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Article

Association of a TGFBI Mutation with Congenital Glaucoma in GAPO Syndrome

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Abstract: Purpose: To investigate the molecular basis of congenital glaucoma in a family with GAPO (growth retardation, alopecia, pseudoanodontia, and progressive optic atrophy) syndrome. **Methods**: We report ocular features of 3 girls with GAPO syndrome born of consanguineous marriage in a multi- generation consanguineous family. The proband (4year old girl) and her younger sibling (1 year old girl) were operated for bilateral congenital glaucoma in both eyes. The elder sibling (10year old female) had features of GAPO syndrome but did not manifest features of glaucoma. **Results:** A genetic evaluation using whole exome sequencing revealed a homozygous *ANTXR1* mutation in all 3 affected siblings with GAPO. No other mutations were detected in the genes associated with glaucoma. A rare missense mutation in *TGFBI* gene was shared in the two siblings with congenital glaucoma and GAPO syndrome. **Conclusions:** Mutations in *TGFBI* gene could have a role in the pathogenesis of congenital glaucoma.

Keywords: congenital glaucoma; GAPO; GAPO syndrome; *TGFBI*; *ANTXR1*

1. Introduction

GAPO syndrome is an extremely rare genetic disorder, with only about sixty cases reported till date. The ocular features of GAPO syndrome include puffy eyelids, sparse eyelash hair, poliosis, hypertelorism, ptosis, strabismus, nystagmus, megalocornea, keratoconus, keratopathy, optic atrophy, myelinated retinal nerve fiber layer and congenital glaucoma (buphthalmos) (1).The diagnosis of GAPO is usually made early due to the characteristic premature 'geriatric' appearance of the patients, the presence of cardinal features like alopecia and pseudoanodontia, as well as the associated features like dwarfism, prominent supraorbital ridges, frontal bossing depressed nasal bridge, long philtrum and a wide open anterior fontanelle. Late onset alopecia has also been frequently documented (2-3). Patients with GAPO have a reduced life span and usually die in their third or fourth decades of life due to generalized interstitial fibrosis of the lungs and atherosclerosis (4-5).

The invariable consanguinity in these families with GAPO, points towards an autosomal recessive mode of inheritance, caused by mutations in *ANTXR1* on chromosomal position 2p14, a protein essential for intracellular actin assembly (6-7). Defective production of this protein leads to altered cell adhesion properties, leading to excessive deposition of extracellular matrix (ECM) secondary to reduced turnover, resulting in the various phenotypic features of this syndrome (7-8).

We describe a multi-generation consanguineous family with three girls affected with GAPO syndrome, two of whom had congenital glaucoma. While there are reports of the occurrence of glaucoma among patients with GAPO syndrome, (5,9-13) it is not known whether mutations in *ANTXR1* gene itself or some other (glaucoma associated) genes,

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lead to the development of congenital glaucoma in these patients. This report analyses the genetic background of two children with GAPO syndrome and congenital glaucoma.

2. Subjects and Methods

A multi generation consanguineous family presented to us, where four girls, three of whom were affected with GAPO, out of whom two also had congenital glaucoma (**Figure 1**). The family belonged to North India with a strong tradition of consanguinity. The three cases of the family described here are of the three girls who had features of GAPO syndrome.

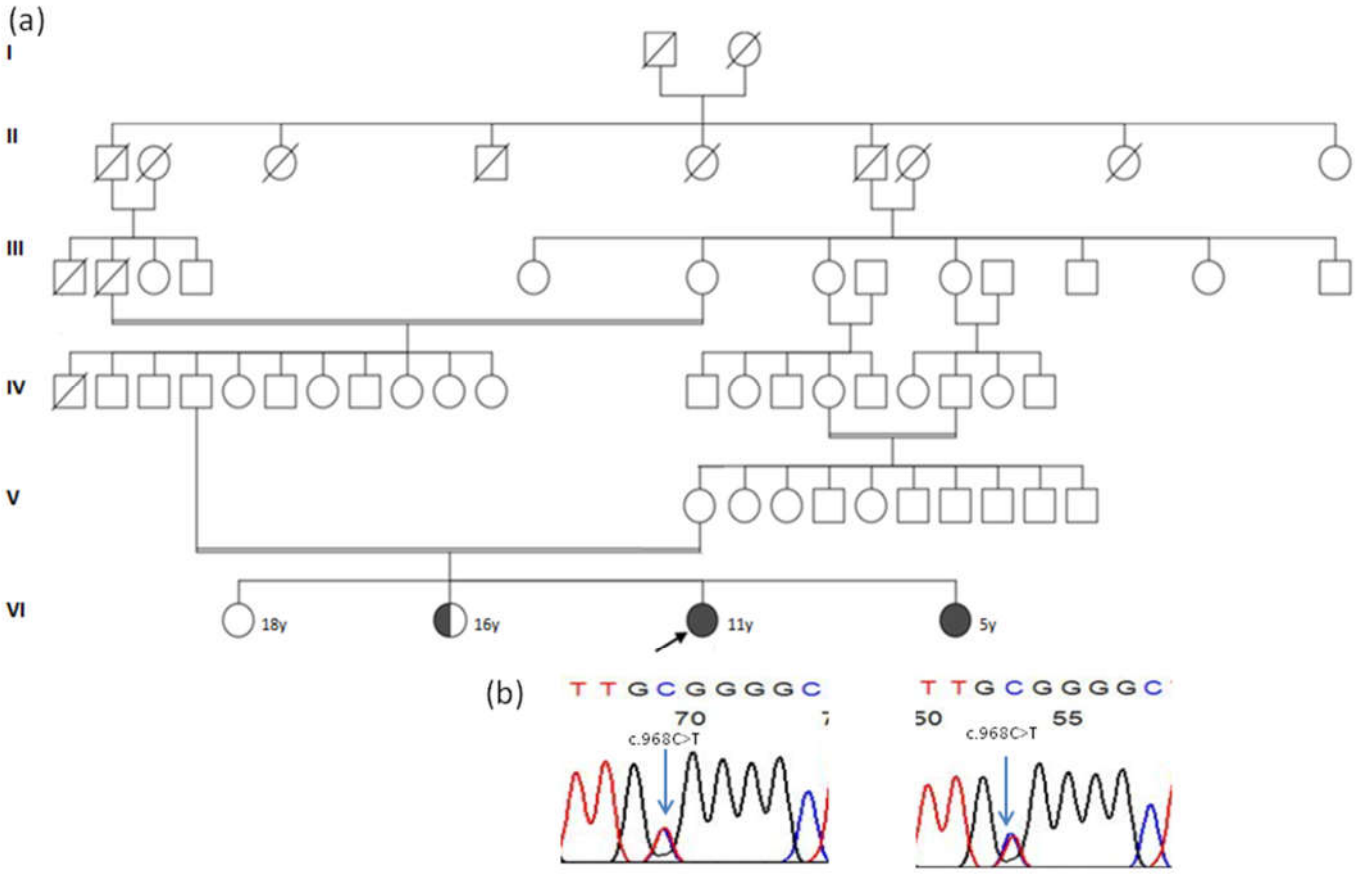

Figure 1. (a)Pedigree chart of the family with three children affected with GAPO syndrome showing at least three generations of consanguinity. The half shaded circle depicts the child having only GAPO syndrome, but not glaucoma. The younger two siblings had glaucoma with GAPO syndrome depicted as full shaded circles. The ages mentioned in the pedigree are those at their last follow up. (b) Chromatograms showing heterozygous, *TGFBI*;NM_000358.3:c.968C>T; p.Ala323Val mutation found in the two girls with congenital glaucoma and GAPO syndrome.

2.1. Case 1 (Proband)

A 4year old girl, born of a consanguineous marriage, presented to our glaucoma clinic with chief complaints of watering and an asymmetric corneal enlargement of the right eye (RE). Physical examination revealed progressive frontal alopecia with a receding hairline, frontal bossing, high forehead, prominent supraorbital ridges, depressed nasal bridge, anteverted nostrils, long philtrum, umbilical hernia, sparse eyebrows and an appearance of premature aging (**Figure 2A1-4**). Intraoral examination revealed absence of

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normal dentition pattern (**Figure 2A3**); a radiograph of the teeth revealed impacted dentition, confirming pseudoanodontia. Her weight (12kg) and height (92cm) were below the 3rd percentile. The mental status of the patient was found to be normal and there was no developmental delay.

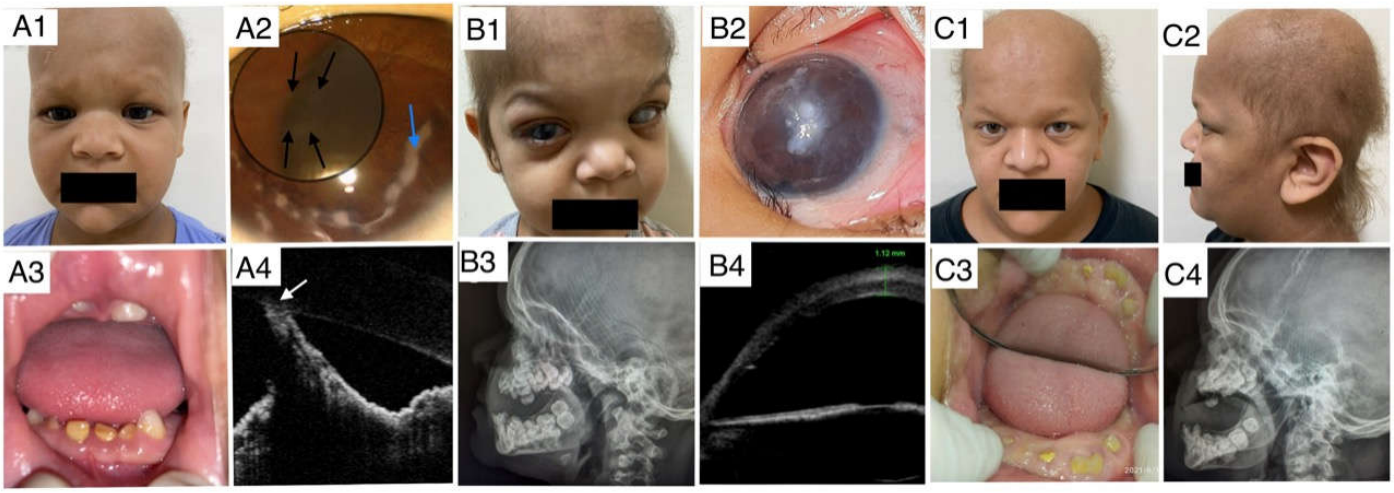

Figure 2. Clinical photographs of Case 1 (A1-4), Case 2 (B1-4) and Case 3 (C1-4). Front facial profile and side facial profile of the patients illustrate the presence of a characteristic geriatric appearance, with alopecia, sparse eyebrows, frontal bossing, prominent supraorbital ridges, depressed nasal bridge, anteverted nostrils and a long philtrum. Clinical photograph of the oral cavity shows impaction of teeth with a reduction in its number. Radiograph of the face (lateral view with open mouth) reveals a normal number of teeth, confirming pseudoanodontia. Anterior segment photograph of Case1 (A2) reveals the presence of megalocornea with prominent iridocorneal adhesions and keratopathy (blue arrow). Corneal opacities are also seen (black arrows; magnified inset). AS-OCT image of the same patient (A4) confirms the iridocorneal adhesions (white arrow). Central keratopathy can be seen in the anterior segment photograph of RE of Case 2 (B2). An ultrasound biomicroscopy (UBM) of the same Case revealed central corneal thickening with thinned out iris and ciliary body (B4).

Examination under anesthesia (EUA) revealed RE enlarged corneal diameters with an IOP of 30mmHg, with corneal edema precluding a detailed anterior and posterior segment evaluation. Her left eye (LE) had clear cornea with an IOP of 16mmHg. The patient was taken up for RE trabeculectomy with mitomycin. On subsequent EUA (post-operatively) when the cornea had cleared up, an anterior segment evaluation revealed the presence of Haab's striae and peripheral keratopathy with iridocorneal adhesions that were also seen on an ASOCT examination in the RE (**Figure 2A3, 2A4**). Her optic disc examination showed a vertical cup disc ratio (CDR) of 0.4:1 with temporal disc pallor in RE; while LE showed a healthy disc with a CDR of 0.2:1. Eventually, she developed increased IOP in her LE, for which she was taken up for LE trabeculectomy with mitomycin, three years after the RE surgery. Her IOPs have been controlled in both eyes (BE) ever since.

An USG abdomen revealed the presence of normal kidneys and ovaries. An MRI of the brain did not detect any intracranial abnormality. Other investigations, including complete blood counts, serum and urine biochemistry, hormonal assays and echocardiography, were normal.

2.2. Case 2

The younger sibling of the proband presented at 1 year of age with complaints of watering BE. Till 6 months of age, she had lush black hair followed by progressive hair loss There was a prominent supraorbital ridge, depressed nasal bridge, high forehead, wide anterior fontanelle and a premature aged look (**Figure 2B1-4**). She also had

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pseudoanodontia. Just like her elder sister, she had growth retardation, with her weight and length below the 3rd percentile for her age.

An EUA revealed BE horizontal corneal diameter of 13.5mm, along with the presence of a diffuse corneal haze in LE. She also had a central keratopathy in RE (**Fig 2B2**). Her IOP was 28mmHg in RE and 32mmHg in LE. An ultrasound biomicroscopy (UBM) revealed central corneal thickening and a thinned out iris and ciliary body. (**Fig 2B4**). She had a cup disc ratio of 0.6:1 in BE. She was operated for BE trabeculectomy with ab externo trabeculotomy with mitomycin. The surgery was uneventful and she maintains normal IOP.

2.3. Case 3

The 10 year-old elder sister of the proband was also evaluated for GAPO features. Just like the proband, she was observed to have all the phenotypic features of this syndrome, in addition to reduced eye lashes (**Figure 2C1-4**). Intraoral examination also revealed pseudoanodontia, and her height (120cm) and weight (20kg) was below the 3rd centile for her age. She had no developmental delay and her mental status was normal. Her visual acuity was found to be 6/6 in both the eyes, and IOP was 14mmHg and 16mmHg for the RE and LE respectively. Her corneae were clear and gonioscopy revealed wide open angles without any abnormality. Her optic nerves were found to be normal.

Table 1 shows the ophthalmic features of the three siblings with GAPO syndrome.

Table 1. Ocular features of the 3 girls with GAPO.

(Pedigree notation)	Case 1 (VI iii)	Case 2 (VI iv)	Case 3 (VI ii)
Glaucoma	+	+	-
Optic Atrophy	-	-	-
Keratopathy	-	+	-
Frontal bossing	+	+	+
Sparse eyebrows	+	+	+
Sparse eyelashes	+	+	+
White eyelashes	-	-	-
Prominent globes	+	+	+
Swollen eyelids	+	+	+
Prominent supraorbital ridges	+	+	+
Epiblepharon	+	-	+

None of the other members of the family examined had any features of GAPO or glaucoma.

2.4. Genotyping

Blood samples were withdrawn from the four children, the parents and the paternal grandmother after an informed consent taken from the parents of the children. The study was carried out according to the tenets of the declaration of Helsinki and an Ethics committee approval was obtained from our Institutes ethics committee. A signed informed consent according to the guidelines of the Institute Ethics Committee was provided by the family.

Genomic DNA was extracted from peripheral blood lymphocytes using PAXgene Blood DNA Kit (Qiagen, Germany) for genetic evaluation. DNA was run on 0.8% agarose gel to check for quality and quantified by Nanodrop.

Whole Exome Sequencing (WES) capture was performed using the Sure Select Clinical Research Exome V2 kit (Agilent Technologies, Santa Clara, CA). Variant analysis was performed using GenomeAnalysisTK-3.6 toolkit. The variant call files (VCF), containing the variant call results, generated were analyzed using Golden Helix VarSeq Software

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v.1.2.1 (Bozeman, MT). VarSeq variants with read depth <15 and genotype quality score <20 were excluded. To identify rare mutations, variant frequency databases were used to remove variants that are present at high frequencies among large population groups. The remaining variants were filtered according to minor allele frequency (MAF) <0.001 in multiple databases including Exome Aggregation Consortium(ExAC) (http://exac.broadinstitute.org/) and gnomAD (http://gnomad.broadinstitute.org/). Variants specifically in the two sisters with glaucoma were filtered, based on only those exonic variants (Non-synonymous missense variants, frame shift and indels and splice region variants) that were present exclusively in the two sisters and absent in the other family members and 20 healthy controls. Inherited variants that were present in both the affected sisters with congenital glaucoma and one of the parents were also looked at, for any association with the known glaucoma genes. Copy number variant (CNV) analysis was performed to look for CNV in the known genes for glaucoma or others with a strong association with glaucoma pathogenesis. The CNV's were annotated with RefSeq gene annotations and further with Database of Genomic Variants v107. The CNV's were then classified to assess the pathogenicity using classify CNV. The CNV's common in both affected individuals were visually inspected using IGV.

We used Homozygosity mapping to identify long stretches of homozygous haplotypes in genes associated with glaucoma. Regions of Homozygosity (ROH) were identified by using the AutoMap software (Quinodoz et al., https://automap.iob.ch/) on WES data (14).

Further functional impact of the protein was predicted by bioinformatic tools; variant effect predictor (VEP), Mutation Taster, Polyphen, FATHMM. The identified variants were confirmed by Sanger sequencing.

3. Results

We found a missense homozygous *ANTXR1* gene mutation in all three children affected with GAPO (NM_032208.2:c.572T>C, p.Ile191Thr). This change is novel and predicted to be disease causing by mutation taster (0.99), PolyPhen-2 (1.0) and PROVEAN (-4.0). Another change at this position c.572T>G, p.Ile572Ser is reported in the COSMIC database (COSV100362660). Homozygosity mapping applied to WES data of the consanguineous family, detected one large (11Mb) homozygous region involving the *TEK* gene (i.e. chromosome 9) in only one of the two sisters with congenital glaucoma, among the genes known for glaucoma. However, neither any CNV, nor any intronic splice region variant was detected in the *TEK* gene in either of the sisters.

No pathogenic variants or CNV were detected that co-segregated with glaucoma in the two girls with congenital glaucoma (Case 1 and 2) at any of the known loci for Mendelian forms of glaucoma (GLC1A, GLC1B, GLC1D-Q) or PCG (GLC3A-D) including the known causative genes namely, *MYOC* (GLC1A), *CYP1B1*(GLC3A), *WDR36* (GLC1G), *ASB10* (GLC1F), *OPTN* (GLC1E), *NTF4* (GLC1O), *TBK1*(GLC1P), *LTBP2* (GLC3C), *FOXC1*, *PITX2*, *TEK* and *PAX6*. Exonic variants specific to the two sisters with congenital glaucoma and the variants they inherited from either of the parents are listed in **Suppl Table 1.**

Four missense mutations exclusive to the two sisters with GAPO and congenital glaucoma (case 1 and case 2); *PTPN4*, *PCDHB4*, *GGT2* and *TGFBI*, were observed. The variants on *PTPN4* and *PCDHB4*, were rejected as they were found to be benign. The *GGT2* variant was not taken in to consideration as it was earlier reported that hGGT2 does not encode a functional enzyme and therefore is unlikely to play a role in the glaucoma pathogenesis. A missense heterozygous variant in *TGFBI* (Transforming Growth Factor Beta Induced),NM_000358.3:c.968C>T NP_000349.1:p.Ala323Val **(Fig 1.a)** was found, that is reported to be damaging by the variant prediction tools PROVEAN (-2.5), FATHMM-MKL (0.825), PolyPhen-2 (0.89) and disease causing by Mutation Taster (0.99). The variant is highly conserved with a Genomic evolutionary rate profiling (GERP) value 5.65. Sanger sequencing confirmed

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heterozygous missense p.Ala323Val mutation in both case 1 and case 2 and was absent in case 3 and other family members of the pedigree. The gnomAD frequency of the variant was found to be 0.001450. The *Clinvar* star rating score, extracted for the variant, was found to be 1/4 with two submissions; one being for corneal dystrophy.

We then looked for the presence of *TGFBI* gene mutations in another cohort of 40 patients with early onset glaucoma (before 25 years of age) in whom WES was previously done. We found two *TGFBI* mutations present in two unrelated juvenile onset open angle glaucoma (JOAG) patients. Neither of these 2 patients had any other mutations in the known glaucoma genes. In one patient a *TGFBI* heterozygous missense mutation was found in the same codon as observed in the described cases of GAPO, but with a different residue amino acid.; NM_000358.3:c.968C>A, NP_000349.1:p.Ala323Glu. The second was a novel mutation in the other JOAG patient. This was a null variant (frame shift mutation); NM_000358.3:c.1944del, NP_000349.1:p.Ser649LeufsTer22. These variants were of uncertain significance and likely pathogenic respectively as per ACMG classification. The former was damaging by Mutation taster (0.99), PolyPhen-2 (0.89) and PROVEAN (-2.5). The gnomAD frequency of NM_000358.3:c.968C>A was found to be 0.00003269 and the frequency of (NM_000358.3):c.1944del is not reported in gnomAD.

4. Discussion

This family with three children affected with GAPO, two of whom presented with bilateral congenital glaucoma gave us an opportunity to study the genetic association of glaucoma with GAPO syndrome.

Glaucoma is an ophthalmological manifestation of GAPO syndrome, and has been reported in ten cases till date (2-3,5,8-13). Glaucoma in five of these patients was early onset open angle glaucoma (2-3,12-13). Primary congenital glaucoma (PCG), is described in five patients (5,9-13) presenting with Haab's striae and buphthalmos. Asymmetric glaucoma, as seen in Case 1 at presentation has also been documented, (5,9) while others have described a late presentation with end stage glaucoma (9-10,13). The pathogenesis of bilateral congenital glaucoma in children with GAPO syndrome is not clearly understood. Mutations in the *ANTRX1* gene itself have been postulated to be the cause of glaucoma and the variable expression of *ANTRX1* mutation could be the reason why the elder sister (case 3) with *ANTRX1* mutation and GAPO syndrome did not have glaucoma. Even if we consider a variable expressivity in *ANTRX1* as the reason for one sibling with GAPO syndrome, not developing congenital glaucoma in this family, we believe this variable expression may have been influenced by the presence of the *TGFBI* mutation.

The abnormal expression of *TGFBI* is related to the occurrence and development of some types of cancers as well as different types of corneal dystrophies; lattice corneal dystrophies (LCD) and granular corneal dystrophies (GCD) (15) while the role of *TGFBI* in glaucoma is not known. The human protein TGFBIp encoded by *TGFBI* has four FASI domains and the mutated amino acid observed in our two patients corresponds to FAS1-2 domain of TGFBIp. However, the *TGFBI* mutations known for a variety of corneal dystrophies are located in the FASI-1 and FASI-4 domain (16). The *TGFBI* gene is also within the linkage area mapped as a glaucoma locus 5q22.1-q32. (17). A gene expression profile of human trabecular meshwork(TM) tissue by SAGE (serial analysis of gene expression) has shown a higher expression for *TGFBI* along with other glaucoma causing genes and genes involved in typical TM maintenance functions (18). A study by Kim et al using Alb-hßigh3 transgenic mice showed that over expressed human βigh3/ (hßigh3)/ TGFBIp in blood may be involved in anterior segment morphogenesis and eye development in mice and the phenotype observed in transgenic mice is similar to human eye disorders such as anterior segment dysgenesis and Peters' anomaly (19). These observations support the role of *TGFBI* in congenital glaucoma as observed in the two sisters with GAPO. A string analysis also showed that both *TGFBI* and *LTBP2* (associated with congenital glaucoma) co-express, along with a possible interaction with *MYOC* and *CYP1B1*. There is also a report of glaucoma observed in a patient with *TGFBI* , R124H

mutation, though the phenotypic details of this patient are not known (20). We also found 2 patients of ours with early onset open angle glaucoma with *TGFBI* mutations in a separate cohort. A high degree of phenotypic variability and incomplete penetrance is known for *TGFBI* mutations and the fundamental reason as to why different mutations cause morphologically distinct phenotypes remains elusive. Our study is the first to report an association of *TGFBI* with congenital glaucoma. However, gene expression and functional studies using cell-based assays and transgenic animal models of the mutant are further needed to establish a cause and effect relationship. Moreover, an interaction between *ANTRX1* and *TGFBI* in the causation of glaucoma, also needs to be explored.

Based on the findings of this preliminary report, *TGFBI* could be well considered a candidate gene for glaucoma, however more studies in a larger patient population as well as functional studies are required to further elucidate its role in glaucoma pathogenesis.

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Data Availability Statement: Data supporting the findings of the study are available from the corresponding author (VG) on request.

Conflicts of Interest: The authors declare no conflict of interest.

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