



Session P18 - Genetic epidemiology/Population genetics/Statistical methodology and ev...

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P18.10B / B - Identification of incompletely penetrant variants by a population genetic approach

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Poster Area

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Abstract

Autosomal recessive (AR) disorders are typically completely penetrant. We recently identified the first variant (*NPHS2*, p.R229Q), that is pathogenic only with specific trans-associated mutations. We aimed to identify other incompletely penetrant variants (IPV) in AR disorders. We collected clinical and genotype data from 9,283 Caucasian patients with biallelic HGMD mutations in 19 genes responsible for frequent AR disorders (*ASL*, *ATP7B*, *CAPN3*, *CFTR*, *CTNS*, *DHCR7*, *GAA*, *GALNS*, *GALT*, *IDUA*, *MUT*, *NPHS1*, *NPHS2*, *PAH*, *PCCB*, *PKHD1*, *PMM2*, *SLC26A4*, *TYR*) in the medical literature. Variants that were less frequent in the patient population than in the general European non-Finnish population of gnomAD were considered non-pathogenic and were excluded (n=28). The penetrance of each pathogenic variant (n=2141) was calculated as its enrichment in the patient population as compared to that of the loss-of-function (LOF) mutations. *DHCR7* and *PMM2* LOF mutations were underrepresented in the patient population suggesting in utero lethality. Out of the 82 variants that were frequent enough to assess their penetrance, we found 23 (28%) *ASL*, *CAPN3*, *CFTR*, *GAA*, *NPHS2*, *PAH* and *PKHD1* variants to be incompletely penetrant, including the known IPVs (*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 IPVs are hypomorphic (16/23, 70%) vs. 19/59, 32% of completely penetrant variants, p=0.0002). Frequent IPVs can be identified by this computerized population-genetic approach and are more common than expected. Proper genetic counseling requires their knowledge. This work was supported by MTA-SE Lendület Research Grant (LP2015-11/2015).