Association of hydrocephalus and renal dysplasia with a homozygous \textit{DLG5} frameshift variant in an alternatively spliced exon

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Background
- \textit{DLG5} is a large gene (32 exons) encoding the large DLG protein (1,919 residues).
- \textit{DLG5} has multiple cellular functions.
- Knockout of the murine homologue Dlg5 causes variably severe hydrocephalus and renal cysts.
- Certain \textit{DLG5} haplotypes have been suggested to predispose to inflammatory bowel disease.
- Monogenic \textit{DLG5}-related phenotypes have not been described.

RESULTS I:
Unusual combination of clinical symptoms

![T1-weighted MRI and ultrasound](image1.png)

Figure 1: Imaging findings. (A) Sagittal brain MRI reveal severe hydrocephalus. (B) Ultrasound of the liver. Note increased echogenicity and fine parenchymal coarsening (arrow). Additional symptoms, not depicted here, include atrial septal defect type II, and cleft lip and palate.

RESULTS II:
Consanguineous background and positive family history

![Pedigree](image2.png)

Figure 2: Pedigree. The parents of the index patient are first degree cousins. A male infant, who had been born with similar external malformations, died shortly after birth.

*available for genetic analysis

RESULTS II:
Homozygous truncating \textit{DLG5} variant in our patient, but paucity of healthy heterozygous carriers

![Genetic observations](image3.png)

Figure 3: Genetic observations. (A) Sanger sequencing traces. The initial whole exome sequencing-based finding of the homozygous \textit{DLG5} frameshift c.3081\_3106del26 (p.Arg1027fs) in the index patients was confirmed, and both parents were found to be heterozygous carriers. (B) Data from the Exome Aggregation Consortium suggest that heterozygous loss-of-function variants in \textit{DLG5} are pathogenic (based on the probability of loss-of-function intolerance [pLI] value, highlighted in red).

Model for differing consequences of truncating \textit{DLG5} variants

![Gene model](image4.png)

Figure 4: Alternative splicing of \textit{DLG5} and isoform-specific susceptibility to nonsense-mediated mRNA decay (NMDD). (A) The two major \textit{DLG5} isoforms as expressed in brain and kidney (exons as black boxes, drawn to scale and numbered above) differ as regards presence/absence of the in-frame exon 15. Encoded protein domains are depicted as ovals (A, CARD; B, DUF622; C, F, PDZ, G, SH3; H, guanylate kinase). (B) A truncating variant in exon 15 (star), as reported here, spares the exon15-missing isoform from NMDD. (C) A truncating variant in any of the other exons is predicted to result in NMDD-mediated degradation of both isoforms.

Conclusions
- \textit{DLG5} is a novel disease gene in humans.
- Truncating \textit{DLG5} variants in exon 15
  - are benign in heterozygosity
  - cause hydrocephalus and renal dysplasia when present on both alleles.
- Truncating \textit{DLG5} variants in exons other than exon 15
  - may entail an unknown phenotype when heterozygous
  - may be embryonically lethal when present on both alleles.

Disclosure of conflict of interest:
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