Review of genes associated with primary congenital glaucoma

CYP1B1, which encodes a monooxygenase, has been characterized from the first mapped locus GLC3A, and pathogenic variants in the gene account for 20-100 % of familial cases with recessive inheritance pattern (OMIM# 231300).[1–3] More than 200 pathogenic variants have been reported to date in the human gene mutation database (HGMD), the majority of which result in loss of function due to alterations in protein stability, abundance, or enzymatic activity.[4,5] However, the exact role of *CYP1B1* in the formation of the anterior segment is not yet fully understood. So far, no genes have been associated with the second (GLC3B, OMIM# 600975) and third locus (GLC3C, OMIM# 613085).[6,7] In a large Pakistani family, a fourth locus (GLC3D, OMIM# 613086) was identified, which is controversial due to its proximity to GLC3C.[8] *LTBP2*, an extracellular matrix protein, was mapped to GLC3D.[9] However, it is disputed whether *LTBP2* pathogenic variants lead to megalocornea with zonular weakness and lens-related secondary glaucoma, rather than primary congenital glaucoma (PCG).[10] The gene *TEK* is also associated with PCG. Souma et al. observed compromised aqueous humor outflow in *Tek*-null-mice, but there was marked variable expressivity in human subjects.[11] Similarly, *ANGPT1/2* were shown to play a role in the development of Schlemm's canal in mice, however incomplete penetrance of *ANGPT1* variants was observed in two out of three families with PCG.[12] Siggs et al. recently emphasized that a significant number of patients lacking pathogenic variants in *CYP1B1* carried *FOXC1* pathogenic variants or copy number variations.[13] *FOXC1* is a member of forkhead box family transcription factors involved in the formation of the anterior segment (OMIM# 601090).[14] The whole range of gene alterations have been described as causes of autosomal dominant anterior segment defects, often classified as part of the ARS-spectrum (OMIM# 180500, OMIM# 601499, OMIM# 602482).[14–17] The majority of variants are located within the DNA-binding forkhead domain, although pathogenic variants in the N- and C-terminal activation- and inhibition domains have also been identified.[18,19] Both hypomorphic and hypermorphic variants were shown to alter transcriptional activity of *FOXC1*.[20]

Table S1 Gene list used for filtering of whole-exome-sequencing data

Genes associated with childhood glaucoma	Gene symbol
a. Primary congenital glaucoma	*ANGPT1*[12], *CYP1B1*[2], *FOXC1*[14], *LTBP2*[9],*TEK*[12,21]
b. Juvenile open angle glaucoma	*MYOC*[22]
c. Secondary/syndromic childhood glaucoma	*ADAM9*[23], *ADAMTSL1*[24], *B3GLCT*[25], *BMP4*[26], *COL1A1*[27], *COL4A1*[28], *CPAMD8*[23], *CREBBP*[29], *DDX58*[30], *FBN1*[31], *FOXE3*[32], *FZD5*[33], *GJA1*[34], *GJA8*[35], *HCCS*[36], *ISPD*[37], *JAG1*[38,39], *LAMB2*[40], *LMX1B*[41], *NDP*[42], *NF1*[43], *NHS*[44], *NOTCH2*[45], *NPHS1*[46], *PAX6*[47], *PEX1*[48], *PIK3R1*[49], *PITX2*[50], *PITX3*[51], *PLOD1*[52], *POMT1*[53], *PXDN*[54], *SBF2*[55], *SH3PXD2B*[56], *SLC4A4*[57], *TFAP2A*[42], *TRIM44*[58]
d. Conditions mimicking childhood glaucoma	*CHRDL1*[59], *COL8A2*[60,61], *SLC4A11*[60,62]
Candidate genes	
e. Primary and/or juvenile open angle glaucoma	*ASB10*[63], *ATOH7*[64], *B4GALT3*[65], *BEST1*[36], *CARD10*[66], *CD5*[67], *CDKN2B*[68], *CNTN4*[69], *COL8A2*[70], *DMXL1*[67], *EFEMP1*[71], *FAM27E5*[67], *GAS7*[68], *GPR180*[72], *IMMT*[67], *NPHP1*[67], *NT5C1B*[67], *NTF4*[73], *OLFM2*[74], *OPTC*[75], *OPTN*[76], *PAK5*[67], *PRPF8*[77], *RPGRIP1*[78], *SIX6*[79], *TBK1*[67], *TMCO1*[68], *TP53BP2*[80], *TULP3*[67], *WDR36*[81]
f. Angle closure glaucoma	*ANGPTL7*[82], *COL11A1*[83], *COL18A1*[84], *CRYAA*[36], *CRYBA4*[36], *CRYGC*[36], *CRYGD*[36], *DIP2A*[84], *EYA1*[36], *GDF6*[36], *KERA*[85], *MFRP*[86], *MMP9*[87], *PRSS56*[88], *VSX2*[86]
g. Genes highly expressed in the trabecular meshwork identified[89]	*ACTB, ACTN2, ALP, APOD, ARGBP2, ARPC2, ARPC3, ARPC1, CALD1, CAPZA1, CCN2, CDT6, CFL2, CHI3L1, CNB1, CNN3, COL1A2, COL3A1, COL4A5, COX7C, CTTNBP2, CTTN, DCN, DMN, DSTN, EEF1A1, EFEMP1, EID1, FN1, FOS, GNAS, GSN, IGFBP7, IMPG1, KLHL2, KRT12, LAMB1, LAPTM4B, LUM, MACF1, MGP, MGP, MYL6, NACA, NDUFA5, PALLD, PCP4, PMCA, PTMA, RGS, RPL12, RPL23, RPL23A, RPL27, RPL31, RPL37, RPL37A, RPL41, RPL5, RPL6, RPL7, RPL9, RPS20, RPS24, RPS25, RPS27A, RPS3A, RPS8, SEMA3E, SGCE, SMOC2, SORBS2, SPARC, SPARCL1, SPARCL1, SPP1, TMSB4X, TMSB4X, TPM1, TPT1, UQCRB, VIM, ZAKA*
h. Genes highly expressed in the trabecular meshwork and within GLC3B or GLC3C locus[89]	*AL13727, CTD6, c-FOS, EIF4C, EIF4G3, FLJ10199, FLJ10521, FLJ13553, FLJ22042, HNPR, LOC1269, LOC57862, LTBP2, MFN2, MIG6, MLH3, NPC2, P29, PINK1, PMSCL2, RERE, RPL11, S164, SFRS5*

i.	**Genes harboring copy number variants identified in primary congenital glaucoma patients by Lee et al.**[90]	*ACVR1C, ADAMTSL3, ANO7, BTAF1, CSNK2A2, EXO5, FAM120A, GATA6, GNB5, GPR12, HEY1, LRRC4, MAP6, PGAM5, PHIP, RAD54B, SLC4A3, TAL1, TCF7L1, TCF7L2, TECTA, XKR4, ZNRF1*
j.	**Predicted functional partners of *CYP1B1, MYOC, LTBP2, PAX6, PITX2, PITX3, FOXC1, FOXE3, EYA1, LMX1B* and *MAF* according to Lee et al.**[90]	*ACYP1, ALX4, ANPEP, BACH2, BDNF, CCND2, CHMP4B, COK4A3, COL4A4, COMMD, COMT, CTNNB1, CXCR4, CYP1B1, CYP1B1, DACH1, DLL4, ELN, EPHX1, ESYT3, FGF2, FLNA, FN1, FOXA2, FOXC1, FOXE3, FOXF2, FOXH1, GCG, GDNF, GIPC1, GPM6A, GPR161, GSTA1, GSTM1, GSTM3, GSTP1, HDAC9, HEY2, HRAS, IL4, IPO13, IRF4, LDB1, LEF1, LOXL1, LRP6, LTB, MFAP2, MITF, MSX2, MTA1, MYB, MYOG, NEUROG2, NFATC1, NFE2, NPHS2, NPRL3, NPS, NR4A2, OLFM3, OPTN, PAX1, PAX2, PAX3, PAX6, PITX2, PKNPX1, POU5F1, PRODH2, RGS1, RGS2, RGS7, RSRFR2, SERPINF, SHH, SIX1, SIX2, SIX3, SIX5, SLC18A2, SLC6A3, SMAD2, SMAD4, SNCG, SOX2, SOX3, SUCLG1, TGFBI, TH, TIMP1, TLX1, TMTC1, TRIM11, UGT1A1, UGT1A6, UGT1A9, UGTB7, WDR36, WHSC1, WNT7A, ZNF185*
k.	**Other:**	*BCO2*[23], *COL4A2*[91], *COL4A3(12), DGKQ*[23], *DNAJB1(54), DPT*[92], *FOXC2*[93], *GPATCH3*[94], *MMP1*[95], *MMP12*[96], *MMP13*[96], *MMP14*[96], *MMP2*[95], *MMP3*[95], *MMP9*[95], *NFATC1*[92], *OPA1*[97], *RELN*[23], *SALL2*[98], *SOX1*[99], *TIMP1*[87], *TSP1*[100], *TSP2*[100], *TULP2, ANGPT2*[12]

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