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A Case of 22q11.2 Deletion Syndrome with Peters Anomaly, Congenital Glaucoma, and Heterozygous Mutation in *CYP1B1*

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We read with interest the recent publication by Tarlan et al (1) describing a patient with 22q11.2 deletion syndrome and ocular features of right microphthalmia and left anterior segment dysgenesis. While anterior segment dysgenesis disorders are occasionally reported with 22q11.2 deletions (2–5), this remains a rare association. We report here an 8-year-old patient with 22q11.2 deletion syndrome and bilateral Peters anomaly with congenital glaucoma; in addition, our patient was found to have a single heterozygous mutation in *CYP1B1*, c.83C>T (p.Ser28Trp).

This 8-year-old mixed Caucasian and Hispanic female was diagnosed with bilateral Peters' anomaly and glaucoma shortly after birth, and had bilateral penetrating keratoplasty performed. Oligonucleotide microarray demonstrated a 2.7 Mb deletion at 22q11.21 (chr22:17,085,801-19,835,558 (hg18)); her extraocular anomalies were consistent with this diagnosis. She had a ventricular septal defect, small kidneys, prominent ventricles on MRI, narrowed C-T and C-3 spaces on skeletal x-ray, possible immune deficiency, developmental delay with low tone, and had a gastric tube for feeding. She has short stature (117 cm, <5th centile) with microcephaly (48.6 cm, <3rd centile). Other dysmorphic features included brachycephaly, short philtrum, cupid's bow upper lip, and mild mid-face hypoplasia as well as 2–3 syndactyly of the right foot. Parental samples are not available for testing and family history is unremarkable.

Mutations in *CYP1B1* have been associated with primary congenital glaucoma (PCG) (6), Peters anomaly/anterior segment dysgenesis (ASD) with glaucoma (7), and adult-onset primary open-angle glaucoma (POAG) (8). Individuals with PCG or ASD typically have homozygous or compound heterozygous mutations in *CYP1B1* whereas non-familial cases of POAG are more likely to carry a single heterozygous mutation (9).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Screening of *CYP1B1* in this patient identified a heterozygous c.83C>G, p.(Ser28Trp) variant which was not present in ~13000 chromosomes available in the Exome Variant Server (http://evs.gs.washington.edu/EVS/). This variant was previously reported as a heterozygous mutation in a single patient with adult onset primary open angle glaucoma (POAG) (10) but has not been reported in association with pediatric phenotypes. The p.(Ser28Trp) variant showed normal catalytic activity but decreased protein stability, suggesting it may be a hypomorphic allele (11). In addition to the p.(Ser28Trp) variant in exon 2, the patient was heterozygous for a known common polymorphism in exon 3, c.1358A>G, p.(Asn453Ser). Screening of other genes that have been previously reported in association with Peters anomaly, such as *PITX2*, *PITX3*, *FOXE3*, *BMP4*, and *B3GALTL*, did not identify any other potentially damaging variants.

22q11.2 deletion syndrome is a widely variable disorder; typical features include conotruncal heart defects, immune deficiency, skeletal and renal anomalies, hypoparathyroidism, and developmental delay. Posterior embryotoxon is present in almost half of affected individuals (compared to ~7% frequency in the general population (12)), suggesting that a gene within this locus is involved in the development of the anterior segment of the eye, but other anterior segment abnormalities are only occasionally seen (4,13). Several cases of unilateral Peters anomaly in patients with chromosome 22q11.2 deletion syndrome have been published (2–5) but neither bilateral Peters anomaly nor glaucoma have been reported. Screening of ocular genes has not been undertaken in the previously reported cases. The heterozygous *CYP1B1* mutation identified in the patient reported here is likely to contribute to the ocular phenotype in this patient, in combination with the 22q11.2 deletion. Interestingly, *TBX1*, one of the genes in the 22q11.2 region and the major gene implicated in the 22q11.2 phenotype, has been linked to the retinoid acid, PITX2, and BMP4 pathways (14–19). A similar genetic interaction is suggested by a recent study of five patients with Sturge-Weber syndrome and congenital glaucoma which identified mutations in *CYP1B1* in two (20). Examination of *CYP1B1* and other ocular genes in patients affected with 22q11.2 deletion syndrome and anterior segment dysgenesis is likely to provide additional information about this possible association.

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