The role of biobanks in elucidating prevalent genetic diseases in Saudi Arabia

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Summary

Biobanking entails large-scale collection of human biological specimens that are linked to the donors’ health and personal information, and has several applications in clinical research. Human biological specimens, such as blood, urine and tissue, have become immensely important to medical research: they offer a valuable source of genetic material that researchers can use to identify disease-associated genetic variation and to determine interactions between genes and environmental factors. Identification of genetic contributions to disease can lead to the development of new diagnostic tests and targeted treatments. Over the last decade, both common diseases and rare genetic disorders have been reported in Saudi Arabia. The need to generate extensive genetic data on these diseases has led to the establishment of several Saudi Arabian biobanks. Fortunately, these vital efforts have the support of the Saudi Government and researchers. However, the success of any biobank also requires public support and the willingness of the population to donate their biological material along with information on their medical records. Thus, the Saudi public needs to be informed of the benefits of maintaining biobanks, their participation needs to be encouraged through donation of biological material, and any public concerns regarding the confidential treatment of medical data need to be addressed. This article reviews the most common genetic diseases identified in the Saudi population, it describes biobanks and it examines how biobanks can support biomedical research in the area. Moreover, this article proposes measures that might help to increase public awareness of biobanks and the preparedness of the Saudi Arabian population to donate biological material.

Keywords: Consanguinity, donation, willingness of donors

1. Introduction

Over the past decade, there has been remarkable interest in the study of genetic disorders in Saudi Arabia, and many researchers have highlighted the need for more intensive studies to help prevent genetic diseases in this region. In 2006, the Yörtürk Foundation declared that genetic diseases have spread among the people of Saudi Arabia (1). Several other studies have reported differences in the incidence of some genetic diseases in Saudi and Caucasian population (2,3). Moreover, inter-ethnic variations have recently been reported with regard to not only the incidence of genetic diseases but also drug pharmacokinetics (4). Indeed, studies comparing Middle Eastern Arabs and other populations found variations in the effective drug doses for treating several diseases. This variability in pharmacokinetics has been attributed, by the authors, to population-specific genetic, environmental, and nutritional factors (4). Due to these reasons, researchers in Saudi Arabia have greatly increased their efforts in studying common genetic diseases. Today, studies mainly at the King Faisal Specialist Hospital (KFSHRC) and National Guard and Health Affairs Hospital (NGHA) in Riyadh have indicated that certain genetic diseases are of substantial medical concern in Saudi Arabia (5,6). These studies have categorized the most prevalent genetic diseases in Saudi Arabia as inherited...
metabolic, neurological, hematological, endocrine, rheumatological, ophthalmological, and congenital malformations. Some rare genetic syndromes that are specific to the Saudi population have also been identified. The most common inherited disorders are as shown in Supplementary Table S1 (http://ddtjournal.com/docindex.php?year=2016&kanno=4).

The main reason for the increased frequency of genetically inherited diseases within the Saudi population has been attributed to the high rate of consanguineous marriages. Consanguineous marriages are generally defined as marriages between blood relatives; however, in genetics research, consanguineous marriages refer to marriages between first or second cousins. Consanguinity increases the risk of inherited diseases such as congenital anomalies and autosomal recessive diseases; the closer the relationship, the higher the risk. For the children of first cousins, the risk of congenital and autosomal recessive diseases is increased by 2-4% (7). Nonetheless, consanguineous marriages are quite common in many parts of the world, with the highest rates occurring in Africa, the Middle East, and Asia.

The average consanguinity rate in Saudi Arabia is very high, and the overall rate of consanguinity was found to be 56% in 2007, with 33.6% of marriages consisting of first-cousin marriages (8). A study has reported that the highest prevalence of consanguinity is in the Njad Region, which includes Riyadh, and in Makkah, Madinah, and the Eastern Province. The structure of society within these regions is largely tribal, and tradition encourages marriages between first cousins from the same tribe. However, there are significant variations in the prevalence of consanguinity between regions, as well as between rural and urban settlements (8). For example, consanguinity is less frequent in areas such as Jiddah, where foreigners come for Hajj and later settle and intermarry with the resident population. Surprisingly, despite recent developments in many aspects of life in Saudi Arabia, the consanguinity rates have remained unchanged over the last decade (9).

As long as the consanguinity problem persists in Saudi Arabian society, and genetic diseases will spread, as confirmed by Recent studies (5,6), biobanks must be established. Biobanks offer the possibility of studying and developing preventive measures and cures for genetic diseases using biological samples donated by affected individuals. They provide the basis for more detailed molecular and pharmacological studies of individuals with genetic diseases that are prevalent in a certain population, such as the Saudi population.

The success of biobanks depends on public support and the willingness to donate. In order for biobanks to be effective, large numbers of participants need to be recruited. Typically, biobank participants voluntarily contribute their samples for research, though in most cases public support cannot be taken for granted. If biobankers knew exactly what prospective donors were thinking, they would be able to address their concerns and increase participation by planning suitable educational programs that increase awareness of biomedical research and biobanking in particular. Over the past few years, several universities, hospitals, and biobanks around the world have surveyed people, asking what makes them want to participate in a research biobank. Among the top factors that were suggested to play a role in a donor's decision are altruism, personal and family benefits, availability of research results, and the influence of religious permission to donate biospecimens (10). Fortunately, there appears to be broad-based support for the biobanking process and the use of biosamples in research. A previous study on the rate of willingness to participate in biomedical research revealed a satisfactory attitude towards participation in Saudi Arabia (11), but more studies are needed to clarify public attitudes towards participation specifically in biobanking-related research.

This paper summarizes the most common genetic diseases in the Saudi population and it highlights the possible role that biobanks can play to support relevant biomedical research. This paper also suggests future educational and awareness programs that provide the information needed to increase public understanding and participation in biobanks.

2. Definition and function of biobanks

In order to understand the complex interactions that exist between genetic and environmental factors, large-scale studies of human populations need to be carried out. Biobanks are suitable tools for generating data needed to undertake these studies, as they contain large collections of human tissue linked to patients' medical records. They facilitate the opportunity to identify environmental risk factors or genetic variants that are associated with genetic diseases prevalent in a community. The generated data are analyzed to obtain statistically significant results correlating gene variants with disease phenotypes (12,13).

There are various definitions of biobanks in the literature, and one exhaustive definition is as follows: biobanks consist of large repositories of biospecimens that are linked to clinical data. They combine two major aspects of biomedical research: i) The capacity to collect and handle large amounts of biological material (e.g., tissues, DNA, and proteins) and ii) The collection, storage, and integration of the clinical records of patients (14).

Another definition of a biobank is that it is a large set of data consisting of personal and health-related information, including medical records, family history, genetic background, and lifestyle. This set of data is linked to a set of stored tissues and cells. Biobank data differ from data stored in a patient registry or
in electronic medical records because these other repositories do not contain related biological specimens. However, such records can be complementary to biobanks, as they also provide information that can assist in human medical research, and particularly information relating to patient populations, and also general healthcare information on hereditary data and mortality.

When a biobank is established, biological samples are systematically collected from patients and/or other healthy donors. These samples are then sorted and stored, together with relevant medical information, primarily for the purpose of medical research and for research into genetic diseases.

2.1. The history and emerging roles of biobanks

On August 26, 1996, the research company deCODE genetics, Inc. was founded in Delaware, US, and later that year the company established its subsidiary, Íslensk erfðagreining, in Reykjavík, Iceland. The aim of deCODE genetics was to establish a gene bank by utilizing the already existing medical and genealogical records of the Icelandic population and to combine this information with genetic information obtained from tissue samples of the entire population. Their aim was to understand the genetic basis of the most common genetic diseases in the Icelandic population and to use the results to develop novel treatments. In December 1998, the Icelandic biobank was established as the world’s first genomic biobank (15). Soon after, biobanks were established in several countries (e.g., the Estonian Genome Project, the UK Biobank, Generation Scotland, and the CARTaGENE project in Quebec, Canada)(16,17).

Today, biobanks are established around the world as an important tool in genetic, medical, and behavioral science (18), and several countries now have well-developed national biobanking programs. Norway, Sweden, Estonia, Canada, and the UK are several countries with the most active biobanks, covering large populations. Furthermore, many recent efforts have been made to connect biobanks through networks that span countries and continents, such as EuroBioBank, TuBaFrost, the Public Population Project in Genomics (P3G), the Telethon Network of Genetic Biobanks, and the Biobanking and Bimolecular Resources Research Infrastructure (BBMRI) (19). Biobank networks facilitate the trans-national sharing of biobank resources. For example, the BBMRI project has recruited 270 organizations and has linked 20 million samples in 33 countries. Similarly, EuroBioBank created a network that offers access to relevant biological samples from biobanks across the region. The network consists of 16 biobanks in eight European countries and has an online database listing more than 440,000 human DNA, cell, and tissue samples linked to rare diseases. In addition to large-scale, national biobanks, several small-scale regional biobanks have also been established around the world. Unlike large-scale biobanks, which include population biobanks and biobanks for therapy and transplantation purposes and involve multiple investigators, ethics professionals, and lawyers, small-scale biobanks may involve a single investigator and a limited number of samples.

Apart from scale, modern biobanks also differ on the basis for the nature of their stored biological specimens, purpose, their target donors, and ownership. The biological specimens in a biobank may include one or a combination of tissues, macromolecules, bodily fluids, or organs. Sample types currently being stored in biobanks are blood, the buffy coat, plasma, serum, frozen tissue, buccal cells, formalin-fixed or paraffin-embedded tissues, cultured cells, donor-derived cell lines, proteins, RNA, and DNA.

The utility of a biobank can be for diagnostic purposes (such as pathology, forensics, or transplantation), for therapeutic treatment (e.g., blood banks, bone marrow, cord blood, and stem cells), or for pure research. The research can be focused on a specific population or on a specific disease, such as cancer, diabetes, heart disease, or a genetically inherited disease (20). Thus, the target population of a biobank can be either healthy people, such as all newborns, adults, or pregnant women, or patients with a specific disease. Disease-oriented biobanks are normally linked to a hospital, where specialized staff members collect samples that represent different diseases to help with the identification of biomarkers linked to a disease (21). Population-based biobanks need not be linked to a particular hospital because they collect their samples from a variety of donors from the general population (e.g., when conducting research on biomarkers for disease susceptibility) (22), and the participants may be of different ages, ethnicities, and exposed to different environments.

The ownership of a biobank can be private, public, or a partnership spanning multiple sectors. Biobanks can be run by the government, non-profit organizations, or commercial companies or by hospitals or universities (23). Different biobanks have different approaches to coding, privacy, and the extent to which data linkage is possible.

3. Saudi Arabian biobanks and their role in biomedical research

The high incidence of rare genetic diseases in Saudi Arabia, partly due to the custom of consanguineous marriage, has increased the need to establish Saudi biobanks that fully cater to and are closely tied to local needs. Currently, there are several biobanks in Riyadh, Saudi Arabia. These include: the Biological Repository Center at the King Faisal Specialist Hospital.
(KFSHRC); the Saudi Biobank at the King Abdullah International Medical Research Center of the National Guard & Health Affairs (NGHA); and the Eye Bank at the King Khaled Eye Specialist Hospital (KKESH). The procedures Saudi biobanks follow to receive, process, store, discard, and release samples have been adapted from different established international biobanks. As an example, the NGHA biobank follows the procedures of the UK Biobank. All Saudi biobanks have departmental policies and procedures (DPP) that apply to all biobank members. DPP describe the policies and procedures for efficient and effective management of the biobank and cover in detail all of the steps involved in processing samples. Moreover, all Saudi biobanks, like international biobanks, are obligated to obtain informed consent from all participants prior to participation. Withdrawal of consent at any time is a right granted to participants (27).

The Biological Repository Center was established in 2004, and its primary function is the preservation and storage of archived frozen tumor and normal tissue samples. These samples will be used for DNA and RNA extraction and for subsequent analysis, including mutational analyses and differential expression analyses (24). The NGHA Saudi Biobank, which was established in 2007, aims to conduct an extensive study on the influence of genes, the environment, and lifestyle in common diseases (25). The Biobank includes four sub-biobanking facilities: the DNA Bank; the Community Biobank; the Disease Biobank; and the Tissue Biobank. The Community Biobank stores biological material from healthy individuals, whereas the Disease Biobank stores biological material from individuals with various genetic and chronic diseases. The Tissue Biobank stores breast, colon, kidney, liver, lymph node, and thyroid tissues. The Saudi Bio-bank Project plans to recruit 200,000 volunteer patients from NGHA hospitals and clinics in order to study the most common diseases in Saudi Arabia (such as diabetes, cancer, coronary artery disease, hepatitis, obesity, bronchial asthma, chronic renal impairment and failure, stroke, and inherited genetic diseases (25). The Eye Bank was established in 1984 for eye donation, and it primarily provides tissues for KKESH surgeons, who perform more than 400 corneal transplantations annually (26).

Until recently, all medical treatments in Saudi Arabia were developed through the study of non-Saudi populations. Moreover, there has been a lack of large-scale research based on populations in the region. Since many Saudi biobanks have been established or in the process of being established, scientists are obtaining access to Saudi biological samples along with health information from Saudi patients and healthy volunteers. Records of the bio-bank participants’ lifestyles, gathered via questionnaires, interviews, and physical examinations, constitute the initial Saudi bio-bank database. This knowledge will allow researchers to better understand diseases that affect Saudi populations and will lead to tailored healthcare and personalized medicine.

4. Social and ethical issues associated with the willingness of donors in Saudi Arabia and the success of biobanks

The need for significant statistical results correlating gene variants and disease phenotypes necessitates the presence of large numbers of volunteers and a respective large-scale collection of biospecimens (12,13). Many successful biobanks pool large numbers of samples and related data by recruiting large numbers of participants who voluntarily contribute samples for research. deCODE genetics has banked the genetic samples of 100,000 Icelandic volunteers that are linked to both the Icelandic Health Sector Database and genealogical records (15). Similarly, the Estonian Genome Project is establishing a national genetic/medical database of one million volunteers (16). The National Institute of Health (NIH/USA) has facilitated biobanking by developing a centralized data repository, the database of Genotypes and Phenotypes (dbGaP). In addition, the NIH has outlined several data-sharing procedures that will allow researchers to share data obtained from NIH-supported genome-wide association studies (GWAS) (28).

As long as the success of biobanks depends primarily on public support and willingness, biobanks need to adopt mechanisms to maximize public interest, to maintain trust between the donors and the biobank, and to encourage people to donate samples and their medical information for research purposes (29). Individuals who contribute their tissues and personal information also need to feel secure in their involvement with the biobank. Generally, people have a positive opinion towards genetic research (30-32), but they may still harbor a negative attitude towards their own participation and sample donation (33,34).

There are considerable social and ethical issues associated with the functions of biobanks in Saudi Arabia. There, religion, tradition, and public awareness can greatly affect people’s attitudes towards participation. These issues need to be addressed for the Saudi Arabian population and the preparedness of the Saudi people to participate in biobanks needs to be assessed so that Saudi biobanks can be established.

4.1. Willingness of donors in Saudi Arabia to participate in comparison to Western donors

In Western countries, several studies have addressed the public’s level of willingness and the reasons that encourage volunteers to participate in biobanks or in other forms of genetic research (32,35,36). Western populations have more access to higher education and
are generally considered to be more familiar with the link between healthcare and research. The public are willing to participate when they understand and believe in the benefits of genetic research, and they are more likely to donate biological material to biobanks if they are assured that their information will be treated with confidentiality and they are aware that there will be no unwarranted access to their samples and information (37).

A previous study in the US by Kelly et al. (35) reported that altruism is one of the primary reasons for public participation in biobanks, as the majority of participants wanted to make a positive contribution to research after facing an illness themselves. Another motivation was the desire to contribute to scientific and medical knowledge and to assist researchers in identifying genes that might aid in the treatment of incurable disease. The authors indicated that ease of participation, where no additional blood samples or time was required, was also an important factor for encouraging donation of biological material to biobanks. Studies among the general population in Finland showed that the willingness to participate was associated with a belief in the benefits of genetic research (38-40). A similar study in Singapore reported different reasons for donation and willingness (41); the authors found that the most common reasons for the willingness to donate blood were: for medical advancement (81.9%), to benefit future generations (81.1%), and to create employment in life-science research (40.4%). They also reported that the reasons for not donating blood included the fear of pain, needles, injections, and blood (38.1%); no self-benefit (24.8%); the fear of finding out that they have a disease (22.3%); and the fear of discrimination by employers and insurance companies (18.7%).

Few efforts have been made to assess the concerns and willingness of Saudi individuals to participate in the country's current biobanks, and little is known about the reasons that might influence their willingness to do so (11). Information on public attitudes to biobank participation in the literature cannot be readily applied to the Saudi population because of the variability in education, culture, traditions, and basic assumptions. Most Saudis, excluding the educated sector, are not fully cognizant of the benefits of participation in genetic research. The general public is unfamiliar with the concept of genes, DNA, or genetic research; therefore, these issues need to be addressed before encouraging widespread public participation in the nation's biobanks. Interestingly, however, the results of two recent surveys conducted at Abdulaziz Medical City in Riyadh, Saudi Arabia indicated that the public is highly willing to contribute to genetic research (87%) and most respondents appear to have positive attitudes towards donation (11, 42). This high level of willingness is consistent with that found in studies conducted previously in highly developed countries, such as Sweden and the US (31, 32).

The similarity between the Swedish, American, and Saudi Arabian populations with regard to the relatively high level of willingness to donate, despite social, cultural, and educational differences, can be explained by findings presented by David Wendler, who summarized the data obtained from 30 studies and more than 33,000 individuals. His studies yielded consistent findings, despite the different nationalities of the participants, and he found that most participants favor donation and biobank participation (43). In addition, a comparison of the factors associated with willingness among groups that are aware of genes versus those that are not yielded very similar results for both groups (43). In order to encourage Saudi willingness to participate in biobanks, social, religious, and ethical factors need to be addressed and public awareness of biobanks needs to be increased. The tribal structure that deeply influences people's social behaviour, beliefs, and ethics is specifically influential and detrimental to the development of biobanking.

4.2. Culture and religion

The cultural setting in Saudi Arabia is deeply religious, conservative, traditional, and family-oriented. Islam is the state religion and the source of the legal system. Islam is turned to for guidance in all aspects of life, including research and medical issues. Saudi people respect their religious leaders and are guided by religious teachings. Accordingly, Saudi biobanks should be designed in a manner to respect not only international guidelines but also Islamic/Sharia values. Muslims' religious and cultural attitudes have to be taken into account when considering issues such as informed consent, privacy, and concerns about justice (42, 44). Islamic sources will be consulted to ensure that the biobank is compliant with and observable of Islamic Sharia law. These sources include the Quran, Sunnah, and fatwas, which are legal opinions concerning a specific matter in Islamic law handed down by an Islamic religious leader. Both researchers and Islamic medical organizations use these institutional fatwas when they encourage participation. However, Saudi biobanks need more specialized fatwas to clarify Islamic judicial views on many issues, including informed consent, privacy, and confidentiality. Fatwas that might hinder harmonization with international biobank standards need to be avoided (45). A recent study in Jordan, a neighboring Muslim country, found that religious permission had a strong positive influence on the respondent decision to participate (46). In Saudi Arabia, very little research has been done on the effect of religion on the willingness of people to allow use of their private information and biological samples for research (11, 42). As religious institutions have a social
authority in the Saudi society, they can effectively collaborate with biobank personnel to encourage the Saudi people to accept the types of ethical guidelines that are widely followed by healthcare professionals worldwide.

4.3. Ethics

An essential component of establishing a Saudi biobank is to set an ethical framework that gains public trust and consent and that facilitates donor recruitment with an ethics review board. The ethical framework should address the concerns of the donors and the principles, policy, research rules, and guidelines of biobanks.

Many countries have developed national and international guidelines for biobanks, such as the UK Biobanks Governance national guidelines (47), the Guidelines for Human Biobanks and Genetic Research Databases from the Organization for Economic Cooperation and Development OECD (48), and the International Declaration on Human Genetic Data by the United Nations Educational, Scientific, and Cultural Organization (UNESCO) (49).

Despite the fact that there has been a lack of published guidelines on genetic or general research ethics with regard to specimen donation in most countries of the Eastern Mediterranean region, Saudi Arabia is fortunate in already having special national guidelines concerning research ethics and efforts are underway to define all research ethics. Different documents regulating research ethics have been drafted, including general guidelines for biomedical research and official legal documents issued by the Council of Ministers. The Saudi Food and Drug Authority (SFDA) guidelines contain 15 of the protections mentioned in international guidelines on research ethics, such as the ICH-GCP, the CIOMS guidelines, and the Declaration of Helsinki (45). However, national regulations on research ethics and guidelines in Saudi Arabia have some deficiencies in comparison to their international counterparts (45). In most Saudi biobanks, e.g. NGHA biobank, the Institutional Review Board (IRB) is an independent body consisting of medical, scientific, and non-scientific members whose responsibility in part is to oversee ethical issues such as protection of the rights, safety, and well-being of human subjects involved in research and regulations on the use of donated samples. As all biobanks exist within institutions, whether they be academic or medical, the biobank IRB work together with the institution' ethical review board to approve all biobanking and to make decisions about biobank access for research.

Gaining donors' trust and confidence is essential for Saudi biobanks to function and it requires, in addition to well-established and clear ethical policies and rules, close collaboration between clinicians, researchers, and information technologists. Fortunately, substantial efforts are being made by the Saudi Government and researchers to address this issue and provide biobanks with expert medical personnel or clinicians to collect biospecimens and to properly manage the samples before storage. In addition to the proper handling and transportation of samples, a pathology review, and the use of qualified laboratories for subsequent molecular biology analyses, such as DNA extraction or the collection of any blood constituent, Saudi donors need to be informed of most, if not all, of the safety procedures that will be followed regarding their donated samples.

In addition, the secure storage of patient medical data and information should be ensured by the biobank. Donors should be informed of the absolute confidentiality of their medical records. The social characteristics and tribal structure of Saudi Arabia still strongly influence people's attitudes regarding their privacy and necessitate strict confidentiality regarding their personal issues. Accordingly, Saudi biobanks should adopt different mechanisms to guarantee the confidentiality of personal information. The stored samples and data should be coded and/or anonymized and kept under strict control and protected by a good security system. The data collected from medical records, medical workers, interviews, or other sources should be formatted for secure storage in a modern coded digital format. All of the digital formats must also allow easy and rapid access to code and decode the information used on specimen labels. Modern types of optically accessible barcoding systems are becoming widespread in all types of massive data storage, and this is especially true for biobanks (50). Finally, infrastructure would ideally be in place before any data are collected, since it will become increasingly important when the size and scope of the biobank increases.

4.4. Education on the usefulness of biobanks

Educational programs that clarify the benefits of participation in genetic research need to be instituted and individual fears and concerns about sample donation need to be addressed in order to establish effective and functional biobanks in Saudi Arabia. As the decision to participate is often made in concert with one's extended family, educational programs should include all family members. A general public education program can be implemented in schools by incorporating basic information into the early educational curriculum. Providing the public with genetic counseling services is also crucial, as is increasing public awareness with the help of mass media.

5. Conclusion and prospects for the future

Biobanking has the potential to be of significant benefit
to genetic research in Saudi Arabia by providing researchers in the country with the opportunity to study and draw conclusions about the role(s) of genes in the development of diseases. The true value of a biobank in Saudi Arabia is likely to be realized only in a climate of cooperation and sharing of resources and experience, both domestically and internationally.

The time has come, in Saudi Arabia, to encourage public discussion to promote the future establishment of a functional biobanking system with clearly defined pathways for obtaining consent from participants, collecting, transporting, and storing samples, and secure data analysis and retrieval. Success in this endeavor will ultimately facilitate a number of valuable research projects. Saudi Arabia can make a unique contribution to the field of genetic disease research, given the prevalence of several inherited conditions in the area and the familial structure. Concerted and well-coordinated efforts are required to increase public understanding and to address any potential concerns regarding genetic research. The public must be educated and encouraged to participate in genetic research, and the public needs to be involved in the development of a genetic research policy. Saudi researchers and the Saudi public are known to have a strong sense of social responsibility and a desire to comply with religious teachings. Thus, all biobanking activities need to be redesigned and reframed to fully comply with Sharia guidance. Accordingly, approvals by or fatwas from prominent clerics in support of biobanking will be crucial to biobanking efforts.

The establishment of highly functional biobanks in Saudi Arabia in collaboration with other biobanks worldwide, and particularly in neighboring Arab countries, will encourage future collaboration and greater discussion and harmonization of guidelines. A broader biobank program in Saudi Arabia will greatly enhance and support efforts to research diseases in surrounding Arab countries.

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(Received July 1, 2016; Revised August 11, 2016; Accepted August 12, 2016)