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The analysis of variants R43W and S133C in the GATA4 gene in (CHD) congenital heart disease

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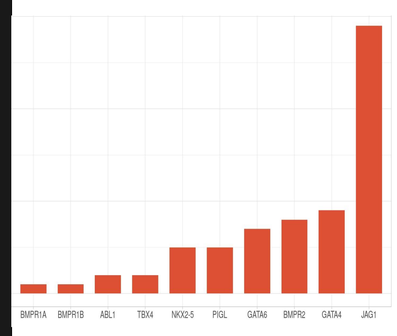
ABSTRACT

Congenital cardiac defects are the source of the symptoms of heart disease. One of the most prevalent diseases in neonates is congenital heart disease. This study aims to shed light on genetic determinants which are the underlying cause of congential heart disease and their symptoms, particularly to congential heart disease. Human disorders have been connected to missense mutation genes and cardiac abnormalities in GATA4. In both mice and humans, proper heart development and homeostasis depend on the zinc transcription factor GATA4. Simple ClinVar was used to identify GATA4 gene that was linked to the congential heart disease. Consequently, this gene has a significant detrimental impact on the development of the heart. Computational tools like SIFT and Polyphen-2 were used to evaluate the pathogenicity of mutations on the protein. The protein's structure was determined through the application of SWISS modeling. GATA4 is a part of the GATA-N superfamily which is the conserved domain. The N-terminal is one of the domain hits of GATA and it's where transcription starts. GATAN is the transcription activator family which is represented by this family. The missense mutations under study was Ser133Cys and Arg43Trp. Ser133Cys is 0.1 and Arg43Trp is 1.0, meaning that it may be harmful. Ser133Cys has a score of 0.09, replacement at pos 133 from S-C is where it's expected to be tolerated, whereas a value 0.00 for Ser133Cys indicates that substitution at position 43 from R to W will have an impact on protein function. The expression of this gene is predominantly seen in the heart and PolyPhen2 predicts R43W to be damaging.

INTRODUCTION

Congential means that you're born with such condition. Congential heart diesease (CHD) is one of the causes of childhood diesases and mortality is mainly triggered by environmental and genetic factors. Congential heart disease in adults and children can change the way blood flows through the heart. There are different types of congential heart defects. It's an abnormality in the heart that can develop before birth. Congential heart defect is one of the most common types of birth defects. The symptoms that may occur is abnormal heart rhythms, shortness of breath, failure to feed or develop normally, and swollen body tissue or organs. In addition to the heart, GATA4 plays important role in the reproductive system. GATA4 is a present in many genes and regulates genes involved in embyrogensis and myocardial differentiation. GATA-4 interacts with many members of the splicesome complex in human induced pluripotent stem cell-derived progenitors. In this study it results in the embryonic stem cells to become damaging. Congential disease is passed down through birth 1% of the time. In this study congential heart diease is causing abnormality in the genetic determinants.



METHODS

- Simple-Clinvar was used in this study to observe GATA4 gene in congential heart disease.
- Swiss Modeling was used to obtain the 3-D model of GATA.
- PolyPhen-2 was used to predict the serio of the gene variations associated with GATA4.
- SIFT programming which takes the sequence to predict whether an amino acid substitution will affect the protein function.

RESULTS

SIFT

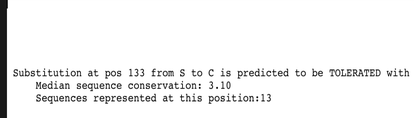


Figure (1a) Ser133Cys variant affecting GATA4 with a score of 0.09.

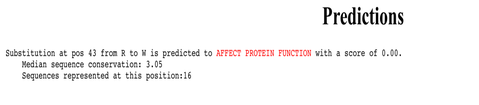


Figure (1b) Arg43Trp variant affecting GATA4 with a score of 0.00

Poly-Phen

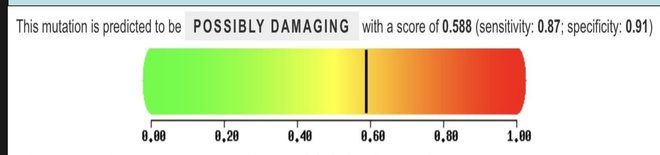


Figure (2a) Ser133Cys variant which is damaging 0.6.

Figure (2b) Arg43Trp variant which is damaging with of a score of 1.000.

Conserved Domains

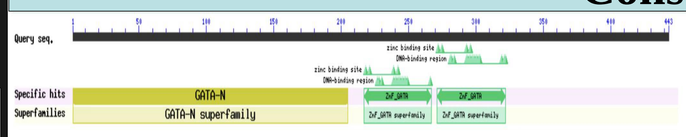


Figure (3a) GATA4 being apart of the GATA-N superfamily. GATA-N is one of the domain sites at intervals 1-205, ZnF_GATA at intervals 217-267. GATA-N is where transcription activates at N-terminal.

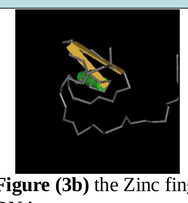
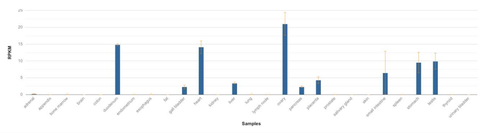


Figure (3b) the Zinc finger DNA binding domain binds specially to DNA consensus sequence [AT] GATA[AG]



Figure(3c): graph of GATA4 encoding in different tissues

Swiss Modeling

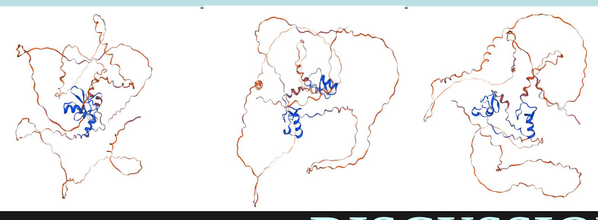


Figure (4): 3D structures of GATA4

DISCUSSION AND CONCLUSION

- GATA4 binding protein 4 gene is on chromosome 8 and encodes for various genes known has zinc transcriptional factor that has a critical role in cardiac hypertrophy, heart failure.
- GATA4 binding protein 4 is present in the GATA-N region. This protein is to regulate genes involved in embryogensis and in myocardial differentiation.
- The mutationArg43Trp and Ser133Cys is a missense mutation in GATA4 which is causing pathogenesis in transcription for DNA to properly bind to GATA4 protein.
- Congential heart disease (CHD) is very rarely seen in 1% of live births.
- Arg43Trp and Ser133Cys variants of the GATA4 is expressed highly in the ovaries.
- Defects in alternative splicing are associated with many cardiac septal defects yet relatively little is known about the cell type or alternative splicing is achieved in the heart.
- The activation of GATA4 occurs various cell signaling events. The discovery of interactions of GATA4 with nuclear factor for activated T cells (NFAT) revealed the importance of calcium signaling in the activation of GATA4. GATA4 can also be phosphorylated by mitogen activated protein kinases and protein kinase A. Lysine modifications also occur on the GATA4 molecule including acetylation and sumoylation. Both reactive oxygen-dependent and –independent antioxidant-sensitive pathways for GATA4 activation. The GATA4 activity is also regulated by modulating the level of GATA4 expression transcriptional as well as translational mechanisms.
- Mutations in this gene have been associated with ventricular septal defects (VSD) which is a common form of congential heart diesase.
- These findings will impact the medical community by increasing an understanding of the connection between the relationship of GATA4 being produced in the reproductive system which would cause the abnormality of the gene determinants among possibly infants that expressed the GATA4 gene.

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