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FBN1 Gene Analysis and Role in Mitral Valve Prolapse

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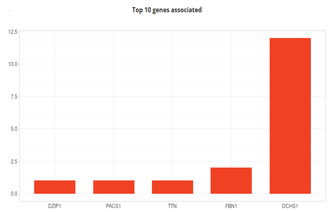
ABSTRACT

Mitral Valve Prolapse, also known as Barlow syndrome, is a heart disease affecting the valve between the left heart chambers. The mitral valve flaps are weak due to tissue weakness and are unable to close properly. Upon researching the genes associated with Mitral Valve Prolapse using simple clinvar, FBN1 was identified. The purpose of this study is to analyze the impact of the FBN1 gene and its mutations on Mitral Valve Prolapse. The FBN1 gene encodes and provides instructions for making a member of the fibrillin family of proteins known as the fibrillin 1 gene. Fibrillin-1 is an extracellular matrix glycoprotein essential for structure serving as a structural component of calcium-binding microfibrils. These microfibrils provide force-bearing structural support in elastic and nonelastic connective tissue throughout the body. The active conserved domains of the protein include EGF_CA, vWFA, Fibrillin_U_N, FXa_inhibition, EGF_3, cEGF, and TB domains. In this study, the missense mutations analyzed were Cys1242Tyr, Gly1127Ser, and Arg2726Trp. After using Polyphen-2 and SIFT Cys1242Tyr and Gly1127Ser mutations were deemed pathogenic impacting protein function, and the Arg2726Trp was deemed benign, likely not impacting protein function. Although Mitral Valve prolapse is not the only disease linked to the FBN1 gene, this research can help advance further studies into how FBN1 is linked to other diseases and what can be done to overcome the challenges possible mutations can cause on patients.

INTRODUCTION

Mitral Valve Prolapse is a heart disease that affects the valve between the left heart chambers. The mitral valve flaps/leaflets are floppy and weak, unable to close tightly. Because of the tissue weakness, they become enlarged or stretched and bulge into the left atrium as the heart contracts with each heartbeat. The role of the mitral valve is to control the flow of blood from the hearts left atrium to the left ventricle. If prolapsed, the valve may leak blood backward through the valve to the atrium causing the condition mitral valve regurgitation. This disease often exists without symptoms, but some may develop overtime such as a racing heartbeat, dizziness, difficulty breathing, fatigue, etc. It is typically an inherited cardiovascular disease affecting 3% of the population and is seen twice as much in women than men. There is not much known about the exact cause of mitral valve prolapse, but it is a lifelong disorder that can run in families as an inherited cardiovascular disease. It also may be linked to other conditions such as scoliosis, graves' diseases, Marfan syndrome and more.

Of the top genes associated with Mitral valve Prolapse, FBN1 showed up with a lower frequency of 2. This could mean the mutations in this gene play a role in why there is tissue weakness in the mitral valve. The goal of this study is to determine which specific errors or mutations can occur in the FBN1 gene and what affects they can have on cellular functions. The FBN1 gene encodes for the fibrillin 1 gene that is essential for structural support in elastic and nonelastic connective tissue throughout the body.

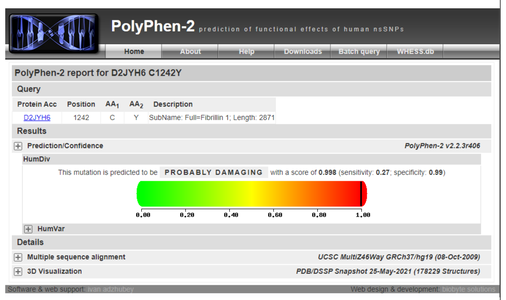


METHODS

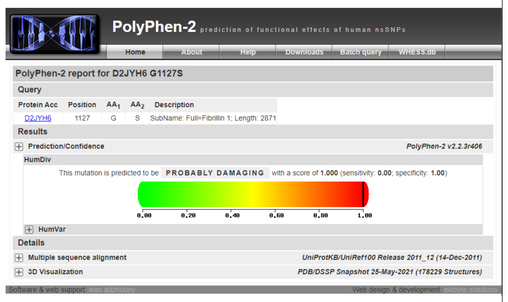
- **Simple Clinvar:** used to initially detect the genes involved in mitral valve prolapse and further analyze the phenotypes expressed and mutations associated with the FBN1 gene.
- **PolyPhen-2:** Used to analyze specific missense mutations among the amino acids in the FBN1 gene and how damaging each mutation could be.
- **SIFT:** Used to analyze sequence homology determining how or if it affects protein functions.
- **Swiss Model Protein:** Used to obtain an actual automated model of the FBN1 protein.
- **NCBI:** Used for further analysis of which tissues the FBN1 gene is expressed and the conserved domains

RESULTS

PolyPhen-2 & SIFT Results



Predictions



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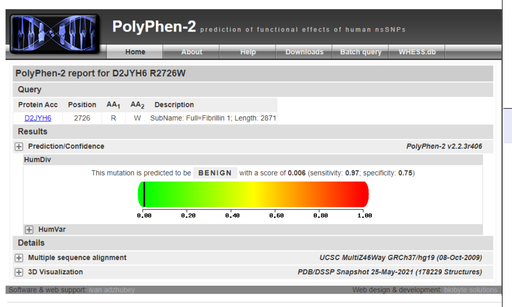
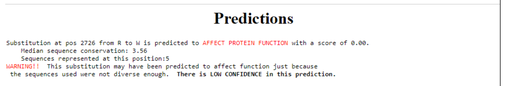
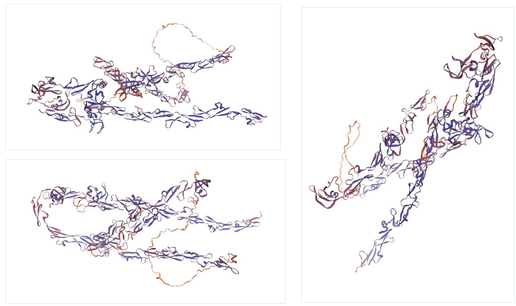


Predictions



There were a total of 2249 possible mutations of the FBN1 gene. The 3 analyzed were Cys1242Tyr, Gly1127Ser, and Arg2726Trp. Cys1242Tyr and Gly1127Ser mutations were both deemed as probably damaging, affecting protein function of cells whereas the Arg2726Trp mutation was deemed benign most likely not to affect protein function.

FBN1 Protein Homology



Conserved Domains

EGF_CA Domain

Calcium-binding EGF-like domain, present in many membrane-bound and extracellular (mostly animal) proteins.

vWFA Domain

Involved in a wide variety of important cellular functions. These include basal membrane formation, cell migration, cell differentiation, adhesion, haemostasis, signaling, chromosomal stability, malignant transformation and in immune defenses.

cEGF Domain

They are found in blood coagulation proteins such as fibrillin, Clr and Cls, thrombomodulin, and the LDL receptor.

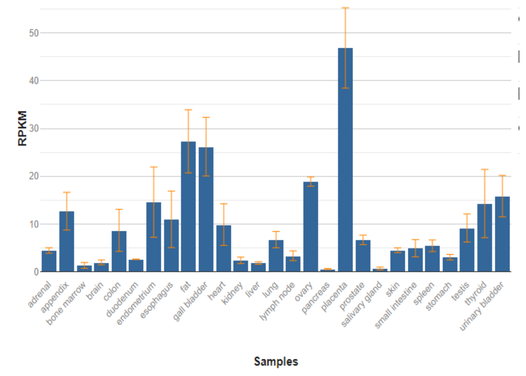
TB Domain

This domain is also known as the 8 cysteine domain. This family includes the hybrid domains. This cysteine rich repeat is found in TGF binding protein and fibrillin.

Fxa_inhibition Domain

This short domain on coagulation enzyme factor Xa is found to be the target for a potent inhibitor of coagulation, TAK-442.

Locations of Gene Expression



DISCUSSION AND CONCLUSION

- The FBN1 gene encodes for fibrillin-1, which is essential for structure, serving as a structural component of calcium-binding microfibrils found in elastic and connective tissues throughout the body.
- Mutations in this gene contribute to diseases such as Mitral Vave prolapse of the heart. The FBN1 gene was confirmed to be expressed in heart tissues but expressed highly in the placenta. This could explain why women are more likely to be diagnosed with mitral valve prolapse and could possibly mean that it is a maternal disease. This would need further research and investigation.
- The mutations of Cys1242Tyr and Gly1127Ser were confirmed to be damaging, affecting protein functions. Because FBN1 is related to structure of connective tissues, the proteins that would be affected would most likely be contractile and structural proteins in the mitral valve tissues of the heart. The calcium-binding microfibrils found in the heart are weakend and prolapse because of this.
- FBN1 is also associated with Marfan syndrome and the related MASS phenotype, as well as ectopia lentis syndrome, Weill-Marchesani syndrome, Shprintzen-Goldberg syndrome and neonatal progeroid syndrome.
- In conclusion, my hopes are that further studies can be done on the FBN1 gene, as it has thousands of possible damaging mutations, possibly affecting thousands of people with not just mitral valve prolapse but any disease related to this gene.

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