Leveraging polygenic risk scores to target genetic modifiers in families with clinically heterogeneous epilepsy

Karen L Oliver[1,2], Ingrid E Scheffer[2], Samuel F Berkovic[2], Melanie Bahlo[1]

1. Walter and Eliza Hall Institute of Medical Research, Parkville, Australia, 3052
2. Epilepsy Research Centre, University of Melbourne, Heidelberg, Australia, 3084

Background

The developmental and epileptic encephalopathies (DEEs) are:[1]

- a heterogeneous group of rare disorders
- characterised by early-onset seizures, developmental delay and regression
- largely conceptualised as sporadic, *de novo* dominant disorders
- small number of DEE cases will have a family history of mild epilepsy.[2]

Hypothesis

Epilepsy risk, due to common genetic variation, is enriched in familial versus non-familial epilepsy cases and modifies the effect of rare monogenic variants segregating in phenotypically heterogenous families.

Methods

Calculated polygenic risk scores (PRS) in 90 unrelated patients with DEE using 11 genome-wide significant SNPs.[3]

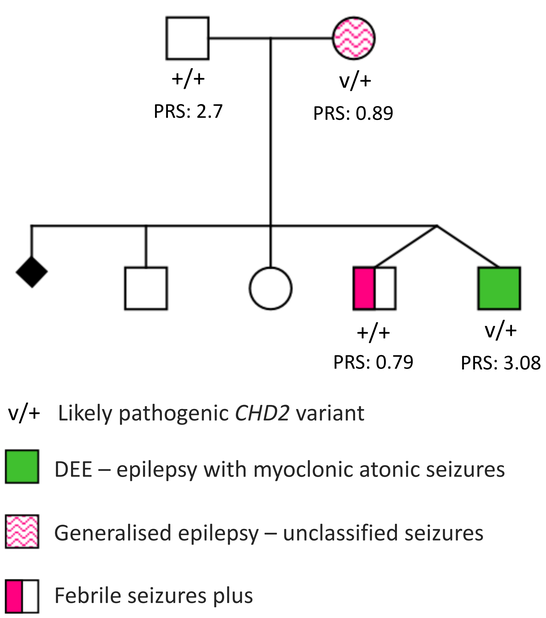
DEE cohort divided into those with an affected first degree relative (n=50; “familial”) versus those without (n=40; “non-familial”).

Scores compared for the two groups using linear regression adjusted for sex and the first three ancestry principle components.

Results

We found significant PRS enrichment for familial versus non-familial DEE cases (p-value = 0.02).

Figure. Polygenic risk scores in family with heterogeneous phenotypes



One familial DEE case, was known to have a maternally-inherited, pathogenic variant in *CHD2*.

The proband’s mother also had epilepsy, but her phenotype was milder (Figure).

Mother’s PRS much lower than her more severely affected child’s (standardised PRS; 0.89 versus 3.08 respectively).

Significance

Preliminary data consistent with our hypotheses being supported.

Future potential to help clarify the interplay between rare and common variants and provide a pathway for targeting important phenotypic modifiers.

References

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