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System Biology approach for identification of glaucoma disease-associated genes and variants influence

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Abstract

Glaucoma is a heterogeneous group of disease characterised by progressive optic nerve degeneration with a complex genetics basis. It is broadly classified into primary and secondary based on their etiology and aqueous humor dynamics. Primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) occurs most commonly. In this study, disease-causing genes network was designed using cystoscope software. The DisGenNet plugin is used for mining the data from curated and BeFree database source. In this network, 89 (28.25 %) genes were reported with Genetic variation, Causal Mutation 6 (6.7%), Biomarker 220 (69.8%) in 25 subtypes of glaucoma. In this disease 179, genetic variations in 50 genes were associated with the glaucoma disease. Maximum gene found with intron variant around 38.70% followed by missense variant around 38.20%. In this study, it is found that a maximum number of the generic variation shown the modifier impact on the disease. The Designing gene-disease network helps in understanding the role of genes in the complex disease. It is a new approach to predict gene-disease association based on network analysis.

Keywords: Glaucoma; open angle glaucoma; angle closure glaucoma; Gene-disease network.

Research Article

1. INTRODUCTION

Glaucoma is a complex group of disease with multiple molecular mechanisms which results in damage to the optic nerve, leading to vision loss. In most cases, the elevated pressure in the eye triggered by backup of fluid in the eye is majorly responsible for origin of glaucoma. Genetic factors are recognised to have key role in all major forms of glaucoma with involvement of various genes or different genetics mechanism in the disease [1]. Damage to the optic nerve and trabecular meshwork (TM) degeneration occurs gradually with passing time [2-4]. It is to reported 60.5 million people with primary glaucoma in 2010 and 79.6 million by 2020 resulting in bilateral blindness in 8.4 and 11.2 million people by the corresponding years, respectively [8]. WHO (2016) reported nearby 12 million people affected by glaucoma and causes 12.8 % the total blindness in the India. It is measured to be the second most common cause of blindness [5]. Two major groups of glaucoma primary & secondary are broadly documented, POAG (Primary open angle glaucoma) may be associated with or without an elevated IOP and has an adult onset (usually >35 years) or juvenile onset (usually <35 years) [9]. Secondary glaucoma also reported as PACG (Primary angle closure glaucoma) is characterised by the involvement of

predisposing ocular or systemic disease such as trauma, uveitis and diabetes resulting in an alteration of aqueous humor dynamics. It is reported that this mode of inheritance in adult-onset POAG and PACG is complex in nature. [1, 6-8]

POAG is the most common form of glaucoma, occurs in the over-50 age group in our country [14]. Any symptoms don't associate with POAG. Several genes have been reported in the case of POAG, including myocilin (MYOC, GLC1A) [10], optineurin (OPTN; GLC1E) [11-12], WD repeat domain 36 (WDR36, GLC1G) [13] and neurotrophin-4 (NTF4, GLC1O) [28] etc. PACG is the second most common form of glaucoma and affects over 16 million people globally (http://www.glaucoma.org/). In this form of glaucoma, the drainage angle closes over time, blocking the pathway to the drainage system and causing high eye pressures. Currently, numerous significant genetics study reports genetic variants that are associated with POCG [21].

Primary congenital glaucoma (PCG) is the most occurs in childhood affecting children from birth to age 3 and is a major cause of blindness in this young population [23,25]. Mutations in the CYP1B1 gene in locus GLC3A is reported to cause PCG in children [24]. The genes currently known to be associated with these forms of glaucoma include LTBP2 [27], FOXC1 and MYOC [26].

In this paper, starting from the construction the gene-disease network through the quarrying the data from the DisGenNet application for instigation the genes that are associated the glaucoma disease. It is potential approach to visualization and analysis the complex disease such as glaucoma. In this study will detect the genes that associated types and their impact. Genetic base study also will be obliging refining patient care, investigation, and treatment outcomes in the glaucoma disease.

2. Material and Methodology

2.1. Cytoscape Software

Cytoscape is open-source software dedicated to building network visualisation molecular interaction and biological pathways. Software “Core” provides basic functionality to layout and query to visually integrate the network with expression profiles, phenotypes, and other molecular states; and to link the network to databases of functional annotations [16]. It is also used in conjunction with large database of gene-gene disease; protein-protein and genetics interactions that are increasingly available for humans and model organisms [15]..Numerous plugin are available for human disease analyses. It also supports additional file format, scripting, and connection with databases. http:// Cytoscape.org

2.2. DisGenNet Application

DisGeNET is a plugin application creating for Cytoscape to query and analyse a network

representation of the datashown in Figure 2. It is useful tool creating gene-disease associations (GDAs) network from several public data sources and the literature [20]. The current version contains (DisGeNET v4.0) contains 429,036 associations, between 17,381 genes and 15,093 diseases, disorders and clinical or abnormal human phenotypes, and 72,870 variant-disease associations (VDAs), between 46,589 SNPs and 6,356 diseases and phenotypes [17].

2.3. Generation of gene-disease networks

Gene-Disease Associated network builds a network including all Glaucoma-related diseases. In order to search the query related to Glaucoma Disease using set the parameter. In search box Select CURATED human as Source, “ANY” for Association Type and Disease Class “EYE”, but specifying * Glaucoma * in the search field to restrict the search to the genes annotated to this disease term pattern, and press Create Network shown in Figure 1(a). In order to know if there are other genes described in the literature but not recorded in the CURATED Dataset so those genes were retrieved form the BeFree Dataset. The Same query was performed as before only same parameter and press the create the network shown in Figure 1(b)

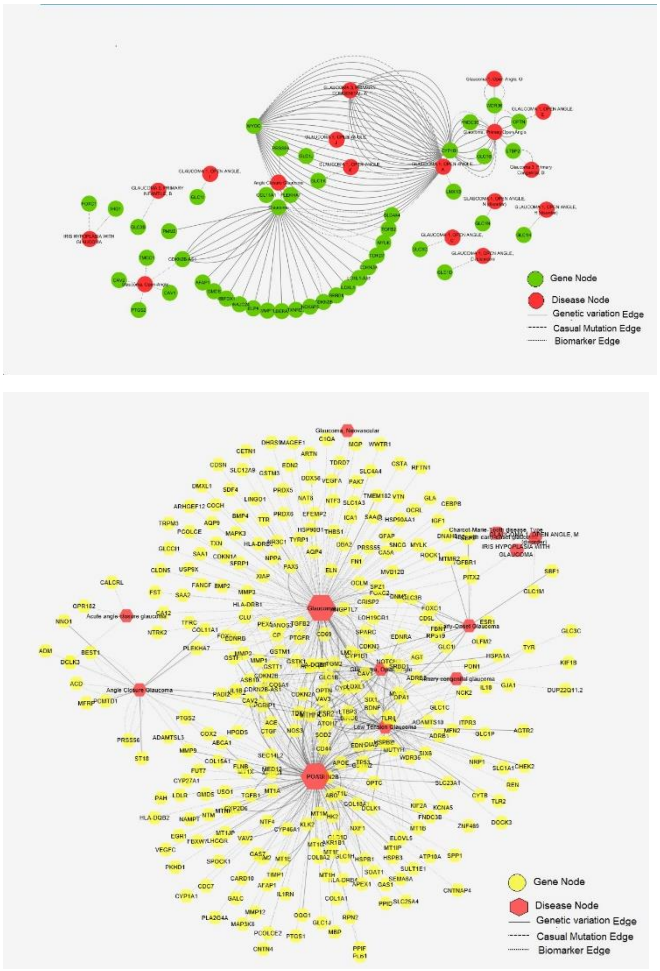

Figure.1 (a) Gene Associated type in the Gene-Disease Network (b) Associated all consequence in the disease

2.4. Variant Effect Predictor (VEP)

Variant Effect Predictor (VEP) tool was used to determine the effect of the variants (SNPs, insertions, deletions, CNVs or structural variants) associated with disease genes, transcripts, and protein sequence, as well as regulatory regions. Using the default option 179 Variant gene id were pasted into large text box and run the job. http://asia.ensembl.org/info/docs/tools/vep/index.html.

Result and Discussion

In this study, Gene-disease association data were retrieved from the DisGeNET Database (CURATED and BeFree). A network has been constructed using Cytoscape software. In both networks around 305 genes were associated with 25 types of Glaucoma disease phenotypes and 37 genes were reported as a share, retrieve from CURATED & BeFree data source shown in Table.1. In the network, maximum 168 genes investigated from BeFree database source and 22 genes from curated database source associated with glaucoma (umls: C0017601). In POAG (umls: C0339573) 6 genes from curated and 167 genes are from BeFree database were investigated. Low Tension Glaucoma (umls: C0152136) 42 genes, PACG (umls: C0017606) 25 gene were also investigated from BeFree database source (Supplementary Table S1). It is observed that 220 (69.8 %) genes were reported Biomarker followed by Genetic variation 89 (28.25 %), Causal Mutation 6 (6.7%), shown in Figure 2(a). Associated 179 genetic variations were processed for analysis the Consequence and their impact on glaucoma. Maximum gene found is intron variant around 38.70% and missense variant 38.20%. Some genes have been that non-coding transcript exon variant 1.10%, regulatory region variant 2.80%, stop gained 0.56%, synonymous variant, 1.10%, upstream gene variant 7.80% in glaucoma as shown in Figure. 2(b).

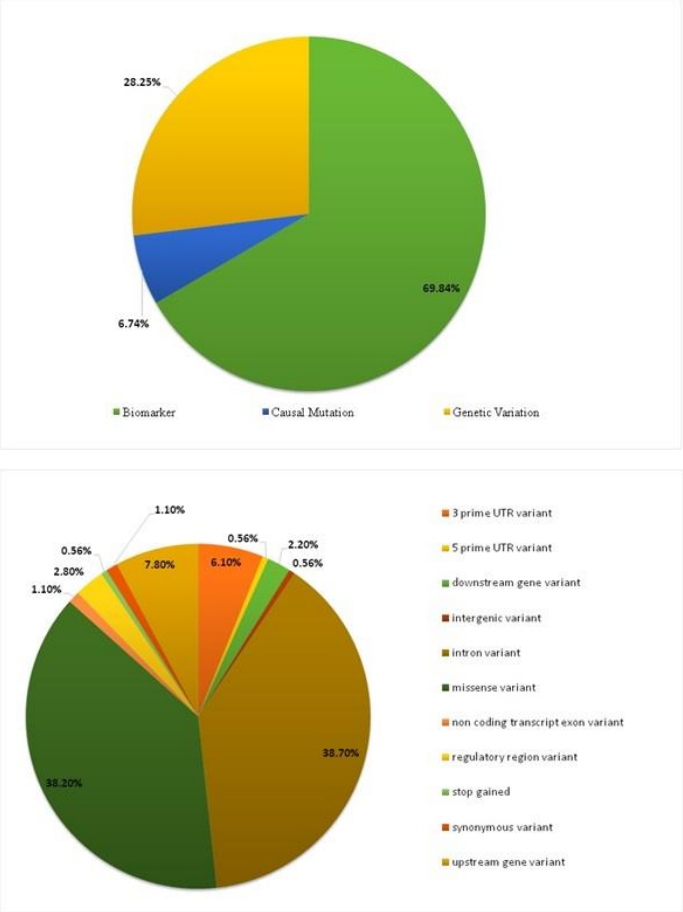

Figure.2 (a) Gene Associated type in the Gene-Disease Network (b) Associated all consequence in the disease

The compressive view of related genetic variations in the glaucoma disease is shown in Figure 3.

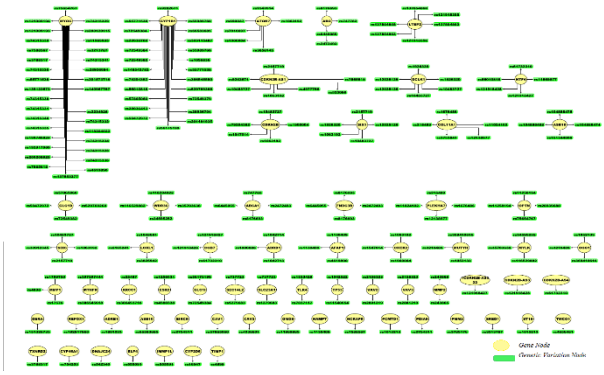

Figure 3. The compressive view of gene associated variations Network in the glaucoma disease.

This study shows the MYOC, CYP1B1, CDKN2B-AS1, SIX1, ASB10 ATOH7,

DCLK1, CDKN28-AS1, CDKN28, COL11A1, NTF4, LTBP2, ABO, ABCA1, FNDC38, GLC10, PLEKHA7, OPTN and WDR36, genes associated the maximum number of genetic variations in glaucoma disease. MYOC gene associated 24 missense variant having moderate impact on the glaucoma disease, CYP1B1 gene has 21 genetic variations. Out of 21 genetic variations, 13 genes variation is downstream gene variation, 4 regulatory region variant which associated as a modifier in glaucoma disease, 3 missense variants have a moderate impact. OPTN gene has 4 missense variation with moderate impact on glaucoma disease, WDR36 gene has 4 genetic variations, 2 downstream gene variant,1 on-coding transcript exon variant and 1 missense variant having modifier impact on glaucoma. CDKN2B-AS1 gene is having 4 non-coding transcript variant with modifier impact. ATOH7 gene having 4 genetic variants, out of 4, 1 genetic variation is found 5_prime_UTR_variant, has modifier impact. LTBP2 gene having 6 genetic variant, out of 6, 4 geneiticvariant are found missense variant have moderate impact. PLEKHA7 gene having 4 genetic variant, out 4, 2 genetic aviation are found intron variant have modifier impact. FNDC3B gene having 4 genetic variants out of 4, 1 genetic variant is found intron variant have modifier impact. COL11A1 gene is having 6 genetic variations, out of 6, 2 genetic variations are found missense variant have a moderate impact and 1 genetic variant has intron variant with modifier impact in the glaucoma disease. CDKN2B gene has 5 genetic variants, out of 5, 1 genetic variant is found 3_prime_UTR_variants has modifier impact. ABO gene is found 4 genetic variations, out of 4, 1 genetic variants is found intron variants has modifier impact.NTF4 gene is found 4 genetic variations, out of 4, 2 genetic variation are found, 1 downstream gene variant with modifier impact and 1 missense variant with moderate impact. DCLK1 gene is found 4 genetic variations, out of 4, 1 genetic variant is found intron variant has modifier impact. ABCA1 and GLCD associated with 4 genetic variations nevertheless found impact in the glaucoma disease. It is also found that maximum number frequency An allele (34.74%) and T allele (25.10%) on genes as shown in Figure 4. The impact of the genetic variant on the phenotypes is of significant attentiveness in genetics.

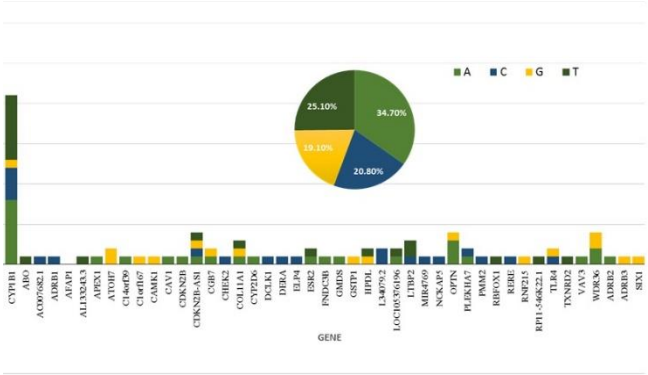

Figure 4. Allele frequency of gene associated with glaucoma disease.

Genetic Variant interpretation is also significant clarification of the impact of the disease. The 'Sorting Tolerant from Intolerant'

SIFT algorithm and Polymorphism Phenotyping (PolyPhen) algorithm were used for prediction the impact of the mutation in the glaucoma. In this study, 129 genetic variant id were analysed, out of 169, 90 genetic variants associated modifier impact that changes the phenotypic expression of the gene at the locus and 39 genetic variants associated the moderate impact in the glaucoma disease. All the genetic variants were analysed using the PolyPhen and SIFT algorithm, and that probably damaging (16), possibly damaging (5) using the PolyPhen algorithm and deleterious (24), tolerated (38) using SIFT algorithm in glaucoma disease as shown in Figure 5.

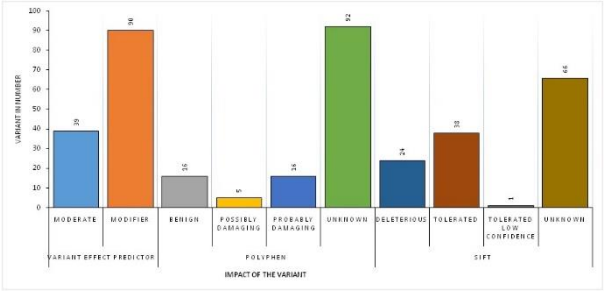

Figure 5. A number of genetic variant impact prediction by VEP, POLYPHEN and SIFT algorithm.

Names	Total	Genes
BEFREE & CURATED	37	GLC1D;LTBP2;GLC1J;TGFB2;SRBD1;OPTN;GLC1H;WDR36;SBF2;PTGS2;PLEKHA7;LMX1B;FNDC3B;CAV2;ASB10;MYLK;GLC1C;AFAP1;TDRD7;GMDS;FOXC1;COL11A1;GLC1I;CDKN2B;CDKN2A;PMM2;CDKN2B-AS1;MYOC;CAV1;GLC1B;SLC4A4;GLC3B;TMCO1;PRSS56;CYP1B1;LOXL1;OPA1
BEFREE	268	ACE;MT1G;CD44;MMP2;GAS1;TLR4;MT1B;CSTA;ROCK1;TRPM3;CDSN;NPPA;EDN1;TYR;HSPB1;OCLM;LOH19CR1;DNAH8;IGF1;SAA;PITX2;SULT1E1;SLC1A3;CETN1;CYTB;PEX5;TP53;SLC23A1;ICA1;ADRB1;MT1F;COX2;TNF;NTM;HSPB2;MAP3K8;DCLK3;SOD2;WWTR1;NAT8;GAS7;IL1A;HLA-DRB1;HLA-DRB4;AQP9;MMP3;FST;SIX6;DUP22Q11.2;PLA2G4A;HLA-DRB5;LHCGR;ZNF469;LDLR;CDKN1A;VEGFC;ELN;KLK2;NRP1;PCOLCE;NTF4;TTR;CLDN5;GJA1;NAMPT;ELOVL5;PRDX6;BEST1;MBP;FOXC2;MT1E;CYP2D6;EDNRB;TYRP1;TGM2;DDX58;NTRK2;TMEM182;GRIN2B;GSTM1;TBK1;ADM;PAK7;SPP1;MT1JP;ARHGEF12;COL1A1;SBF1;DNMT1;XIAP;MTHFR;RPGRIP1;BIRC6;CYP2B6;DBA2;EDN2;OPTC;PLB1;SDF4;HLA-DQB2;CD5L;USO1;GALC;HPGDS;CNTNAP4;RFTN1;PPID;SLC25A4;ACD;NNO1;TGFBR1;SIX1;MT1L;CARD10;IL1B;REN;MAGEE1;VTN;IL18;GSTK1;LINGO1;NCK2;CNTN4;CA5A;FLNB;NOTCH2;COL15A1;ADAMTS10;MT1H;APOE;GLC3C;BMP2;MGP;ESR1;MT1A;HSPA1A;PON1;GLC1P;SLC1A1;BMP4;BDNF;RPN2;MT1IP;TXN;SPARC;SLC12A9;HSPB3;ABCA1;C1QA;SAA2;PTGS1;CYP27A1;DMXL1;DOCK3;FUT7;PRSS55;PRDX5;COL8A2;HOOK2;SPZ1;CLU;CD69;COL18A1;ADRB2;TLR2;NXF1;HK2;VEGFA;XRCC1;CYP46A1;DCLK1;ANGPTL7;TGFB1;VAV2;EDNRA;APEX1;ABO;PPIF;CEBPB;TFRC;EFEMP2;CALCRL;MFN2;GSTM2;THBS1;CYP1A1;ABCC5;CRISP2;PCOLCE2;FOXE3;MT1X;MAPK3;ATOH7;ADAMTSL3;FBN1;TIMP1;FANCF;AKR1B1;CDKN3;ESR2;AGTR2;AGT;SOAT1;PCMTD1;COCH;HSP90B1;NTF3;PAX5;KIF1B;AQP4;CP;NANOS3;SFRP1;VAV3;SNCG;CHEK2;PKHD1;LTBP3;KIF2A;MTNR1A;OCRL;MUTYH;GLA;GSTT1;HGF;MT1M;MMP1;RPS19;CA12;NOS3;GSTP1;CTGF;MED12;MMP12;HLA-DQB1;GSTM3;CDC7;KCNA5;EGR1;PADI2;SEMA6A;OGG1;PTGFR;SAA1;FBXW7;PAH;SLCO6A1;FN1;DHRS9;ST18;ARTN;MVB12B;MTMR2;ATP10A;HSP90AA1;MFRP;IL1RN;SEC14L2;USP9X;ITPR3;MMP9;GLCCI1;NR3C1;PDIA5;OLFM2;SPOCK1;OPA3;GFAP
CURATED	11	ELP4;TXNRD2;NCKAP5;DERA;GLC1K;IHG1;RBFOX1;IMMP1L;DNAJC24;GLC1M;LOXL1-AS1

Conclusion

Research Article

It is a major challenge to solve the complex biological problem related to human health and understand the mechanisms of glaucoma disease. In this study, an effort has been spent on determining genes associated to complex glaucoma diseases and their impact disease on progression. It has been observed that around 315 genes are associated directly and indirectly with glaucoma disease, out of which 220 genes (69.8%) are associated with Biomarker gene, Causal Mutation 6 (6.7%), and 89 genes (28.25 %) are associated with genetic variation. This study shows the MYOC (24 genetic variant), CYP1B1 (21 genetic variant), LTBP2, ATOH7, DCLK1 (6 genetic variant), CDKN2B-AS1, SIX1, CDKN28-AS1, NTF4, CDKN2B, COL11A1 (5 genetic variant), ASB10, ABO, ABCA1, FNDC38, GLCD, PLEKHA7, OPTN and WDR36 (4 genetic variant), genes have the maximum number of genetic variations in glaucoma disease. This study assists researcher to understand and investigate glaucoma diseases with respect to their genetic variant. The genetic variant analysis of glaucoma disease associated genes also helps in improving patient care, surveillance, and new treatment outcomes in glaucoma.

Compliance with ethical standards

Conflicts of interest: authors have no conflict of interest to declare.

Research involving human participants and/or animals: No

Informed consent: No

Additional Information Supplementary information accompanies from DisGeNET database at http://www.disgenet.org/

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