# Case report with biallelic variants in *GCNT2* implicates exon 1B in congenital cataracts

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Poster #295

## BACKGROUND

- Congenital cataracts (CC) is associated with more than 30 different genes. Diagnosis of CC is complicated by high genetic heterogeneity[1,2,3].
- *GCNT2* is a rare cause of autosomal recessive CC. Fewer than 10 cases have been reported[1].
- *GCNT2* has 3 major transcripts, each with a different first exon[4,5]. Exons 1A and 1B are both hypothesized to be important for the ocular phenotype (Figure 1A, Table 1).
- Previous reports have not confirmed which first exon is critical for CC.

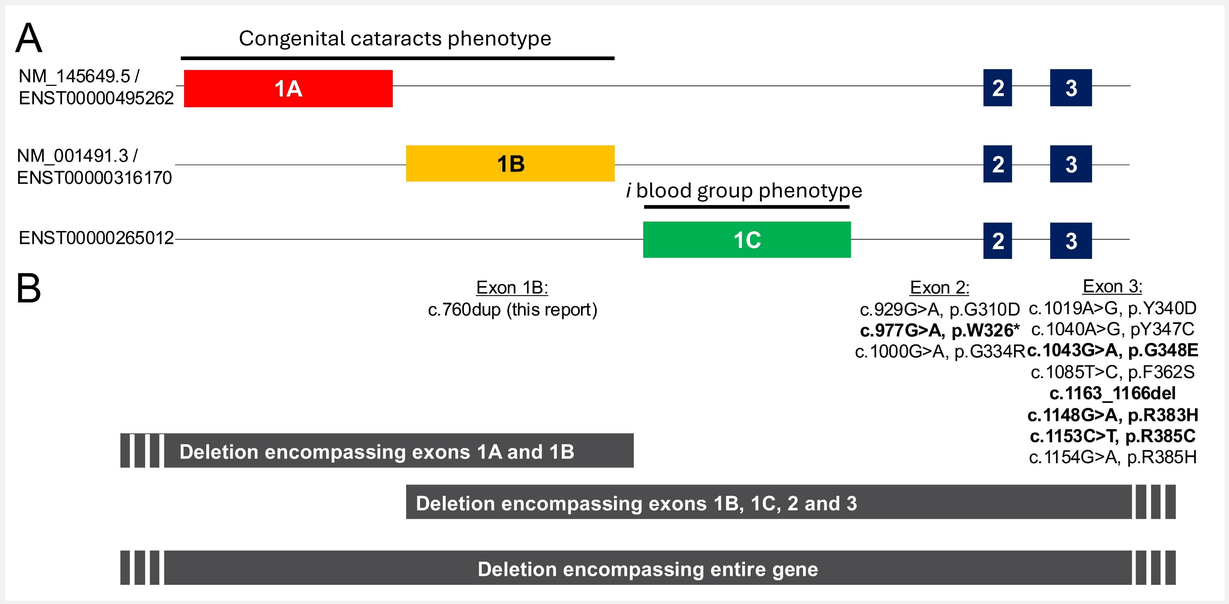


**Figure 1 -** *GCNT2* transcript structure and variants reported in association with CC. A. Isoforms A, B, and C depicted; isoform A is the MANE Select transcript. B. Variants reported in patients with CC. Recurrent small variants are in **bold**.

| Alternative exon 1 | Refseq / Ensembl identifiers | Expression[5] | Unique variants and associated phenotype |
|---|---|---|---|
| 1A | NM_145649.5 / ENST00000495262 | blood | Deletion of 1A and 1B --> CC |
| 1B | NM_001491.3 / ENST00000316170 | blood; lens epithelial cells | Deletion of 1B and 1C --> CC |
| 1C | ENST00000265012 | blood; reticulocytes | Variant in exon 1C--> *i* blood group phenotype[6] |

**Table 1.** Description of *GCNT2* transcripts.

**REFERENCES**
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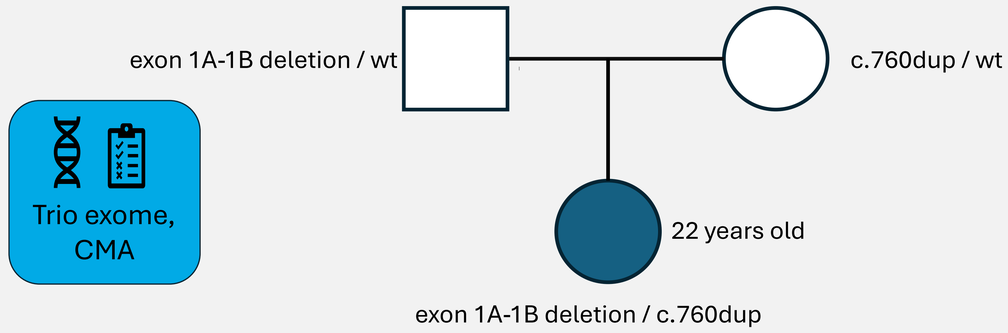
4. Irum, B., et al. (2016). *PloS One*, *11*(12), e0167562.
5. Yu, L.-C., et al. (2003). *Blood*, *101*(6), 2081–2088.
6. Lin, M., Hou, M.-J., & Yu, L.-C. (2006). *Transfusion*, *46*(11), 1982–1987.

## CASE DESCRIPTION




### Ocular features

- Bilateral congenital cataracts, corrected by surgery:
  - Cataract extraction
  - Strabismus surgery
  - Intraocular lens implantation
- Residual features:
  - Bilateral myopia
  - Astigmatism
  - Nystagmus
  - Hypoexotropia

### Non-ocular features

- Herlyn-Werner-Wunderlich syndrome
  - left renal agenesis, didelphys uterus, and longitudinal vaginal septum
- Catamenial anaphylaxis
- Optical migraines
- Hirsutism and alopecia areata
- Hashimoto's thyroiditis
- Delayed dental eruption
- Joint hypermobility and pain
- Anxiety, ADHD

## RESULTS

**CC phenotype was explained by two variants in *GCNT2***

- Maternal NM_001491.3: c.760dup p.H254Pfs*2, in exon 1B
- Paternal exon 1A and 1B deletion
  - Chromosomal microarray detected a ~75 kilobase CNV deletion (hg19 chr6:10,500,208-10,575,042del)

**Non-ocular phenotypes still unexplained**

- No variants in genes hypothesized to be associated with Herlyn-Werner-Wunderlich syndrome were identified, namely *CHD1L*, *TRIM32*, *TGFBR3*, *WNT4*, *RET*, *FRAS1*, *FAT1*, *FOXF1*, and *PCSK5*.
- Rare SNVs in other genes did not meet our reporting criteria

## TAKE HOME POINTS

- **This is the first report of a CC variant limited to exon 1B of *GCNT2*.**
- **Isoform B (NM_001491.3) is a clinically relevant transcript for CC.**
- **We can now apply full PVS1 weight for truncations in exon 1B of *GCNT2*.**
- **Caveat: Given that no cause for the non-ocular features was found, we cannot completely rule out a syndromic form of CC.**