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IDENTIFICATION OF INCOMPLETELY PENETRANT VARIANTS BY A POPULATION GENETIC APPROACH

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Text of the abstract

Introduction

Autosomal recessive (AR) disorders are typically completely penetrant. We recently identified by population-genetic approach the first variant (NPHS2, p.R229Q), that is pathogenic only with specific trans-associated mutations.

Aims

We aimed to identify other incompletely penetrant variants in AR disorders.

Methods

We collected clinical and genotype data from 12 119 patients with biallelic HGMD mutations in 17 genes responsible for frequent AR disorders (ASL, ATP7B, CAPN3, CFTR, CTNS, DHCR7, GAA, GALNS, GALT, IDUA, MUT, NPHS1, NPHS2, PAH, PKHD1, PMM2, SLC26A4) in the medical literature. Variants that were less frequent in the Caucasian patient population than in the general European non-Finnish population of gnomAD were considered non-pathogenic and excluded (n=27). The penetrance of the pathogenic variants (n=2046) was assessed based on their allele count in the patient population (AC_{patient}) and in the general European

population of gnomAD (ACcontol) as compared to the loss-of-function mutations.

Results

Patients with biallelic DHCR7 and PMM2 LOF mutations were underrepresented in the patient population indicating in utero lethality. Among the 15 remaining disorders, we found significant diminishment of the missense alleles in seven (ASL, CAPN3, CFTR, NPHS2, PAH, PKHD1, TYR-related disorders) indicating incomplete penetrance.

Out of the 81 variants that were frequent enough to assess their penetrance, we found 22 (27%) ASL, CAPN3, CFTR, GAA, NPHS2, PAH and PKHD1 variants to be incompletely penetrant, including the three known incompletely penetrant variants (NPHS2 R229Q, CFTR R117H and L997F). No other but the R229Q variant was subject of interallelic interactions. Based on the associated phenotype, most of the incompletely penetrant variants are hypomorphic (16/23, 70%) vs. 18/58, 31% of completely penetrant variants, $p=0.0002$).

Conclusion

Frequent incompletely penetrant variants can be identified by our computerized population-genetic approach and are more common than expected. Proper genetic counseling requires their knowledge.

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Data of the presenter

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