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Brief Report

Marfan Syndrome

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Introduction

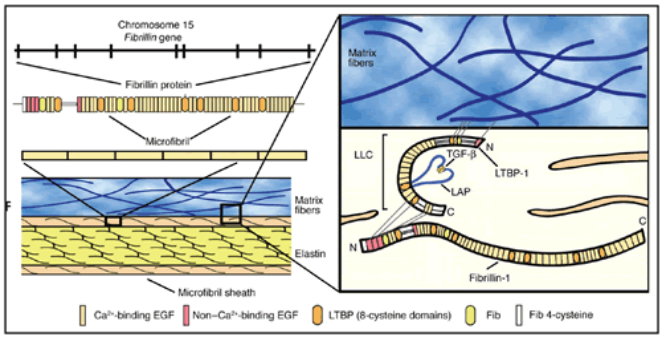
Marfan syndrome is a rare hereditary disorder. Cohort studies conducted on this disease claim that the birth incidence for such disorders is 1 patient per 4268 people [1]. According to Cook, et al. [2], cardiovascular abnormalities are among the main reasons behind the increased rates of morbidity, as well as mortality in the syndrome, along with other clinically related diseases. Moreover, there is a pathogenic contribution of the deregulated growth factor, which eventually affects the signaling process and impairs it. The following essay highlights the overview of the disease, the pathophysiology of Marfan syndrome, the genotypic and phenotypic analysis of the disease, along with the various risks and barriers associated with the personal environmental backdrop, as well as their effect on the social cultural society.

Overview of the Disease

Marfan syndrome is a genetic disorder affecting the connective tissues of the body. The connective tissue plays an important role in holding cells, tissues, and organs of the body together, while simultaneously helping in the proper development and growth of the body. Almost 1 out of 5,000 people suffer from Marfan syndrome, which is inclusive of men and women irrespective of races and ethnicity. About 3 out of 4 people suffer from Marfan syndrome through the genetic mutation inherited from their parents. However, spontaneous mutations occur in some people where they are the first people to inherit the disease. Genetically, there is a 50 % chance of a person with Marfan syndrome passing the genetic mutation to their progeny. Children suffering from Marfan syndrome are young and do not usually develop symptoms like aortic enlargement or other signs of the disease until they are adults [3].

Pathophysiology

Marfan syndrome is a connective tissue disorder which is an inherited in an autosomal dominant manner. Marfan syndrome is mainly caused by gene mutations, often on the FFBN1 gene. The gene is important for Fibrilin 1 which is a glycoprotein. Fibrillin 1 is the main constituent that make up the micro fibrils that is part of the extracellular matrix.



Source:http://www.interactive-biology.com/3290/what-is-marfan-syndrome/

According to Dietz, et al. [4], Marfan syndrome is caused by the heterozygous mutations in the gene FBN1, which encode extracellular matrix protein Fibrillin 1. Missense mutations are common, which have a very high frequency of substitutions that either lead to the destruction or creation of cysteine residues present in repetitive growth factors, such as growth transforming factor TGBβ. FBN1 mutations involves insertions as well as deletions inclusive of altered spliced events that alter the coding sequence, but maintain the open reading frames which helps in the creation of termination codon. The phenotypic-genotypic correlations in Marfan syndrome include allelic heterogeneity, along with the fact that most of the phenotypes often show genetic variation and potentially influence the genetic, as well as environmental modifiers of the disease. Reductions and abnormalities in the gene causes weaknesses in the tissue, which lead to increased signaling of the growth beta factor, loss of interactions of the cell matrix, and ultimately to various phenotypic manifestations of the Marfan syndrome. The most important clinical manifestations of Marfan syndrome is cardiovascular involvement [5].

Punnett squares are useful in determination of genotypes through proper crossing or breeding experiments. From the

evaluation of the Punnett Square for Marfan syndrome, the genotypes of the parents have been considered with the alleles M and m. The combinations of the alleles have been represented through Punnett Square and it can be seen that almost 50 % chance of disease transmission is there. Among the possible genotypes of the off-springs, one of them is a carrier and the other is not a carrier. Overall, the result of getting the disease from the parents is 50-50.

This is the proband pedigree with Marfan syndrome. +/- is a representation of the heterozygous type while -/- is the wild type. The circles and squares are represented by the females and males. The filled symbols in black are a representation of the symptoms affected with Marfan syndrome as shown by the arrow. From the evaluation of the pedigree charts, it can be found that most of the patients with Marfan syndrome often develop cardiovascular diseases. Moreover, it has affected only males of the family. This disease can be either an X linked or Y-linked disorder. The son of the second generations are tall and lanky with extended arms and fingers. Thus, a pedigree chart is important for the analysis of human inherited diseases. From this chart, the inheritance of the allele for Marfan syndrome is evident. It is an autosomal dominant disease because the disease can occur due to presence of genes in one of the parents, which is a characteristic of the dominant type. Additionally, it is autosomal as it is inherited from a non sex-chromosome.

Discussion of Research Studies

Various genotype phenotype relations can be evaluated for the correlation of Marfan syndrome with cardiovascular involvement. Early observations by Aoyoma, et al. [6] have shown that mutations often lead to deposition of the fibrillin 1 protein in very small amounts. Moreover, the low levels of protein have been associated with various shortened event-free survivals, along with various cardiovascular complications. Furthermore, previous studies have found that patients having premature terminations codons have worse prognosis and increased chances of aortic surgery, aortic complications, and mortality rates. Similarly, the author has found that there is a relation of truncation mutations in Marfan syndrome with mutation carriers [7,8]. Alberts, et al. [8] have observed that data on DNA analysis of 184 patients suffering from Marfan syndrome have carried FBN1 mutations which influence the phenotype. The relationships between the genotypes and the phenotypes in left ventricular dilatation have been occurring due to non-sense mutations. Also, haplo-sufficiency is often believed to the main reason leading to the disease.

Impact of Heredity

Marfan syndrome is an autosomal dominant disease. However, a minimum of 25 % of the disease syndrome occurs due to new mutations in the FBN1 gene. Thus, this disease can occur in people where there has been no history of the disorder in the family.

The mechanisms by which the genes cause an increased risk of development of the diseases include mutations in the FBN1 gene, especially on chromosome 15, cause the specific disorder which eventually weakens the ligaments, tendons, and connective tissues. FBN 1 is mainly located at the chromosome 15q, consisting of 65 exons and encoding 2871 structural proteins like fibrilin 1, which is further a 360 kDa glycoprotein having 47 epidermal growth factors. According to the mutations of the Universal Mutation Database, almost 3000 mutations including 1745 mutations have been documented. Moreover, a missense mutation in Exon 14 of FBN1 has occurred where substitution of the cysteine has been changed by glycine, ultimately leading to non-consanguineous family for generations [9]. Thus, these specific changes in the genes have continued for generations, which increase the risks for the development of the Marfan syndrome for continuing generations.

Risks and Barriers with Testing

The costs of genetic testing are huge, which varies upon the nature, as well as the complexity of the tests. Moreover, the costs increase when multiple tests are required for obtaining a proper and meaningful interpretation of the test. Although health insurance policies mean to cover most of the expenses, most of the times, increased costs are not covered completely under the health insurance. Additionally, state privacy protection laws are important for consideration for appealing to governmental health policies. Without the affirmation from governmental organizations, insurance companies cannot give health insurance. Thus, it can be seen the increased cost of the diagnosis of genetic hereditary disorders, such as Marfan syndrome, show that there are various financial barriers and risks, which are very important for consideration of the stability of the present condition [10].

There are further barriers to the tests for diagnosis of the disease which can affect the individual personally. For instance, for carrying out eye tests, in order for glaucoma to be checked, the pressure of the eyeball of should be examined and can affect the individual while testing. Also, the risks are enhanced for old people with heart diseases. Regular echocardiograms done for the diagnosis should be done carefully and is hectic for the older citizens. Physical risks are often very negligible as they require small amounts of blood samples. However, the same procedures are risky for pregnant women because there is an increased risk of losing the pregnancy since the tests require a sample of the amniotic fluid and tissue samples from the fetus [10]. The prevalence of methods such as genetic testing has specific environmental exposures. It affects the gene-gene and gene-environment interactions among a huge population. Also, there are increased chances of Single Nucleotide Polymorphisms (SNPs), which affect the genetic constitution of the environment. Moreover, premature transferals of genetic testing procedures into practice affect the balance in the environment.

Impact on Legal, Ethical, Socioeconomic Factors

Various ethical issues are involved in the testing procedures of Marfan syndrome. Availability of the informative test in the workplace helps workers to perform, while being informed and well known about the kind of jobs taken by them. Genetic testing procedures create a hazardous environment. The safety of the worker regarding procedures like genetic testing is of primary importance. For instance, in the US, specific chemical companies have been closed due to the failure to include a specific employee in proper cytogenetic testing programs, which have led to the development of leukemia. Thus, considerations of ethical issues are important for carrying testing for the disorders [11].

There are various legal considerations which have to be kept in mind while carrying out diagnosis-based tests for Marfan syndrome and related hereditary disorders. Firstly, communication of the test results is important for discussing with patients in a proper understandable and compassionate manner. Results should only be released to those individuals only with consent of the patient. Patients should be careful while considering direct consumer genetic testing procedures who are encouraged for discussing the results of the tests with their respective healthcare professionals. Health providers should confirm the confidentiality of the information of the patients. They should not inform other members of the family without the prior permission of the patients. Healthcare professionals should not discuss test results with the members of the family. As far the social effects of the Marfan syndrome are concerned, people suffering from genetic disorders often face emotional as well as social issues. Changes in outlook and lifestyles are affected. Restriction of activities for Marfan syndrome often has a negative impact on the social effect of the person. Such people often feel angry and afraid. They are often stressed about their hereditary characteristics and suffer from anxiety regarding the passing on the disease to their progeny [12].

Genetic Testing and Impact on the Disease

Genetic testing is actually defined as the study of a person's DNA for identification of genetic differences, as well as susceptibility to various diseases and abnormalities. Genetic testing in Marfan syndrome helps in confirming, as well as ruling out the diagnosis procedure as required. Moreover, it facilitates discussion involving preimplantation genetic diagnoses and prenatal diagnosis as well. Whenever diagnosis cannot be used for the determination through clinical evaluation, genetic testing may be helpful in those cases.

However, there are several limitations regarding genetic testing. Only particular populations are required for more than usual testing procedures for identification of the alterations. Mutations in FBN1 syndrome might cause other conditions apart from Marfan syndrome. Most of the time, it is difficult for the prediction of the condition by expecting the mutation. Current best estimates suggest that no mutation is found in about 5-10 percent of people with clear-cut Marfan syndrome. This occurs due to the nature of the change in the gene mutation or a variety of technical problems. Furthermore, family members having same mutations can show a wide variety of presentations regarding the timing of its onset and the severity of various complications. Another limitation of genetic testing procedure for Marfan syndrome is the increase in costs for the procedure. Additionally, the increased costs cannot be covered by health insurance companies most of the time [10]. Genetic testing has a positive impact in the diagnosis of the disease. The clinical management of various diseases, including the Marfan syndrome, has been improving due to the specific incorporation of genetic testing procedures. Moreover, prognosis of the patient can be estimated easily due to the determination of specific genetic risks. Thus, preventive measures can be adapted, and the therapeutic procedure can be incorporated successfully. Marfan disease and its clinical diagnosis often acts as an example of the clinical benefit of genetic testing [13].

It can be concluded that there are various factors to be considered while suffering from the disease. Marfan syndrome is a rare autosomal dominant hereditary disorder where half of the progeny is affected, and half are carriers. This disease occurs due to the missense mutation in the FBN1 gene which shows phenotypic characteristics such as extended arms, feet, legs and fingers. One of the most important disorders related with the development of the disease include cardiovascular disease. Diagnostic procedures mainly used for the diseases are echocardiograms and genetic testing methods. However, genetic testing methods include cultural and ethical barriers. Furthermore, there are several legal considerations to be made during genetic testing procedures. The mechanism by which the genes influence the heredity of the diseases are mainly mutations in the specific chromosome, especially chromosome 15 q. The patient suffers in terms of social impact the disorder has, especially the impact of the community and the environment. Taking all the factors into consideration, Marfan syndrome is a rare inherited disorder which need to carefully keep in mind the social, cultural, and environmental factors for the establishment of a healthy community and for enhancing the mental health of patients in the future.

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