Confirmation of ACER3-related recessive neurodegeneration, and preliminary evidence for feasibility of biochemistry-based ACER3 variant classification

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Background

- Ceramidases cleave ceramides into fatty acids and sphingosine.
- They are thereby important players in lipid metabolism.
- Knockout of the murine alkaline ceramidase 3 (Ac3r) entails a late onset gait phenotype, Purkinje cell degeneration and dysregulation of several ceramides.
- A homozygous missense variant in the human homologue ACER3 has been associated with leukodystrophy and abnormal ceramide/sphingolipid profiles in two patients from a single family.

CLINICAL PICTURE I:
Severe spasticity in two unrelated pediatric patients

Figure 1: Photographs taken at approximately two years of age.

CLINICAL PICTURE II:
Additional clinical description

Table 1: Following a neonatal period of normal development, there was a highly similar course of loss of acquired milestones and generalized deterioration.

RESULTS I:
Homologous inactivating ACER3 variants in both patients

Figure 2: Whole exome sequencing-based findings and predicted consequences at protein level. c.537C>T (p.L18P, patient 1) maps to the luminal N-terminus in close proximity to a previously described variants which has been shown to catalytically inactivate the protein. c.399delC (p.T133Tfs, patient 2) maps to a transmembrane domain (TMD), is predicted to trigger nonsense-mediated mRNA decay and, thus, defines a bona fide loss-of-function (LoF) allele.

RESULTS II:
Apparent impact of ACER3 genotype on the plasma metabolome

Figure 3: Metabolomic profiling of plasma from individuals with or without variants in ACER3. (A) Representative data from targeted analysis of 50 selected metabolites (ceramides ["Cer"], dihydroceramides ["DHCer"], glycosylceramides, sphingomyelins) in patient 2 and her parents, and in 10 controls. Note that the heterozygous (!) parents are largely in between index and controls (box plots). (B) Unsupervised clustering of data derived from untargeted metabolomics profiling. Enrolled individuals were selected based on ACER3 genotypes. Note that presence of a heterozygous, rare, potentially pathogenic variant impacts on the position in the dendrogram, while the genotype for a frequent missense SNP does not.

Conclusions

- ACER3 is now a confirmed gene for severe, recessive neurodegeneration.
- Pathogenic variants may be missense or truncating, and likely act via LoF.
- Biochemical profiling may enable variant classification for ACER3 in heterozygous carriers.
- A relevance of this concept for other metabolic disorders is being tested.

Disclosure of conflict of interest:
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