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Pharmacogenomic analysis of TGFB1 towards uterine leiomyomas

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Abstract
Uterine leiomyomas commonly called fibroids are benign monoclonal tumors of uterine smooth muscle found in women of reproductive age. Variations in TGFB1 gene hold a significant role in enhancing the growth of Uterine leiomyoma. The pharmacogenetic and pharmacogenomic analysis of the mutation have been carried out to characterize the individual variation in the proneness of the disease. The SNPs rs146182311, rs148552731, rs1800471, rs104894722 and rs111033611 have been identified as the genetic signatures behind proneness of the disease. During epigenetic analysis, the attributes, 'Evolutionary history and Transcriptome' have been pointed out as the major variant responsible for DNA methylation and further mutation. It has been found that the chromosome region, 41341952-41352971 stands out as the most sensitive positions corresponding to population wise variation. Moreover, the European, South Asian and African populations have been identified as most prone to the mutation. The pharmacogenomic analysis reveals the involvement of TGFBR1, TGFBR2, DCN, SMAD3 and SMAD2 genes for the tumor growth.

Keywords: Uterine leiomyoma, pharmacogenomics, transforming growth factor beta gene, metagenomics, missense, deleterious, single nucleotide polymorphism

Introduction
Uterine leiomyomas are benign solid tumors of the uterine smooth muscle cells that usually affects women of reproductive age. Though available treatment options for symptomatic fibroids include medical therapies, surgical procedure and interventional radiology procedures, Hysterectomy stays the common offered treatment for symptomatic fibroids. Research on designing drugs that women may depend without much side effects and thus can improve the quality of life have to be focused.

Uterine leiomyomas may occur due to mutations or dysregulation of genes including those with functional roles in cell proliferation, differentiation and extracellular matrix production [1]. TGF beta (Transforming Growth Factor) is a cytokine that possess a key role in cell growth and differentiation. An altered expression of TGF beta is observed to play a remarkable role in leiomyoma [2, 3, 4]. Studies indicate the over expression of TGFB1 gene as a cause for tumor progression and also report the influence of certain drugs in down regulating TGFB1 thereby reducing the myoma growth. Thus, targeting TGFB1 could lead to drugs that may directly affect leiomyoma regression [2, 3]. Normally TGF betas act by binding to their receptors and then affect SMADs to activate gene transcription. An altered TGFB1 can influence the activities of all the related genes in signaling pathway.

The present study focusses on variations in TGFB1 encoded by TGFB1 gene to identify the individual variations towards TGFB1 responsiveness. The investigation includes genetic, epigenetic, metagenetic and environmental factors. Since TGFB1 is a member in signaling pathway, the other genes occurring in the pathway have also been investigated. The genetic variants –SNPs referred to as genetic signatures which holds a pivotal role in specifying the susceptiveness to the disease have been accessed from National Centre for Biotechnology Information Database. The proneness of the disease among different populations have also been studied to figure out the most affected ones globally. The attributes significant in contributing to DNA methylations have been identified using the online tool EpiGRAPH, which performs based on machine learning algorithms. Metagenomic study have been undertaken to consider the microbes responsible for inducing the disease and to identify the chromosome region where microbial infection could occur. Besides environmental factors such as chemicals, drugs that could have an effect on the disease have also been analyzed.

Materials and Methods

The present study involves the Pharmacogenomic approach identifying the genetic, epigenetic, metagenomic and environmental factors that risk a person to disease.

Dysregulation of TGFB1in the promotion of fibroid growth has been identified through literature survey. The detailed information on TGFB1 gene has been obtained from Genecards and NCBI (National Centre for Biotechnology and Information). SNPs (single Nucleotide Polymorphism) are genetic markers to track the proneness towards a disease. The genetic markers of TGFB1 gene have been retrieved from NCBI database. The missense, pathogenic and deleterious SNPs found using online supports Gwass central (Genome – wide association study) and Ensembl. The population wise analysis-showing the population likely to have a great risk to disease have been generated using the online tools Exac Browser and Ensembl. Since methylations in CpG islands is the target of mutations, DataBase of CpG islands and Analytical Tool (DBCAT) database is used to detect the methylated regions in the genes which could affect gene expression regulation by providing the fasta sequence of the TGFB1 gene in the space.5 From the methylated and non-methylated region obtained using DBCAT database, the attributes leading to methylation have been analyzed using EpiGRAPH Tool. Microbes act on those regions having similarity with it. Similarity sequence regions have been performed using NCBI Blast to find those regions. The environmental factors contributing to fibroid development have been listed from CTD (Comparative Toxicogenomics Database).

The associated genes of TGFB1 gene have been identified from Genecards and STRING an online bioinformatic tool, as they can also indirectly influence TGFB1 gene to stimulate fibroid growth.

Results and Discussion

SNP analysis

In the present study, the TGFB1 gene responsible to regulate the growth of fibroids has been examined to identify the genetic variants-SNPs and its consequences [7]. Two hundred and ten missense SNPs have been identified in the TGFB1 gene in which nine of them are pathogenic. Five of the identified missense SNPs have been reported as deleterious and is provided in the table 1. establishing the significance of various attributes contributing to epigenetic variations, 847 promising attributes classified into 10 groups - DNA sequence, DNA structure, Repetitive DNA, Chromosome Organization, evolutionary history, population variation, Genes, regulatory regions, transcriptome, and epigenome and chromatin structure have been identified with the help of EpiGRAPH a web based SVM tool [6]. On analyzing the epigraph result, two attributes evolutionary history and trancsriptome have been found to have a remarkable role in DNA methylation leading to the disease. Evolutionary history indicates the hereditary nature of the disease.

Metagenomic study

Metagenomic studies conducted reveals the contribution by microbes for inducing the disease. The chromosomal position within the range 41352762-41352964 have been found more sensitive to microbial attack favoring fibroid growth. None of the SNP's were found to be within this range indicating less tendency to be affected from pathogens.

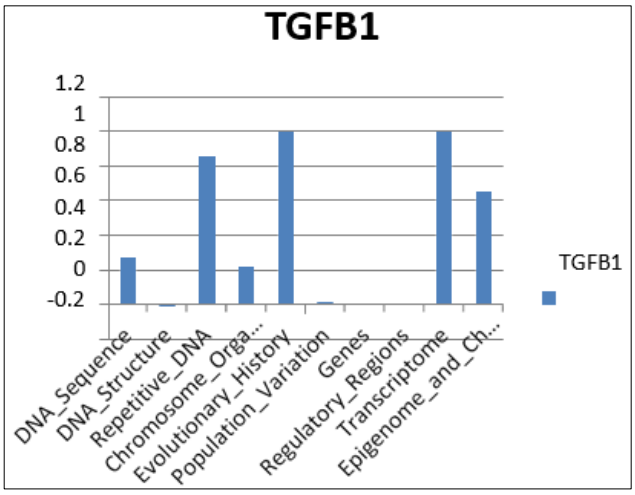

Fig 1: Bar diagram depicting the variation of the attributes of epigenetic

Environmental factors

Comparative Toxicogenomics Database an online database provides the lists of environmental or external factors influencing the disease. From the database, estradiol and progesterone steroid sex hormones were identified which helps to stimulate fibroid growth by acting on these genes. It have been also found that nutritional supplements such as curcumin enhances UL apoptosis [5] and genistein a phytoestrogen downregulate the genes associated in TGFbeta pathway [6]. Drugs such as raloxifene hydrochloride and tamoxifenes, mifepristone, Goserelin, Danazol also lead to positive effect in fibroid regression [13].

Gene-Gene Interaction

The associated genes of TGFB1 has been found out using STRING an online tool. Eleven genes have been identified to have significant influence with the gene TGFB1.

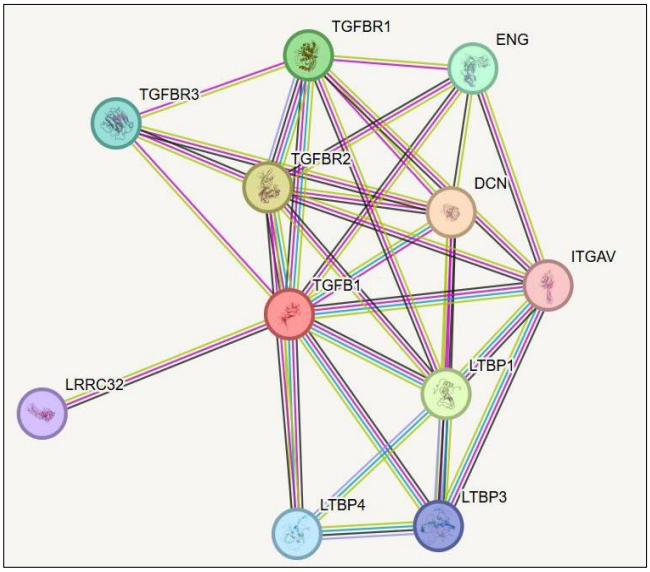

Fig 2: Association of gene TGFB1 with other genes

There are several signaling pathways that contribute to leiomyoma development and growth. TGFBR1, TGFBR2 and TGFBR3 are the receptors which are activated by TGFB ligands and responsible for initiating TGFB1 signaling pathways [14]. Abberations in these associated genes may also

contribute to leiomyoma proliferation.

Conclusion

The genetic signature behind the proneness of the disease have been identified. Epigenetic analysis confirms evolutionary hereditary and transcription as significant attributes responsible for DNA methylation. Studies also reveals the influence of the bacterium kleptom to induce disease when conditions favour. The intake of curcumin and genistein have been found to lower the risk of fibroid progression. Population wise variation have been found to be within the region 41341952-41352971. The responsiveness of genetic variants towards the disease have been identified for different global population. European population have been identified to be more sensitive to the disease. Estrogen and progesterone – sex hormone have been found to promote fibroid growth whereas the inclusion of curcumin, epigallocatechin gallate and genistein lowers the risk for leiomyoma.

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