Review

Review of the principles of complexity in business administration and application in financial statements

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This paper introduces the background and fundamental aspects of chaos and complexity together with the differences and the links between chaos and complexity, and the distinction between complicatedness and complexity with reference to issues in business administration. There is a need to be cautious when using chaos and complexity models in business administration, not to provide a superficial characterization of reality within a confused narrative. Besides, the application of these theories and models is accompanied with several rationales and logic, such as dialogic reasoning, circumscription, the logic of belief, paraconsistent logic, adductive and default reasoning. All these logic and rationale are applied in business administration and specifically in financial statements analysis, management discussion and analysis and notes to financial statements. There seems to be a need and an opportunity for the use of chaos and complexity in business administration; new logic and models are ready to be applied with solid foundations, but they require new forms of thinking.

Key words: Business administration, management, chaos, complexity, financial statements.

INTRODUCTION

BACKGROUND AND FUNDAMENTAL ASPECTS OF CHAOS AND COMPLEXITY

The sciences of chaos and complexity have been introduced in business administration and their possibilities have been explored (Lewin, 1999); management science is also interested in this new form of approaching reality and its developments. Complexity is evident in papers dating back as early as the 1900s concerning government, in which it is shown how some methods produce paradoxical effects and how simple ideas result in complex methods (Rogers, 1900). In particular, national government growth has been understood to be a product of external complexity, whereas at lower levels of government, growth comes from internal complexity (Appleby, 1954). Complexity can also be found in problems of land registration (Brewter, 1904). In relation to interaction among scientific disciplines, it has been argued that stating this term serves to mask our scientific insufficiency (Bain, 1929). Furthermore, expressive richness has also been defined in terms of complexity (Kemeny, 1955), amongst other concepts.

Later on, Simon (1962) defined a complex system as one made up of a large number of parts, with non-simple interactions among them, in an architecture of levels. Still later, Kauffman (1971) stated the idea that a complex system can be decomposed into different perspectives or non-isomorphic parts, and Wimsatt (1972) described a complex system as characterized by decomposition into parts with non-coincident boundaries.

Finally, regarding information, complexity can be defined as the utility or probability changes that information can produce in a maximal open system (Driver and Streufert, 1969), the amount of information that a
proposition holds (Good, 1974), the inherent difficulty implied in the message of a sentence (Williams, 1979), or the information that makes a predicate capable of expressing more than others (Kemeny, 1955).

These stimulating definitions have endured through time but as part of a non-unified set of theories. Complexity is an intriguing concept (Ekstig, 2010) and scientists must deal with a plurality of incomplete and partially contradictory/supplementary theories (Wimsatt, 1972) as complexity is not a unified set of thoughts or theories (Bousquet and Geyer, 2011). However, the sciences in which the notion of complexity is employed share certain principles (Dooley, 1997), such as basic elements interacting one with another and with the environment, resulting in non-linearity with a feedback loop and self-regulation. Furthermore, complexity theories have in common the idea that the whole is different from its basic elements and emerges from them (Klijn, 2008), that it is more than the sum of its parts.

The notions of a multivalent reality, patterns and indetermination (Dooley, 1997) make complexity an interdisciplinary concept (Mitchell, 2009, p. 4), consisting of methods, reasoning, logic, formulations and narratives about reality. However, core to these approaches are the ideas of non-linearity and uncertainty. Uncertainty permeates many organizational activities, such as planning (Magellan, 2011); complexity, on the other hand, comprises scales and levels that reconcile the whole (Pribam, 1996, p. 41) with interrelations among every part of the system (Richardson, 2008) in a non-linear manner. Complexity also includes one mapping for each micro and macro level (Wimsatt, 1972).

Within complex adaptive systems, there are several models and characteristics, among which Dooley (1997) identifies the following:

a) Complex Adaptive Systems: patterns determining system evolution, attractors, chaotic structures, emerging control and order, transition between equilibrium points, adaptation and self-organization;

b) Autopoiesis: structural change, self-renewal, reproduction, ontology of structural change, dynamics of change, adaptation and self-organization;

c) Dynamic systems: large-scale modeling, nonlinearity and self-regulation,

d) Dissipative systems: conditions far from equilibrium, triggering by events, paradoxical dynamic stability and randomness;

e) Dynamics of chaos: chaotic nature of changes, alternation between inertia and change, moves away from equilibrium and cumulative changes.

Thus, complexity introduces a rich set of concepts and models, but it is necessary to make a clear distinction between concepts and models to avoid confusion in their application. While linear models are intuitively easy to understand, complexity needs to be accessible conceptually before its application. Usually, the popular narratives of complexity that exist in management science describe uncertainty and multiple elements as characteristics that impede understanding and control of a system and the making of predictions.

However, in the absence of understanding of a system, it is not possible to operate within it, so to model it as complex requires a rigorous application of the principles of complexity theory. There is a lack of control and predictability in complexity theory; however, once a system can be modeled as complex, it is possible to operate it by introducing some variations in parameters. This is not like the classical deterministic approach to science, but rather concerns the circumscription of reality, its logic and the application of known models of complexity. Moreover, just as chaos is not unpredictability and disorder (Morin, 2007), so it is with complexity. Yet, the principle of uncertainty implies that variations in parameters tend not to be provided by a rigid set of conditions but by a large number of conditions, which are mostly unknown.

DIFFERENCES AND LINKS BETWEEN CHAOS AND COMPLEXITY

The concept of chaos has received wide spread attention within complexity theory; studies on chaos in complex systems and co-evolution (Anderson, 1999) and chaotic behavior in organizations (Dooley and Van de Ven, 1999) show the links between chaos and complexity. Chaos theory is attributed to the second generation of complexity theory (Alhadeff-Jones, 2008) and connected to the theory of catastrophe (Jakimowicz, 2010; Mckelvey, 1999).

The dynamics of chaos comprise irregular periodicity, sensitivity to initial conditions and lack of predictability (Brown, 1995), and it is sufficient that the system is sensitively dependent on initial conditions (Lorenz, 1995, p.8). Chaos theory involves the qualitative study of unstable and non-periodic behavior in deterministic nonlinear dynamical systems (Kellert, 1993, p.2).

Meaningful information seems to be located between order and chaos (Adriaans, 2009) and consequently chaos is associated with disorder (Villacís, 2005). Complex systems seem to have a more robust structure (Cilliers, 2000). Nevertheless, deterministic chaos is composed of well-defined formulations and analytical solutions (Alligood et al., 1996) that provide a clear structure to chaotic models. Moreover, chaotic mathematical models show that simple models result in complex properties (Morel and Ramanujam, 1999).

Complex systems and chaos can have a weak relationship (Cilliers, 2000) and differences between them could have their origin in narrative and metaphorical language, rather than a deterministic and mathematical perspective. In this regard, several types of language can
be related to chaos and complexity, but each generates different explanations and models that do not converge. Both chaos and complexity show the potential for generalization and large doses of subjectivism, which are necessary qualities in dealing with uncertainty and unknown information, but this promotes non-convergence.

Although complex systems do not imply chaos and chaos does not imply complexity (Morel and Ramanujam, 1999), it is possible that chaos is a part of complexity. Concerning this possibility, chaos theory could be part of complexity theory (Klijn, 2008), and chaos may be a class of behavior within complex systems (Dooley, 1997). Both chaos and complexity belong to a category of models that deal with unknown information, indeterminism, and a certain and partial representation of reality. In relation to both chaos and complexity, a circumscription is made about reality and models are derived from that circumscription. However, the many factors affecting the parameters of the models also confer uncertainty. With regard to this, complexity is a humble approach within which there is recognition of its limits in relation to predictability and control (Bousquet and Geyer, 2011).

Moreover, circumscription is a type of non-monotonic logic; in this logic, certainty is not accomplished through the accumulation of knowledge and error reduction. Defining the system involves determining its characteristics of non-linearity, openness and environmental interaction through a construction comprised of identified patterns. In this sense, a single measure of all-over complexity is not realistic (Bunge, 1962).

**THE DISTINCTION BETWEEN COMPLICATION AND COMPLEXITY AND ASSOCIATED LOGICS**

Simplicity is not easy to accomplish and ultimately simplicity itself is a complex concept (Bunge, 1962). Bunge (1962) defines the material and ideal objects to be classified within the categories of simplicity and complexity. Whereas it is possible for complexity to be a state of the world, complication is a state of mind (Norman, 2010, p.2); this introduces a distinction between the logic of decision making and the logic of the real world. Managerial or business logic acts upon a world which is never fully known, so the first step is defining partial systems or worlds.

Certainly, it is not easy to build a logical architecture every time a manager needs to make a decision. Furthermore, conceptual complexity might obscure the organization’s true situation (Michael, 1968) in the case that it is not based on solid foundations. If complexity spreads across different levels of the world, the boundaries in the part in which we are interested define the level at which complexity arises and the levels where basic elements are located. Complexity arises from simplicity in a hierarchical manner (Simon, 1962) and comprises hierarchical stages (Lamport, 2008).

However, it may be difficult to distinguish between what is complex and what is complicated (see Richardson, 2008), and it might the case that business administration could be operating on a complicated basis while subjacent processes in the world are operating on a complex one. Vasconcelos and Ramirez (2011) argue that organizations cope with both complexity and complication and state that natural complexity guides the actions of the organization. They follow Atlan (1979) in his distinction between complication as algorithmic complexity and complexity as contextual or natural complexity.

Thus, contextual complexity constitutes a right to act in a context in which there is incomplete information, intuitive notions, or contextual pattern recognition concerning the course of action or consequences (Juárez and Contreras, 2012, pp. 15–16). In acting, it is necessary to be adaptive and a precondition for survival is the ability to distinguish between the world as sensed and the world as acted upon through an iterative process (Simon, 1962). That is, information is obtained through action; the complex nature of the world does not allow the development of a framework with complete information, rather it is action that provides information in terms of consequences. Thus, actions can comprise complicated algorithms developed from a complex and unknown world.

Prediction implies complication. Whilst prediction may be based on a well-defined set of premises, in complex contexts it depends on the interaction between elements (Sargut and McGrath, 2011). This means that prediction depends on actions, but is not reduced to them. Furthermore, interaction is circumscribed by the operations of the observer, determining a part of reality as complex. Ultimately, it is impossible artificially to differentiate between what is complicated and what complex as both are, to some degree, present any context (Juárez and Contreras, 2012, p. 19).

Accordingly, managers operate on the basis of a logic that does not follow the rules of classical logic, i.e., they do not follow the condition $p \rightarrow q$, or the law of the excluded middle, $A \lor \neg A$. This logic admits different states and dynamics of reality. For instance, in circumscription, a minimal set of elements of reality, $C(Business\ Reality) = (Cm | Cm \text{ is a minimum set of Business Reality})$, is determined by $Cm = \{x_1, x_2, \ldots, x_n\}$, comprising all the basic interacting units associated by the circumscription.

In paraconsistent logic, different and opposite states must be taken into account in relation to simultaneous existing and decision-making needs. Moreover, dialogic reasoning overcomes the law of the excluded middle (Morin, 2007). Accordingly, $B$ and $C$, being $C = \neg B$, coexist and the decision-making process can verify that one of them is true if $\rightarrow$ and only if $\rightarrow$ the other is false.

The final logic considered here is the logic of belief (Smullyan, 1986), which consists of analyzing the beliefs held on the part of the person reasoning. That is, for all propositions $p$, $tp (Bp \rightarrow (B')p)$, and any belief $B$ that a person holds in relation to a proposition $p$ implies another
believe in $p$, $B^\prime$, or just $p$ being true.

This set of logics (for a detailed description, see Juárez, 2013) helps to address complexity and allows the application of minimum rules in complex daily situations at the managerial level.

**SOME CONCEPTUAL CAUTIONARY REMARKS ON APPLYING CHAOS AND COMPLEXITY IN BUSINESS ADMINISTRATION**

In business administration, metaphors help to build strategies and planning. However, the metaphor of complexity sometimes results in a confused narrative and instead of describing a circumscription of business reality, introduces a superficial characterization. To avoid this, several types of language related to complexity and chaos are useful in business administration. Neo-reductionist, metaphorical and critical pluralistic languages (Richardson, 2008) refer to complexity in different ways.

Based on simulation studies and under the assumption that empirical-analytical formulations can give an account of complexity, neo-reductionist language searches for objectivity in testing hypotheses; in contrast, metaphorical language is the language of daily interactions and is highly subjective. Everyday language does not represent objective neo-reductionist models, but creates new models, employing implicit knowledge that uses non-classical logics in their simple forms. Critical pluralism avoids the excesses of the other two (Richardson, 2008) and consists of a critical reflection, a deconstruction and construction of reasoning about complexity.

The use of these different narratives and complexity models indicates that translating business reality into an intelligible and considered explanation it is not an easy task. It is necessary to avoiding common-sense recommendations. The world is complex (Elsner et al., 2010; Urry, 2011), but the fact that complexity is an intriguing concept with no agreed definition (Ekstig, 2010) and that many models comprise complex properties (Morin, 2007) does not justify an excessive simplification of logic.

**INSIGHTS INTO THE APPLICATION OF CHAOS AND COMPLEXITY IN FINANCIAL STATEMENTS**

There are many applications of chaos and complexity in the field of business administration. In particular, in relation to corporate finance, there are examples of chaotic models of macroeconomics explaining failure, transformations and sources of economic complexity (Jakimowicz, 2010), or explaining how financial markets correct their mistakes (Haley, 2010), as well as chaotic and complex models of financial health (Juárez, 2010a, 2010b, 2011a, 2011b).

Furthermore, the notion of complex adaptive systems has been applied in supply chains (Choi et al., 2001), breeding programmes (Teisman, 2008), government (Teisman and Klijn, 2008), strategic public management (Bovaird, 2008), management (Boisot and Child, 1999; Salamadra et al., 2008; Sterman and Wittenberg, 1999; Tait and Richardson, 2008), organization and capabilities (Augier and Teece, 2006), bargaining games (Chatterjee and Sabourian, 2000), market analysis (Gale and Sabourian, 2005), competitive advantage (Stefanović et al., 2011), the development of new products (Kim and Wilemon, 2007), and landscape design (Levinthal and Warglien, 1999).

Other areas of interest in applying complexity to business administration are entrepreneurship (Swanson and Zhang, 2011), leadership (Denis et al., 2000; Hannah and Lester, 2009; Hooijberg et al., 1997; Juárez and Contreras, 2012; Ussahawanitchakit, 2011), and culture generation (Frank and Fahrbach, 1999).

No doubt many of these studies have had an impact on financial statements, but it seems that the financial statement remains embedded in a normative paradigm. Financial accounting as a whole is rather normative (Frezatti et al., 2009) and as such is not permeated by chaos and complexity approaches. Many issues in financial statements are under scrutiny, for instance intangibles (Lev, 2008; Skinner, 2008a, 2008b), and are the subject of disagreement among experts (Springer and Borthick, 2004), as are competency-based education (Boritz and Carnaghan, 2003), human resources accounting (Grant et al., 1976), natural resources accounting (Harris and Fraser, 2002), goodwill (Ketz, 2002), codes of conduct (Neill et al., 2005), and critical accounting policies (Levine and Smith, 2011).

Moreover, basic concepts have been discussed in relation to Financial statements, such as income (Bedford, 1951), Assets, Liabilities and Equity (Chambers, 1975), cash flow (Gombola and Ketz, 1983), earnings management (Jiraporn et al., 2008), financial distress (Purnanandam, 2008; Titman and Tsyplakov, 2007), and financial health and chaos theory (Juárez, 2010a, 2010b, 2011a, 2011b; Juárez and Farfán, 2012). In addition, the use of concepts from biology (Máràcine and Delcea, 2009; McKelvey, 1999; Morel and Ramanujam, 1999) in terms of syndromes such as bankruptcy (Scarlat and Delcea, 2011) has been introduced in the analysis of financial statements.

Accordingly, critical thinking is necessary (Camp and Schnader, 2010; McBride et al., 2005) due to the presence of uncertainty in estimates (Billings, 2011) and accounting principles (Manninen, 1997), as well as the fact that financial information admits different interpretations (Bjurklo, 2008). Another logic allowing for uncertainty and the existence of contradictions could provide a different view.

Regarding the fundamental aspects of accounting, the basic model Assets = Liabilities + Stockholders’ Equity is based on logical reasoning and not a mathematical computation. A well-established set of standards for
accounting sustains this model. However, from a different viewpoint, the sum of liabilities and stockholders’ equity is not equal to assets; they are different categories. In general, we could say that assets comprise real amounts, and liabilities and stockholders’ equity are claims against those assets. Classical logic, which does not allow for the existence of opposites, cannot explain this; something cannot be and not be at the same time (the principle of the excluded middle).

Other logics are capable of explaining the operations in financial statements, i.e., dialogic reasoning allows for the existence of contradictions (Morin, 2007) and default reasoning explains the assignment of transactions to items in the absence of examples that contradict the rule. Also, abductive reasoning makes it possible to perform a transaction whenever an adequate explanation exists, by a rule of generalization.

Moreover, it might be possible to define a proposition \( p \) by applying a true-false value, for example, "transaction X is made in unearned service revenue". Now, bearing in mind the principles of circumscription logic (McCarthy, 1980), a proposition is considered true only if necessary and if it is possible that a proposition is false, it is false. In this case, it is possible that proposition \( p \) is false because the service could not be provided and thus, according to circumscription logic, this explanation, which did not exist in initial premises, must be taken into account. Accepting the minimum of truth means applying circumscription logic to financial statements.

In addition, the Management Discussion and Analysis (MD&A) section in financial statements, Critical Accounting Policy (CAP) and Critical Accounting Estimates (CAE) present uncertainties, and estimate determination and accuracy (O’Shaughnessy and Rashty, 2005, 2007), but all of them are highly subjective. In the same manner, Notes to financial statements deal with policies and information concerning doubts in financial statements. These reports tend to contain contradictory sentences – violating classical logical principles – and to be based on a set of beliefs.

This can be overcome through paraconsistent logic, which admits contradictions. According to this, and assigning true (\( T \)) and false (\( F \)) values, it is possible to say that a sentence is true if and only if the opposite is false: \( T(B) \iff F(\neg B) \). Thus, the contradiction is solved by a logical relationship between contrasts. Furthermore, Notes to financial statements are based on a set of assumptions that are sustained as long as none of them fail. This set of beliefs \( B(b_1, b_2, b_3, \ldots) \) makes reasoners of financial analysts. Thus, there are several options, depending on the reasoner (Smullyan, 1986) engaging in the analysis and the degree of certainty that the analyst attributes to himself or herself. Moreover, the analyst can always change some beliefs.

Finally, the use of logarithmic transformation results in chaotic distribution in many items of financial statements (Juárez, 2010a, 2010b, 2012, 2013). Logarithmic transformations are examples of the emergence of complex systems or patterns from initially simple origins (Morel and Ramanujam, 1999).

**CONCLUSION**

A link is needed between complexity/chaos theory and management and financial statements. This link must be explained in management language and logic using different approaches based on models of the social and natural world. This means avoiding linguistic idealism (Manninen, 1997), unrealistic experimental tasks (Booth and Cocks, 1990), and living in an “ivory tower” (Elwin, 2008). Management and financial statements demand new explanations. It is not possible for business administration to make a transition to chaos and complexity models while continuing to base financial statements on the same principles that have been in force for decades. There is a new logic (Lewin, 1999) to be applied to organizational routines (Morel and Ramanujam, 1999) and new forms of thinking about these routines are needed.

**REFERENCES**


Entrepreneurial Orientation in Marketing:
An empirical study of small businesses
in the Swedish fashion industry

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Abstract

Entrepreneurial orientation (EO) can be defined as strategic processes encouraging entrepreneurial actions to support businesses in recognizing and exploiting new opportunities. Previous studies have shown that businesses with higher levels of EO, characterized through actions that are innovative, proactive and risk-affine, perform better than the ones that lack such orientation. Therefore, EO is considered to be a crucial aspect when businesses seek to gain a competitive advantage. Little has been investigated by using an approach that combines EO literature with regards to marketing activities, and therefore this study contributes to the research field by applying EO theory in marketing context. The study employs three core elements of EO as a framework to analyze small businesses’ marketing activities and related competitiveness. The study applies a qualitative approach of analysis and conducts semi-structured interviews with four small businesses owners within the Swedish fashion industry to collect data.

The three sub-dimensions of EO were found to be highly related to each other, which means that all of them were encouraged with regard to the firm's marketing activities in order to enforce a competitive advantage. The results also show that businesses in the fashion industry mainly concentrate on product and market innovation, whereas administrative innovation was not encouraged in any of the cases. More specifically, introducing new concepts, experimenting with marketing activities, entering new markets, building a relationship to customers, adapting alternative distribution and supply channels were the key activities that increased a competitive advantage. An unexpected outcome was that small businesses in the Swedish fashion industry actually tend to cooperate with their competitors and form strategic alliances in order to benefit from economies of scale, share industry experiences, as well as understand and satisfy latent customer needs, and therefore overcome liability of smallness.

This paper also contributes to the research field by advancing EO theory, i.e. incorporating two new strategic actions: building a relationship to customer and full control of the production process, which were not previously discussed in EO literature. Additionally, this study provides the Entrepreneurial oriented marketing model, which contributes not only for small businesses within the fashion industry, but also indulges a better understanding what issues are important when seeking to gain a competitive advantage through the use of entrepreneurial orientation in marketing activities.

Keywords: Marketing, Small businesses, Entrepreneurial marketing, Entrepreneurial orientation, Innovativeness, Proactiveness, Risk-taking, Competitive advantage.
Introduction

As highlighted by numerous scholarly investigations, small businesses are a vital component of economic wealth, since they account for a major source of employment (Eggers et al., 2013; OECD, 2000). When investigating factors that promote economic wealth, the concept of Entrepreneurial Orientation (EO) has often been considered, as EO enhances competitiveness and consequently the performance of small businesses (Keh et al., 2007). Besides other areas, such as strategy and firm culture, EO has a strong impact on the marketing of a business. In fact, the integration of EO in marketing activities constitutes a specific research area called Entrepreneurial Marketing (EM), which helps small businesses that are resource-constrained and face a liability of smallness, to be competitive and successful in the market.

Many studies have investigated the effect of EO and EM on performance and organizational strategies, but little has been investigated when it comes to small businesses’ marketing activities that lead to a competitive advantage. Even though the relationship between EO and EM is obvious (due to overlapping dimensions), EM theory solely focuses on entrepreneurial and marketing concepts and little investigates competitiveness, meanwhile EO theory studies entrepreneurial attribution and competitiveness, but does not analyze marketing concepts. Therefore, by linking these two theories we create an alternative framework of analysis and look at marketing activities and competitiveness from different lens, where only three EO (and EM) sub-dimensions are taken into consideration.

Previous studies have found that three sub-dimensions of EO, risk-taking, proactiveness and innovativeness, have the highest impact on businesses’ performance. Therefore, this study analyzes these sub-dimensions of EO as elements of the marketing strategy to understand how small businesses gain a competitive advantage. Hence, the research question is formulated as follows:

How do small businesses gain a competitive advantage through EO in their marketing activities?

To provide a structured answer to the research question the remainder of this paper is divided into six chapters. First, marketing in small businesses, entrepreneurial marketing and entrepreneurial orientation are introduced as the basis for the theoretical framework. The second chapter introduces the research methodology: background, empirical context and sampling selection, data collection as well as the method of data analysis. Subsequently, the empirical results are presented, followed by the analysis and discussion as well as the introduction of a guideline for small fashion business owners. Finally, conclusions and directions for future research are emphasized and limitations are highlighted.
Background and theoretical framework

Marketing in small businesses

The American Marketing Association describes marketing as “the activity, set of institutions, and processes for creating, communicating, delivering, and exchanging offerings that have value for customers, clients, partners, and society at large” (American Marketing Association, 2014). Despite the standard definition, small business owners approach their marketing efforts in different manners than professional marketing managers in large businesses (Carson & Cromie, 1989). One of the main reasons for this differentiation might be the nature of small businesses itself. It has been found that small businesses are resource-constrained and face liability of smallness (Aldrich & Auster, 1986; Kraus et al., 2010). According to Morris et al. (2002) and Gilmore (2011), limited resources and underdeveloped marketing skills often lead to unsophisticated and unplanned marketing activities. Therefore, marketing is crucial for the success and survival of small businesses. Thus, in order to remain competitive, small businesses frequently rely on creativity and innovation (Morrish, 2011). These firms employ “marketing activities with an entrepreneurial mindset” (Kraus et al., 2010, p. 19).

Entrepreneurial marketing

Very often Entrepreneurial Marketing (EM) is related to marketing activities in businesses that are resource constrained (Morris et al., 2002). However, it is also recognized that EM is relevant for all types of businesses, i.e. small and large businesses (Jones & Rowley, 2011), since the utilization of EM often enhances business performance irrespective of the firm size.

Morris et al. (2002, p. 5) define EM as “the proactive identification and exploitation of opportunities for acquiring and retaining profitable customers through innovative approaches to risk management, resource leveraging and value creation”. EM is also characterized as opportunistic and intuitive marketing activities, since EM aims to offer customers something different or more than competitors, i.e. add value to the customer (Gilmore, 2011).

As a result of the interface between entrepreneurship and marketing, EM is characterized by proactiveness, innovativeness, calculated risk-taking, opportunity focus, resource leveraging, customer intensity, and value creation (Morris et al., 2002). The first five elements highly relate and overlap with EO concepts. A clear relationship between EO and EM intrigues to combine them into an alternative study framework in order to analyze how entrepreneurial oriented marketing activities could increase competitiveness.
Entrepreneurial orientation

For decades, EO has been emphasized as the core value of innovative businesses and found to promote a competitive advantage. EO can be defined as strategic processes encouraging entrepreneurial actions, such as recognizing and exploiting new business opportunities (Lumpkin & Dess, 1996; Wiklund & Shepherd, 2003). More specifically, EO is the key factor affecting organizational strategy, firm culture, leadership, and marketing (Phokha & Nonsrimuang, 2013). In consequence, it has been proved that enterprises with higher levels of EO perform better than the ones with a lack of such orientation (Keh et al., 2007).

Prior studies have found EO to be a significant factor when seeking to gain a competitive advantage. For example, Lechner’s et al. (2014, p.53) found that “entrepreneurial behavior acts through the development of a competitive strategy”. In other words, EO has to be related to the strategic goals, when seeking to gain a competitive advantage. Despite the importance of EO with regard to competitiveness, EO theory does not analyze the effect of EO on marketing concepts. To complete this research gap we compared the dimension of EM with the construct of EO. The three sub-dimensions, namely proactiveness, innovativeness and risk-taking, were found to overlap and have a strong impact on firm performance (Rauch et al., 2009). Consequently, we focus on those three dimensions to investigate the effect of EO on marketing activities in small businesses within the Swedish fashion industry. A combination of EO and EM theories not only complements previous research, but also forms a new framework of analysis, which accredits better understanding how small businesses gain competitive advantage through EO in their marketing activities. Hence, the following sections will introduce each dimension in details.

Innovativeness

Very often innovativeness is highly related to the “organization’s tendency to engage in and support new ideas, novelty, experimentation, and creative processes that may result in new products, services or technological processes, as well as the pursuit of creative, unusual, or new solutions to problems and needs” (Madhoushi et al., 2011, p. 310). In other words, technological development or product innovation can be utilized when pursuing new opportunities or seizing a competitive advantage (Knight et al., 1995; Lechner et al., 2014; Lumpkin & Dess, 1996; Thoumrungroje & Racela, 2013).

However, encouraging and managing innovativeness can be very challenging, as it requires abandoning established practices (Dess & Lumpkin, 2005). For example, technological
innovativeness requires research and engineering efforts when introducing new products and processes, product innovativeness demands market research, product design, and innovative marketing techniques, whereas administrative innovativeness is built on “novelty in management systems, control techniques, and organizational structure” (Dess & Lumpkin, 2005, p. 150).

In fact, a number of authors propose the link between innovation and creativity, new product or service development, and new approaches to marketing issues (Knight et al., 1995), enhances the generation of a competitive advantage (Kandampully, 2002; Martin & Rana, 2001; Stokes, 2000) and opportunity recognition (Hulbert & Brown, 1998; Nonaka & Takeuchi, 1995; Raymond et al., 1998; O'Dwyer’s et al. 2009). However, existing studies analyzing EO are rather focusing on the organizational strategy than marketing. Therefore, this study finds an intrigue to examine how an innovative approach in marketing activities might affect competitiveness.

Innovativeness in marketing

Innovative marketing approach is defined as a gap “between innovation and market positioning to achieve a sustainable competitive advantage” (Gardner, 1991, p. 18), whereas later studies often label innovative marketing as a part of entrepreneurial marketing (Schindehutte, 2009). Hence, one can sum up that innovativeness in marketing can be perceived through entrepreneurial marketing activities.

Traditional marketing activities are hardly affordable to financially restricted small businesses. Consequently, firms are looking for new ways to gain a competitive advantage rather than employing expensive marketing campaigns. One way to seek a competitive advantage through an innovative approach is to employ strategic alliances as a marketing tool, which allows small businesses to act with the capacity of a large company, “expanding their resources, skills and abilities and geographic spread” (O'Dwyer et al., 2011, p. 91-92).

According to Carson et al. (1998) and Stokes (1995), the primary components of innovative marketing are: product improvements, alternative distribution channels and methods, exploration of new markets, alternative marketing mix and new operational systems. Meanwhile, a later study does not support the previous findings such as distribution channels and uniqueness as elements of small businesses innovative marketing practices. In fact, it demonstrates the integrity of the emergent innovative marketing concepts of small businesses’
image, strategic alliances and product quality to innovative marketing activities (O'Dwyer et al., 2009).

**Proactiveness**

Proactiveness refers to the ability to recognize new opportunities and shape the environment (Merlo & Auh, 2009). In other words proactiveness within the EO framework seeks to identify opportunities in products and/or technologies as well as in markets and consumer demand (Lumpkin and Dess, 2001).

Proactive behavior is highly coherent with understanding customer and competitors, as well as monitoring trends and changes in the industry and the overall environment. Certainly, recognizing and proactively reacting to those changes might lead to great business opportunities. However, it is not only about “recognizing changes, but also willingness to act on those insights ahead of the competition” (Lumpkin and Dess, 2005, p. 150).

According to Lumpkin and Dess (2005), proactiveness might lead to a first mover position or industry leadership. In fact, businesses benefit from proactiveness in terms of profits, brand recognition and market shares. However, it is unknown whether small businesses in the fashion industry are able to enhance their competitive position by being proactive with regard to their marketing activities. Hence, we find the proactive approach as an important aspect to examine with regard to marketing activities when seeking a competitive advantage.

**Proactiveness in marketing**

The majority of scholarly research defines proactive marketing actions as comprehensive market information utilization, i.e. understanding customers and competitors in order to improve strategic decisions in marketing (Keh et al., 2007). Thoumrungroje and Racela (2013), and Lamore et al. (2013) complement the definition by adding active opportunity-seeking and forward-looking strategic actions to understand, redefine and satisfy latent customer needs which in consequence creates value. Other studies have acknowledged the importance of creating value based on market demands or trends and consequently being the first-mover in the market in order to gain a competitive advantage (Lumpkin & Dess, 1996; Lumpkin & Dess, 2001; Hills & Sarin, 2003; Martin-Consuegra et al., 2008; Venkatraman, 1989). In summary, it can be assumed that proactive marketing actions stimulate a competitive advantage (Hunt & Madhavaram, 2006).
**Risk-taking**

According to Eggers et al. (2013), risk-taking refers to the organization’s agreement to commit resources with uncertain outcome. Dess and Lumpkin (2005) distinguish three types of risk that businesses encounter: business risk, personal risk, and financial risk. Business risk emerges when for instance new markets are entered, which involves unknown chances of success, whereas personal risk-taking refers to the risks that a business owner takes when choosing a strategic action, which certainly influence the direction of the business. Financial risk-taking is involved when a business invests large amounts of its resources with the intention to grow.

Frequently, the risks mentioned above are taken with the purpose to gain high returns by taking opportunities in the market (Memili et al., 2010). However, even though many businesses tend to be risk-averse, March and Shapira (1987) state that small businesses should take well-calculated risks in order to be successful (Caliendo et al., 2010). In fact, by detailed market research relevant information of potential consequences can be found out to elaborate possible scenarios and outcomes.

**Risk-taking in marketing**

Morrish (2011) states that risk-taking implies a company’s propensity to offer a product that is not well known or accepted within the market. In other words, a company might take a risky strategy when introducing a product, which serves customer needs that do not yet exist, rather than solely serving expressed customer needs. However, in order to obtain a competitive advantage, businesses need to take risk to some extent, e.g. introducing new products or services in new markets (Dess & Lumpkin, 2005).

According to Morris et al. (2002), in order to reduce and manage risk, marketers attempt to redefine components of the external environment, as for example, collaborating in marketing projects with other businesses, developing joint-projects, testing staged productions, working with lead users, implementing strategic alliances or handling resources in different ways. Another method to lower risk is active networking. According to Gilmore (2011), as small business owners do not implement conventional marketing activities, but rather adapt the traditional frameworks to their own situation, they frequently use their peers as well as other business contacts in order to collect relevant information. Therefore, networking can also contribute to promote a competitive advantage. Another way to reduce and better manage risk is to use a customer-centric approach, i.e. maintaining a close relationship to customers in
order to receive feedback, which is in turn less expensive than formal market research (Morrish, 2011). In conclusion, it can be said that only well-calculated risks might benefit when seeking a competitive advantage.

**Summary of literature review**

The main finding in the literature review is that EO in marketing activities is an important factor for small businesses that seek to gain a competitive advantage. For instance, the development of innovative products, the formation of strategic alliances, entering new markets, the implementation of novel operational processes, proactiveness towards industrial changes, actively monitoring and adjusting to changes in the external environment, and taking well-calculated risks, all help to promote a competitive advantage.

The literature review has also shown that different theories and their combinations (Entrepreneurship, Marketing, EO, EM) focus on different elements. For example, EM is a combination of entrepreneurial and marketing concepts, however little investigates the competitiveness. Meanwhile, EO focuses on entrepreneurial attribution, and competitiveness, but does not analyze marketing concepts. A combination of EO and EM theories complements previous research and forms an alternative framework of analysis, which accredits better understanding how small businesses gain a competitive advantage through EO in their marketing activities. In other words, this study framework complements previous research, by combining EO and EM theories and allowing a comprehensive analysis on EO in marketing activities. Furthermore, there is little knowledge when it comes to small businesses in competitive industries, such as the Swedish fashion industry. Therefore, in this study, we use the three core dimensions of EO (risk-taking, proactiveness and innovativeness) as elements of the marketing strategy to analyze and understand how small businesses gain a competitive advantage.
Research methodology

In the following chapter the research methodology is described. This includes the background of the study, empirical context and sampling selection, method, data collection process as well as method of analysis.

Background

The motivation for academic research emerges either from a problem or a research gap. In this regard, either a new theory is developed or an existing theory is applied to a new context (Sandberg & Alvesson, 2011). The present study is based on a research gap and tries to advance existing theories in EM and EO, combining them to a new framework i.e. applying EO theory when analyzing marketing activities and competitiveness. As emphasized in the literature review, a number of studies have been conducted on EO and its relation to firm performance. However, there is a research gap in how small Swedish fashion businesses gain a competitive advantage by applying EO in the marketing activities. The assumption that a competitive advantage can be gained by applying EO in the marketing activities is retrieved from the circumstance that enterprises with higher levels of EO are found to perform better than the ones lacking such an orientation (Keh et al., 2007). In consequence, our study “does not question the assumptions underlying established literature <...rather advances…> already influential theories” (Sandberg & Alvesson, 2011, p. 131).

Empirical context and sampling selection

The fashion industry is an important source of employment in Sweden, since it provides approximately 50.000 job positions, being comparable to the size of the Swedish food industry with regard to employment (Association of Swedish Fashion Brands, 2013). The competitive nature of the fashion industry implicates the phenomena of fast reaction to changes, such as quick introduction of new collections, constant threat of new entrants in the market and high focus on innovation (Hauge et al., 2009). Hence, the fashion industry is highly important for the Swedish economy and therefore serves as a good research object for the study. Moreover, by linking established theories (EO and EM) to an underexplored context (the Swedish fashion industry) we contribute to the entrepreneurship field in order to better understand how small businesses can gain a competitive advantage (Zahra, 2007).

Regarding the research focus, we solely selected small businesses. According to the Official Journal of the European Union (2003), small businesses are companies that employ less than
50 people with an annual turnover or total annual balance sheet that does not exceed 10 million Euros. To select potential participants for our study, we carefully screened the members of the Association of Swedish Fashion Brands (ASFB) as well as some other Swedish fashion brands that are not members of the ASFB, always considering the turnover and the number of employees (Allabolag.se) to verify their categorization as a small business. Consequently, twenty fashion businesses were selected and asked to contribute to this study by sending a formal e-mail and/or phone calls. Regarding selection criteria, we also considered to interview heterogeneous companies since this type of sample would enhance the quality of the research in comparison to analyzing similar cases. Four fashion businesses (Conservative, Nerdy by Nerds, Nikolaj d’Étoiles, and Tailor Store) agreed to contribute to the study. We believed that analyzing these companies, which have different business models, operate in different locations and are diverse in age, could benefit the study since data is less biased, consequently providing more legitimate findings that can be generalized for this particular industry. For instance, Conservative, Nerdy by Nerds, and Tailor Store offer customized products, whereas Nikolaj d’Étoiles offers ready-to-wear fashion. Conservative, Nerdy by Nerds, Nikolaj d’Étoiles are mainly acting in the Swedish market, meanwhile Tailor Store exports to 70 countries. Conservative and Nerdy by Nerds are located in Malmö, Tailor Store has its headquarters in Helsingborg, meanwhile Nikolaj d’Étoiles is based in Stockholm. Nicolaj d’Étoiles and Tailor Store were established in 2003, whereas Conservative was founded in 2010 and Nerdy by Nerds in 2011. Therefore, we considered these four companies as potential providers of valuable information for this study.

**Method and data collection process**

Due to the identified research gap the present study applies a case study approach based on semi-structured interviews (Yin, 2009). A case study is characterized by richness in data collection, meaning that the study does not focus solely on one data collection method but rather uses several sources of verification (Yin, 2009). Therefore, besides the semi-structured interviews, the study was supported by secondary sources, such as internal strategic documents, information on the company websites, and the Allabolag’s database. As emphasized by Yin (1994), semi-structured interviews are one of the most important sources of qualitative research as it provides the possibility of descriptive and free responses, whereas the interviewer is able to add or modify questions during the interview. Furthermore, contrary to quantitative research, qualitative research serves to develop respectively advance a theory.
(Bryman and Bell, 2011) and enables to ask specific questions as well as to observe on certain behaviors and attitudes.

An interview guideline was elaborated by taking questions into consideration that have been developed by previous studies (Dess & Lumpkin, 2005). Seeking to gain legitimate and truthful answers in order to conduct a valid research, semi-structured questions were used rather than leading, close-ended questions. Three interview sessions/rounds within each company were conducted. The first round interviews aimed to gain an overall picture of the company and its background as well as getting first insights on their marketing activities. Subsequently, the second interview with each company concentrated on the main themes, namely innovativeness, proactiveness, and risk taking. The third interview was a follow-up of the first two interviews to assure that each theme was covered, and to ensure a proper interpretation. Three companies were interviewed in person, and one via phone call.

**Method of analysis**

Analyzing qualitative empirical data is a systematic process, with the main focus on patterns and regularities in order to advance existing theory. Due to the narrative structure and deviated responses, the data has to be analyzed in divergent ways. (Eisenhardt, 1989)

The process of our qualitative analysis includes: description, systematization, categorization, and final combination (Eisenhardt, 1989). First, each company is presented separately, including a short background and recent marketing activities. Second, at the systematization stage, a thematic analysis with regard to innovativeness, proactiveness and risk-taking in terms of marketing activities was conducted. At the categorization stage the responses of the four companies were screened for similarities and differences in order to search for hidden relationships and categorize them into sub-themes respectively. To improve the accuracy the two authors analyzed the interviews separately. Moreover, a member check method was adopted to improve accuracy and credibility of the analysis, once the data was categorized. This step involved the verification of the results and the researchers’ interpretation. Therefore, the cases were sent to each company in order to verify the accuracy of the interpretations. Last, in the final combination stage, the main findings and practical implications were discussed by drawing connections to findings of the literature review.
Empirical results

This chapter will highlight the results of the interviews that have been conducted with the companies that agreed to participate in our study. The empirical results of each case company will be presented in themes, namely proactiveness, innovativeness and risk-taking with regard to their marketing activities. Table 1 provides some background information on each company.

Table 1: Interviewed companies

<table>
<thead>
<tr>
<th>Name</th>
<th>Number of employees</th>
<th>Total annual turnover (TKR)</th>
<th>Activities</th>
<th>Year of foundation</th>
<th>Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>0</td>
<td>436</td>
<td>Tailor made clothes</td>
<td>2010</td>
<td>Malmö, Sweden</td>
</tr>
<tr>
<td>Nerdy by Nerds</td>
<td>2</td>
<td>1,679</td>
<td>Customized jeans</td>
<td>2011</td>
<td>Malmö, Sweden</td>
</tr>
<tr>
<td>Nicolaj d'Etoiles</td>
<td>1</td>
<td>699</td>
<td>Ready-to-wear</td>
<td>2003</td>
<td>Stockholm, Sweden</td>
</tr>
<tr>
<td>Tailor Store</td>
<td>14</td>
<td>46,296</td>
<td>Tailor made clothes</td>
<td>2003</td>
<td>Helsingborg, Sweden</td>
</tr>
</tbody>
</table>

Sources: Allabolag, 2014; Nerdy by Nerds, 2014

Conservative

Background

Conservative is a classic and timeless fashion brand located in Malmö, with the main focus on made to measure clothing (Conservative, 2014). The company was founded when the owners have noticed a so-called trend for craftsmanship. The main competitive advantage of this business is a personalized communication as well as a long-term services based on a close relationship with customers (personal attachment, where the cost of choosing an alternative is too high). Furthermore, the location itself is a great advantage, considering the second fashion adopters approach in Malmö, which allows foreseeing the main trends for the following year.

Marketing

One of the initial marketing activities of Conservative was direct communication to potential customers with high income and social position leaders. A number of calls, a showroom in the
city center and folders with personal letter inviting to see the craftsmanship concept, have lead to their first and long-term high-end customers. Moreover, the founders of Conservative acquired a retail-shop that offers ready-to-wear brands - Engelska Herr in December 2013. The retail-shop and the Conservative studio are located in the same building, which was a strategic decision. For instance, if a customer is not satisfied with a ready-to-wear suit in Engelska Herr, he can directly be introduced to the Conservative studio downstairs where personal measurements can be taken to tailor a perfectly fitting suit. This way the co-founders combine and complement two businesses based on two different concepts.

In regards to traditional media, Engelska Herr has two ads a year in the newspapers *Sydsvenkan* and *Vellingeposten* to promote their sales. However, Conservative’s main marketing activities remain in social media. Different to the other interviewed companies, for Conservative the brand recognition is not important, being word-of-mouth between high-end customers the most powerful marketing technique in this business. Customer loyalty and high-end products do not require large quantities, but rather time for personalized service and direct communication with customers.

**Innovativeness**

Conservative is quite traditional and does not follow the latest trends. The company rather focuses on late adopters in Southern Sweden by imitating last year’s trends from Stockholm. The concept of made to measure clothing is very traditional, however it has been used little in the past decades. Therefore offering the “forgotten” old fashion way of making suits has become a sort of “innovation”. Besides, the young co-founders encourage experimentation (by having a “try-out” approach) and often introduce new attractions to customers. For instance, this autumn Conservative will make an art-show in the store with cooperation of a gallery in Halmstad, inviting their largest clients and the press to the event. The combination of a physical and online store is another “try-out” activity aiming to satisfy different customer groups. To better reach potential customers and to strengthen marketing activities, Conservative cooperates with accessory retailers, photographers, galleries. Furthermore, they take a novel approach by cooperating with competitors in order to overcome liability of smallness.
**Proactiveness**

To differentiate themselves from the aggressive competitors in the clothing industry, Conservative strictly focuses on their strength – made to measure clothing with personalized service. The co-founders are also proactive towards the increasing e-commerce boom, and therefore will open an online store in July 2014. The online store will include the ready-to-wear collection available in Engelska Herr, as well as the offers from Conservative. Furthermore, Conservative proactively reacts to economic and behavioral changes. For example, when sales are decreasing, Conservative bargains with suppliers for better conditions and therefore reduces one of the business risks. Conservative visits fairs and follows trends in bigger fashion cities such as London (first adopter) and Stockholm. This way the company stays alert and proactively satisfies customer needs.

**Risk-taking**

As outlined before, Conservative focuses on late adopters in the Malmö region, therefore it is a low risk business. Furthermore, as the brand of Conservative is not famous yet, the company has not experienced that competitors so far tried to imitate their business model.

In order to reduce common risks within this industry (such as investing in large stocks or expensive marketing activities with unpredictable outcome, etc.) the business critically reflects on each marketing activity, has an established budget, and solely commits on short-term bases.

**Nerdy by Nerds**

**Background**

Nerdy by Nerds (NBN) is a small manufacturing business specialized in customized, tailor made jeans with a novel concept in Europe. The novelty of the concept and full control over the factory are the main components of NBN’s competitive advantages. The business was established when the co-founders noticed a gap and a demand in the market - customers liked the idea to have tailor made jeans and were curious about how the manufacturing process works. Today NBN offers not only a great customer experience in the shop-factory in Malmö, but also sells online. This spring NBN is opening a second shop in Stockholm and plans to enter other European markets, such as Berlin and London.
**Marketing activities**

The marketing strategy of NBN has two main components: brand building and sales marketing. Brand building is well controlled and based on creating awareness of the concept and the brand in the press. NBN receives a lot of attention from the media since the concept is new and sustainable, which is a good strategy to create brand awareness without incurring expenses. Furthermore, the realization of a crowdfunding campaign not only has increased brand awareness and funds, but also gathered investors that contribute with their knowledge and expertise within the field of fashion. However, sales marketing is much more complicated and concentrates on the customer value. Currently, the marketing efforts are mainly focused on social media (Facebook, Instagram, Twitter, Tumblr) as well as PR team that constantly searches for brand ambassadors, such as fashion bloggers or people in the music industry, etc. In order to overcome challenges in marketing, NBN mainly tries out and checks if an activity increases the sales and only invests further into the strategies that bring desirable outcomes.

**Innovativeness**

Even though the product offered by NBN is traditional, the concept of “shop factory” is novel in Sweden (Nerdy by Nerds, 2014). Furthermore, NBN stimulates innovation and experimentation, by introducing the concept for serving a new niche - women. One of the strategic decisions of NBN was to start a crowdfunding campaign, which is a relatively novel and little researched marketing technique. Concerning NBN’s concept and the nature of business (manufacturing based on customer orders) there is little space left for creativity. However, the team has frequent meetings for brainstorming and experimenting new designs. Specifically in marketing, experimentation is a learning process, meaning that they try out different marketing strategies in order to find out which one works best for NBN. For example, to understand the market NBN is cooperating with students from universities who organize focus groups and research market.

**Proactiveness**

To satisfy customers, NBN proactively reacts to industry changes and trends. For instance, NBN is aware of a growing trend regarding conscious customers, and therefore encourages product quality and social responsibility. Furthermore, by possessing full control in the production (own factory), rapid changes can be implemented.
NBN also attends fashion fairs in Stockholm, Copenhagen, Berlin and Paris in order to stay up to date, discover new trends, and establish contacts with suppliers and people within the fashion industry. Furthermore, NBN is proactively listening to their customers (new ideas, prices, etc.) For example, if several customers ask for something specific, they consider introducing it to the market.

NBN constantly does market research. For instance, the owners have noticed that the majority of Swedish fashion businesses are located in Stockholm. To increase sales and obtain market share, NBN has decided to open a second store in Stockholm. Moreover, they are analyzing the possibility to offer the products through retailers as well as introducing the concept within other European markets.

**Risk taking**

The business concept does not require having large stock, hence there is no large financial risk involved. As risk-taking remains within various parts of the NBN’s strategic decision processes, most of the actions are based on experimentation. For example, to minimize risks NBN adopts a “try-out” approach and short-term commitments, to find activities that actually enhance the company’s outcomes. In order to take well-calculated decisions, the NBN team also conducts market research. For example, before engaging in the crowdfunding campaign, NBN’s founders did some research in order to minimize the risk of losing control. Nevertheless, they are aware that planning does not secure from failure due to the fact that certain aspects cannot be foreseen.

**Nikolaj d'Étoiles**

**Background**

Nikolaj d'Étoiles (NdE) is a small business, representing a luxury fashion brand for menswear in Scandinavia. NdE reinvents classical garments by combining them with innovative design (Nikolaj D’Étoiles, 2014). The business has been established when the co-founders have noticed the gap in the market and customers’ interest in high quality menswear. Today the main business operations include building and designing three collections per year, marketing and sales as well as the day-to-day collaboration with vendors, and searching for new opportunities such as opening an online store or a physical store. So far NdE mainly cooperates with retailers in Sweden and Norway, namely VOLT Magasin, Jupiter, Awesome Rags, Divanti and Rådhuset, but plans to enter new markets in a near future.
**Marketing activities**

NdE has recently invested in a PR agency in order to be more visible in the press and stay on the top in the fashion industry. Opposite to most traditional businesses, NdE does not use any traditional marketing instruments, except advertising through Volt magazine (their main partner and retailer in Norway). Furthermore, NdE is active in social media (Facebook and Instagram), however it remains selective and content-driven concerning the target customer and brand values. Their competitive advantage is highly related to their marketing strategy of solely offering high quality, caring about fabrics and details, as well as aiming for new trends by designing classic but arrogant styles.

**Innovativeness**

NdE is a traditional brand, however in 2003, when NdE was established, a luxurious menswear fashion concept in Scandinavia was underdeveloped. In the past decade the concept has been evolving and attracting more and more competitors. Therefore, NdE considers entering new markets in Europe. To some extent innovation is also encouraged in product development. For example, NdE introduces both new and conventional materials, and applies an innovative approach to combine and turn them into a unique menswear style. In regards of marketing activities, NdE has admitted not using any innovative marketing techniques; on the other hand the company does not use traditional marketing either. Slight experimentation appears in one of their latest marketing activity – PR agency. NdE has decided to try and see whether it will work and bring desirable results. In fact, NdE does not conduct lots of market research either. However, the NdE team constantly visits fairs, reads fashion magazines, and follows latest trends to understand their customers and competitors.

**Proactiveness**

As highlighted before, to understand their customers and competitors, the NdE team constantly visits fairs, screens fashion magazines, follows latest trends and responds to changes in the environment proactively. NdE also tries to stay one step ahead of competitors by continually introducing new lines and designs. NdE also acknowledges that fashion is quite a proactive industry itself and working within the fashion industry requires constant change and being aware of up-to-date trends. Furthermore, even though NdE aims for long-term relationships with suppliers and distributors, the company is always looking for new distribution channels and better conditions from suppliers.
**Risk taking**

NdE is a high-risk business, since competition is high and it is hard to foresee the number of retailers and buyers. Furthermore, various strategic processes and actions require up-front payment with unknown results. The production and quality are one of the issues that bear the biggest risks in this business. To calculate and foresee those risks NdE employs highly experienced personnel to work with textile (17 years’ experience), and constantly visits and keeps close relationship with the factory in Lithuania where production has been outsourced to. The marketing activities were found to involve rather low-risk, but remain costly with late return and always containing uncertainty in the result. Similar to the other interviewed companies, NdE does not tend to sign long-term commitments and thereby minimizes uncertainties and remains flexible with regard to their marketing activities.

**Tailor Store**

**Background**

Tailor Store (TS) is a company selling tailor made clothing online with leading edge technique. All the marketing and logistics activities are located in Sweden whereas the production is based in an owned factory in Sri Lanka (Tailor Store, 2014). TS focuses on exports, being 62% of their turnover from 70 countries, whereas 38% of sales are within Sweden. As a strategy to outstand from competitors, TS bases its production in a subsidiary in Sri Lanka. Owning the factory gives TS total control of management and production, which leads to greater control of prices, quality, working conditions, and lead time among others.

**Marketing activities**

Concerning marketing activities, TS focuses on communicating a clear statement on why customers should wear custom made clothes; a perfect fit tailored to the unique preferences and wishes of each and every customer. Even though TS is selling in 70 countries, the business conducts marketing activities only in 15 countries. TS spends much of its marketing budget and efforts on search engine optimization (SEO), i.e. buying search words such as “made to measure shirts” in different languages in order to be well positioned in search engines and therefore attract more potential customers. TS also relies on search engine marketing (SEM), which is related to the previously mentioned SEO. Furthermore, TS works
with affiliate networks, which manage thousands of other sites to advertise the banners, and campaigns that TS has previously prepared. Customer relationship management (CRM) is also a part of TS marketing, which is weekly newsletters (that keep customers up to date), and mails before and after the order. Another marketing activity is a “display” - buying space in websites where TS would like to be in order to get traffic to TS’s website. Additionally, TS uses social media in order to maintain direct contact with customers, and manage customer service related questions. TS considers that synchronization of all the activities mentioned before is very important to get the highest impact.

So far TS has focused on digital marketing activities, however they are introducing some traditional marketing in order to reach specific segments. TS campaigns are available in some magazines, such as Café and Lifestyle in order to reach high-income people. TS considers this specific group to be influencers of other groups, and therefore dedicates efforts on this small but important segment.

**Innovativeness**

In 2003, when the company was established, the business model was novel, since there were only few small competitors offering customized fashion online. Furthermore, the algorithm for measurements and other codes were written by TS. For example implementing a 3D model to visualize designs was one of many experiments. Besides, TS encourages different activities to find out which ones work the best. For instance, the company is now experimenting with marketing channels such as radio and TV, which are new for TS since they have mainly focused on digital marketing in the past. Another experiment is the pilot store that will be established in Stockholm in April 2014. Certainly, innovativeness and experimentation are fundamental part of TS’s culture.

**Proactiveness**

TS is aware of current changes and therefore tries to react proactively. Even though the trend of online purchases is increasing, people still like to see and feel materials before purchasing. Hence, TS has decided to open a first physical store in Stockholm and offer customers this possibility before ordering a customized product.

TS also aims to attract customers and take market share from the regular clothing stores, thus a physical store might be a very important strategic move. To cope with competition TS is
elaborating an entirely new interface, a new generation of website that will offer better reproduction, colors, and layout.

Considering suppliers, the TS team is always looking for better alternatives when visiting fabric fairs and communicating with people in the industry. However, the company is conscious that establishing long-term relations always bring benefits. Additionally, TS also tries to observe what is happening in the industry by screening fashion magazines and reports. This way TS analyzes trends, new technical introductions, and see new opportunities, however they do not aim to be the first ones in fashion trends, but rather quick followers.

Furthermore, TS constantly aims to enter new markets. As mentioned before, the company is currently operating in 70 countries and researching markets abroad for potential opportunities. For example, the next markets that will be entered are Poland and the USA. If the pilot store in Stockholm turns out successful, TS will continue opening other physical stores as well.

**Risk taking**

TS has been involved in number of situations with high risks, such as the implementation of the 3D model, which represented a high financial risk for the company. Another example of financial and personal risk was the construction of the factory in Sri Lanka. In order to well-calculate risks, TS plans activities precisely and sets budgetary limitations. However, they are rather flexible and rarely follow plans entirely.

Meanwhile, in digital marketing activities, TS has the advantage of being able to calculate risk through the access to concrete numbers and the impact of their marketing efforts, such as the number of website visitors, purchases and money spent for certain actions. This way most of the risks are minimized and well-calculated decisions are made.

Nevertheless, TS also uses traditional marketing, where risks are higher and harder to measure comparing to the previously discussed digital marketing. As a way to reduce those risks, TS does not engage in long-term commitments and thereby leaves a chance to an exit if a strategy appears to be not efficient.
Analysis and Discussion

This chapter will discuss the previously described results in a comparative manner by taking the theoretical framework into consideration. The aim of this chapter is to observe similarities and differences and to categorize them in order to better understand how the interviewed companies applied an entrepreneurial orientation within their marketing activities. Thereby, the three EO sub-dimensions will be further sub-categorized based on the findings.

Innovativeness

As outlined before, innovativeness is defined as an “organization’s tendency to engage in and support new ideas, novelty, experimentation, and creative processes that may result in new products, services or technological processes, as well as the pursuit of creative, unusual, or new solutions to problems and needs” (Madhoushi et al., 2011, p. 310). Innovativeness has been found in diverse ways with regard to the marketing activities of the interviewed companies. In the following, different characteristics that have been identified are presented.

Introduction of novel materials, techniques, and/or concepts

Some of the interviewed companies have named the fashion industry as an innovative industry itself due to constant changes and new trends. Hence, to some extent innovation is encouraged in all interviewed companies. For example, NdE stimulates an innovative product development by introducing new materials and combining them into a unique style for menswear. Meanwhile, TS focuses on leading edge technique, the creation of their own algorithm for measurement in product development as well as the 3D modeling. Likewise, NBN introduced the “shop factory” concept, the first store with its own factory in Europe.

Experimentation

According to Carson et al. (1998), one of the primary components of innovativeness is an alternative marketing mix. Even though the interviewed businesses were not introducing any innovative marketing techniques (digital marketing and traditional media are dominated), experimentation was stimulated in all cases. For example, NdE, TS, and NBN experimented with their marketing activities (e.g. NBN experimented with a crowdfunding campaign, TS with TV and radio advertisement, and NdE with PR agency) by investing small amounts of money to different marketing techniques in order to see whether it brings desirable results or
not. TS also experiment by opening its first physical store, whereas Conservative is opening an online store, running an art-show event, and cooperating with their competitors.

**New market entry / Serving niche markets**

Entering new markets or serving a niche that has not been served before are frequently related to innovativeness (Stokes, 1995). To be precise, the interviewed small businesses were not the first ones to enter the market. However, the “old-new” concept of made to measure clothing (Conservative), tailor made jeans (NBN), luxurious menswear fashion (NdE), and tailor made clothes (TS) were quite new at the time the businesses were founded, which evolved over the years and lead to a competitive advantage of each business in its respective niche. Gradually, all of the interviewed businesses are considering entering new markets in the future.

**Reduced bureaucracy**

Administrative innovativeness is built on “novelty in management systems, control techniques, and organizational structure” (Dess & Lumpkin, 2005, p. 150). However, none of the interviewed businesses were encouraging administrative innovativeness since they all consider administration to be a distraction for creativity, and therefore try to simplify the administrative activities. In fact, for small fashion businesses a simplified administration might facilitate flexibility and eases internal process that subsequently can create room for innovation.

**Strategic alliances and collaborations**

One way to seek a competitive advantage through an innovative approach is to employ strategic alliances (O'dwyer et al., 2011). For example, Conservative is cooperating with their competitors for being able to make larger orders at suppliers in order to benefit from economies of scale, and with accessory retailers to make their products visible in their store. Meanwhile, NdE outsources various processes, for instance, production is outsourced to a factory in Lithuania, whereas marketing activities are employed by a PR agency. Furthermore, through the crowdfunding campaign, NBN had the opportunity to connect and to work with experienced people in the fashion industry.
Alternative distribution channels and suppliers

Alternative channels and distribution methods are factors defining a firm’s innovativeness (Lumpkin & Dess, 2005). All interviewed companies aim for long-term relationships with suppliers and distributors. However, all of them are constantly looking for better distribution channels as well as superior conditions from suppliers. Thus, NdE is considering the possibility to start an online store to show their full collection, TS is opening a physical store in Stockholm as a new distribution channel in order to gain market share from big clothing chains. Likewise, NBN is analyzing the possibility of implementing a further distribution method such as selling ready-to-wear jeans through retailers.

Proactiveness

Proactive behavior in business is highly coherent to “understanding customer and competitors, monitoring trends, changes in the industry and overall environment; recognizing and proactively reacting to those changes might lead to great venture opportunities” (Lumpkin and Dess, 2005, p. 150). The strategies and factors that are described in the following were implemented by the interviewed companies and considered to enhance each firm’s competitive advantage.

Understanding customers and changes in the external environment

To understand their customers and competitors, the interviewed companies constantly visit fairs, screen fashion magazines, follow the latest trends and react to changes proactively. Proactiveness also emerges when “introducing new products or technological capabilities ahead of the competition” (Lumpkin and Dess, 2005, p. 150). For example, NBN and TS proactively reacts to the “conscious buyers” trend, that claims for ethically responsible companies, by offering sustainable products. NBN showed proactiveness by offering the possibility to see how jeans are produced in shop-factory, while TS and Conservative apply a “quick follower” respectively “second adopter” strategy. Furthermore, NBN and Conservative proactively realized an opportunity in cooperating with competitors.

The circumstance that NBN, TS and Conservative offer customized products can also be considered as proactiveness, as certainly a need has been identified for tailored respectively individualized cloth rather than mass productions. Thereby, understanding customers and foreseeing their desires certainly plays a major role that helped these businesses to create a competitive advantage in the respective niche in which they are operating.
**Building a relationship to customers**

According to Keh et al. (2007), understanding customers and competitors enhances strategic decisions in marketing. Therefore, competitiveness can be achieved through a close relationship to customer. All interviewed companies basically practice active participation in social media and thus well maintain relationships to customers. By proactively keeping customers up to date of current developments and products, among others, and taking care of questions and customer desires through channels like social media, certainly promotes loyalty and is an important aspect for the success of the interviewed companies.

**Alternative distribution channels and suppliers**

Alternative channels and distribution methods are factors defining not only a firm’s innovativeness but also its proactiveness (Lumpkin & Dess, 2005). As outlined before, all interviewed companies aim for long-term relationships with suppliers and distributors. However, they are proactive and search for new suppliers and channels if the current ones are not satisfying their expectations. For instance, TS decided to open a physical store in order to reach customers who prefer to see and feel the fabrics before purchasing. Meanwhile, Conservative proactively introduces an online store in July. This way the company tries to gain further market share through physical presence at different locations.

**Risk-taking**

Risk taking refers to an organization's’ commitment to uncertainty, and thus potentially encounter harmful failure (Eggers et al., 2013). However, in order to be successful and hence to obtain a competitive advantage, businesses somehow need to take a certain amount of risk, e.g. introducing new products or services in new markets (Dess & Lumpkin, 2005).

**Willingness of taking calculated risks**

Previous studies suggested that small businesses have to take well-calculated risks in order to be successful (Caliendo et al., 2010). All interviewed companies take risks to some extent. Especially Conservative that not only produces customized products, but also offers ready-to-wear products, bears the risk of hardly being able to foresee the acceptance of the offers and quantity of sales. Furthermore, NdEs’ decision to outsource the production to a factory in Lithuania as well as TSs’ decision to build a factory in Sri Lanka involves risk due to
uncertainty regarding the product quality and cultural differences, among others. Likewise, NBN took risk by introducing the shop-factory concept in Sweden. Concerning marketing activities, the interviewed companies are not willing to take high risks, but rather well calculated ones, and therefore mainly choose a low risk marketing activity - social media. All companies emphasized that before taking any risky action, profound research has been undertaken to better estimate potential outcomes and reduce uncertain outcomes as far as possible.

**Full control of the production process**

Previous research concentrates on taking well-calculated risk as one way to increase competitiveness, however does not analyze strategies such as full control of the production process as a way to leverage risks. For example, to minimize risks related to production, NdE employs highly experienced personnel and regularly does personal visits at the factory to keep close relationship and to ensure the compliance of quality standards. In fact, taking full control of the production process (prices, quality, lead times), is part of TSs’ competitive advantage. When looking at NBN and Conservative, there is less risk involved with regard to production due to the circumstance that the production is realized in-house, which eases the fulfillment of quality standards, among others.

**“Try-out” approach in marketing campaigns**

Both traditional and digital marketing activities bare uncertainties, and therefore the interviewed companies have introduced and applied a so called “try-out” approach as another way to minimize risk. Subsequently, the companies did not commit to any marketing technique on a long-term, until they have found effective marketing strategies. This approach is in line with previous findings (Caliendo et al., 2010), claiming that only well controlled risks are likely to enhance the business performance.

**Summary**

As it can be seen in the analysis, by using an entrepreneurial orientation in their marketing activities, the interviewed companies were able to gain a competitive advantage. This statement can be supported by the fact that by implementing EO actions, these companies were able to survive in a competitive market when actually, according to research, most of the
new established companies tend to disappear after a few years of establishment (Brüderl et al., 1992). Furthermore, these companies are not just surviving but also expanding, e.g. all of them are adding new distributions channels by opening new stores in Sweden and/or abroad, adding an online store, among others, which means that the strategies taken so far have benefited them. These two facts mentioned before can be considered as a result of a gained competitive advantage by an EO approach in the companies’ marketing activities.

Based on the identification and discussion of important aspects that increase the competitiveness of small businesses through an EO in the marketing activities, an integrated model has been elaborated (figure 1). This model shows the strategic actions taken by the interviewed companies within the three sub-dimensions – innovativeness, proactiveness, and risk-taking.

**Figure 1: Entrepreneurial oriented marketing model**

<table>
<thead>
<tr>
<th>Innovativeness</th>
<th>Proactiveness</th>
<th>Risk-taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of novel materials/techniques and/or concepts</td>
<td>Forseeing and adapting to changes in the external environment</td>
<td>Willingness of taking calculated risk</td>
</tr>
<tr>
<td>Experimentation</td>
<td>Active screening for new materials, techniques, and/or designs</td>
<td>Full control of the production process</td>
</tr>
<tr>
<td>New market entry / Serving niche markets</td>
<td>Sustainability and ethical responsibility</td>
<td>“Try-out” approach in marketing campaigns</td>
</tr>
<tr>
<td>Simplified administration</td>
<td>Customization of products and services</td>
<td></td>
</tr>
<tr>
<td>Strategic alliances and collaborations</td>
<td>Understanding customers</td>
<td></td>
</tr>
<tr>
<td>Alternative distribution channels and suppliers</td>
<td>Building a relationship to customers</td>
<td></td>
</tr>
<tr>
<td>Foreseeing and adapting to changes in the environment</td>
<td>Active participation in social media</td>
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</tr>
</tbody>
</table>

After analyzing the strategic actions, that have been summarized in the figure 1, we have observed certain patterns among those actions that share similarities to some extent. Therefore we have grouped the similar strategic actions into clusters such as explorative approach, simplified administration, and collaborative partnerships within innovativeness; dynamic response to the environment and customer focus within proactiveness; and risk management within risk-taking (figure 2).
By assembling the strategic actions into these six clusters, we provide a comprehensive model to better understand how an explorative approach, simplified administration, collaborative partnerships, dynamic response to the environment, customer focus, and risk management could increase competitiveness. Therefore, by considering not only the three sub-dimensions of EO in marketing activities, but also the six clusters and its strategic actions, small business owners would increase the chances to gain a competitive advantage. Consequently, this model serves as a guideline for small business owners in the Swedish fashion industry to promote a competitive advantage by being entrepreneurial oriented with regard to marketing activities.
Conclusions

Little has been investigated by using an approach that combines EO literature with regard to marketing activities. A combination of EO and EM theories complements previous research and forms an alternative framework of analysis, which accredits better understanding how small businesses gain a competitive advantage through EO in their marketing activities. In line with previous studies, one of our main findings is that the three sub-dimensions of EO, innovativeness, proactiveness, risk-taking, have a strong and valuable effect on marketing activities. The analysis has shown that the interviewed companies were able to gain a competitive advantage by using EO in their marketing activities, which can be supported by the fact that those companies have not only survived, but also expanded.

This study has shown that companies in the Swedish fashion industry manage both production and marketing activities in an innovative manner. For example, to remain competitive the interviewed businesses introduce new concepts and constantly offer new products and designs. Furthermore, all companies focus on personalized and direct communication to customer, which is in some cases associated to the business model of offering customized products. One of the unexpected outcomes was that small businesses in the Swedish fashion industry cooperate with their competitors and form strategic alliances in order to benefit from economies of scale, to share industry experiences, as well as to better understand and satisfy latent customer needs. Furthermore, it was noticed that the analyzed businesses have a rather simplified administration that facilitates flexibility.

In regards to proactiveness, the study has shown that small fashion businesses in Sweden are aware of the increasing consciousness of consumers in terms of social and ethical responsibility and react proactively by offering sustainable products promoting transparency. Companies are also proactive in networks and constantly look for better distribution channels. Besides, it was observed that the interviewed companies were acting proactively to the external changes in order to better understand and satisfy latent customer needs.

Concerning risk-taking, the companies encourage well-calculated choices in order to promote competitiveness. Furthermore, all interviewed businesses leverage risks by following a “try-out” approach (experimentation) and short-term commitments in order to reduce the harm in case an activity turns out to be unsuccessful. Moreover, it has been found that offering customized products does not require having large stocks that in turn reduces financial risks of large prior production investments.
In conclusion, a close relationship with customers, cooperation with competitors, creativity and experimentation in marketing activities, reduced bureaucracy, proactive behavior in environmental changes and well-calculated actions enhance a small businesses’ competitiveness. Thus, it can be highlighted that the use of EO positively affects the marketing activities and increases competitiveness.

During the process of analysis it was noticed that some of the strategic actions were not emphasized in previous research. For instance, building a relationship to customer and full control of the production process were not previously discussed as EO actions that enhance competitiveness. However, the study has shown that these two strategic actions had actually increased competitive advantage, and thus it can be assumed that small businesses within the fashion industry could benefit by applying these two strategic actions in their marketing activities. Therefore, this paper contributes to the research field by advancing EO theory.

A practical contribution is the *Entrepreneurial oriented marketing model*, which benefits not only small businesses within the fashion industry, but also indulges a better understanding what issues are important when seeking to gain a competitive advantage through the use of entrepreneurial orientation in marketing activities.

**Limitations and Future research**

In terms of limitations, we are aware of certain particularities by which the fashion industry is characterized. In fact, the study is context dependent (region and industry) and consequently might not be relevant to other industries or regions. Hence, the outcome of this study cannot be generalized. Furthermore, according to Saunders et al. (2003), the main weakness and limitation of the interview method is the reflection bias. Different background and experience might lead to different understanding and perception of the events. Therefore, the reflections both on entrepreneurial orientation and marketing activities are subjective and might be biased. However, to decrease a potential bias, secondary sources were incorporated within the analytical framework. Furthermore, we are aware that the study could have been performed in another way, for example by conducting a single or multiple embedded case analyses, or gathering data differently. However, we are convinced that the chosen research design is appropriate to investigate the particular research question.

One of the main suggestions for future research is to conduct a study in different context (industry and region). By comparing outcomes from different context, the research field would benefit from more generalized results on how EO increases competitiveness in
different industries. We also recommend to further investigate the effect of the EO dimensions on marketing activities considering potential determinants and antecedents, such as experience, financial resources or networks since this study has not considered those elements. Likewise, this paper has not taken into account factors such as age in order to compare if EO actions differ depending on the company age. Therefore, it would be interesting to investigate more profoundly potential differences between younger and older firms. Finally, we believe that analyzing the effect of the EO dimensions on marketing activities over time in a longitudinal study would help to better understand the analyzed phenomena.
List of references


Appendix 1

Interview Guideline

Main question: How small businesses seek to gain a competitive advantage through entrepreneurial orientation in the marketing activities

Task: Make sure to cover every topic that is listed in the guideline. Also, try to reveal issues that we haven’t thought of yet (what else influences decision-making?).

Company and Background

1. Name, year founded, number of employees
2. What are the main company activities?
3. Has your company been founded by customer needs or did you create the market for your product?
4. What are the biggest problems/pains in your company?
5. How does your company outstand from competitors?

Marketing Activities

1. Could you please describe the marketing activities of your company?
2. Did you make any changes regarding the marketing activities? Did the changes have any impact (positive/negative)?
3. What problems do you face when it comes to marketing?
4. How do you solve those marketing problems?
5. Which marketing activities do you consider that helps the company to outstand from competitors?
6. Does your firm invest a large share in marketing and product development?
Innovativeness

1. Does your product target a new market/market niche that hasn’t been served before?
2. Does your firm encourages and stimulate product, marketing and administrative innovation?
3. (How often) do you introduce customer with new products or product improvements (experimentation, innovativeness)? Does your firm stimulate creativity and experimentation? How? (Specially in marketing)
4. How often do you change your marketing strategy (differentiation, tendency to experiment, engage, and support new ideas and creative processes?)
5. How do you conduct market research and how do you use this information?
6. Do you have strategic alliances? If yes, how do you use them and what result do they bring?
7. Is it hard for competitors to imitate your innovative initiatives?

Proactiveness

1. How do you react to changes within your industry? (How do you use it to gain a competitive advantage?)
   · Customers’ behavior (how?)
   · Competitors’ behavior (how?)
   · Suppliers’ behavior (also funding) (how?)
2. How do you try to understand your customer and competitors?
3. How do you discover and satisfy latent customer needs?
4. Does your firm continuously monitor trends and identify future needs of customers and/or anticipate future demand conditions?
5. Does your firm introduce new products and technologies ahead of the competition? Does it continuously seek for new product or service offerings?
6. Do you consider alternative channels and distribution methods, if the current ones work fine?
7. Do you intend to explore new markets in the future?

Risk-taking

1. Are you more risk affine or risk averse regarding business, financial and personal issues?
2. Does your firm analyze risks in order to minimize uncertainty and how? (E.g. Research and planning)
3. How are your marketing activities? How risky do you consider them? Why?

Is there anything else you would like to add? Thank you for your time!!!
The Implications/Reflections of European Economic Integration in Kosovo’s Business Environment Managers’ Attitude towards European Economic Integration Process

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Abstract

This research study does seek to investigate and presumably explore managers’ prospect and attitude towards the implications/reflections of European economic integration in Kosovo’s business environment. In this regard, in order to have rich data twenty-four (24) in-depth semi structured interviews have been conducted with different managers’ that currently are working in fourteen (14) variety organizations. This particular research study explicitly argues the importance and relevance of economic integration process in managers’ conviction towards creating a wide range of business opportunities as a result of removing the current trade barriers. This comprehensive process does prompt organizations to expand their business scope of activities as well as developing business ties with foreign counterparts that could have direct impact in improving organizations competitive advantage. In addition, even though, this economic process is conceived as great source of creating new opportunities from managers’ prospect, the main concern though is whether the current Kosovo’s organization does have the intellectual, technical, infrastructural and logistical capacities to embrace this economic process accordingly.

Key words: economic integration, kosovo, business environment, managers’

1. Introduction

In the current global economy, organizations do confront with numbers of challenges like: globalization process, the fast rate of development technology, and internet revolution that lead organizations to dramatically shift its focus towards fulfilling customers needs and demands (Frels, Shervani & Srivastava, 2003; Khan & Bashar, 2010). In this regard, the process of European economic integration it does create tremendous opportunities and challenges for number of business organizations to augment the existing volume of trade and investment in a unique and integrated market through increasing the mobility of capital that in the last instance it does help economies to grow (Shadlen, 2008). Therefore, the economic integration process opens the doors for new countries that so far are left behind in order to provide the likelihood for making real progress of goods and services as well as investing their capital overseas (Martin, 1998) that induced and accelerated growth athwart the community and most likely ensures an internal stability as an upshot of augmenting trade in goods or by augmenting flows of ideas (Rivera-Batiz & Romer, 1991). Insofar, though, the benefits that deriving from this comprehensive process outweigh the costs that certainly occurs through embracing this positive and conducive process (Andrei, 2012). In this respect, removing trade barriers, tariffs and fees that are some of the restrictions and cost driven certainly do increase the opportunity for organizations to embrace a strategy of reducing marginal costs as well as reducing the substitutability of the current products via making supplementary investment in new product innovation (Braun, 2008).

In addition, the process of innovation most importantly reflects organizations inclination to support the creative process of flourishing new products and services or technological ideas and novelities (Lumpkin & Dess, 1996). Thus, the process of innovation in this economic integration is crucial in creating a strong competitive advantage due to product differentiation that enlarges the likelihood for successfully penetrating in foreign markets as well.
as strengthening the position with regard to the competition (Lin & Saggi, 2002; Andrei, 2012). This is the main argument that triggers Krugman & Venables (1993) to emphasize the importance of such a process to prove the benefits of involving different countries in this comprehensive economic integration process that innovation will flourish, customers will benefit from new products and services and economies in real circumstances will grow. Therefore, this economic integration certainly augments the long-run scale of economic growth of the countries that decide to join this union and exploiting their resources in scaling up the research and development sector (Rivera-Batiz & Romer, 1991) that ultimately is linked with coming up with new conducive ideas that lead organizations to improve their position in competing with foreign competitors (Shadlen, 2008; Andrei, 2012).

Nevertheless, so far, it does appear that the European economic integration process it does require to be further investigated as well as explored especially when it does come to the countries that are facing the transition period like Kosovo. In this regard, this particular research paper endeavors to address in more extensive terms the implications/reflections of the European economic integration process in Kosovo’s business environment. In this regard, the particular research study is structured in four main sections. The first section is focused in exploring the contemporary literature on EU economic integration and the actual economic crises and, the role of business organizations in this process. The second section is focused in presenting the scope of this particular research and the way that the particular research study was conducted. The third section presents the findings whereas the last one discusses the main results as well as does come up with research conclusions.

2. Literature Review

2.1 The Effects of the Current Crisis on European Economic Integration

The current European economic crises has indicated that it can spill over swiftly amid closely integrated economies, either via developing trade channels or most likely financial channels, or most of the time both (Moro, 2013b). Insofar, though, the evidence of the current crises lie in the fact that apparently since the onset of the European Monetary Union (EMU), countries that joined this euro area have faced terrific diverse macroeconomic development (More, 2013b). Insofar, though, the wide financial crises that hit the majority of the European countries undoubtedly had an effect in this context as well. Therefore, the reflection of availability of low interest credit rate did lead toward an unsustainable enlargement of private (in Ireland, Portugal and Spain) as well as public (in Greece and Portugal) debt in the actual crises that hit these countries (More, 2013b). In addition, dropping the real interest rate in different countries after they joined the Eurozone area as well as the incoming capital increased unmaintainable development, comprising excess credit dynamics as well as real estate bubbles in different countries like Spain (Moro & Nuño, 2012) and a rapid increase in fiscal spending for instance in Greece. Likewise, it did reduce the stress for pursuing a comprehensive economic reform to recover competitiveness in the EMU in order to allow countries to finance easily their existing account deficits via abundant incoming working capital (Bindseil & König, 2012). In this respect, adopting a single currency did lead converging the interest rates in periphery countries in that extend with the basic countries, and combining with the increase of capital income led to better financial integration (Lin & Treichel, 2012), higher economic growth, augment government revenues and spending.

Therefore, the current financial crises determines that every sovereign state in the Eurozone it is flawed as an upshot of the lack of an integrated fiscal institution that does create the room for individual countries to pursue their own political as well as financial agendas (More, 2012; More, 2013a; More 2013b). It is important to emphasize the fact that some countries did see huge improvement in external demand as well as a substantial improvement in their account balances throughout the period of the European crises. This economic development was vividly endorsed by the increase of competitiveness, which does reflect significantly in reducing the labor costs in relation to the trading counterparts (Bindseil & König, 2012). But, in the other hand, other countries did experience a constant loss of their competitiveness power, which mainly is linked with increasing the macroeconomic challenges as well as account deficits. The persistent of competitiveness losses has been associated with the booms in their domestic demand after the nominal interest rate declined substantially as well as consumers and firms were desperately optimistic due to an increase in the future incomes in the majority of the euro area countries (More, 2013a). In this regard, Bernanke and Gertler (1995) point out that in real circumstances an excessive demand in economic crises linked with the credit rate will cause macroeconomic problems in terms of augmenting the domestic as well as the external debt especially in different countries that so far suffer from the economic structural reforms.

Furthermore, in different authors view undertaking structural reforms is the vital step that should be done in order to restore Europe’s economic crises, but in this economic circumstances these decisions are not easy to be made, because such decisions do imply extraordinary risk after the crises hit almost the whole economic chain.
(De Grauwe & Ji, 2012a; More, 2012; 2013b). In addition, pursuing structural reforms it is necessary and inevitable due to indebted countries in order to enrich productivity and augment competitiveness in the current markets (De Grauwe & Ji, 2012a). This structural reform undoubtedly does create better economic outcomes but the matter of the fact is that this approach it is long-term oriented solution. Hence, in this constellation, in the short term the coherent, pragmatic and possible solution to overcome the current economic crises is to stock up a new period of economic growth at European countries in order to endorse a significant augment in employment, which will stabilize the financial situation in affected countries (Moro & Nuño, 2012).

2.2 Benefits of Economic Integration in National Economy

The benefits of the economic integration process are well acknowledged amid scholars. In their research, different scholars emphasize the role and influence of this process especially when it does come to the transition countries that this process creates the preconditions for economic growth by facilitating the trade opportunities (Hausman, 2005) that augments the internal economic development through successfully spreading the wealth and reducing trade deficit (Tapsell & Woods, 2010). The same argument was supported by Michael and Pearce (2009) in their research though, that vividly do mention some important factors that every country will certainly benefit as an upshot of developing the organizations scope of business activities especially for countries that face the transition period this will reduce the unemployment rate, ostensibly increase the domestic product, reduce the import that certainly does trigger the economy to be in a better shape. In this respect, it is vital to accentuate the fact that scholars in their research they do evaluate the positive aspects of this comprehensive process that in the last instance is indisputable and irrevocable. Insofar, though, economic integration is perceived to accelerate and facilitate organizations way to sustain their operation activities to develop a wide range of products as well as services in order to seek out enriching the internal development and creating macroeconomic stability (Mahemaba & De Brujin, 2003).

Although the economic growth is accentuated extensively in this research, another important factor that needs to pay close attention is macroeconomic stability. So, Bleaney (1996) points out that there is a robust evidence that triggers us to believe that developing economic relationship between countries it does produce a macroeconomic stability though, which is certainly related with fostering economic growth and increasing the foreign direct investment as long as the economy is in expansion period. Moreover, other authors expand this argument by identifying the main channels that are solely related with macroeconomics stability that include: increasing foreign investment, reducing unemployment and deficit which are vital in ensuring this macroeconomic stability that in the last instance does provide huge opportunity for a real economic prosperity as a consequence of economic integration as well as are necessary in fostering economic growth, even though, over long period has substantial impact (Fischer, 1993; Yusuf, 1994). In addition, this sequential connection amid economic integration and macroeconomics stability is closely linked as long as the entire economic capillary are working properly and not having any possible fluctuation that puts at stake the whole economic chain that certainly spreads the consequences in other economies too (Oksanen & Rilla, 2009). Therefore, there is a broad acknowledgment among scholars point of view that the consequences of a recession that possible hits a particular country its impact can be spread swiftly in other countries that are part of this economic integration and the majority of those countries will face consequences throughout the period that recession hit (Nancy & Geoffrey, 2005; Siddiqui, 2009). This argument does trigger some authors to hold a conservative approach as well as skeptical conviction due to creating an integrated economic market that could be conducive for all countries and, in particular for countries that still are in a transition period and have structural as well as conceptual problems in organizing the whole economic system (Ghosh, 2012; Rustow, 2012). Hence, Kormai (1994) in his research points out that in order this economic integration process to be successful as well as being far away from oscillation cycles there are necessary to be set some policies that evaluate the current economic situation of the countries that so far have make their aspiration officially to join this broad and comprehensive process.

2.3 The Impact of Economic Integration in Business Organizations

The economic integration process that certainly integrates different economic markets it does create new competitiveness among business organizations (Isaksen, 2001). Moreover, it is crucial to understand that as a consequence of a comprehensive economic integration process organizations need to understand the complexity as well as the odds that will be created as an upshot of shrinking borders, removing barriers like tariffs, fees and reducing costs that ultimately are associated with the likelihood for expanding the business affiliation in foreign markets (Nayak & Ketteringham, 1986). But, in the flip side, understanding the complexity of this process and the consequences that mainly comprise economic and financial results, the internal difficulties in embracing the
necessity standards in the production process and the risks it does necessitate from organizations to be aware about the final outcome that derives from this process (Leifer, McDermott & O’Connor, 2000).

Insofar, being able to understand the benefits that derive from this process it does drive organizations to expand their scope of activities as well as paying more attention in improving the internal operation activities in order to survive in this volatile, complex and global market (Cooke, 2007). Therefore, putting much effort in understanding the main trade preconditions and increasing the internal capacities that could raise the competitive advantage in existing markets is the key indicator of envisioning the importance and relevance of this process (Marques & Ferreira, 2009). In addition, this comprehensive process certainly it prompts business organizations to invest further in embracing the mechanisms that increase organizations competitive advantage in competing with different competitors in foreign markets for new customers as well as new market share (Leifer et al., 2000). In this regard, building strategic capabilities through competitive advantage is the cornerstone of creating the necessary potential in competing into the global markets with different competitors as a result of the possibility that the economic integration provides to different domestic business organizations (McIvor, 2009). In addition, developing capabilities in order to be able to compete in the global economy it does strength organizations position in the market as well as it does augment the odds for sustaining the operation activities through developing trade in other countries and in wider markets that facilitates organizations growth (Barney, 1991; Ireland, Hitt & Vaidyanath, 2003).

In this respect, organizations benefit from economic integration in terms of expanding their business ties and creating new business partners that has a huge impact in developing know-how. This process creates the likelihood for organizations to combine and facilitate the existing knowledge and the know-how process, and creating and diffusing new knowledge that ultimately is related with new innovation ideas in production or services (Wolfie & Brawell, 2008) that induce organizations overall performance. Thus, developing knowledge through building business partnership apparently it does help organizations to attain unique competency from this partnership in exploring and embracing new conducive methods in organizing and leading organizations towards reaching the market peak (Pfeffer & Salancik, 1978). Likewise, another conducive way that organizations can improve their learning process and develop their knowledge is through close internal cooperation that helps the partners to increase the intellectual abilities, technical as well as analytical skills and business experiences, which are indispensable factors for exploiting properly and in a successful way the business learning activities (Cohen & Levinthal, 1990; March, 1991). Therefore, the benefits of this comprehensive process in terms of developing business partnerships and sharing the know-how it does make organizations aware when it does come to have a vivid picture about the foreseeable of the future (Mabert & Venkataraman, 1998). This collaboration process does have prominent impact in organizations tendency to pursue a wide range of collaboration between organizations from different countries and to share the positive success through this collaboration (Porac & Thomas, 1990). Hence, there is plenty of scientific evidence that vivly supports the view that this form of collaboration through knowledge sharing has been successfully and extensively developed over time (Barringer & Harrison, 2000; Ketokivi & Schroeder, 2004) that drive organizations towards raising the rate of sales and market share (Bartb, 2003) as well as increases internal efficiency and effectiveness (Davies &Waters, 2004).

2.4 The Rationale of the Study

The argument mentioned above do accentuate two critical issues that need to be emphasized: Economic integration process and its impact upon organizations business environment. The literature does emphasize profoundly the current economic crises that hit the majority of European countries and the consequences that mainly causes in the whole economic chain. In particular, the current statement of knowledge accentuates macroeconomic problems that different countries of euro zone facing with. But, the main argument that derives from the literature is related with the benefits and opportunities that this process provides for organizations in expanding their operation activities (McIvor, 2009). Therefore, the main conclusions that can be obtained from the abovementioned literature are presented in general without discussing particular cases and specific circumstances that different countries are facing with in terms of facilitating organizations way of seeking out new opportunities and the effect that this comprehensive process may cause in domestic circumstances. The vital question that needs to be addressed nowadays is not only linked with the likelihood that this economic integration process is irrevocable process that organizations have to join in order to benefit from the wide range of opportunities that this process provides, but also it is necessary to observe deeper organizations current situation whether they are able to embrace and overcome such a challenge or still they do need additional time to be able to face such a difficult process. Economic integration process do appear to be a huge opportunity and
responsibility for organizations to join this process in order to build business alliances and partnerships with foreign businesses that has comprehensive consequences in organizing and leading the whole business activities. Nevertheless, what does appear to be not vivid in the literature, obviously after we do not have any previous research that addressed so far the particular phenomenon under investigation is the fact whether Kosovo’s organizations do have the necessary capabilities to embrace such a process? Is any particular issue that has a huge impact in restricting Kosovo’s organization to embrace this challenge? In this regard, the particular research study endeavored to investigate and presumably provide answers in these two critical research questions through conducting a profound investigation due to managers’ responses on the implications/ reflections of European economic integration in Kosovo’s business environment.

3. Research Methodology

3.1 Research Approach and Justification

In order to pursue a deep investigation due to the research questions that were mentioned above, throughout this research study it was used a qualitative approach. In this way, certain researchers uphold the view that for a profound exploratory study the qualitative research it is the most appropriate approach to be taken (Creswell, 2003; Christy & Wood, 1999; Goodman, 1999). Likewise, qualitative research it has been well known amid variety of researchers as the appropriate method that should be embraced, because it does provide powerful and meaningful data due to the research questions (Gilmore & Carson, 1996). Moreover, Creswell (2003) in his research points out that pursuing an exploratory qualitative study it does mainly imply that not so much has been written due to the specific topic or mainly to the “population being studied”, who ostensibly researchers are looking for participants’ contribution in order to outline a clear understanding for the specific phenomenon under investigation. In this respect, however, this logic is entirely applied to the current study that aims to explore this specific field that fewer things have been investigated and written so far. In particular, the study of the implications/ reflections of European economic integration in Kosovo’s business environment do appear to be less accentuated and developed so far, which in turn does mean that the particular research by embracing an exploratory mode and a profound qualitative approach, will certainly have the opportunity to achieve profound understanding of the particular topic under investigation.

In this regard, in-depth semi structured interviews were conducted with different managers working in variety of private organizations. Johns and Lee-Rose (1998) point out the fact that this research method does certainly provide better, reliable and accurate information for the researchers as well as does tremendously reduce the distance and the vagueness between interviewer and interviewee. Likewise, Palmerino (1999) in his research emphasizes the role and impact of this method in researchers’ objectives by underlining that this method does provide more in-depth information regarding the study, it is more efficient and effective as well as adds more value, which does make the research more reliable. So, by adopting the qualitative method the current research study endeavored to investigate in-depth managers’ awareness and attitudes towards the implications/ reflections of European economic integration in Kosovo’s business environment. Open and free interviews were conducted with managers, in which every interviewee did have the possibility to express his/her thoughts in any way they did want that did give the researchers the opportunity to discuss a lot of key issues related to the aim of the particular study.

Likewise, it is important to underline that although the process of interviews were based on a free and open discussion, the researchers did use a semi-structure questionnaire that facilitates their efforts and guarantee that all critical issues have been addressed and deeply discussed. The semi-structured questioner included aspects like managers’ personal information, questions about EU, questions about Economic integration with particular focus in Kosovo’s business environment, questions about the role of economic integration in domestic organizations capabilities to embrace this process, and questions about the role of Kosovo’s organization in developing their scope of activities in foreign markets as an upshot of this comprehensive process. Hence, it needs to be mentioned that the focus was stressed mostly in two factors “EU Economic Integration” and “Implications/Reflections in Kosovo’s business environment”.

3.2 Sampling

The sample of organizations and managers that we did work with them was selected based on purposive judgmental technique of non-probability sampling (Gregoire, Schreuder & Weyer, 2001). Therefore, specific criteria have been set for opting organizations and managers. Specifically, organizational criteria that have been used were (1) the size of the current organizations, (2) the years of market operations, and (3) the industry that these organizations pursue their operation activities. The rationale behind this decision was to investigate an extensive sample of organizations that comprise both medium and large size companies, with a common
established culture and procedure of work and finally, organizations that cover all three main industries namely, manufacturing, service and retail.

In this respect, the range of the respondents that participated in our research was selected following specific criteria like (1) the current position of the interviewees in their companies, (2) the work-experiences, and (3) the specific involvement that they have in relation to managing employees in their organizations. The sample of interviewed managers and the variety of the positions of the respondents did allow the researchers to capture a more complete understanding due to the management approach towards the issue under investigation. The rationale of this particular study focused on managers and not including employees in this particular study was based on the fact that managers and especially those in the middle level can be considered as key figures in setting organizational policies and future strategies (Floyd & Wooldridge, 2000; Psychogios, Wilkinson & Szamosi, 2008).

3.3 Data Collection

Overall twenty-four (24) interviews were conducted with different managers working in fourteen (14) variety private organizations. The demographic features of them varied across age, education, and years of the work experiences.

The interviews did take place between August and October of 2013. The process was based on identifying the organizations that basically fulfilling the criteria mentioned above. Then these organizations have been contacted in order to nominate one or two potential managers that can contribute as interviewees in this research study. Subsequently the managers were contacted in order to obtain their arrangement and approval of participating in the interviews. Likewise, details of the interviews have been arranged. During this communication the researchers underlined the importance of this research study by explaining and clarifying the whole aim and ensuring the confidentiality of information (Seidman, 1998) that certainly preserves the ethical part of this research investigation (Malhotra & Peterson, 2001). All interviews did take place at managers’ offices. Hence, every interview lasted roughly 50 to 60 minutes. The interviews were tape recorded after receiving the permission of the interviewees. Likewise, throughout the entire discussion the researcher have taken written notes. Moreover, after the entire interviews were done researchers professionally transcribed the discussion, and coded the data that vividly facilitate their analysis. Finally, the data gathered by interviews have been subjected to the content analyses. Content analysis is considered to be an accurate research technique that creates the opportunity to replicate the valid interpretations from existing data to their structure (Krippendorff, 1980).

4. Findings

In our research that we carried out with medium and large organizations managers due to the implications/ reflections of European integration in Kosovo’s business environment, 24 managers have participated in this qualitative research. In addition, 6 of them were females and 18 males. The interviewed managers experiences in business was satisfactory enough 8.3 years, which will be conducive for our study. Also, it is important to emphasize that their level of education was high. All interviewed managers hold a master degree in different fields like: business, economics, marketing as well as finance and accounting.

The process of European economic integration it does play a significant impact in doing business in managers’ point of view. They seem to relate economic integration with creating the basis for internal stability within organizations.

“... I think economic integration will have broad benefits for businesses in our country, starting from enriching the opportunities to cooperate in variety of fields through building strong business ties as well as expanding our scope of knowledge by benefiting from comprehensive relationship with foreign organizations that will help us in establishing their approaches, which apparently it contributes to ensuring our stability (Marketing manager)”.

“... In the last 10 years we have started a new cooperation with one of the best manufacturing organization in Europe. Our cooperation basically comprise importing raw material, but it does include providing trainings for our staff twice a year as well, and the most important financial aid, which ultimately it is a strong evidence that makes us to sustain our operation activities (Production manager)”.

The notion of ensuring stability as a result of European economic integration it does link organizations in sharing ideas, concepts as well as organizing different forums, seminars and workshops that managers will be able to learn more about the effects as well as the significance of such an indispensable process. This does seem to be the view of several managers:
“... Certainly, I believe that this process will have an extraordinary effect in building our professionalism and establishing the best European practices that will create a smooth process of workflow through variety of interactions that will take place. This process will comprise different conducive sources like: trainings, exchanging experiences and seminars that will enhance our skills and abilities that are necessary in doing business (Operation manager)”.

“... European economic integration in terms of business in my point of view it means that we will have better opportunities to develop further the cooperation with our counterparts all around Europe. Also, in my opinion the most important thing is to try to adapt some approaches that will drive us to improve the overall information technology within our organizations, which apparently means additional trainings in order to exploit this technology (IT managers)”. 

Besides the fact that the economic integration process from managers’ point of view is related with positive outcomes in developing organizations capabilities, it is important to emphasize that managers hold a pragmatic view due to this issue. They do seem to realize the opportunities that presumably will be created to export their products as a benefit of trade as well as the importance of trade in sustaining their operation activities as an additional input in increasing their capacities:

“... I think economic integration brings extraordinary benefits when it comes to increasing our sales out of the country, opens new opportunities for boosting our business, and it helps our economy to generate new jobs. This process is not only beneficial from organizations prospect, but from the countries perspective as well, because the benefits of this process will be spread in the entire country by boosting exports and reducing the trade deficit that is one of the biggest problem of our economy (Finance manager)”.

“... As an economist that my specialization is in international economics, I can say that economic integration for businesses will mean a lot. It is sufficient that the door for promoting and selling goods and services overseas will be opened. As a new process of free economic trade our customers will have products with higher quality and reasonably price, because in the European markets will survive only organizations that indeed produce products with high quality and high efficiency (HR manager)”. 

Therefore, from these managers the critical point in this solely process is the opportunity that will be created in developing their scope of activities in other markets that is related with the likelihood of boosting their sales, creating new jobs and the most important developing a new powerful system of competition. Insofar, though, European integration process in these managers point of view is extremely related with creating the preconditions for one particular country to improve its economic healthy system as long as new opportunities are opened for businesses that are the cornerstone of keeping the economy on the right track:

“... In my view, this EU economic integration process for businesses it is a challenge that we have to overcome. The positive argument though is that it creates better opportunity for new partnership as well as robust internal collaboration between government in one side and businesses in the other side, because it is a win-win situation that spreads the benefits in the entire country (Operation manager)”.

“... I tend to believe that from this process there is no loser. We all benefit from such a conducive and comprehensive process. The government has a huge interest in boosting the exports and initiating a new campaign in subsidizing internal businesses, because this creates wealth, lifts people out of the poverty, and most importantly urges the economy to grow as a consequence of new internal business movements. In the other side, businesses are driven to compete in other markets for new customers with current competitors that increases the likelihood for expanding their impact in other markets and expanding their scope of business as well (Marketing manager)”. 

“... I think this process has two crucial points that need to be addressed. First, it is the benefits that derives from eliminating trade restrictions as an upshot of this economic integration, after we face a lot of difficulties in selling our products out of our borders that provides new opportunities for creating new alliances and join ventures in the way of targeting new markets. Secondly, the government has an interest in this process as well. The benefits that are linked with the government are purely destined to the overall economic development that improves the whole economic system (Sales manager)”. 

Despite the fact that this process does provide new opportunities for current businesses, the matter of the fact is that in these managers prospect the sparks of this process will be spread in the whole national economy. Thus, the benefits in most cases are tangible; meaning that as a result of penetrating in new markets and increasing the market shares in foreign markets as an upshot of the economic integration process this will derive better
outcomes with respect to augmenting the influx of money in the whole economy and raising the possibility for new internal investment, which is the key for transition countries to build and shape a better economic prospect.

“... So far, I think our businesses can benefit from this process, because we do not have plenty of opportunities in penetrating new foreign markets. Even though, so far, we have an agreement with CEFTA countries for a free trade economy and we are seeing the impact that derives from such an agreement, and I think expanding this market with EU countries opens new extensively paths for our businesses to expand our operation activities that are associated with the new opportunities (Production manager).”

In this respect, the last interviewer explicitly accentuate the opportunity that will be created for domestic businesses in expanding their business operation activities when it does come to develop a new and conducive business appearance in foreign markets that emerges as necessity nascent that is occurring from the economic integration process. In this context, the pragmatic argument that derives from managers prospect is solely linked with the notion that such a process it will prompt organizations to increase their efforts in developing employees working skills in order to enrich efficiency and effectiveness inside the working environment. Therefore, the vast majority of managers in their conceptual analyses emphasize such a view as well:

“... In my analyses this process it is not easy as it may look like in the first glance. It is an intricate process, because it necessitates huge internal investment starting from accepting and accordingly implementing the international standards in the production process, like ISO standards that provides a clear indication about our products quality, which in the last instance require a lot of endeavors and money in developing our employees skills in order to augment our efficiency in competing with international competitors (Quality manager).”

“... This integration process that you are referring, despite the fact that has certain benefits that will make our products more acknowledged in international markets, in the other hand it raises one important question whether we have the necessity capacities to embrace such a vital process accordingly? I think we still have some deficits in embarking our journey toward foreign markets, which is the main concern so far (Strategic manager).”

Albeit the fact that managers emphasize the role and the importance of economic integration, still there is a doze of skepticism and reluctance whether the current organizations do have the intellectual, technical, infrastructural and logistical capacities in pursuing such an important journey in expanding their businesses in other markets. Therefore, in these managers point of view, this process does require a thorough and profound analysis in evaluating the advantages and disadvantages about the role and the impact of the existing organizations in their homeland as an upshot of EU economic integration. This already is the view of several managers in their analyses:

“... I want to emphasize the fact that not every process that it seems to be beneficial in the infancy stage in real terms it is though. I think this process will cause different internal problems, even though our politicians always are trumpeting for joining the EU. I very much cast my doubts that this process will be useful in our economic perspective and especially for our organizations that the vast majority striving in this period of financial crises (Finance manager).”

“... With all respect for such a process, but I am reluctant whether our organizations will be able to enlarge their business activities. It will be difficult to compete with foreign competitors in such a situation when you struggle to sustain your operation activities as an outcome of lack of cash circulation that we are facing with (Operation manager).”

Hence, in these managers prospect, they concede the fact that this process is much complex and volatile in embracing and joining for the explicit reasons that currently organizations are facing with. Therefore, these managers strait accentuate the existing situation that is inseparable of the next steps that need to be taken with regard to a comprehensive process of EU economic integration, and the most important the challenges and difficulties that may be created on the ground mainly do express these managers attitudes and concerns toward EU economic integration process.

5. Discussion

The European economic integration it does appear to capture these managers’ consciences and attitudes when it does come to the benefits and consequences that derive mainly from this comprehensive process. Even though, the findings that were presented above vividly emphasize these managers’ notions and attitudes toward the benefits that Kosovo’s organization will have from this conducive process, still there is a concerns amid these managers’ whether this is the appropriate time for emerging and embracing this economic process accordingly. Although, some countries as soon as they embark a profound evaluation process of economic integration they
most likely outweigh the benefits that deriving from this process in comparison with the cost that occurring throughout this path in order to have a vivid picture whether this is the right decision to be made. The logic behind such a carefully approach is solely related to elude the risks that may be appeared though and cause tremendous negative effects in the whole economic chain.

The main findings that are mentioned above solely indicate these managers’ positive prospect due to the implications/reflections of European economic integration in Kosovo’s business environment. The main explanation that basically can describe such a positive attitude from these managers’ is linked with managers education who the majority of the interviewees comes from economics filed that increases the likelihood for understanding and perceiving accordingly the core of this process in the whole business environment and national economy respectively. Therefore, these managers’ do appear to recognize the benefits and opportunities that will be created from this comprehensive process for their organizations as well as for the entire country. Insofar, the integration of different markets it does create better opportunities for new collaboration amid business organizations from different countries as well as creates a healthy competition as a result of reducing, eliminating and removing trade barriers in order to simplify trade amid different nations (Doz & Hamel, 1998). Thus, from this comprehensive and conducive process organizations benefit in terms of reducing their costs that are mainly linked with the economic operation activities, likewise it is associated with eliminating the fees, and tariffs that facilitates the accessibility of trade business partners that seeking out to benefit from such a process in penetrating other markets.

In this respect, these managers do seem to embrace the fact that EU economic integration will facilitate the opportunity for building business ties with foreign counterparts in having accessibility in new markets. In addition, it is important to accentuate the fact that the economic integration process opens new chapter for internal organizations in creating internal stability through developing business cooperation from these managers point of view. Moreover, it is important to address the fact that these managers’ do perceive this process as a huge chance to build close business ties with foreign counterparts that could be conducive for the whole domestic organizations by establishing new approaches that will lead to better business outcomes as well as will simplify their way of penetrating into new markets through collaboration and partnerships. Therefore, this economic integration in these managers mindset explicitly is perceived to boost the opportunity to create business alliances and joint ventures that in the last instance will help to augment sales out of the country. In this respect, creating business alliances and joint ventures as an outcome of economic integration it does mean that Kosovo’s organizations will benefit not just in penetrating other markets, but also in increasing their intellectual capabilities that augment the possibility to successfully launching products or services in foreign markets that mainly impact organizations sustainability and growth (Yasamorn & Ussahawanitchakit, 2011). The process of know how is crucial in such a period that Kosovo’s organization are facing with. Hence, the broad collaboration process with such businesses do mean organizing seminars, training sections and workshops where the know how will be passed by, which certainly will make Kosovo’s organization to be better prepared to embrace this economic integration in a smooth way that increases the competitive advantage in domestic markets as well as creates a better positioning in targeting new foreign markets.

In this regard, this research study suggests that the EU economic integration process is positively related in these managers’ prospect with Kosovo’s business environment and with the necessity of creating the same preconditions for all countries in doing business. So far, the current situation is a break hearted, because Kosovo’s organizations are restricted in the whole process of doing business with other countries as a result that still we are out the EU membership and in this context different obstacles appear. Therefore, this process will remove the current barriers that are in place, and most probably will create a new chapter in the economic relationship between Kosovo and EU countries. Nevertheless, managers do appear to conceive this new opportunity as new light in boosting their sales out of their country and in this way to reach to expand their businesses in other markets as well. This process does help Kosovo’s organizations to increase their scope of activities and to augment their efficiency and effectiveness when it does come to exploit their resources wisely in production process in one hand, and in the flip side it will produce extraordinary benefits for the whole economy. Moreover, these managers’ vividly highlight the fact that the outcomes of this process will be spread in the whole economy by alleviating the poverty, reducing unemployment and improving the trade deficit that contemporarily are the main issues that grasp the attention of Kosovo’s government.

Although one crucial lesson that can be derived from such a process is that when the whole economies are in a good shape certainly other economies that are part of the economic integration process will flourish and they will surely have an economic growth as long as this growth is spread in the whole economic chain. Likewise, though, in the flip side the same philosophy will be applied when the economies will face with recessions. The
critical economic situation that the vast majority of European countries are facing currently it does raise the main concern whether such a process indeed will produce positive outcomes for other countries that want to join this broad family (Andrei, 2012), especially for countries that are in transition like Kosovo that still face different challenges to recover from the previous centralist economy towards free market economy. Moreover, whether the existing domestic organizations are ready to be able to compete with foreign competitors, which mainly are some of the concerns in these managers’ mindset. Therefore, the EU economic stability that currently is at stake it does have an impact in these managers reluctance as well. Nevertheless, in these managers’ conviction there is no doubt that EU economic integration process is the right decision that should be made, but the main concern is related with internal capacities and capabilities that organizations currently do hold to overcome such a challenge. Especially when it does come to invest in embracing some of the European standards that in most cases do require a huge investment in establishing in the whole organizations philosophy. Hence, this doze of skepticism in these managers’ prospect purely is related with organizations intellectual, technical, infrastructural and logistical capacities in pursuing such an important journey in expanding their businesses in foreign markets.

6. Conclusions and Research Limitation

This particular research study does seek to explore managers’ prospect as well as attitudes regarding the implications/ reflections of European economic integration in Kosovo’s business environment. The literature review about economic integration and the impact upon business environment explicitly emphasizes the benefits that business organizations will have as a result of the broad opportunities that will be created which is the key indicator of envisioning the importance and relevance of this process (Marques & Ferreira, 2009). In addition, in order to have a vivid picture about this process certainly it is necessary to investigate and understand profoundly the main aspects of implications/reflections of European economic integration in Kosovo’s business environment that prompts organizations to increase the awareness about the steps that need to be undertaken in order to be competitive in the market. Therefore, this economic integration process it does provide a wide range of opportunities for Kosovo’s organizations in expanding their scope of activities and developing their business ties with foreign counterparts that could have a direct impact in improving organizations performance. Likewise, it is important to underline the fact that was supported by managers that economic integration is perceived as conducive opportunity in resolving some of the main economic problems that Kosovo is facing with like: unemployment, trade deficit and fostering economic growth. In this regard, though, managers’ do seem to evaluate and emphasize the benefits that derive from this comprehensive economic integration process, but the main concern though is whether the current organizations do have the intellectual, technical, infrastructural and logistical capacities in embracing such an important economic integration process. This is the main conclusion that can be drawn from this research study. This concern is based on the current financial situation that the majority of Kosovo’s organizations are facing with the lack of cash disposal in one hand and, in the other hand some basic standards that need to be established in the process of organizations philosophy in order to be competitive in this global market that certainly requires additional resources.

Albeit, this particular research study vividly shows robust results due to the topic under investigation, it is important to highlight the fact that further research will always be helpful regarding exploring the implications/reflections of European economic integration in Kosovo’s business environment. In particular, pursuing this research analysis with particular organizations of the same industry can certainly provide with better results. Last, pursuing a robust qualitative approach for instance observation can provide rich and powerful outcomes due to this area that is so important for Kosovo’s economic future.

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This study was about knowledge management practices role in enhancing business performance. To achieve the objective of the study, primary data were collected with the aid of questionnaire. Two organizations; one each from the public and private sectors, were selected for the study to represent the major two sectors in the Nigeria economy. One hundred and twenty copies of questionnaires were administered to the personnel of the organization out of which one hundred and two were recovered fully attended to. Data collected were analyzed with percentages and tested the research hypotheses with contingency (χ²) statistics. Findings revealed that managers and employees were generally convinced that knowledge management was positively related to key indicators of performance. The study then concluded that there was a direct relationship between both concepts. Hence, managers and business leaders were advised to continue to innovate by constantly acquiring knowledge to enable them remain competitive in the industry they operate.

Keywords: Knowledge Management, Knowledge Capabilities, Organizational Resources, Business Performance.

I. Introduction

Knowledge management utilization has increasingly become important due to the dynamism in business operations, to provide strategic directions for organizations to enhance their performance and competitiveness. According to Mostafa and Golnessa (2011), a knowledge base economy is emerging, and knowledge management (KM hereafter) is being rapidly disseminated in academic circles, as well as in the business world. While an increase number of companies have launched knowledge management initiatives, large portion of these initiatives retain a technical perspective. Knowledge management is important because it is one of the most strategic weapons that can lead to sustained increase in profit (Choi and Lee, 2002; Janepuengporn and Ussahawnitchakit, 2011), and it is increasingly considered as the main source of competitive advantage for corporations. From a practice perspective, Zack (1999) opines that firms are noticing the importance of managing knowledge if they want to remain competitive and grow. Thus, many companies everywhere are beginning to actively manage their knowledge and intellectual capital, since in the future (DeTienne et al., 2004; Drucker, 1993; Grant, 1996; Teece, 1998), the only sustainable competitive advantage will be the creation of organizational knowledge and its proper management. More also, to establish long-term competitive advantage from an information and knowledge management point of view, (Mostafa and Golnessa, 2011), it is no longer sufficient solely to have efficient access to internal and external information resources. Today it is a business requirement to efficiently exploit what the business actually knows and not only what it owns.

The purpose of this paper is to examine the role knowledge management play in enhancing business performance. Performance is perceived to entail various measures such as profit growth, competitive
success and business expansion. The arrangement of the remaining parts of this paper is as follow: Review of relevant literature which will be geared toward understanding the main concept (knowledge management), Knowledge management capabilities and the role of knowledge management in enhancing organizational performance. Hypotheses will be stated immediately. Others are methodology(Materials and Method), results and discussion, conclusion and finally make recommendation as appropriate.

II. Literature Review

Knowledge Management is one of the magnificent concept possessed by organizations to improve their performance. This approach originated in management science (Mostafa and Golnessa, 2011), and has been applied successfully in commercial organizations. Wiig (1995) defines knowledge management as a group of clearly defined process or methods used to search important knowledge among different knowledge management operations. As a process, Filemon and Urritarte (2008) argued that knowledge management is a broad process of locating, organizing, transferring, and using the information and expertise within an organization. As a procedure, Bukowitz and Williams (1999) also defined Knowledge management as the procedure used by the organization to create capital from its intellectual or knowledge based assets. Lang (2001) emphasized that intellectual capital is the key element in knowledge creation. Further, knowledge is both produced and held collectively rather than individually in knit groups, or communities of practices. According to Janepuengpor and Ussahawitchakit (2011), it is the effective application of management best practices and information technologies that benefit an enterprise in attaining their objectives efficiently and effectively. Hence (Stankosky, 2002) Knowledge management is the key to competitive advantage. Knowledge is the fundamental basis of competition (Zack, 1999; Grant, 1996) and an optimal ingredient to be innovative and more effective (Lee and sukoco, 2007; Chen and Huang, 2008; Martinez-Cañas et al., 2012). Particularly tacit knowledge can be a source of advantage because it is unique, imperfectly mobile, imperfectly imitable and non – sustainable. Knowledge management helps boulder the capacity of an organization by developing, organizing, retaining and utilizing, human and knowledge resources which contribute directly to its survivability and profitability. With better recognition placed on the practical relevance of knowledge management to business (Davenport and Prusak, 1998), organization are beginning to invest in ad-hoc projects initiatives to leverage on knowledge for business uses. Thus, many company every where are beginning to actively mange their knowledge and intellectual capital (Detienne et al., 2004). Most large companies in USA and many in Europe have some sort of knowledge management initiatives in place (Davenport and Volpel, 2011). From the foregoing, we deduced that knowledge management is a process, procedure and strategy of taking advantage of intellectual capital and knowledge assets for organization success. With increased realization of the value of knowledge and the need to exploit it in day - to - day operations, both public and private sector organizations have embraced and embarked on knowledge management initiatives.

2.1 Knowledge Management Capabilities

Organizations have developed knowledge Management capabilities to help support a range of vital operational and innovative activities (Mohamad et al., 2012). The interest in organizational capabilities has created a focus on the development and implementation of knowledge management processes and infrastructure required to support daily work practices. Knowledge capabilities can be understood as the capabilities of organizations to effective perform the knowledge process on which their successes depend. According to Birinder and Darren (2011), knowledge management is a systematic approach to develop capabilities which accelerate the evolution of knowledge into key organizational resources. From the organizational perspective of effective knowledge management (Andrew et al., 2001), the perspective suggests that knowledge infrastructure consisting of technology, architecture, and culture along with knowledge process and protection are essential organizational capabilities or preconditions for effective knowledge management. For others, different resources make up the knowledge capability of a firm. These include technology infrastructure, organizational structure and organizational culture which are linked to a firms knowledge infrastructure capability; and knowledge acquisition, knowledge conversion, knowledge application and knowledge protection which are linked to the firms knowledge process capability (Alavi and Leidner, 2001; Gold et al., 2001). These organizational resources putting together, (Alavi and Leidner, 2011; Gold et al., 2001) determine the knowledge capability of a firm, which in turn has been linked to various measures of organizational performance.

2.2 Role of Knowledge Management in Business Performance

Given the increasing role of knowledge management in upgrading business competition, the interest of
managers, in measuring and evaluating both knowledge management performance and its benefits, is not surprising. To manage knowledge successfully, it must be measured (Mostafa and Golnessa, 2011). A study by Abdel et al., (2012), examine empirically the issues of effective knowledge management from the perspective of organizational capabilities. They found that knowledge infrastructural capability and knowledge process capability are the drivers of organization effectiveness. Jelena et al., (2012) argued that one of the benefits of introducing knowledge management practices in organizations is its positive impact on organizational performance. Susan and Kasim, (2010) studied the significant role of knowledge management practices in improving the performance of organization. The result shows that the level of knowledge management practices were important criteria for determining and improving organizational performance. Also, Chang and Chaung (2011) showed empirically the effectiveness of knowledge management processes from the roles of infrastructure capability and business strategy in enhancing firm performance. Hence, organization with knowledge management strategy tends to achieve its better performance. Thus the following hypotheses are proposed with the integration of key performance indicators, to adequately address whether knowledge management enhance business performance as evidenced by preview studies.

Hypothesis a: There is significant positive relationship between knowledge management and productivity.

Hypothesis b: There is significant positive relationship between knowledge management and firm’s profitability.

Hypothesis c: There is significant positive relationship between knowledge management and market share.

Hypothesis d: There is significant positive relationship between knowledge management and sales growth.

Hypothesis e: There is significant positive relationship between knowledge management and innovativeness.

Hypothesis f: There is significant positive relationship between knowledge management and competitiveness.

Hypothesis g: There is significant positive relationship between knowledge management and cost performance.

It is expected that results will be positive in line with findings of previous studies. This is because organizations that genuinely acquired knowledge, convert it to suit the organization’s strength and needs, applied it where appropriate, protect it from being transferred or copied and permanently store it for the organization’s uses will always outperform competition and achieve their objectives.

III. Materials and Methods

The main objective of the study is to examine the role of knowledge management in the enhancement of business performance of two selected organizations in Nigeria. The study is designed around field survey. To achieve the objective of the study, a questionnaire was designed to collect the required information. Two organizations were under study. Industrial and General Insurance Plc (private sector) and NICON Insurance Plc (Public sector). The selection was based on their experience, geographical coverage, convenience and representativeness of the basic sectors, private and public ones. After several consultations with the organizations, they agreed to participate in the exercise. In all, 120 personnel 60 each from the organizations were solicited to take part. 43 of them were heads of various units; others are senior staff of the organizations. A total of 120 questionnaires were distributed with the aid of paid field workers. Participants were asked as to rate their perception towards knowledge management role in enhancing their organization’s performance on a five point likert-type scale with anchors from 1- agreed to 5- strongly disagree. The items on the instrument i.e questionnaire were directed to the points and easily understood, and does not required much supervision. After two weeks of administering the questionnaire, only 102 were recovered representing 85% returned rate. And 10 of the returned questionnaires were not filled and were discarded. The data collected were analyzed quantitatively with percentages and were presented in tables. The hypotheses of the study were manually tested with chi-square ($\chi^2$) to determine whether there is relationship between the variables being measured at 0.05 level of significance.

IV. Result and Discussion

This section is used to present the data collected from the field on knowledge management role in the enhancement of business performance. This will be geared toward testing the hypotheses, upon which conclusion and recommendation will be based.
Table 1: Characteristic Distribution of Respondents

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<th>Distribution</th>
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</table>

The above shows the distribution of respondents on the role of knowledge management in the enhancement of business performance. From the table, about 38 (41.3%) respondents fall between the age 41 – 50. This mean that respondents were matured enough to understand the subject under investigation. About 41 (45%) of the respondents had Bachelor Degree, this mean that their response is reliable. 39 (42.4%) of respondents have spent above 12 years in service. The implication of this is that the information they provided is dependable. Also, 43 (47%) of the respondents are managers and heads of various units, this can be assumed that they are the policy formulator and implementer of the organizations. Thus, their information represents the actual truth and can be trusted.

Table 2: Knowledge Management and Organizational Performance

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<tr>
<td>productivity:</td>
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<tr>
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<td>27.2</td>
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<td>sale growth:</td>
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<td>45</td>
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<td>3</td>
<td>-</td>
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</table>
From the above, on whether knowledge management leads to productivity, 29 (32%) participants agreed; 39 (42.4%) strongly agreed; 5 (5.4%) were uncertain; 13 (14.1%) disagreed while 6 (7%) strongly disagreed. On the argument that knowledge management lead to firm’s profitability, 31 (34%) participants agreed; 47 (51.1%) strongly agreed; 5 (5.4%) disagreed; 9 (10%) strongly disagreed and none stood for uncertain. For whether knowledge management lead to increase market share, 25 (27.2%) participant agreed; 39 (42.3%) strongly agreed; 7 (8%) were uncertain 14 (15.2%) disagreed while 7 (8) strongly disagreed. More also, whether knowledge management lead to sales growth, 31 (34%) participants agreed; 45 (49%) strongly agreed; none were uncertain; 11 (12%) disagreed while 5 (7%) strongly disagreed. Participant agreed that knowledge management lead to innovativeness as 26 (28.3%) stood to it; 37 (40.2%) strongly agreed; 9 (10%) were uncertain; 12 (13.0%) disagreed and 8 (9%) strongly disagreed. Further, participants firmly believed that knowledge management leads to competitive advantage as agreed by 37 (40.2%) of them; 51 (55.4%) strongly agreed; none were uncertain; 4 (4.3%) disagreed but non of the participant strongly disagreed. Finally, participants 25 (27.2%) agreed that knowledge management leads to reduced costs; 40 (43.5%) strongly agreed; 9 (10%) were uncertain; 11 (12%) disagreed and 7 (8%) of the participants strongly disagreed that knowledge management leads to reduced cost of general operation of business.

From the contingency test below, a number of decisions can be made; the table value of Chi-square (0.05) is 3.84, the computed in the table below is higher, it then mean that there is significant positive relationship between knowledge management and organizational (business) productivity, profitability, market share, sales growth, innovativeness, competitiveness as well as cost performance. This validates the previous studies on the role of knowledge management practices in improving the performance of organization.

### V. Conclusions

The study examines the role of knowledge management in enhancing the performance of business organizations. A significant number of researches have been carried out on the effect of knowledge management on the performance of an organization; factors like technology, culture, structure and human resources has been said to have affected knowledge management practices and adoption, but all of these research shows positive correlation between knowledge management and organizational performance. In line with the previous studies, the finding of this study revealed positive relationship between knowledge management and business performance. Relationships were drawn between knowledge management and key indicators of organizational or business performance including productivity, profitability, market share, sales growth, innovativeness, cost performance and competitiveness. All of which proved positively correlated. Hence, there is direct and positive relationship between knowledge management and business performance of the organization studied.
VI. Recommendations

Having reviewed relevant literatures on previous studies, based on the finding of this study, the researchers recommend that: Managers and business leaders should endeavour to acquire new knowledge as the need arises. Though may be capital intensive but the long run benefits is important if the business must remain successfully competitive. These knowledge when acquire should be digested and converted to an easily understandable process for those that should use it in the organization. The beauty of knowledge is that it brings new innovation, thus should be applied in all line of product and services offered by the organization. For an organization to remain competitively successful, it means other firms in the same industry have no knowledge of what they possess. Hence, knowledge must be protected and properly stored to avoid linkage and deterioration.

Table 3: Chi – Square ($\chi^2$) Contingency test

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References


Ogbadu et al., 23

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This study was about knowledge management practices role in enhancing business performance. To achieve the objective of the study, primary data were collected with the aid of questionnaire. Two organizations; one each from the public and private sectors, were selected for the study to represent the major two sectors in the Nigeria economy. One hundred and twenty copies of questionnaires were administered to the personnel of the organization out of which one hundred and two were recovered fully attended to. Data collected were analyzed with percentages and tested the research hypotheses with contingency (χ²) statistics. Findings revealed that managers and employees were generally convinced that knowledge management was positively related to key indicators of performance. The study then concluded that there was a direct relationship between both concepts. Hence, managers and business leaders were advised to continue to innovate by constantly acquiring knowledge to enable them remain competitive in the industry they operate.

Keywords: Knowledge Management, Knowledge Capabilities, Organizational Resources Business Performance.

I. Introduction

Knowledge management utilization has increasingly become important due to the dynamism in business operations, to provide strategic directions for organizations to enhance their performance and competitiveness. According to Mostafa and Golnessa (2011), a knowledge base economy is emerging, and knowledge management (KM hereafter) is being rapidly disseminated in academic circles, as well as in the business world. While an increase number of companies have launched knowledge management initiatives, large portion of these initiatives retain a technical perspective. Knowledge management is important because it is one of the most strategic weapons that can lead to sustained increase in profit (Choi and Lee, 2002; Janepuengporn and Ussahawnitchakit, 2011), and it is increasingly considered as the main source of competitive advantage for corporations. From a practice perspective, Zack (1999) opines that firms are noticing the importance of managing knowledge if they want to remain competitive and grow. Thus, many companies everywhere are beginning to actively manage their knowledge and intellectual capital, since in the future (DeTienne et al., 2004; Drucker, 1993; Grant, 1996; Teece, 1998), the only sustainable competitive advantage will be the creation of organizational knowledge and its proper management. More also, to establish long-term competitive advantage from an information and knowledge management point of view, (Mostafa and Golnessa, 2011), it is no longer sufficient solely to have efficient access to internal and external information resources. Today it is a business requirement to efficiently exploit what the business actually knows and not only what it owns.

The purpose of this paper is to examine the role knowledge management play in enhancing business performance. Performance is perceived to entail various measures such as profit growth, competitive
success and business expansion. The arrangement of the remaining parts of this paper is as follow: Review of relevant literature which will be geared toward understanding the main concept (knowledge management), Knowledge management capabilities and the role of knowledge management in enhancing organizational performance. Hypotheses will be stated immediately. Others are methodology(Materials and Method), results and discussion, conclusion and finally make recommendation as appropriate.

II. Literature Review

Knowledge Management is one of the magnificent concept possessed by organizations to improve their performance. This approach originated in management science (Mostafa and Golnessa, 2011), and has been applied successfully in commercial organizations. Wiig (1995) defines knowledge management as a group of clearly defined process or methods used to search important knowledge among different knowledge management operations. As a process, Filemon and Uritarte (2008) argued that knowledge management is a broad process of locating, organizing, transferring, and using the information and expertise within an organization. As a procedure, Bukowitz and Williams (1999) also defined Knowledge management as the procedure used by the organization to create capital from its intellectual or knowledge based assets. Lang (2001) emphasized that intellectual capital is the key element in knowledge creation. Further, knowledge is both produced and held collectively rather than individually in knit groups, or communities of practices. According to Janepluengporn and Ussahawitchakit (2011), it is the effective application of management best practices and information technologies that benefit an enterprise in attaining their objectives efficiently and effectively. Hence (Stankosky, 2002) Knowledge management is the key to competitive advantage. Knowledge is the fundamental basis of competition (Zack, 1999; Grant, 1996) and an optimal ingredient to be innovative and more effective (Lee and sukoco, 2007; Chen and Huang, 2008; Martinez-Cañas et al., 2012). Particularly tacit knowledge can be a source of advantage because it is unique, imperfectly mobile, imperfectly imitable and non – sustainable. Knowledge management helps boulder the capacity of an organization by developing, organizing, retaining and utilizing, human and knowledge resources which contribute directly to its survivability and profitability. With better recognition placed on the practical relevance of knowledge management to business (Davenport and Prusak, 1998), organization are beginning to invest in ad-hoc projects initiatives to leverage on knowledge for business uses. Thus, many company every where are beginning to actively mange their knowledge and intellectual capital (Detienne et al., 2004). Most large companies in USA and many in Europe have some sort of knowledge management initiatives in place (Davenport and Völkel, 2011). From the foregoing, we deduced that knowledge management is a process, procedure and strategy of taking advantage of intellectual capital and knowledge assets for organization success. With increased realization of the value of knowledge and the need to exploit it in day - to - day operations, both public and private sector organizations have embraced and embarked on knowledge management initiatives.

2.1 Knowledge Management Capabilities

Organizations have developed knowledge Management capabilities to help support a range of vital operational and innovative activities (Mohamad et al., 2012). The interest in organizational capabilities has created a focus on the development and implementation of knowledge management processes and infrastructure required to support daily work practices. Knowledge capabilities can be understood as the capabilities of organizations to effective perform the knowledge process on which their successes depend. According to Birinder and Darren (2011), knowledge management is a systematic approach to develop capabilities which accelerate the evolution of knowledge into key organizational resources. From the organizational perspective of effective knowledge management (Andrew et al., 2001), the perspective suggests that knowledge infrastructure consisting of technology, architecture, and culture along with knowledge process and protection are essential organizational capabilities or preconditions for effective knowledge management. For others, different resources make up the knowledge capability of a firm. These include technology infrastructure, organizational structure and organizational culture which are linked to a firms knowledge infrastructure capability; and knowledge acquisition, knowledge conversion, knowledge application and knowledge protection which are linked to the firms knowledge process capability (Alavi and Leidner, 2001; Gold et al., 2001). These organizational resources putting together, (Alavi and Leidner, 2011; Gold et al., 2001) determine the knowledge capability of a firm, which in turn has been linked to various measures of organizational performance.

2.2 Role of Knowledge Management in Business Performance

Given the increasing role of knowledge management in upgrading business competition, the interest of
managers, in measuring and evaluating both knowledge management performance and its benefits, is not surprising. To manage knowledge successfully, it must be measure (Mostafa and Golnessa, 2011). A study by Abdel et al., (2012), examine empirically the issues of effective knowledge management from the perspective of organizational capabilities. They found that knowledge infrastructural capability and knowledge process capability are the drivers of organization effectiveness. Jelena et al., (2012) argued that one of the benefits of introducing knowledge management practices in organizations is its positive impact on organizational performance. Susan and Kasim, (2010) studied the significant role of knowledge management practices in improving the performance of organization. The result shows that the level of knowledge management practices were important criteria for determining and improving organizational performance. Also, Chang and Chaung (2011) showed empirically the effectiveness of knowledge management processes from the roles of infrastructure capability and business strategy in enhancing firm performance. Hence, organization with knowledge management strategy tends to achieve its better performance. Thus the following hypotheses are proposed with the integration of key performance indicators, to adequately address whether knowledge management enhance business performance as evidenced by preview studies.

**Hypothesis a:** There is significant positive relationship between knowledge management and productivity.

**Hypothesis b:** There is significant positive relationship between knowledge management and firm’s profitability.

**Hypothesis c:** There is significant positive relationship between knowledge management and market share.

**Hypothesis d:** There is significant positive relationship between knowledge management and sales growth.

**Hypothesis e:** There is significant positive relationship between knowledge management and innovativeness.

**Hypothesis f:** There is significant positive relationship between knowledge management and competitiveness.

**Hypothesis g:** There is significant positive relationship between knowledge management and cost performance.

It is expected that results will be positive in line with findings of previous studies. This is because organizations that genuinely acquired knowledge, convert it to suit the organization’s strength and needs, applied it where appropriate, protect it from being transferred or copied and permanently store it for the organization’s uses will always outperform competition and achieve their objectives.

### III. Materials and Methods

The main objective of the study is to examine the role of knowledge management in the enhancement of business performance of two selected organizations in Nigeria. The study is designed around field survey. To achieve the objective of the study, a questionnaire was designed to collect the required information. Two organizations were under study. Industrial and General Insurance Plc (private sector) and NICON Insurance Plc (Public sector). The selection was based on their experience, geographical coverage, convenience and representativeness of the basic sectors, private and public ones. After several consultations with the organizations, they agreed to participate in the exercise. In all, 120 personnel 60 each from the organizations were solicited to take part. 43 of them were heads of various units; others are senior staff of the organizations. A total of 120 questionnaires were distributed with the aid of paid field workers. Participants were asked as to rate their perception towards knowledge management role in enhancing their organization’s performance on a five point likert-type scale with anchors from 1- agreed to 5—strongly disagree. The items on the instrument i.e questionnaire were directed to the points and easily understood, and does not required much supervision. After two weeks of administering the questionnaire, only 102 were recovered representing 85% returned rate. And 10 of the returned questionnaires were not filled and were discarded. The data collected were analyzed quantitatively with percentages and were presented in tables. The hypotheses of the study were manually tested with chi-square ($\chi^2$) to determine whether there is relationship between the variables being measured at 0.05 level of significance.

### IV. Result and Discussion

This section is used to present the data collected from the field on knowledge management role in the enhancement of business performance. This will be geared toward testing the hypotheses, upon which conclusion and recommendation will be based.
Table 1: Characteristic Distribution of Respondents

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The above shows the distribution of respondents on the role of knowledge management in the enhancement of business performance. From the table, about 38 (41.3%) respondents fall between the age 41 – 50. This means that respondents were matured enough to understand the subject under investigation. About 41 (45%) of the respondents had Bachelor Degree, this means that their response is reliable. 39 (42.4%) of respondents have spent above 12 years in service. The implication of this is that the information they provided is dependable. Also, 43 (47%) of the respondents are managers and heads of various units, this can be assumed that they are the policy formulator and implementer of the organizations. Thus, their information represents the actual truth and can be trusted.

Table 2: Knowledge Management and Organizational Performance

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Table 2 continues

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<table>
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</table>

Notes: 1 = Strongly agree, 2 = Agree, 3 = Uncertain, 4 = Disagree and 5 = Strongly disagree

From the above, on whether knowledge management leads to productivity, 29 (32%) participants agreed; 39 (42.4%) strongly agreed; 5 (5.4%) were uncertain; 13 (14.1%) disagreed while 6 (7%) strongly disagreed. On the argument that knowledge management lead to firm’s profitability, 31 (34%) participants agreed; 47 (51.1%) strongly agreed; 5 (5.4%) disagreed; 9 (10%) strongly disagreed and none stood for uncertain. For whether knowledge management lead to increase market share, 25 (27.2%) participant agreed; 39 (42.3%) strongly agreed; 7 (8%) were uncertain 14 (15.2%) disagreed while 7 (8) strongly disagreed. More also, whether knowledge management lead to sales growth, 31 (34%) participants agreed; 45 (49%) strongly agreed; none were uncertain; 11 (12%) disagreed while 5 (7%) strongly disagreed. Participant agreed that knowledge management lead to innovativeness as 26 (28.3%) stood to it; 37 (40.2%) strongly agreed; 9 (10%) were uncertain; 12 (13.0%) disagreed and 8 (9%) strongly disagreed. Further, participants firmly believed that knowledge management lead to competitive advantage as agreed by 37 (40.2%) of them; 51 (55.4%) strongly agreed; none were uncertain; 4 (4.3%) disagreed but non of the participant strongly disagreed. Finally, participants 25 (27.2%) agreed that knowledge management leads to reduced costs; 40 (43.5%) strongly agreed; 9 (10) were uncertain; 11 (12%) disagreed and 7 (8%) of the participants strongly disagreed that knowledge management leads to reduced cost of general operation of business.

From the contingency test below, a number of decisions can be made; the table value of Chi-square (0.05) is 3.84, the computed in the table below is higher, it then mean that there is significant positive relationship between knowledge management and organizational (business) productivity, profitability, market share, sales growth, innovativeness, competitiveness as well as cost performance. This validates the previous studies on the role of knowledge management practices in improving the performance of organization.

V. Conclusions

The study examines the role of knowledge management in enhancing the performance of business organizations. A significant number of researches have been carried out on the effect of knowledge management on the performance of an organization; factors like technology, culture, structure and human resources has been said to have affected knowledge management practices and adoption, but all of these research shows positive correlation between knowledge management and organizational performance. In line with the previous studies, the finding of this study revealed positive relationship between knowledge management and business performance. Relationships were drawn between knowledge management and key indicators of organizational or business performance including productivity, profitability, market share, sales growth, innovativeness, cost performance and competitiveness. All of which proved positively correlated. Hence, there is direct and positive relationship between knowledge management and business performance of the organization studied.
Table 3: Chi – Square ($x^2$) Contingency test

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VI. Recommendations

Having reviewed relevant literatures on previous studies, based on the finding of this study, the researchers recommend that: Managers and business leaders should endeavour to acquire new knowledge as the need arises. Though may be capital intensive but the long run benefits is important if the business must remain successfully competitive. These knowledge when acquire should be digested and converted to an easily understandable process for those that should use it in the organization. The beauty of knowledge is that it brings new innovation, thus should be applied in all line of product and services offered by the organization. For an organization to remain competitively successful, it means other firms in the same industry have no knowledge of what they possess. Hence, knowledge must be protected and properly stored to avoid linkage and deterioration.
References


Urine homogentisic acid and tyrosine: Simultaneous analysis by liquid chromatography tandem mass spectrometry

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ABSTRACT

Alkaptonuria (AKU) is a rare debilitating autosomal recessive disorder of tyrosine metabolism. Deficiency of homogentisate 1,2-dioxygenase results in increased homogentisic acid (HGA) which although excreted in gram quantities in the urine, is deposited as an ochronotic pigment in connective tissues, especially cartilage. Ochronosis leads to a severe, early-onset form of osteoarthritis, increased renal and prostatic stone formation and hardening of heart vessels. Treatment with the orphan drug, Nitisinone, an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase has been shown to reduce urinary excretion of HGA, resulting in accumulation of the upstream pre-cursor, tyrosine. Using reverse phase LC–MS/MS, a method has been developed to simultaneously quantify urinary HGA and tyrosine. Using matrix-matched calibration standards, two product ion transitions were identified for each compound and their appropriate isotopically labelled internal standards. Validation was performed across the AKU and post-treatment concentrations expected. Intra-batch accuracy for acidified urine was 96–109% for tyrosine and 94–107% for HGA; inter-batch accuracy (n = 20 across ten assays) was 95–110% for tyrosine and 91–109% for HGA. Precision, both intra- and inter-batch was <10% for tyrosine and <5% for HGA. Matrix effects observed with acidified urine (12% decrease, CV 5.6%) were normalised by the internal standard. Tyrosine and HGA were proved stable under various storage conditions and no carryover, was observed. Overall the method developed and validated shows good precision, accuracy and linearity appropriate for the monitoring of patients with AKU, pre and post-nitisinone therapy

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1. Introduction

Alkaptonuria (AKU) was the first inborn error of metabolism described by Garrod, in 1902 [1] (OMIM # 203500). It is a rare autosomal recessive disorder, which results from a deficiency in homogentisate 1,2-dioxygenase activity in the liver [2,3] (Fig. 1). In the absence of the enzyme, homogentisic acid (HGA) is excreted in the urine in gram quantities [4–6] (equivalent to mmol/L concentrations), which turns black upon standing or alkalinisation. HGA circulates at lower concentrations in plasma (μmol/L) and is oxidised to benzoquinones which polymerise and bind to proteins, particularly in connective tissues including cartilage [7–11]. This process leads to ochronosis – a blue-black discoloration of the connective tissues especially cartilage. The mechanism of this remains unclear. Ochronotic pigmentation causes early onset degenerative arthritis of the spine and large weight bearing joints leading to increased pain and premature joint replacement. Aortic stenosis has been described as a cardiac complication of the ochronosis process [12,13] and in severe cases has led to aortic valve replacement. Additionally, an increased incidence of kidney stone formation is reported with an increase in prostate stones in males [5,8]. The formation of benzoquinones results in additional formation of reactive oxygen species and free radicals, which are suggested to play a significant role in the aetiology of AKU arthritis [14].

Although current therapy for AKU is palliative, there have been several reported trials of Nitisinone (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione [5,6,9,15,16]. Nitisinone is a potent inhibitor of the second enzyme in the tyrosine pathway, p-hydroxyphenylpyruvic acid dioxygenase which has been shown to...
lower circulating HGA and completely prevent pigmentation in AKU mice [17]. Nitisinone is approved for treatment of hereditary tyrosinaemia (OMIM #276700). It is currently being used at the National Alkaptonuria Centre (Royal Liverpool University Hospital, UK), in a large multi-centre clinical trial (DevelopAKUre Clinical Trials – www.akusociety.org) to evaluate its effectiveness in the treatment of AKU.

Currently published methods for quantitative and semi-quantitative analysis of HGA employ spectrophotometry, enzymatic spectrophotometry, gas chromatography mass spectrometry (GC–MS) and high performance liquid chromatography (HPLC) and integrated with mass spectrometry LC–MS/MS [17–23]. Urine tyrosine is generally measured as part of an amino acid screen with semi-quantitative reporting as part of a total screen, or quantitative analysis in select panels [24].

The diagnosis of AKU relies on clinical presentation and evaluation and quantitative or semi-quantitative analysis of urine HGA. Due to the instability of HGA in an alkaline environment, the preferred sample collection criterion is acidified urine. The aim of this study was to develop a quantitative method for the simultaneous measurement of urinary tyrosine and HGA using LC–MS/MS. For validation and comparison purposes, the method has been validated in both acidified and non-acidified urine matrices.

2. Materials and methods

2.1. Chemicals and materials

Tyrosine, tyrosine isotope-labelled internal standard (d2-tyrosine) and HGA were obtained from Sigma–Aldrich UK. HGA isotope-labelled internal standard, 13C6-HGA was obtained from Larodan Fine Chemicals (Sweden). LC–MS grade methanol and acetonitrile were obtained from Sigma Aldrich, UK. Formic acid was obtained from Biosolve. Water was purified in-house by DIRECT-Q 3UV Millipore water purification system. All dilutions and sample preparation was performed in glass. Oxygen free nitrogen was supplied by a Peak nitrogen generator.

2.2. Instrumentation and operating conditions

All analysis were performed on an Agilent 6490 Triple Quadrupole mass spectrometer with Jet-Stream® electrospray ionisation (ESI–MS/MS) coupled with an Agilent 1290 infinity UPLC pump and HTC autosampler. All data processing both qualitative and quantitative analysis was performed using Mass Hunter software package.
Chromatographic separation was achieved on an Atlantis C18 column (100 mm × 3.0 mm, 3 μm, Waters) maintained at 35 °C. Initial conditions were 80:20 water:methanol with 0.1% formic acid (v/v) increasing linearly to 10:90 by 2.5 min. The mobile phase was maintained for 1.1 min, increased to 100% organic for 1 min and then returned to starting conditions 80:20. The flow rate was maintained at 0.6 mL/min throughout the run. The column was reconditioned for 2 min prior to the next injection. 2 μL of sample was injected with a total run time of 7.0 min. Optimum operating ESI conditions were gas temperature 150 °C, gas flow 17 L/min; nebuliser pressure 40 psi; sheath gas temperature 320 °C and sheath gas flow 12 L/min. Capillary voltages were optimised to 3500 V in positive mode and 2500 V in negative mode with equal nozzle voltages (1500 V) in both modes. The iFunnel parameters were optimised in both negative and positive mode as 60 V for low pressure RF and 110 V for high pressure RF.

2.3. Preparation of standard solutions

Super stock standard solutions of tyrosine and HGA were prepared: tyrosine in 0.5 N sulphuric acid and HGA in deionised water at concentrations of 100 mmol/L and 400 mmol/L respectively. These were stored at −20 °C.

Internal standards were prepared: l-tyrosine-(phenyl-3,5-d₂) super stock at 100 mmol/L in 0.1 N sulphuric acid. An intermediate stock of 1 mmol/L was prepared by dilution in deionised water, and stored at −20 °C. 13C₆-HGA was reconstituted at 1 mg/mL equivalent to 5.75 mmol/L, in deionised water with an intermediate 250 μmol/L stock in deionised water, stored at −20 °C.

2.4. Preparation of calibrators and controls

To ensure matrix-matched calibration, super-stock aqueous standard solutions were added to either an acidified urine base pool (5 N H₂SO₄, 1%, v/v) or non-acidified urine base pool. The urine base was assayed prior to preparation to identify a low tyrosine pool suitable for standard addition. The super stock standards were diluted to intermediate stocks at ten times the final required concentration. These were then added to urine pool in a ratio:1:9, to create combined calibrators with final concentrations of tyrosine 20 μmol/L to 4 mmol/L and HGA 30 μmol/L to 52 mmol/L, whilst maintaining the integrity of the matrix.

A combined internal standard solution was used as the sample diluent, containing final concentrations of 0.4 μmol/L 13C₆-HGA and 2 μmol/L d₂-tyrosine in 0.1% formic acid (v/v) in deionised water.

Quality controls were prepared in the same manner to the standards, in both acidified and non-acidified urine base pools at concentrations suitable to the dynamic range of the calibration curve. HGA QC values were 90–15,000 μmol/L and Tyrosine QC values at 55–4000 μmol/L. All samples, calibrators and quality controls were assayed on a 1 in 1000 dilution with the internal standard solution. Calibrators and quality controls were spiked from separate stocks of tyrosine and HGA.

2.5. Assay validation

The assay was validated using in-house protocols based on published guidance [25–27].

2.5.1. Linearity

Standard curves were fitted using linear regression with a 1/x weighting factor and a minimum of six calibration points plus urine blank (not a true blank for tyrosine due to endogenous levels) and curve fitting parameters excluded zero. Performance of fitted curves is presented as the coefficient of determination (r²).

2.5.2. Accuracy

Accuracy was determined as closeness to the nominal spiked concentrations, this was determined both intra- and inter-assay with n = 6 and n = 20 respectively. Accuracy was calculated as: [measured concentration−nominal concentration]/[nominal concentration] × 100%.

2.5.3. Precision

Imprecision was determined both intra- (n = 6) and inter-assay (n = 20) using separately spiked urine pools and is expressed as coefficient of variation (CV).

2.5.4. Matrix effects

The presence of ion suppression was evaluated for tyrosine and HGA and their respective internal standards. Deionised water, acidified and non-acidified urines (six individual donors) were spiked with a low, medium and high concentration of tyrosine or HGA or the equivalent of the final concentration of internal standard (prepared as in section 2.4). Matrix factor was determined by calculating the ratio of the peak area in the presence of matrix (spiked with analyte or internal standard) to the peak area in the absence of matrix (deionised water plus analyte or internal standard). Due to the endogenous levels of tyrosine in urine, the matrix spiked with an equivalent volume of water, as used for the spike was also measured. Using the matrix factors calculated, an internal standard normalised matrix factor can be determined (matrix factor of analyte/matrix factor of internal standard multiplied by 100) [25].

2.5.5. Dilution and carryover

Dilution integrity of urine HGA was assessed by pre-analytical dilution of five samples with high HGA in deionised water (due to endogenous tyrosine in urine) at factors of one in three, five and ten with recovery as a percentage of the base (n = 6). Carryover of both tyrosine and HGA and their respective internal standards was assessed by five separate water injections following injection of the top calibrator (approx. 4000 μmol/L for tyrosine and 16,000 μmol/L for HGA). Water was used due to the endogenous tyrosine in urine matrix base pool.

2.5.6. Stability

Stability of tyrosine and HGA in both acidified and non-acidified urine was assessed using three pools representing low, medium and high concentrations of tyrosine and HGA. Stability was determined following three freeze-thaw cycles (at −20 °C), over 24 h at room temperature and over a 24 h period at 4 °C (equivalent to the sample manager 4 °C temperature, attached to the Agilent 6490). Results are expressed as a percentage of nominal values determined against a fresh calibration curve. Samples used for the on-board 24 h stability were also repeatedly analysed over the 24 h period for any deterioration which may limit batch and run times.

2.6. Analysis of analytes in urine samples

HGA and tyrosine levels were determined in three AKU patients, who are on a daily dose of 2 mg of nitisinone, as part of the National AKU Centre at Liverpool. Baseline, three, six and twelve month samples were analysed. 24 h acidified urine collections were analysed for creatinine (Jaffe assay) and samples were prepared at a 1 in 1000 dilution, for analysis.
Table 1  
Parameters for MS detection of HGA and tyrosine.

<table>
<thead>
<tr>
<th>Ionisation mode</th>
<th>Product ion 1 (quantifier)</th>
<th>Collision energy</th>
<th>Product ion 2 (qualifier)</th>
<th>Collision energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGA</td>
<td>Negative</td>
<td>167&gt;122</td>
<td>22</td>
<td>167&gt;108</td>
</tr>
<tr>
<td>$^{13}$C$_6$-HGA</td>
<td>Negative</td>
<td>173&gt;128</td>
<td>22</td>
<td>173&gt;114</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Positive</td>
<td>182&gt;136</td>
<td>14</td>
<td>182&gt;91</td>
</tr>
<tr>
<td>D$_2$-Tyrosine</td>
<td>Positive</td>
<td>184&gt;138</td>
<td>12</td>
<td>184&gt;125</td>
</tr>
</tbody>
</table>

3. Results

3.1. Method Validation

The mass spectrometer was operated in multiple reaction mode (MRM). Two product ion transitions were determined for each precursor ion and the respective collision energies are detailed in Table 1. For optimal sensitivity tyrosine and D$_2$-tyrosine were measured in positive ionisation mode while HGA and $^{13}$C$_6$-HGA were measured in negative ionisation mode. Additional parameters were optimised to ensure suitable operating conditions for method validation as detailed within Section 2.2.

A typical chromatogram is displayed in Fig. 2 for the primary product ion (quantifier) for each precursor, demonstrating the chromatographic separation of tyrosine from HGA in the urine matrix. No difference was observed in retention times of tyrosine and HGA upon comparison of acidified and non-acidified urine matrices. Tyrosine eluted at 1.8 min and HGA at 2.5 min, with neither eluting in a region of ion suppression.

3.2. Linearity

Calibration standard curves (seven points) exhibited a good fit over the range examined, with minimal inter-assay variability; tyrosine in acidified urine $r^2=0.999$ ($n=8$) and tyrosine in non-acidified urine $r^2=0.997$ ($n=8$) over a concentration range of 20–4000 mol/L; HGA in acidified urine $r^2=0.999$ ($n=8$) and HGA in non-acidified urine $r^2=0.997$ ($n=8$) over a concentration range 30–16,000 mol/L.

3.3. Accuracy

Intra and inter assay accuracy was determined (Table 2) in both acidified and non-acidified urine matrices. Results are represented as percentage recovery of a nominal amount of tyrosine or HGA spiked into matrix. Intra-batch accuracy was 96–109% for tyrosine in acidified urine and 97–108% in non-acidified urine. Inter-batch accuracy was 95–110% and 93–116% for tyrosine in acidified and non-acidified urine respectively. With regards to HGA, the intra-batch accuracy was 94–107% and 83–103% for acidified and non-acidified urine respectively; the inter-batch accuracy was 91–109% for acidified urine and 86–1060% for non-acidified urine. Trimming of the Intra-assay data for the low pool for non-acidified HGA reduced the CV to <15% ($n=5$).

3.4. Imprecision

Imprecision (%CV), both intra- ($n=6$) and inter- ($n=20$) was determined in both acidified and non-acidified urine. In the acidified urine matrix, intra-assay precision was <5% for tyrosine (170–4000 mol/L) and HGA (100–16,000 mol/L). Inter-assay precision in acidified urine was <10% for tyrosine (70–4000 mol/L) and <5% for HGA (100–16,000 mol/L). Similar precision was seen in the non-acidified urine matrix for HGA with %CV <5% both intra- and inter-assay. Intra-assay precision for tyrosine in the non-acidified matrix was <12% (170–4000 mol/L) and inter-assay precision was <10% (170–4000 mol/L).

3.5. Limit of Quantification (LLOQ)

The LLOQ in validation protocols is defined as the lowest calibrator which satisfies a CV ≤20%. The LLOQ for HGA in urine was 30 μmol/L with an intra-assay CV of 3.7% ($n=6$) and an inter-assay CV of 6.7% ($n=20$). In addition, urine tyrosine demonstrated acceptable performance at a level of 20 μmol/L.

3.6. Matrix effect

The matrix effect of both acidified and non-acidified urine was assessed across the concentration range for tyrosine and HGA, with five individual urine matrices (both acidified and non-acidified). Results demonstrated a slight matrix effect for acidified urine (12% decrease, CV 5.6%) which was normalised by the internal standard. For both tyrosine and HGA, the %CV of the internal standard normalised matrix factor is <10% in both acidified and non-acidified urine matrices satisfying validation criteria [25–27].

3.7. Dilution integrity

Due to the range of urine HGA concentrations exhibited at the time of diagnosis with AKU (>12,000 μmol/day) and the levels when patients are treated with nitisine (<1000 μmol/day) [unpublished data from the National AKU Centre, Liverpool, UK] the recovery of urine HGA, post-dilution was assessed. Acidified urine demonstrated recovery of 97.8 ± 7.1% at a 1 in 3 dilution; 97.3 ± 4.7% at a 1 in 5 dilution and 96.6 ± 6.6% at a 1 in 10 dilution ($n=6$ for all). Similar recoveries were measured for non-acidified urine with 97.8 ± 4.4%, 95.2 ± 5.4% and 96.5 ± 6.9% at a 1 in 3, 5 and 10 dilution respectively.

3.8. Stability

Stability following three freeze thaw cycles demonstrated average recovery of 95.7 ± 1.8% and 101.4 ± 4.6% for tyrosine and 93.2 ± 3.1% and 97.4 ± 1.8% for HGA in acidified and non-acidified urine respectively ($n=5$ at each of three levels). Samples stored at room temperature demonstrated average recovery of 100.8 ± 5.1% and 101.7 ± 3.2% for tyrosine and 100.1 ± 6.7 and 102.8 ± 3.2 for HGA in acidified and non-acidified urine respectively ($n=5$ at each of three levels). Repeated analysis of 3 urine pools over a 24 h period, stored at 4 °C demonstrated average recovery at $t=24$ hrs of 97.4 ± 1.3% and 97.9 ± 4.8% for tyrosine and 95.1 ± 4.0% and 97.2 ± 2.1% for HGA in acidified and non-acidified urine respectively. There was no significant deterioration in recovery across a 24 h period for either tyrosine (%CV of 3.6% and 2.8%, $n=21$) or HGA (%CV 4.8% and 2.8%, $n=21$) in both acidified and non-acidified urine. In addition, no significant difference was observed between acidified and non-acidified urine ($p=0.87$ for tyrosine and $p=0.07$ for HGA).

3.9. Carryover

Following injection of the top calibrator there was no clear visible peak in either tyrosine or HGA transition windows. Integration of background noise/chromatography gave a calculated % area of
the LLOQ of <1.5% for both tyrosine and HGA in acidified and non-acidified urine. The internal standards were calculated as <0.7% for both d2-tyrosine and 13C6-HGA in both acidified and non-acidified urine matrices.

3.10. AKU urine samples

Three patients were analysed to demonstrate the application to AKU. The creatinine normalised HGA in the three samples pre and post treatment is displayed in Table 3. Urine HGA suppressed in all three patients at three months with 90.5%, 99.0% and 92.2% respectively. There was a concurrent rise in urine tyrosine secretion, as anticipated with the use of nitisinone. Urine tyrosine was variable and there is an additional dietary influence as evident particularly at baseline.

4. Discussion

A method has been validated for the simultaneous quantitation of urine tyrosine and HGA. To date, this is the first published method for quantitation of tyrosine and HGA in urine. The method was validated with a simple sample preparation across a short, seven-minute chromatographical separation. The method has been demonstrated as sensitive and specific with favourable accuracy and precision performance. The validation performance of the method satisfies that of key validation guidelines [25–27]. Data from the National AKU Centre at Liverpool, UK (unpublished) and previously reported trial data [6] demonstrates that HGA is excreted in mmol/L concentration in AKU patients. Once they are commenced upon nitisinone the levels drop to µmol/L, therefore the assay was evaluated over the entire HGA concentration range expected. The calibration curve consists of six standards covering this range and as demonstrated, exhibits an $r^2$ > 0.995 for both tyrosine and HGA with minimal inter-assay variability. In addition, recovery post-dilution proved that the linearity can be extended if required as dilution integrity was maintained up to a 1 in 10 dilution. Dilution greater than this was not examined as matrix integrity should be maintained. Data included on three patients with AKU demonstrates the suitability of the validated assay for analysing urine metabolites both pre and post nitisinone treatment.

To maintain assay integrity, the calibration standards and quality control pools have been matrix matched, in either acidified or non-acidified urine. The variation of matrix was determined to be minimal ensuring reproducibility batch to batch with regards
Table 2

<table>
<thead>
<tr>
<th>Tyrosine</th>
<th>Homogenised acid</th>
<th>Acidiﬁed urine matrix</th>
<th>Non-acidiﬁed urine matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter-assay</td>
<td>Intra-assay</td>
<td>Inter-assay</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
</tr>
<tr>
<td></td>
<td>[CV] %</td>
<td>[CV] %</td>
<td>[CV] %</td>
</tr>
<tr>
<td>386</td>
<td>105.7 ± 36.3 (34)</td>
<td>99.0 ± 31.1 (33)</td>
<td>90.2 ± 41.8 (37)</td>
</tr>
<tr>
<td>1586</td>
<td>105.3 ± 25.2 (25)</td>
<td>94.5 ± 21.1 (29)</td>
<td>93.4 ± 30.4 (30)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urinary HGA μmol/mmol creatinine</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKU1</td>
<td>2135</td>
<td>203</td>
<td>141</td>
<td>61.2</td>
<td></td>
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<tr>
<td>AKU2</td>
<td>2868</td>
<td>27.3</td>
<td>7.9</td>
<td>13.5</td>
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<tr>
<td>AKU3</td>
<td>2520</td>
<td>196</td>
<td>53.6</td>
<td>102</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3**

Urinary concentration of HGA and tyrosine in AKU patients, pre and post-nitisinone treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urinary tyrosine μmol/mmol creatinine</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKU1</td>
<td>34.2</td>
<td>245</td>
<td>246</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>AKU2</td>
<td>6.9</td>
<td>93.3</td>
<td>73.1</td>
<td>97.1</td>
<td></td>
</tr>
<tr>
<td>AKU3</td>
<td>9.9</td>
<td>71.9</td>
<td>77.8</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

to the matrix. Although many methods utilise an aqueous matrix (phosphate buffered saline, water, organic solvents) as a base for in-house calibration standards, this does not contain other key constituents present in patient samples e.g. creatinine, urea, protein and electrolytes. The authors advocate using a matrix as similar to the sample base to be analysed and it is a requirement of several key method validation guidelines [25–27]. In a clinical laboratory environment, with increasing requirements for robust validation of LC–MS/MS methods and in the United Kingdom, the adherence to the ISO 15189:2012 standard requires documented method validation in line with published validation protocols. Determination of the internal standard-normalised matrix factor demonstrated that the slight signal suppression seen with a urine matrix was corrected by the respective internal standard. It cannot be assumed that internal standards will always correct for matrix effects, as is sometimes evident, especially with deuterated internal standards, a phenomenon called differential matrix effects [28].

A characteristic of urine in patients with AKU is that the urine darkens upon standing or alkalinisation, therefore urine samples have been collected under acidified conditions. The assay described herein has been validated for analysis of both acidified and non-acidified samples. Stability of both HGA and tyrosine in a non-acidified urine has been demonstrated as equal to that of the acidified urine matrix, over the stability period examined with no significant under or over recovery of the analytes of interest. Therefore urine samples could be collected without acid preservative and acidified upon receipt within the laboratory, within a 24 h period, or analysed as non-acidified random samples, again within a 24 h period.

Previously published data on excreted levels of HGA in AKU have utilised the method of Lustberg et al. [19], which involves ultra-ﬁltration of acidified urine samples which are then either analysed on a 1 in 100 dilution pre-treatment or neat, post-treatment with nitisinone. The spectrophotometric method indirectly measures urine HGA by measuring benzoquinone-2-acetic acid, an oxidised derivative. This then undergoes adduct formation with diethylentriamine, the product of which is measured spectrophotometrically. More recently a study has been published which used LC–MS/MS for quantitation of HGA [23]. Although the inter- and intra-assay variability was comparable, the method utilised aqueous calibration standards and required 9 min for separation and an additional six for re-conditioning of the column, resulting in 15 min analysis time. In addition, despite commercial availability there was no internal standard used. As demonstrated, there was a slight signal suppression with a urine matrix, but the isotope labelled standard corrected for this, emphasizing the usefulness of matrix matching and internal standards. With regards to tyrosine, published methods using LC–MS/MS are available in urine, serum and whole blood [24,29] which are integrated into panel assays for paediatric metabolic disorders and hereditary tyrosinaemia type I.
5. Conclusion

In conclusion, an assay has been developed to enable rapid biochemical diagnosis of AKU when high HGA levels and normal urine tyrosine levels are characteristic. In addition the assay is suitable for analysis of samples when patients are on nitisinone therapy, where suppressed levels of urine HGA and increased urine tyrosine excretion are determined. An advantage is that the method involves a simple sample preparation and both pre and post treatment samples can be analysed on the same assay. This is due to the sensitivity of the LC–MS/MS, the lack of carry over and the precision of the assay. This method will pave the way for analysis of clinical trial samples to determine the efficacy and response to nitisinone in the treatment of AKU.

Disclosure

ATH, AMM, ASD, PC, GR, JAG, JJD, LRR – no disclosures.

Acknowledgements

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References

Premature termination of SMARCB1 translation may be followed by reinitiation in schwannomatosis-associated schwannomas, but results in absence of SMARCB1 expression in rhabdoid tumors

Theo J. M. Hulsebos · Susan Kenter · Wim I. M. Verhagen · Frank Baas · Uta Flucke · Pieter Wesseling

Abstract In schwannomatosis, germline SMARCB1 mutations predispose to the development of multiple schwannomas, but not vestibular schwannomas. Many of these are missense or splice-site mutations or in-frame deletions, which are presumed to result in the synthesis of altered SMARCB1 proteins. However, also nonsense and frameshift mutations, which are characteristic for rhabdoid tumors and are predicted to result in the absence of SMARCB1 protein via nonsense-mediated mRNA decay, have been reported in schwannomatosis patients. We investigated the consequences of four of the latter mutations, i.e. c.30delC, c.34C>T, c.38delA, and c.46A>T, all in SMARCB1-exon 1. We could demonstrate for the c.30delC and c.34C>T mutations that the respective mRNAs were still present in the schwannomas of the patients. We hypothesized that these were prevented from degradation by translation reinitiation at the AUG codon encoding methionine at position 27 of the SMARCB1 protein. To test this, we expressed the mutations in MON cells, rhabdoid cells without endogenous SMARCB1 protein, and found that all four resulted in synthesis of the N-terminally truncated protein. Mutation of the reinitiation methionine codon into a valine codon prevented synthesis of the truncated protein, thereby confirming its identity. Immunohistochemistry with a SMARCB1 antibody revealed a mosaic staining pattern in schwannomas of the patients with the c.30delC and c.34C>T mutations. Our findings support the concept that, in contrast to the complete absence of SMARCB1 expression in rhabdoid tumors, altered SMARCB1 proteins with modified activity and reduced (mosaic) expression are formed in the schwannomas of schwannomatosis patients with a germline SMARCB1 mutation.

Keywords SMARCB1 · Schwannomatosis · Rhabdoid tumor · Nonsense-mediated mRNA decay · Translation reinitiation · Site-directed mutagenesis

Introduction

Schwannomatosis (OMIM # 162091) is a rare hereditary tumor predisposition syndrome, characterized by the development of multiple schwannomas (often resulting in severe pain) and, in some cases, meningiomas, but no vestibular schwannomas. The tumor suppressor gene SMARCB1 on chromosome 22 has been identified as a major predisposing gene in schwannomatosis, being involved in about 50 % of the familial, but no more than 10 % of the sporadic cases [11, 22]. Very recently, a second predisposing gene, named LZTR1, has been
identified, being involved in about 80% of chromosome 22-related schwannomatosis cases lacking mutation in SMARCB1 [21]. The SMARCB1 protein is a core subunit of the SWI/SNF complex, which plays an important role in the regulation of the expression of many genes through chromatin remodeling [29]. SMARCB1 was originally discovered as being involved in the development of rhabdoid tumors [28]. In contrast to the relatively benign schwannomas, these are aggressive tumors that develop in the brain, kidney or soft tissues of children, who usually die before 3 years of age. Almost all mutations of SMARCB1 in rhabdoid tumors are nonsense or frameshift mutations, which generate premature termination codons (PTCs). Together with deletion of the wild-type copy of SMARCB1, these result in complete absence of SMARCB1 protein in the tumor [1–3, 6, 9, 10, 14, 24, 28]. In the schwannomas of schwannomatosis patients, most germline mutations of SMARCB1 are missense or splice-site mutations or in-frame deletions, which are presumed to result in the synthesis of an altered SMARCB1 protein with modified activity [22]. However, also germline mutations in SMARCB1 that generate a PTC have been reported. Four of these, c.30delC (p.Phe10Leufs*6), c.34C>T (p.Gln12*), c.38delA (p.Lys13Serfs*3) and c.46A>T (p.Lys16*), introduce a PTC in exon 1. Interestingly, the latter type of mutation has not been reported to occur in rhabdoid tumors. The PTC-generating mutations are expected to result in nonsense-mediated mRNA decay (NMD) and failure to encode the SMARCB1 protein. Like in rhabdoid tumors, combined with loss of the second wild-type copy of SMARCB1 in the tumor, these mutations would be then expected to result in complete absence of SMARCB1 protein expression in the schwannomas of the patients. However, in our original report, in which we identified SMARCB1 as a predisposing gene for schwannomatosis, we demonstrated that the c.34C>T germline mutation caused mosaic expression but not complete absence of SMARCB1 protein in multiple schwannomas of a schwannomatosis patient [11]. This mosaic expression of SMARCB1 protein, i.e. expression in only part of the nuclei of the tumor cells, is a characteristic, but so far not well understood feature of schwannomatosis-associated schwannomas [11, 12, 18, 25].

To explain SMARCB1 protein expression in case of the c.34C>T mutation and of the other PTC-generating mutations in exon 1, we hypothesize that in these cases the abrogated protein synthesis is resumed at a downstream AUG codon at position 79 in the mRNA sequence. A translation start prediction program identified this codon, encoding methionine at position 27 in the amino acid (aa) sequence of the SMARCB1 protein, as an efficient start site of translation [20]. Reinitiation at this position would result in the synthesis of a protein missing the first 26 aa residues of the native SMARCB1 protein. Like the shortened or extended SMARCB1 proteins, presumed to result from the splice-site mutations and in-frame deletions that are frequently found in the SMARCB1 gene of schwannomatosis patients, these proteins are expected to remain at least partially functional.

To test this hypothesis, we investigated the available schwannomas for the presence of transcripts with the PTC-generating mutations. In addition, we performed transient transfection experiments with constructs containing the PTC-generating SMARCB1 exon 1 mutations to determine whether the predicted amino-terminal truncated proteins are formed. We also performed immunohistochemistry with a SMARCB1 antibody to investigate the mosaic expression in the available schwannomas of patients with a PTC-generating mutation in exon 1 of SMARCB1.

Materials and methods

Patients and tumors

We studied schwannomas and corresponding blood samples of three schwannomatosis patients. All patients developed multiple schwannomas at various locations, but no vestibular schwannomas. Patient 1 is a 51-year-old female patient without a family history of schwannomatosis. Besides the multiple schwannomas, she had dermal nevi in her face, a giant cell tumor of tendon sheath of the left foot (with recurrent tumor later on), an ossifying fibroma of the upper jaw, and a cerebello-pontine angle tumor on the left side with the MRI appearance of a meningioma. Formalin-fixed paraffin-embedded (FFPE) and frozen samples of the schwannomas were available for further analysis. Patient 2, a male with a family history of schwannomatosis, died at the age of 57 years due to cardiac arrest. His clinicopathologic characteristics have been presented previously [11]. Only FFPE (tumor) tissue blocks were available from this patient. Patient 3 is a female patient of 34 years with multiple schwannomas, with no constitutional or somatic SMARCB1 mutation, but with independent somatically acquired NF2 mutations in the tumors, of which both FFPE and frozen tissue were available. The family history of this patient is unknown. Informed consent of the daughter and wife of deceased patient 2 and of patients 1 and 3 was obtained for using their tissues.

DNA and RNA samples

DNA was extracted from blood samples and FFPE tissue blocks according to standard methods.
Total RNA was purified from FFPE tissue blocks using a commercially available kit (RNase FFPE kit, QIAGEN). One μg of total RNA was used to synthesize cDNA with random priming according to standard methods.

Mutation analysis

SMARC1 was sequenced using genomic or cDNA as substrate for amplification by polymerase chain reaction (PCR). All primers for sequencing were equipped with M13-primers (forward 5′-TGTTAAAACGAGGCTG-3′; reverse 5′-CAGGAAAACAGCTATGACC-3′). For DNA, the mutations in exon 1 were sequenced using forward primer 5′-CCCTCTGTACCTCCGACG-3′ in the 5′-UTR and reverse primer 5′-CGGGCTACCTGAGGCGGAT-3′ in intron 1; the mutation in exon 5 was sequenced by using forward primer 5′-TGATCCATGAGAACACGATCT-3′ in exon 5 and reverse primer 5′-CAGCTAACACACAGGGGT TG-3′ in intron 5. For cDNA, the mutations in exon 1 were sequenced by using forward primer 5′-GCCCTGTCCGCAGGC-3′ in exon 1 and reverse primer 5′-GAACCTC GGAACATCGGAGGTAGT-3′ in exon 2; the mutation in exon 5 was sequenced using forward primer 5′-TGACCCA GCTGTGATCCAT-3′ in exon 5 and reverse primer 5′-GAGGC GTCATCAACTTCTCA-3′ in exon 6. All sequence reactions were performed using ABI Big Dye v3.1 chemistry and the products were sequenced with an ABI 3730 capillary system (Applied Biosystems). Sequences were analyzed using CodonCode Aligner (CodonCode Corporation).

Site-directed mutagenesis

For site-directed mutagenesis the SMARC1 human cDNA clone SC126727 (OriGene Technologies) was used. The clone has a 1,717-bp insert, containing transcript variant 1 cDNA, which was inserted into the NotI site of expression vector pCMV6-XL5. Mutations were introduced into the SMARC1 gene using the QuickChange II Site-Directed Mutagenesis Kit (Stratagene), according to the manufacturer’s instructions. However, TOP10 chemically competent cells (Invitrogen), instead of XL1-Blue cells, were used for transfection of the wild-type and mutant SMARC1 cDNA clones. The mutagenesis primers, developed by using the QuickChange Primer Design program (Agilent Technologies), were as follows: for c.30delC: 5′-TGCGGCTGAGCAAGACCTTGGGCAAGA GC-3′ (sense) and 5′-GCTTCTGCCAACAGGTCTTGCTCAG CGCA-3′ (antisense); for c.34delT: 5′-GCAAGACCTCCGCTAGAAGCCCGTGAAG-3′ (sense) and 5′-CTCCACGGGCTTCTACCGAAGGTCTT GC-3′ (antisense); for c.38del: 5′-AGCAAGACCTTCCGG CAGAGCCCGTGAAG-3′ (sense) and 5′-CTCCACGGGCT CAGCCCGGAGGTCTTGCT-3′ (antisense), for c.46A>T: 5′-GGCAGAAGCCCGTGAAGTCCGAGCTGGAG-3′ (sense) and 5′-CTCCAGCTGGAACACGGGCTCTT GC-3′ (antisense), and for c.79A>G: 5′-ACGGCGAGTT CTACGTATCGGCTCCAG-3′ (sense) and 5′-CTC GGAGCGATACGTGAACCTCGGCAG-3′ (antisense). The coding sequence in the obtained clones was screened for the presence of the respective mutations and absence of additional mutations by direct sequencing using primers that generate overlapping fragments. Besides the introduced mutations, no other mutations were found.

Transient transfection

MON cells [28] were used for transient transfections with the wild-type and mutant SMARC1 cDNA clones. The cells were cultured in RPMI 1,640 medium with 1 % Glutamax-1, 10 % fetal bovine serum and 1 % penicillin/streptomycin (all Gibco). Lipofectamine 2,000 Transfection Reagent (Invitrogen) in OptiMEM-1 (Gibco) was used to transfect 1 μg of each SMARC1 cDNA clone into 50,000 MON cells. Cells were harvested 48 h after transfection, lysed in RIPA buffer (50 mM Tris–HCl pH7.6, 150 mM NaCl, 1 % NP-40, 0.5 % SDC, 0.1 % SDS, 2 mM EDTA) and 1 × protease inhibitory cocktail (Roche), and stored at −20 °C for immunoblotting.

Protein sample preparation and immunoblotting

For sample preparation, 15–20 slices (20 µm) of frozen tumor were lysed in 1,500 ul RIPA buffer and 1 × protease inhibitor cocktail. Samples were run on 8 % SDS-PAGE gels with a 4 % SDS-PAGE stacking gel. After electrophoretic transfer of the separated proteins to a nitrocellulose membrane, the membrane was incubated with blocking buffer (5 % non-fat dry milk, 1 × PBC, 0.05 % Tween 20, 0.1 % BSA), followed by incubation with a mouse monoclonal SMARC1 antibody (Abcam ab58209-100, 1:500, raised against aa 81–181, or BD Biosciences BAF47, 1:500, raised against aa 257–359) in blocking buffer. After incubation with polyclonal Rabbit Anti Mouse/HRP secondary antibody (Dako p0260, 1:1,000) in blocking buffer, bound antibody was visualized using the Lumi-light Western Blotting Substrate kit (Roche). Incubation with mouse monoclonal alpha-tubulin antibody (Abcam ab11304, 1:100,000) in blocking buffer was used as loading control.

Immunohistochemistry

Immunohistochemical analysis of SMARC1 protein expression was performed as described previously using the BAF47 antibody [11]. In test experiments, the Abcam ab58209-100 antibody generated comparable immunohistochemical staining patterns (data not shown).
Results

Translation reinitiation at codon 27 in SMARCB1

The c.30delC (p.Phe10Leufs*6) and c.38delA (p.Lys13Serfs*3) mutations cause a frameshift and generate a premature termination codon (PTC) starting at nucleotide 44 (Fig. 1). The c.34C>T (p.Gln12*) and c.46A>T (p.Lys16*) mutations directly generate a PTC at the respective positions. Because the PTCs in the transcripts are located more than 50–55 nucleotides upstream of the 3′-most exon–exon junction, these transcripts are expected to be degraded by nonsense-mediated mRNA decay (NMD) [17]. However, it has been demonstrated that downstream translation reinitiation can protect such transcripts from degradation [30]. We noted the ATG codon, encoding methionine at position 27 in the aa sequence, as a candidate codon for translation reinitiation. The NetStart 1.0 prediction program [20] indeed identified this ATG codon, besides the four ATG codons at the normal translation start site and those at more downstream positions, as a probable translation start site (score 0.589) in the 5′-terminal part of the coding sequence of SMARCB1.

Transcripts with nonsense codon-generating mutations are present in schwannomas

The c.30delC (p.Phe10Leufs*6) mutation has originally been reported by others [23]. We independently identified a patient (our patient 1) with this mutation. The c.34C>T (p.Gln12*) mutation has originally been found by us (our patient 2, [11]), and, since then, also by others [23, 26]. The c.38delA (p.Lys13Serfs*3) [7] and c.46A>T (p.Lys16*) [8] mutations have been reported by others. From the latter two patients, no materials were available to us. We first investigated whether transcripts with the PTC-generating mutations were present in the schwannomas of patients 1 and 2. The sequence recording in Fig. 2 (left panel) shows that the SMARCB1 copy with the germline c.30delC mutation is retained but that the wild-type copy of SMARCB1 is lost...
Interestingly, the transcript derived from the retained mutant SMARCB1 copy is present and apparently not degraded by NMD in this tumor (Fig. 2, right). The mutation-containing transcript of SMARCB1 was also seen in a second schwannoma in the neck as well as in a chin schwannoma of this patient (data not shown).

For patient 2, with the germline c.34C>T mutation, the schwannomas of the right upper arm and of the right thumb could be investigated for the presence of SMARCB1 transcripts. As reported earlier [11], the right upper arm schwannoma displayed considerable loss of the wild-type SMARCB1 allele, but heterozygosity is retained in the right thumb schwannoma. The sequence recordings for the corresponding RNAs demonstrate presence of the mutation-containing RNA (cDNA) in all tissues. Bottom. The sequence recordings show heterozygosity for the c.544C>T mutation in exon 5 in the right thumb schwannoma DNA, but absence of the mutation-containing transcript in RNA extracted from this tumor

N-terminally truncated SMARCB1 proteins synthesized in tumors and cell lines due to translation reinitiation

Frozen tissue of the chin and of the second neck schwannoma of the patient with the germline c.30delC mutation was available to determine whether the PTC containing transcripts encode an N-terminally truncated SMARCBI protein. For this purpose, we probed a Western blot of protein lysates derived from the two schwannomas (Fig. 4a, lanes 1 and 2) and of a spinal schwannoma (T4) of schwannomatosis patient 3 with no SMARCB1 mutation (lane a3) with a SMARCBI antibody (Abcam, raised against aa 81–181). As shown in the latter lane, the wild-type SMARCBI gene codes for two proteins of 385 and 376 aa residues, respectively. These are translated from two transcript variants (1 and 2), of which transcript variant 2 is 27 nucleotides (corresponding to 9 aa residues) shorter than transcript variant 1 as a consequence of alternative splicing in the 3'-terminal part of exon 2 [4]. Besides the two
wild-type variant proteins, two additional shorter proteins in the size range to be expected on the basis of a reinitiation event at the ATG codon at position 27 (359 and 350 aa residues, respectively) can be seen in the second neck schwannoma (lane a2). However, only faint additional proteins are visible in the chin schwannoma, which was operated 11 years before the second neck schwannoma (lane a1). Others, studying different systems, have reported that they were unable to detect reinitiated N-terminally truncated proteins by Western blot analysis, possibly because these were rapidly degraded [5, 19, 27]. To avoid the latter and to provide further support for our translation reinitiation hypothesis, we overexpressed the wild-type and mutant SMARCB1 genes by performing transient transfection experiments. For this purpose, we introduced the c.30delC and c.34C>T mutations and also the c.38delA and c.46A>T mutations in the wild-type SMARCB1 cDNA sequence, coding for transcript variant 1, by site-directed mutagenesis. We additionally introduced the c.79A>G mutation in the construct with c.30delC mutation. This converts the ATG codon, encoding methionine at position 27 of the SMARCB1 protein, into GTG, which codes for valine, and should prevent reinitiation of translation at that position. Expression vectors containing the wild-type and mutant SMARCB1 cDNAs were used to transiently transf ect MON cells, which are rhabdoid tumor cells without endogenous SMARCB1 protein [28]. We probed Western blots of protein lysates, derived from the various transfec tions and from HeLa cells, with the Abcam SMARCB1 antibody. These are shown in Fig. 4b. As expected, the vector-only transfected cells and the untransfected cells display no SMARCB1 protein at all (lanes b11 and b12). In cells transfected with the wild-type SMARCB1 expression vector only the full-length SMARCB1 protein (385 aa residues, encoded by transcript variant 1) is synthesized (lanes b1, b6, and b14). In cells transfected with the c.30delC containing SMARCB1 construct a prominent band at a position corresponding to that of the additional proteins in the second neck schwannoma of patient 2 (carrying the same SMARCB1 mutation) can be seen (lanes b2 and b7, cf. lane a2). In addition, smaller bands are apparent. The prominent band strongly reduced in intensity after transfection of the c.30delC containing SMARCB1 construct in which the c.79A>G mutation was additionally introduced (lane b3).
However, the smaller bands remained present. The reinitiated SMARCB1 protein and the smaller bands were also present in the lysates derived from cells transfected with the c.34C>T, c.46A>T, and c.38delA containing SMARCB1 constructs (Fig. 4b, lanes 4/8, 9, and 15, respectively).

To confirm the identity of the reinitiated SMARCB1 protein and the smaller proteins, we additionally probed the blot with lanes 1–4 (see Fig. 4b) with the BAF47 antibody, which is specific for the C-terminal part of the SMARCB1 protein (aa 257–359). Except for one additional smaller protein in lanes 2–4 (but not in lane 1), the same bands as for the Abcam antibody (specific for aa 81–181) were visualized with the BAF47 antibody (Fig. 4c).

Mosaic expression of N-terminally truncated SMARCB1 proteins

The mosaic expression of the N-terminally truncated SMARCB1 protein in several schwannomas of patient 2 with the germline c.34C>T mutation has already been reported [11]. The mosaic immunohistochemical staining of the right upper arm schwannoma of this patient is shown in Fig. 5b. Staining with the SMARCB1 antibody also revealed a mosaic expression pattern for the N-terminally truncated SMARCB1 protein in a spinal schwannoma (Th9-Th12) of patient 1 with the germline c.30delC mutation (Fig. 5a). In contrast, homogeneous staining with the SMARCB1 antibody of all tumor cell nuclei was apparent in the spinal schwannoma (Th 4) of patient 3 without a SMARCB1 mutation (Fig. 5c).

Discussion

PTC-generating mutations in SMARCB1-exon 1 in schwannomatosis

In this study, we investigated the sequence of events in schwannomas of schwannomatosis patients with a PTC-generating mutation in exon 1 of SMARCB1 (Fig. 1). It has been shown that, when a PTC is generated within short distance of the normal initiating AUG codon, ribosomes continue scanning and reinitiate protein synthesis at a downstream AUG codon [16]. Reinitiation was found to be optimal after translation of an open reading frame of 13–55 codons [15, 16]. The AUG codon at position 27 is a good candidate for translation reinitiation, because the open reading frames caused by the four mutations have the optimal size (11–15 codons) and this codon is identified as an efficient translation start site by the NetStart 1.0 prediction program. We could demonstrate that transcripts containing the c.30delA and c.34C>T mutations were present and, therefore, protected from NMD in the schwannomas of the respective patients (Figs. 2, 3). Their presence was not the consequence of a general failure for PTC-induced NMD in these schwannomas, because another PTC, in exon 5 of SMARCB1, resulted in total absence of the PTC-containing transcript in the schwannoma (Fig. 3).

Our transfection studies with the four mutant SMARCB1 exon 1-containing constructs demonstrated in each case the synthesis of a major protein, as visualized with the Abcam antibody (against aa 81–181), consistent with
usage of the predicted reinitiation methionine codon at position 27 in the amino acid sequence of the SMARCB1 protein (Fig. 4b). Confirmative support for the specificity of this event was provided by the strong reduction of that protein in cells transfected with the c.30delC + c.79A>G SMARCB1 construct. The additional c.79A>G mutation caused the replacement of the reinitiation methionine codon by a valine codon, thereby preventing a translational start at that position. Besides the major reinitiated protein, additional smaller proteins are present in the lysates derived from the cells transfected with the four SMARCB1 exon 1 mutant-containing constructs and also in the cells transfected with the c.30delC + c.79A>G construct (Fig. 4b). These are clearly absent in the cells transfected with the wild-type SMARCB1 construct. It is plausible that in case of the exon 1 mutant-containing constructs, and also in case of the c.30delC + c.79A>G construct, ribosomes continue scanning and reinitiate SMARCB1 protein synthesis at more downstream AUG codons and, in this way, prevent decay of the mRNA. This notion is supported by our observation that, except for one additional smaller protein, the same reinitiated SMARCB1 protein and smaller bands as for the Abcam antibody are recognized by the BAF47 antibody, the latter being specific for the C-terminal part of the protein (aa 257-359) (Fig. 4c). The additional smaller band that is exclusively visualized by the BAF47 antibody may represent a reinitiated protein that starts at an AUG codon between the sequences that encode the antigenic sites for the Abcam and BAF47 antibody, respectively. The NetStart 1.0 prediction program indeed identified four AUG codons in that region (with scores 0.601, 0.772, 0.522, and 0.700) as candidate translation start sites. However, it cannot be excluded that some of the smaller bands represent degradation products of the reinitiated SMARCB1 proteins.

Interestingly, for rhabdoid tumors no nonsense or frameshift mutations generating a PTC in exon 1 of SMARCB1 have been reported. This is explainable now, given the capacity of MON cells, as demonstrated here, to produce a reinitiated SMARCB1 protein in case the PTC is upstream of the ATG codon at position 79 in the coding sequence of SMARCB1. This type of mutations will, therefore, result in synthesis of a reinitiated SMARCB1 protein, but not in absence of SMARCB1 protein, the latter considered to be instrumental for the development of rhabdoid tumors.

Instability of the reinitiated SMARCB1 protein

It is known from studies in other systems that reinitiated proteins are often unstable and difficult to detect [5, 19, 27]. Prolonged degradation may have caused the almost total absence of reinitiated SMARCB1 proteins in the chin schwannoma of patient 1 displayed in lane 1 of Fig. 4a, which was operated 11 years before the (second) neck schwannoma in lane 2. In contrast, the two wild-type SMARCB1 protein variants in lane 3 displayed no degradation products at all.

The increased instability of the reinitiated proteins may also explain the mosaic staining pattern revealed by probing histological sections of schwannomatosis-schwannomas with a SMARCB1 antibody, as demonstrated for the c.30delC and c.34C>T mutations in Fig. 5. For both mutations, we have shown that the mutant SMARCB1 gene is retained and that the second SMARCB1 gene is lost or its transcript degraded by PTC-induced NMD in the schwannomas of the patients (see Figs. 2, 3). Therefore, all schwannoma cells should carry a mutant SMARCB1 gene, which encodes an immunoreactive reinitiated protein, as demonstrated for the c.30del mutation in Fig. 4 (lanes a2, b2, and b7). We hypothesize that the reinitiated protein is degraded and that not all degradation products are recognized by the antibody. Being a random event, this process may result in the accumulation of immunologically not-reactive SMARCB1 protein degradation products in part of the schwannoma cells. If so, then the mosaic staining pattern observed in other schwannomatosis-associated schwannomas might also be explained by the increased instability and random degradation of the encoded mutant SMARCB1 proteins [11, 12, 18, 25]. Our observation that the wild-type SMARCB1 protein variants of patient 3 are not degraded and display a homogeneous staining pattern with the SMARCB1 antibody (Fig. 5c) supports this concept. On the other hand, mosaic SMARCB1 staining has also been reported to occur in NF2-associated non-vestibular schwannomas [18]. Although no information was given about the somatic mutational status of the SMARCB1 gene in those tumors, one may assume that at least in some of the schwannomas the gene was wild-type. However, under certain conditions, even wild-type SMARCB1 protein may be subjected to random degradation, as was recently demonstrated for synovial sarcomas in which the SMARCB1 protein could not be incorporated into the SWI/SNF complex [13].

Conclusion

We demonstrated that in schwannomatosis-associated schwannomas PTC-generating mutations in SMARCB1-exon 1 can result in N-terminally truncated SMARCB1 proteins via translation reinitiation. As such, PTC-generating mutations in SMARCB1-exon 1 are absent in rhabdoid tumors. We hypothesize that the synthesis of an altered SMARCB1 protein, by translation reinitiation or encoded by the missense or splice-site mutations or in-frame deletions typically found in schwannomatosis patients, prevents
the development of a malignant rhabdoid tumor and results in the synthesis of a (relatively) benign schwannoma. Further functional studies are needed to determine how the activities of the encoded mutant SMARCBI proteins have been changed, how they contribute to the development of the schwannomas in patients with schwannomatosis, and how the selective vulnerability of (precursors of) Schwann cells for this type of SMARCBI mutations can be explained.

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References


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