Association of hydrocephalus and renal dysplasia with a homozygous *DLG5* frameshift variant in an alternatively spliced exon

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Background

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

RESULTS I:
Unusual combination of clinical symptoms

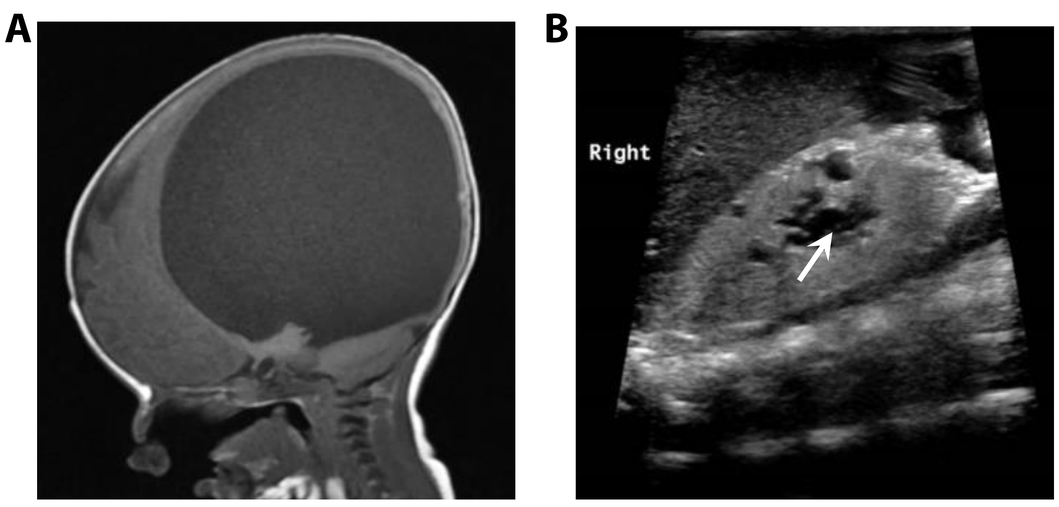


Figure 1: Imaging findings. **(A)** Sagittal brain MRI reveal severe hydrocephalus. **(B)** Ultrasound of the liver. Note increased echogenicity and fine parenchymal coarsening (arrow). Additional symptoms, not depicted here, include atrial septal defect type II, and cleft lip and palate.

RESULTS II:
Consanguineous background and positive family history

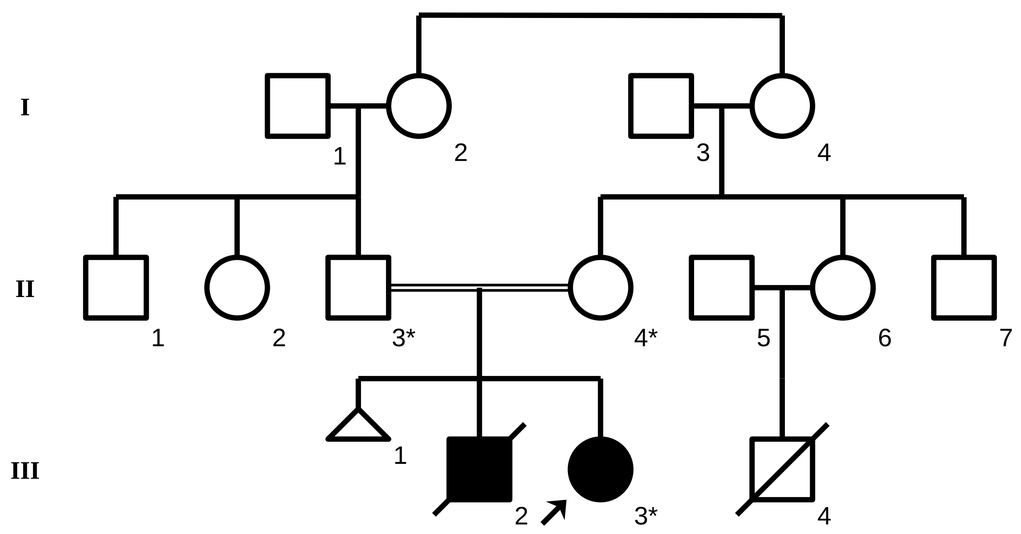
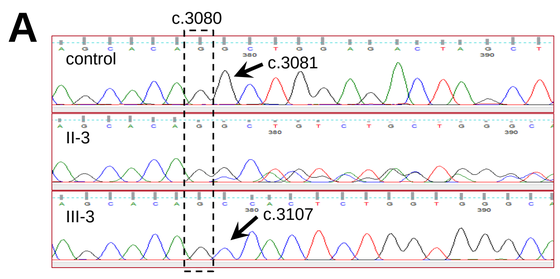


Figure 2: Pedigree. The parents of the index patient are first degree cousins. A male infant, who had been born with similar external malformations, died shortly after birth. *available for genetic analysis

RESULTS III:
Homozygous truncating *DLG5* variant in our patient, but paucity of healthy heterozygous carriers



B

Constraint from ExAC	Expected no. variants	Observed no. variants	Constraint Metric
Synonymous	373.9	360	z = 0.45
Missense	782.9	628	z = 2.71
LoF	54.8	4	pLI = 1.00

Figure 3: Genetic observations. **(A)** Sanger sequencing traces. The initial whole exome sequencing-based finding of the homozygous *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 *DLG5* are pathogenic (based on the probability of loss-of-function intolerance [pLI] value, highlighted in red).

Model for differing consequences of truncating *DLG5* variants

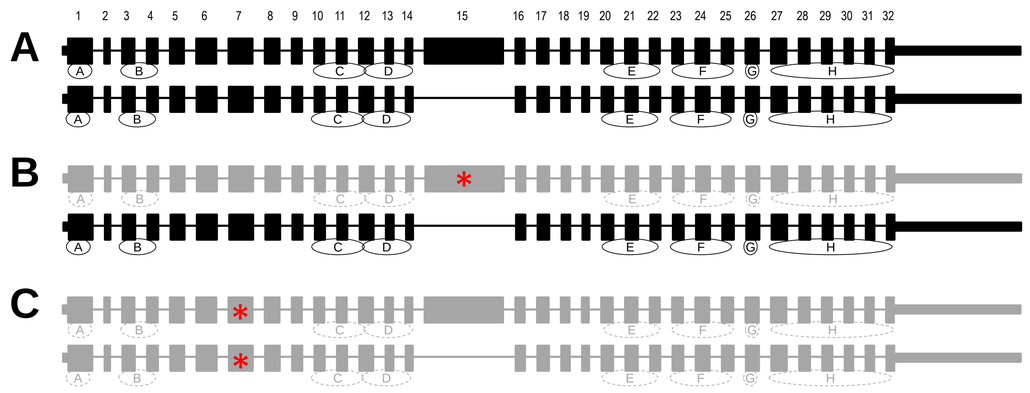


Figure 4: Alternative splicing of *DLG5* and isoform-specific susceptibility to nonsense-mediated mRNA decay (NMD). **(A)** The two major *DLG5* isoforms as expressed in brain and kidney (exons as black boxes, drawn to scale and numbered above) differ as regards presence/absence of the in-frame exon 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 NMD. **(C)** A truncating variant in any of the other exons is predicted to result in NMD-mediated degradation of both isoforms.

Conclusions

- *DLG5* is a novel disease gene in humans.
- Truncating *DLG5* variants in exon 15
- - are benign in heterozygosity
- - cause hydrocephalus and renal dysplasia when present on both alleles.
- Truncating *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:
This study was sustained in part by CENTOGENE AG, Rostock, Germany. FV, ZY, KK, KKK, MW, AMB, AR and PB are or have been employees of CENTOGENE AG.