Marfan Syndrome

Ben Niver, Francis (Ryan) Santos and Pragati Tandon

Marfan Syndrome, first described by French pediatrician Antoine Marfan, affects the connective tissue and manifests as a group of physical signs.[1] As connective tissue is found throughout the body, Marfan Syndrome can affect several body systems: skeletal, cardiovascular, ocular, integumentary, pulmonary and dural. The former three are the most profoundly affected.[2] The molecular basis of this disease is currently under scientific investigation and hints at disruption of fibrillin-1 protein and TGFBR2 functions as underlying causes of this disease.[3] While the etiology of the disease is still under investigation, the management of its symptoms has made remarkable advances in the last thirty years.

Biochemistry and Molecular Biology

Recent scientific research on Marfan Syndrome indicates that various malformations of connective tissue protein contribute to the manifestation of the disorder. More specifically, scientists have looked at the effects of abnormalities in the primary structure of collagen, the main structural protein found on connective tissue. Research has been conducted on fibrillins and their association with this disorder. These proteins are present in the structural regions of the extracellular matrix and are building blocks of microfibrils. Studies using immunoflurescence have shown that humans with Marfan Syndrome tend to have deficiencies in fibrillin network formation including fibrillin synthesis and fibrillin secretion and accumulation in the extracellular matrix. It is theorized that mutations in the gene coding for fibrillin (FBN1 on long arm of chromosome 15) interfere in the proper assembly of microfibrils. Certain mutations may lead to shortened fibrillin-1 molecules. Others cause problems in disulfide bond formation due to insertion or deletion of cysteine residues affecting the folding of the fibrillin-1 protein. Moreover, there are mutations that affect protein functions such as interdomain packing and protein-protein interactions. Hence, these various mutations have deleterious effects on the assembly of the microfibrils. Despite increasing knowledge about the formation of microfibrils and the effects of the mutations in the gene encoding for fibrillin-1 protein, it is not currently known how the mutations in the gene can lead to the manifestation of the symptoms of Marfan Syndrome.[3]

In addition to the fibrillin-1 gene, the TGFBR2 gene has been implicated as causing a type II Marfan Syndrome. This gene is involved in signal transduction pathways that allow signals in the extracellular matrix to communicate with signals inside the cells. Disturbances in this transduction pathway caused by mutations in the TGFBR2 gene may result in underdevelopment of connective tissue resulting in the phenotype of Marfan Syndrome.[4]

Diagnostics

There are a few criteria for diagnosis of Marfan Syndrome. The criteria vary depending if family history of the disorder is present or not. When a patient has no family history, two body systems must be involved in addition to a minor involvement of

a third system. In the presence of family history or identification of a mutation in the fibrillin-1 gene or the haplotype surrounding the mutation, there must be a major involvement of one body system with a minor involvement of a second.

The four body systems that are taken into consideration when assessing for major involvement in Marfan Syndrome are the skeletal, ocular, cardiovascular, and dural systems. For the skeletal system, four of the following must be present: pectus carinatum or excavatum, reduced upper-to-lower segment ratio for age or arm span-to-height ratio, wrist and thumb signs, scoliosis greater than 20 degrees or spondylolisthesis, reduced elbow extension, medial rotation of medial malleolus and protrusio acetabulae. In the ocular system, dislocated lens is a major involvement. For the cardiovascular system, major involvement includes either dilation of the ascending aorta at the sinuses of Valsava or dissection of the ascending aorta. Finally, for the dural area, lumbosacral dural ectasia is considered a major involvement. Minor involvement includes the integumentary and pulmonary systems in addition to the afromentioned body systems. There are various degrees of signs and symptoms that are taken into consideration from these systems for minor involvement.[2] See attached chart from Gene Reviews.

There are various tests available for assessing for Marfan syndrome including protein-based tests and molecular genetic tests. The protein-based test employs immunohistochemical or pulse-chase methods of detecting anomalies in fibrillin-1 protein from dermal tissue. Molecular genetic tests are used for confirmation of diagnosis, predictive testing in the presence of a family history or for prenatal testing. Methods used include sequencing of cDNA of the FBN1 gene with a detection rate up to 90% or the direct sequencing of the 65 exons of the fibrillin-1 gene with a detection rate between 70-90%. Linkage analysis is also being used to detect the presence of an allele of the FBN1 gene that causes Marfan Syndrome.[2]

Genetics and Disease Risks

Marfan Syndrome is a heritable disease transmitted in an autosomal dominant manner. Seventy-five percent of affected individuals inherit the disease from an affected parent, while twenty-five percent of individuals have a *de novo* mutation[2] on the fibrillin-1 gene on chromosome 15.[5] Over 500 mutations have been identified, and most are unique to an individual or family.[6] About two-thirds of mutations are missense mutations that change one of the amino acids in this 65-exon gene, while approximately 20% are frameshifts which cause downstream nonsense mutations and 12% are splice site mutations.[7] Fibrillin is a glycoprotein and the major building block of microfibrils which are the structural components of suspensory ligaments, elastin, and other connective tissues. Abnormal fibrillin does not aggregate and prevents proper aggregation for microfibril formation. Due to its variable expressivity, the diagnostic statistics of Marfan Syndrome are not necessarily indicative of its incidence in the population. Current estimates suggest a frequency of 2-3 per 10,000 live-births in the United States. Marfan syndrome is panethnic and affects all races.[8] Thus, the disease risk to the siblings of affected individuals is 50% if a family history is known. If the affected individual suffers from a *de novo* mutation, the siblings are at no greater risk of developing the disease. Affected individuals have a 50% chance of passing on the mutated form of the FBN1 gene to their offspring.

Prognosis and Treatment

While there is no cure for Marfan Syndrome, its symptoms and signs are becoming increasingly better managed. Data collected in 1972 demonstrated that the life expectancy for patients with Marfan Syndrome was remarkably short – patients' mean age of death was 32 years old without intervention. A similar study conducted in 1995 showed significant increases in the life expectancy of patients suffering from Marfan syndrome. The mean age of death was 41 years old.[9] This is largely attributable to advances made in cardiovascular management, since the main cause of death in patients with Marfan Syndrome is cardiovascular: aortic dissection, congestive heart failure, or cardiac valve disease being the main contributors.[8] Likewise, quality of life preservation has increased, which is largely attributable to early recognition and better informed clinicians.

Advances in cardiothoracic surgery have been a key component in the lengthening of life amongst patients with Marfan Syndrome. Due to frequent aortic aneurysm and subsequent dissection, or mitral or aortic valve prolapse, surgery has been the default treatment for Marfan surgery for the last 30 years. Repair of the aorta is indicated for patients with a demonstrated diameter of 5 centimeters or a growth rate of greater that 1 cm per year.[8]

Recent advancements, however, have brought about a change in the protocol for surgical intervention. David, *et al.*, have pioneered an aortic valve-sparing surgery that reduces the risks of thromboembolism and spares the patient a lifetime dependency on anticoagulants.[10] No long term clinical trials have been explored; however, the short term results are encouraging.[8] Additionally, early recognition efforts have strongly reduced the need for surgical intervention. In patients lacking rapid growth of the ascending aorta or already enlarged ascending aorta, the use of β-blockers and/or ACE inhibitors have been shown to preserve enough function to delay or forgo surgery.[8]

In addition to the advances in cardiovascular care, the quality of life of many Marfan Syndrome patients has been increased. Patients now immediately begin a long-term relationship with an opthalmologist to manage ocular dislocation through special contact lenses and to monitor for glaucoma or cataracts.[2] Additionally, preventative efforts and studies have created better management during pregnancy. The early use of β-blockers or ACE inhibitors spare the risks associated with anticoagulants to the fetus.[8] Moreover, studies have also cleared many potential mothers for pregnancy by demonstrative proof that in a setting of an aortic root size less than 1 cm, the risks during pregnancy to the mother are quite low.[8]

Despite these wonderful advances in the treatment of Marfan syndrome, lifestyle modifications are necessary. Due primarily to the risks of aortic dissection, heavy exercise is strictly forbidden. Only light exercise with constant monitoring is indicated.[8]

Conclusion

Currently, while the treatment of Marfan Syndrome has advanced considerably in the last 30 years, the medical treatment of Marfan Syndrome is still focused on treating the signs and symptoms. Variable expressivity and the variable range of the age of onset results in Marfan Syndrome being under diagnosed.[2] Therefore, current statistics about the prevalence of this disease may be unreliable. All encompassing therapies are being

explored that combine the fields of molecular biology, genetics and pathophysiology. Indeed, Marfan Syndrome is one of many syndromes that stands to benefit greatly from the advancement of the basic sciences in clinical practice.

Table 1 from Gene Reviews[2]

Table 1. Marfan Syndrome: Diagnostic Criteria

System	Criteria	
	Major	**Minor**
Skeletal	Presence of at least four of the following components: • Pectus carinatum, OR pectus excavatum requiring surgery • Reduced upper-to-lower segment ratio for age (<0.85 for older children or adults) or arm span-to-height ratio (>1.05) [1] • Wrist (Walker-Murdoch) and thumb (Steinberg) signs [2] • Scoliosis of >20° or spondylolisthesis • Reduced extension at the elbow (<170°) • Medial rotation of the medial malleolus causing pes planus • Protrusio acetabulae (abnormally deep acetabulum with accelerated erosion) of any degree (ascertained on radiographs)	Two major components or one major component and at least two of the following: • Pectus excavatum of moderate severity • Joint hypermobility • Highly arched palate with tooth crowding • Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Ocular	• Ectopia lentis	At least two of the following: • Abnormally flat cornea (as measured by keratometry) • Increased axial length of the globe (as measured by ultrasound) • Hypoplastic iris or hypoplastic ciliary muscle causing decreased pupillary miosis
Cardiovascular	At least one of the following:	At least one of the following:

	• Dilatation of the ascending aorta involving the sinuses of Valsalva • Dissection of the ascending aorta	• Mitral valve prolapse with or without mitral regurgitation • Dilatation of the main pulmonary artery, in the absence of obvious cause, before the age of 40 years • Calcification of the mitral annulus before the age of 40 years • Dilatation or dissection of the descending thoracic or abdominal aorta before the age of 50 years
Pulmonary		At least one of the following: • Spontaneous pneumothorax • Apical blebs (ascertained by chest radiography)
Skin and Integument		At least one of the following: • Striae atrophicae without obvious cause • Recurrent or incisional herniae
Dura	• Lumbosacral dural ectasia (ascertained by CT or MRI)	
Family/ Genetic History	At least one of the following: • Having a parent, child, or sib who meets these diagnostic criteria independently • Presence of a mutation in *FBN1* known to cause Marfan syndrome • Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with Marfan syndrome in the family (ascertained by linkage analysis)	

1. The lower segment (LS) is measured from the top of the symphysis pubis to the floor; the LS is subtracted from the height to obtain the upper segment (US). The arm span is measured between the tips of the middle fingers with the arms outstretched.

2. Walker-Murdoch wrist sign is the overlapping of the complete distal phalanx of the thumb and fifth finger when wrapped around the opposite wrist. The "thumb sign" (Steinberg) is extension of the entire distal phalanx of the thumb beyond the ulnar border of the hand when apposed across the palm.

References

1. Pyeritz R and Gasner C. *The Marfan Syndrome.* Fifth Edition. July 1999, revised 2001.
2. Dietz, Harry C. *Marfan Syndrome*. Gene Reviews. <http://genereviews.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=GU4PDyEpbTIQd&gry=&fcn=y&fw=Ojyj&filename=/profiles/marfan/index.html> .
3. Robinson PN, Arteaga-Solis E, Baldock C, Collod-Beroud G, Booms P, De Paepe A, Dietz HC, Guo G, Handford PA, Judge DP, Kielty CM, Loeys B, Milewicz DM, Ney A, Ramirez F, Reinhardt DP, Tiedemann K, Whiteman P, Godfrey M. *The Molecular Genetics of Marfan Syndrome and Related Disorders.* Journal of Medical Genetics. 2006; 43: 769-787.
4. *Marfan Syndrome*. Medline Plus. <http://ghr.nlm.nih.gov/condition=marfansyndrome>.
5. *Marfan syndrome.* OMIM. <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=154700>.
6. Nollen GJ and Mulder BJ. *What is new in the Marfan syndrome?* International Journal of Cardiology. 2004 Dec; 97 Suppl 1:103-8.
7. P.N. Robinson, P. Booms, S. Katzke, M. Ladewig, L. Neumann and M. Palz *et al. Mutations of FBN1 and genotype–phenotype correlations in Marfan syndrome and related fibrillinopathies*. Human Mutations. 2002; 20: 153–161.
8. Judge DP and Dietz HC. *Marfan's Syndrome.* Lancet. 2005 December 3; 366(9501): 1965-1976.
9. Silverman DI *et al*. *Life expectancy in the Marfan syndrome*. American Journal of Cardiology. 1995 Jan 15; 75(2): 157-60.
10. David TE and Feindel CM. *An aortic valve- sparing operation for patients with aortic incompetence and aneurism of the ascending aorta.* Journal of Thoracic Cardiovascular Surgery. 1992; 103:617-621.