Human Genetics (2019) 138:1043–1049
https://doi.org/10.1007/s00439-018-1878-z

ORIGINAL INVESTIGATION

Congenital glaucoma and *CYP1B1*: an old story revisited

Hessa S. Alsaif[1] · Arif O. Khan[1,2] · Nisha Patel[1] · Hisham Alkuraya[3] · Mais Hashem[1] · Firdous Abdulwahab[1] · Niema Ibrahim[1] · Mohammed A. Aldahmesh[1] · Fowzan S. Alkuraya[1,4,5]

Received: 7 November 2017 / Accepted: 12 March 2018 / Published online: 19 March 2018

Abstract

Primary congenital glaucoma is a trabecular meshwork dysgenesis with resultant increased intraocular pressure and ocular damage. *CYP1B1* mutations remain the most common identifiable genetic cause. However, important questions about the penetrance of *CYP1B1*-related congenital glaucoma remain unanswered. Furthermore, mutations in other genes have been described although their exact contribution and potential genetic interaction, if any, with *CYP1B1* mutations are not fully explored. In this study, we employed modern genomic approaches to re-examine *CYP1B1*-related congenital glaucoma. A cohort of 193 patients (136 families) diagnosed with congenital glaucoma. We identified biallelic *CYP1B1* mutations in 80.8% (87.5 and 66.1% in familial and sporadic cases, respectively, $p < 0.0086$). The large family size of the study population allowed us to systematically examine penetrance of all identified alleles. With the exception of c.1103G>A (p.R368H), previously reported pathogenic mutations were highly penetrant (91.2%). We conclude from the very low penetrance and genetic epidemiological analyses that c.1103G>A (p.R368H) is unlikely to be a disease-causing recessive mutation in congenital glaucoma as previously reported. All cases that lacked biallelic *CYP1B1* mutations underwent whole exome sequencing. No mutations in *LTBP2*, *MYOC* or *TEK* were encountered. On the other hand, mutations were identified in genes linked to other ophthalmic phenotypes, some inclusive of glaucoma, highlighting conditions that might phenotypically overlap with primary congenital glaucoma (*SLC4A4*, *SLC4A11*, *CPAMD8*, and *KERA*). We also encountered candidate causal variants in genes not previously linked to human diseases: *BCO2*, *TULP2*, and *DGKQ*. Our results both expand and refine the genetic spectrum of congenital glaucoma with important clinical implications.

Introduction

Primary congenital glaucoma is trabeculodysgenesis that causes increased intraocular pressure and results in ocular changes such as buphthalmos and corneal haze. Additional clinical features include Haab striae (breaks in Descemet membrane), high myopic refractive errors, and cupping of the optic nerve (Ko et al. 2015). Primary congenital glaucoma is the most common form of pediatric glaucoma and accounts for nearly a fifth of childhood blindness, which reflects its poor prognosis (Gilbert et al. 1994; Tabbara and Badr 1985; Taylor et al. 1999). Incidence varies widely among different populations being highest among certain inbred populations (e.g., 1/1250 in Slovakian Roma) and lowest in outbred Western populations (1/10,000) (Genĉík 1989; Ho and Walton 2004). In the highly consanguineous population of Saudi Arabia, a minimum incidence of 1 in 2766 has been estimated (Abouelhoda et al. 2016).

The identification of *CYP1B1* mutations in patients with primary congenital glaucoma was a major breakthrough in our understanding of the disease (Bejjani et al. 1998). Although it remains unclear how mutations in a member of the cytochrome P450 family of enzymes of intermediate metabolism should result in a developmental defect of the trabecular meshwork, a developmental role in this tissue

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00439-018-1878-z) contains supplementary material, which is available to authorized users.

✉ Fowzan S. Alkuraya
falkuraya@kfshrc.edu.sa

[1] Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[2] Eye Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

[3] Specialized Medical Center Hospital, Riyadh, Saudi Arabia

[4] Department of Anatomy and Cell Biology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

[5] Saudi Human Genome Program, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia

has been proposed (Lewis et al. 2017; Zhao et al. 2013). Many variants in *CYP1B1* have been associated with congenital glaucoma (HGMD lists 240), all acting recessively. Several interesting aspects have emerged from *CYP1B1* genotype–phenotype studies. Variable expressivity has been demonstrated where some variants appear to result in a later onset disease, and some have been shown to cause severe anterior segment dysgenesis and aniridia (Khan et al. 2011a, b, 2013, 2014; Pasutto et al. 2010; Suri et al. 2009; Vincent et al. 2006). Perhaps more surprising is the finding that some of these variants cause congenital glaucoma in some patients but not others, i.e., reduced penetrance, unusual for an autosomal recessive disease (Bejjani et al. 2000). Because *CYP1B1* mutations account for only a variable percentage of primary congenital glaucoma depending upon the specific population [< 20% in Japan and USA, but > 85% in Middle East (Bejjani et al. 2000; Lim et al. 2013; Mashima et al. 2001)], there exists the possibility that non-penetrance may reflect erroneous disease-variant association and that alternative variants in other genes may be causal in those cases.

In this study, we take advantage of the large family size of our population and the streamlined referral system for primary congenital glaucoma to study the penetrance and phenotypic consequences of *CYP1B1*-related glaucoma, as well as the potential causes of *CYP1B1*-negative cases.

Materials and methods

Human subjects

The majority of patients in our cohort were children diagnosed with primary congenital glaucoma by a single experienced clinician (AOK) and referred for genetic counseling. A few were cases he diagnosed as atypical congenital glaucoma (e.g., with ectopia lentis) or as previously misdiagnosed glaucoma (e.g., congenital hereditary endothelial dystrophy rather that glaucoma); for the latter, genetic analysis for congenital glaucoma was done to substantiate the change in diagnosis. Congenital glaucoma was defined as congenital/infantile increased intraocular pressure (typically over 25 mm Hg) with accompanying buphthalmos, corneal haze/scarring, induced myopia, and optic disease cupping. Virtually all cases were evident at birth or early infancy. Phenotyping was based on the parameters affected in primary congenital glaucoma (ocular size, pattern of corneal haze, intraocular pressure level, cycloplegic refraction, optic disc appearance) with careful consideration of conditions that can mimic pediatric glaucoma (Khan 2011). A few cases in our cohort, however, were directly referred from other ophthalmologists who had made the diagnosis of congenital glaucoma. After obtaining informed consent using an IRB-approved research protocol (KFSHRC RAC#2070023), venous blood was collected in EDTA tubes for downstream analysis.

Mutation analysis

DNA was extracted using Gentra Puregene Blood Kit and QIAamp DNA Blood Mini Kit. The entire coding and flanking intronic sequences of *CYP1B1* were amplified by PCR and subjected to bidirectional Sanger sequencing. Variants were assessed for pathogenicity using the standard ACMG criteria. We took advantage of the highly consanguineous nature of our population and genotyped all study participants who did not harbor *CYP1B1* biallelic mutations for autozygome analysis as previously described (Alkuraya 2010). Those who mapped to *CYP1B1* but had no biallelic mutation in the gene underwent RTPCR analysis whenever RNA is available to search for splicing or other regulatory mutations. No copy number analysis of *CYP1B1* was performed. For penetrance calculation, we followed a two-pronged approach. First, we performed full segregation analysis of all relatives of the index who agreed to enroll and gave their informed consent. Second, we queried our database of 2363 ethnically matched exomes for whom detailed clinical information is available to identify all instances of biallelic *CYP1B1* mutations and assessed the presence or absence of primary congenital glaucoma. Where available, relatives of those individuals were sought for recruitment and segregation analysis as well. Eventually, penetrance was calculated for each variant as the ratio of those who are affected and homozygous for that variant or compound heterozygous with another known pathogenic variant to the total number of homozygotes or compound heterozygotes for that variant with another known pathogenic variant.

Novel candidate gene discovery

All patients who had no pathogenic/likely pathogenic biallelic *CYP1B1* mutations were exome sequenced, including those who were only heterozygous. For exome sequencing, samples were prepared according to the preparation guide of Agilent SureSelect Target Enrichment Kit and the resulting libraries were sequenced using the Illumina HiSeq 2000 sequencer. The Genome Analysis Toolkit (GATK) was used for variant calling. We specifically searched for mutations in previously reported congenital glaucoma genes: *TEK*, *LTBP2* and *MYOC*. In addition, we applied the following filters: coding/splicing, within autozygome (where applicable), and novel/rare (MAF < 0.001 based on gnomAD and 2363 in-house ethnically matched exomes). We prioritized variants that are apparently loss of function (frameshift indels, nonsense and canonical splicing) as well as missense variants with strong pathogenicity prediction based on PolyPhen, SIFT and CADD. All candidate variants were

confirmed by Sanger sequencing and segregation analysis was performed in all available family members.

Results

CYP1B1-related congenital glaucoma is highly penetrant

Our cohort consists of 193 patients from 136 families. The yield of pathogenic/likely pathogenic *CYP1B1* mutations (80.8%) was higher among multiplex compared to simplex families (87.5 and 66.1%, respectively, $p < 0.0086$). Homozygous and compound heterozygous mutations represented 94.2 and 5.8%, respectively, of these *CYP1B1* mutations, consistent with the highly consanguineous nature of the study population. All identified *CYP1B1* variants were previously reported (Table S1). The large family sizes of our population allowed us to recruit and test 295 unaffected relatives of the index patients to make a more precise estimate of penetrance. In addition, our database of 2363 carefully phenotyped and ethnically matched individuals who have a wide range of Mendelian phenotypes excluding congenital glaucoma permitted us to identify in an unbiased fashion those individuals who have biallelic *CYP1B1* mutations and perform "reverse phenotyping". Our penetrance estimates for all variants combined were 85.5%. The single most common variant was c.182G>A (p.G61E) ($n = 107$) and its penetrance was 87.7% followed by c.1405C>T (p.R469W) ($n = 40$) with 93% penetrance, followed by c.434_443del10 (p.Arg145Profs*4) ($n = 5$) with 100% penetrance (Fig. 1). Despite the extremely high carrier rate of c.1103G>A (p.R368H) variant in the Saudi population (0.01678, compared to 0.01586 for c.182G>A (p.G61E), it was far less enriched in our cohort compared to c.182G>A (p.G61E) with only one homozygous and two compound heterozygous states and even these had a very low penetrance of 23% (Figure S1). To test whether there is any enrichment at all for this variant in congenital glaucoma, we examined an independent ethnically matched cohort recruited on the basis of intellectual disability (Anazi et al. 2017). Remarkably, we identified three heterozygous individuals (3/147) in that cohort, which reflects no enrichment and suggests that the presence of c.1103G>A (p.R368H) in our congenital glaucoma cohort merely reflects its normal population distribution as a common Saudi SNP. Although we cannot exclude the possibility that c.1103G>A (p.R368H) may have a phenotypic expression later in life, among the

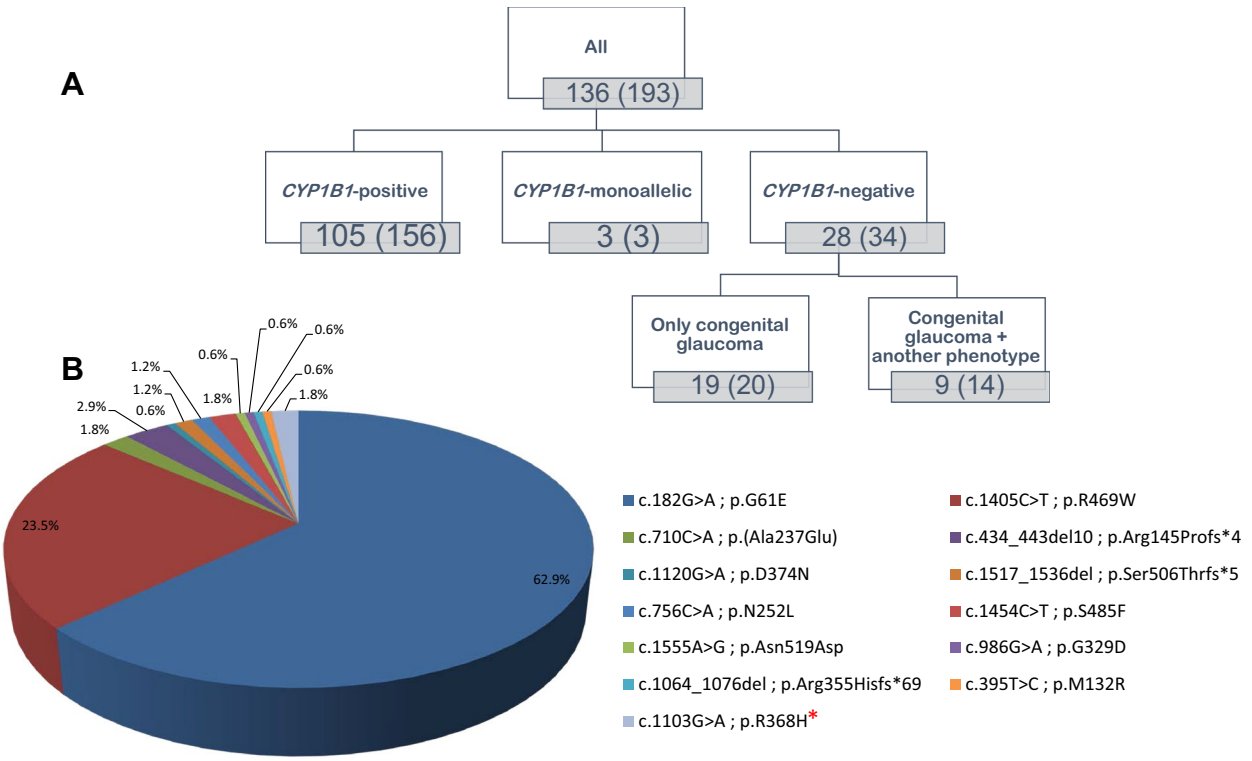

Fig. 1 **a** Distribution of *CYP1B1* mutations in the study cohort. Monoallelic refers to cases where only one pathogenic allele in *CYP1B1* was identified. Numbers denote families and numbers in parenthesis denote absolute counts of individuals. **b** Pie chart distribution of 13 mutations identified in *CYP1B1*. *c.1103G>A (p.R368H) is included in this pie chart simply to show its minimal contribution to the overall allele burden but we conclude in the manuscript that it is not pathogenic (see "Discussion")

7 homozygous and compound heterozygous individuals for this variant in the Saudi non-congenital glaucoma cohort, our findings strongly argue against c.1103G>A (p.R368H) as a bona fide disease-causing variant in the context of congenital glaucoma and this conclusion is consistent with a recent large population genetics study (Lek et al. 2016). This prompted us to recalculate the penetrance of the other *CYP1B1* alleles by excluding those homozygotes and compound heterozygotes for c.1103G > A (p.R368H) and the revised overall penetrance was 91.2%. Furthermore, by reclassifying c.1103G>A (p.R368H) as a benign SNP, we were able to recalculate the minimum incidence of congenital glaucoma in Saudi Arabia to 1 in 5532.

The phenotypes associated with *CYP1B1* are summarized in Table S1. Briefly, virtually all cases (97.1%) were bilateral (only 3 cases were unilateral) and 8.5% were associated with additional ocular findings, e.g., anterior segment dysgenesis, corneal flattening and aniridia.

Expanding the differential diagnosis of primary congenital glaucoma

CYP1B1-negative cases (34 patients from 28 families) underwent exome sequencing. No pathogenic variants in *LTBP2*, *TEK* or *MYOC* were identified. Rather, we identified potentially causal variants in the following genes that are known to cause various ocular phenotypes: *SLC4A4*, *SLC4A11*, *ADAM9*, *CPAMD8*, and *KERA* (Table S1). Of these genes congenital glaucoma is only known to be associated with *SLC4A4*. The phenotype in the three patients with homozygous *SLC4A4* variants included band keratopathy, which had been thought to be secondary to their severe disease and multiple surgeries but in retrospect was a primary effect of the *SLC4A4* mutations (Patel et al. 2017). Patients with mutations in *SLC4A11*, *ADAM9*, *CPAMD8*, and *KERA* did have the expected phenotypic features of corneal dystrophy, cone-rod dystrophy, lens subluxation, and severe anterior segment dysgenesis (prior surgeries may have been a confounding factor), respectively.

Identification of novel candidate genes

A novel homozygous apparently loss-of-function variant was identified in one gene that has not been linked to human diseases: *BCO2* (NM_031938.5:c.10C>T:p.Arg4*). In addition, a missense variant with high pathogenicity scores was identified in *TULP2* (NM_003323.2:c.1081A>C:p.Lys361Gln). Although the novel variant we identified in *DGKQ* (NM_001347.3:c.1148C>T:p.Thr383Met) was predicted benign at the protein level, it was suspicious for an exonic splicing effect by SpliceAid. Indeed, q-RTPCR confirmed marked reduction in the wild-type transcript level (> 70%) compared to controls (Fig. 2). All these variants were confirmed to fully segregate with primary congenital

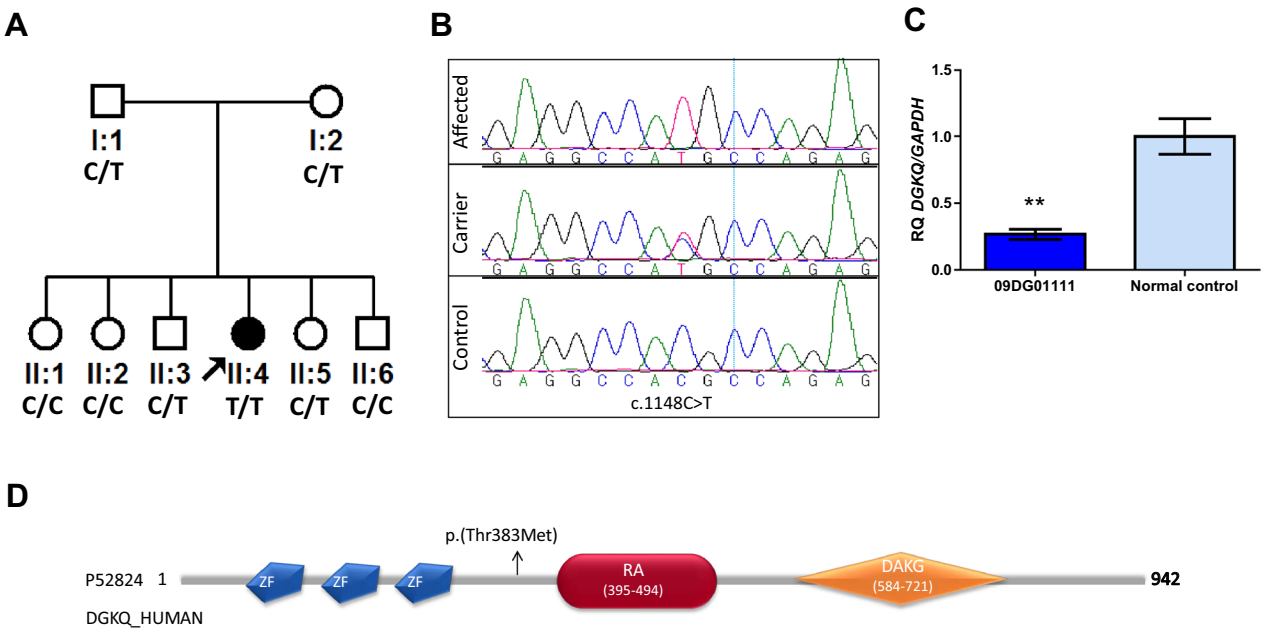

Fig. 2 **a** Pedigree of the family with congenital glaucoma and a novel *DGKQ* variant. **b** Sequence chromatogram of the novel *DGKQ* variant. C) qRT-PCR for *DGKQ* expression in LCL in patient 09DG01111 with a missense mutation in this candidate gene compared to three normal control reveals > 70% decreased in expression. Results are normalized to *GAPDH* and are the average from triplicate readings from three independent experiments. *p* values are based on unpaired student *t* test, $^{**}p < 0.01$. Error bars are standard error ± mean. **d** Cartoon of DGKQ protein and the site of the mutated residue

glaucoma in the respective families and the phenotype was non-syndromic and indistinguishable from *CYP1B1*-related glaucoma.

Discussion

Primary congenital glaucoma is one of the most common genetic diseases in Saudi Arabia with an estimated incidence of 1:2766 (Abouelhoda et al. 2016). Similar to other populations, we found *CYP1B1* to be the most common identifiable mutated gene for this disease, albeit at a much higher frequency. Precise estimates of the penetrance of *CYP1B1*-related congenital glaucoma are lacking despite the large number of studies, presumably because of the limited number of unaffected relatives that could be analyzed. In this study, we show that the disease is highly penetrant and the few cases of apparent non-penetrance are primarily those with c.182G>A (p.G61E), the most commonly encountered pathogenic variant in *CYP1B1*. Unlike c.182G>A (p.G61E), c.1103G>A (p.R368H) lacks functional validation and epidemiological support of pathogenicity so the non-penetrant cases associated with c.1103G>A (p.R368H) may simply represent normal rather than mutated individuals. The observation that despite the comparable general population frequency, c.1103G>A (p.R368H), was > 50 fold less common in our congenital glaucoma cohort, the largest of its kind from the study population strongly argues against its pathogenic nature. Furthermore, we found a comparable frequency of c.1103G>A (p.R368H) in a cohort of intellectually disabled children, which further argues against a causal, even partial, link to congenital glaucoma. We recommend that the status of this variant currently listed in public databases as "pathogenic", to be changed to at least "disputed" if not "refuted", as suggested by the recent ClinGen consortium (Strande et al. 2017). The resulting revision of the disease burden to 1 in 5532 should be taken with caution because it does not account for private mutations as explained before (Abouelhoda et al. 2016).

Although the clinical diagnosis of primary congenital glaucoma is often clear, certain conditions are known to have overlapping phenotypes and can be mistaken for the diagnosis (Khan 2011). *SLC4A11* mutations cause congenital hereditary endothelial dystrophy (CHED), a disease characterized by such significant corneal edema and opacity that the clinical picture may be confused with that of *CYP1B1* mutations (Aldahmesh et al. 2009; Khan et al. 2010), and we indeed identified one family with CHED previously misdiagnosed as primary congenital glaucoma. *SLC4A4* mutations typically cause a syndrome with the triad of band keratopathy, renal tubular disease and intellectual disability. However, we have recently shown that a founder 3′UTR mutation can cause an ocular-limited phenotype and we report here three cases with primary congenital glaucoma and band keratopathy (Patel et al. 2017). *KERA* mutations cause cornea plana and we are not aware of reports, other than the patients described in this study, of *KERA*-related congenital glaucoma. It is conceivable, and perhaps likely, that severe anterior segment involvement predisposed to a secondary angle-closure glaucoma. *CPAMD8* mutations have only recently been reported as a cause for a unique form of autosomal recessive anterior segment dysgenesis that can include ectopia lentis (Cheong et al. 2016). We show that congenital glaucoma can be part of this phenotype. Our study also expands the phenotypes associated with *ADAM9* and *RELN* to also include congenital glaucoma; however, we cannot exclude the possibility that congenital glaucoma in these two families was due to a factor other than homozygous mutations in the identified genes.

The search for additional genetic causes of primary congenital glaucoma has been met with limited success. The observation that despite the relative homogeneity of our study population, we did not identify any recurrently mutated genes in *CYP1B1*-negative cases suggests that the disease is heterogeneous genetically, or perhaps there are important non-genetic causes that need to be considered. Another possibility is that at least some underlying mutations are non-coding and these are not identifiable by exome sequencing, e.g., we did not include CNV analysis in our pipeline. We note here that the percentage of familial cases in the *CYP1B1*-negative cases without alternative etiology in known ocular genes (see above) is curiously small (2.1%), which does raise the suspicion that these cases may not be genetic. Despite this limitation, we highlight in this study novel variants in interesting candidates. For example, we describe the first human "knockout" for *BCO2*:NM_031938.5:c.10C>T:p.R4X. *TULP2* is highly expressed in the retina and we note that *TULP1* mutations are known to cause retinal degeneration, so it is possible that *TULP2* mutation may also cause an ocular phenotype. *DAGK4* is also expressed in the mammalian retina and deficiency of its ortholog in furitfly results in retinal degeneration (Pilz et al. 1995). As with other candidate genes, the link remains tentative until future cases are described. We hope that sharing these candidates will facilitate the identification of additional cases, an approach that has been encouraged to accelerate the establishment of new disease genes in humans (Boycott et al. 2017).

In conclusion, our study defines novel phenotypic and genetic aspects of congenital glaucoma. We confirm the incomplete penetrance of *CYP1B1*-related glaucoma and provide an estimate of penetrance based on a large and unbiased control population. Our study further expands the differential diagnosis of congenital glaucoma and suggests a few novel candidate genes that require future verification.

Acknowledgements We thank the study families for their enthusiastic participation. We also thank the Sequencing and Genotyping Core Facilities at KFSHRC for their technical help. This work was funded in part by KACST 15-BIO3688-20 (FSA), the Saudi Human Genome Program (King Abdulaziz City for Sciences and Technology) (FSA), and King Salman Center for Disability Research (FSA).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abouelhoda M, Sobahy T, El-Kalioby M, Patel N, Shamseldin H, Monies D, Al-Tassan N, Ramzan K, Imtiaz F, Shaheen R (2016) Clinical genomics can facilitate countrywide estimation of autosomal recessive disease burden. Genet Med 18:1244–1249

Aldahmesh MA, Khan AO, Meyer BF, Alkuraya FS (2009) Mutational spectrum of SLC4A11 in autosomal recessive CHED in Saudi Arabia. Invest Ophthalmol Vis Sci 50:4142–4145

Alkuraya FS (2010) Homozygosity mapping: one more tool in the clinical geneticist's toolbox. Genet Med 12:236–239

Anazi S, Maddirevula S, Faqeih E, Alsedairy H, Alzahrani F, Shamseldin H, Patel N, Hashem M, Ibrahim N, Abdulwahab F (2017) Clinical genomics expands the morbid genome of intellectual disability and offers a high diagnostic yield. Mol Psychiatry 22:615–624

Bejjani BA, Lewis RA, Tomey KF, Anderson KL, Dueker DK, Jabak M, Astle WF, Otterud B, Leppert M, Lupski JR (1998) Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. Am J Human Genet 62:325–333

Bejjani BA, Stockton DW, Lewis RA, Tomey KF, Dueker DK, Jabak M, Astle WF, Lupski JR (2000) Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. Hum Mol Genet 9:367–374

Boycott KM, Rath A, Chong JX, Hartley T, Alkuraya FS, Baynam G, Brookes AJ, Brudno M, Carracedo A, den Dunnen JT (2017) International cooperation to enable the diagnosis of all rare genetic diseases. Am J Human Genet 100:695–705

Cheong SS, Hentschel L, Davidson AE, Gerrelli D, Davie R, Rizzo R, Pontikos N, Plagnol V, Moore AT, Sowden JC, Michaelides M, Snead M, Tuft SJ, Hardcastle AJ (2016) Mutations in CPAMD8 cause a unique form of autosomal-recessive anterior segment dysgenesis. Am J Hum Genet 99:1338–1352. https://doi.org/10.1016/j.ajhg.2016.09.022

Genčík A (1989) Epidemiology and genetics of primary congenital glaucoma in Slovakia. Description of a form of primary congenital glaucoma in gypsies with autosomal-recessive inheritance and complete penetrance. Dev Ophthalmol 16:76–115

Gilbert CE, Canovas R, Canovas RK, Foster A (1994) Causes of blindness and severe visual impairment in children in Chile. Dev Med Child Neurol 36:326–333

Ho CL, Walton DS (2004) Primary congenital glaucoma: 2004 update. J Pediatr Ophthalmol Strabismus 41:271–288

Khan AO (2011) Conditions that can be mistaken as early childhood glaucoma. Ophthalmic Genet 32:129–137

Khan AO, Al-Shehah A, Ghadhfan FE (2010) High measured intraocular pressure in children with recessive congenital hereditary endothelial dystrophy. J Pediatr Ophthalmol Strabismus 47:29–33

Khan AO, Al-Abdi L, Mohamed JY, Aldahmesh MA, Alkuraya FS (2011a) Familial juvenile glaucoma with underlying homozygous p. G61E CYP1B1 mutations. J Am Assoc Pediatr Ophthalmol Strabismus 15:198–199

Khan AO, Aldahmesh MA, Al-Abdi L, Mohamed JY, Hashem M, Al-Ghamdi I, Alkuraya FS (2011b) Molecular characterization of newborn glaucoma including a distinct aniridic phenotype. Ophthalmic Genet 32:138–142

Khan AO, Aldahmesh MA, Mohamed JY, Alkuraya FS (2013) Congenital glaucoma with acquired peripheral circumferential iris degeneration. J Am Assoc Pediatr Ophthalmol Strabismus 17:105–107

Khan AO, Aldahmesh MA, Mohamed JY, Hijazi H, Alkuraya FS (2014) Complete aniridia with central keratopathy and congenital glaucoma is a CYP1B1-related phenotype. Ophthalmic Genet 35:187–189

Ko F, Papadopoulos M, Khaw PT (2015) Primary congenital glaucoma. Prog Brain Res 221:177–189

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won HH, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG; Exome Aggregation Consortium (2016) Analysis of protein-coding genetic variation in 60,706 humans. Nature 536(7616):285–291. https://doi.org/10.1038/nature19057

Lewis C, Hedberg-Buenz A, DeLuca AP, Stone EM, Alward WL, Fingert JH (2017) Primary Congenital and Developmental Glaucomas. Human Molecular Genetics 26(R1):R28–R36

Lim S-H, Tran-Viet K-N, Yanovitch TL, Freedman SF, Klemm T, Call W, Powell C, Ravichandran A, Metlapally R, Nading EB (2013) CYP1B1, MYOC, and LTBP2 mutations in primary congenital glaucoma patients in the United States. Am J Ophthalmol 155(508–517):e5

Mashima Y, Suzuki Y, Sergeev Y, Ohtake Y, Tanino T, Kimura I, Miyata H, Aihara M, Tanihara H, Inatani M (2001) Novel cytochrome P4501B1 (CYP1B1) gene mutations in Japanese patients with primary congenital glaucoma. Invest Ophthalmol Vis Sci 42:2211–2216

Pasutto F, Chavarria-Soley G, Mardin CY, Michels-Rautenstrauss K, Ingelman-Sundberg M, Fernández-Martínez L, Weber BH, Rautenstrauss B, Reis A (2010) Heterozygous loss-of-function variants in CYP1B1 predispose to primary open-angle glaucoma. Invest Ophthalmol Vis Sci 51:249–254

Patel N, Khan AO, Al-Saif M, Moghrabi WN, AlMaarik BM, Ibrahim N, Abdulwahab F, Hashem M, Alshidi T, Alobeid E (2017) A novel mechanism for variable phenotypic expressivity in Mendelian diseases uncovered by an AU-rich element (ARE)-creating mutation. Genome Biol 18:144

Pilz A, Schaap D, Hunt D, Fitzgibbon J (1995) Chromosomal localization of three mouse diacylglycerol kinase (DAGK) genes: genes sharing sequence homology to the Drosophila retinal degeneration A (rdgA) gene. Genomics 26:599–601

Strande NT, Riggs ER, Buchanan AH, Ceyhan-Birsoy O, DiStefano M, Dwight SS, Goldstein J, Ghosh R, Seifert BA, Sneddon TP (2017) Evaluating the clinical validity of gene–disease associations: an

evidence-based framework developed by the Clinical Genome Resource. Am J Human Genet 100(6):895–906
Suri F, Yazdani S, Narooie-Nejhad M, Zargar SJ, Paylakhi SH, Zeinali S, Pakravan M, Elahi E (2009) Variable expressivity and high penetrance of CYP1B1 mutations associated with primary congenital glaucoma. Ophthalmology 116:2101–2109
Tabbara KF, Badr IA (1985) Changing pattern of childhood blindness in Saudi Arabia. Br J Ophthalmol 69:312–315
Taylor RH, Ainsworth JR, Evans AR, Levin AV (1999) The epidemiology of pediatric glaucoma: the Toronto experience. J Am Assoc Pediatr Ophthalmol Strabismus 3:308–315
Vincent A, Billingsley G, Priston M, Glaser T, Oliver E, Walter M, Ritch R, Levin A, Héon E (2006) Further support of the role of CYP1B1 in patients with Peters anomaly. Mol Vis 12:506–510
Zhao Y, Wang S, Sorenson CM, Teixeira L, Dubielzig RR, Peters DM, Conway SJ, Jefcoate CR, Sheibani N (2013) Cyp1b1 mediates periostin regulation of trabecular meshwork development by suppression of oxidative stress. Mol Cell Biol 33:4225–4240