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Commentary

The impact of low-risk genetic variants in self-limited epilepsy with centrotemporal spikes aka Rolandic epilepsy

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Epilepsy is a common neurological disorder with a lifetime prevalence of 3%–4%. The disorder is defined by recurrent, unprovoked seizures resulting from abnormal, synchronized neuronal firing in the brain and encompasses a heterogeneous group of disease entities with diverse etiologies and outcomes. Genetic factors are known to play a significant role in epilepsy, either as monogenic causes in rare Mendelian epilepsies, or as multiple genetic risk factors in common epilepsies such as genetic generalized and focal epilepsies. Self-limited epilepsy with centrotemporal spikes, also known as Rolandic epilepsy, is one of the most common epilepsy syndromes of childhood, comprising approximately 15% of children with epilepsy under the age of fifteen years. The seizures in Rolandic epilepsy occur predominantly during sleep and often manifest as focal seizures with altered sensory-motor function of the face, and unilateral facial or arm clonic movements as well as hypersalivation. Previous studies have reported an increased rate of febrile seizures and idiopathic focal epilepsy syndromes including encephalopathy related to status epilepticus during slow-wave sleep (ESES) or Landau-Kleffner syndrome (LKS) in relatives of children with Rolandic epilepsy. However, despite these findings Rolandic epilepsy is assumed to be of multifactorial inheritance. Several rare variants have been linked to Rolandic epilepsy, including variants in *RBFOX1, RBFOX3, DEPDC5, GABRG2, ELP4* [1–3] and duplications at chromosome 16p11.2 [4,5,9], although these variants might be associated with more severe or atypical forms [9]. Furthermore, pathogenic variants in *GRIN2A*, encoding a subunit of the NMDA receptor, have been identified in up to 15% of rare pedigrees with monogenic inheritance of Rolandic epilepsy [5].

In a recent study published in *EBioMedicine*, Shi and colleagues, present the first genome-wide association study (GWAS) on Rolandic epilepsy [6]. The GWAS was performed on 1800 Chinese Han patients with Rolandic epilepsy, and 7090 healthy controls, and although, the authors were unable to identify variants with genome-wide significance, the study suggest that 10% of the heritability may derive from an additive effect of SNPs, which is comparable to larger studies on focal epilepsy [7]. The study found no support for association of previously reported genes or risk loci, however the authors proposed twelve loci with association between $5 \times 10-8$ and $10-5$ as new possible risk loci. It is, however, clear that larger studies and meta-analysis are needed before it is possible to conclude that risk factors for Rolandic epilepsy are situated in these twelve loci. Furthermore, well-powered statistical analysis, will most likely increase the utility of the derived effect-sizes from the GWAS study, e.g., polygenetic risk scores to predict disease risk [8], assessing biological mechanisms [7] or treatment outcome [9]. The study by Shi and colleagues leaves us with several unanswered questions that future studies need to address. From the tentative results of 12 loci harbouring nominal significant variants, a gene-environmental risk interaction was suggested to be part of the causal inference of Rolandic epilepsy. The genetic association derived from a strong transcriptomic effect of the *CHRNA5* gene, encoding the alpha 5 subunit of the cholinergic nicotinic receptor. *CHRNA5* has previously been associated with cigarette smoking, nicotine addiction and smoking associated lung diseases [9], thus, a logical deduction would be that smoking (maternal or paternal perinatal, or postnatal passive, smoking) can increase the risk for Rolandic epilepsy. Mendelian randomization is an approach to assess whether a risk factor has a causal effect on an outcome based on observational data [10]. Statistical models based on Mendelian-randomization, allowing low-risk variants to be used as instrumental variables, have been developed to inform us on causalities.

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The concept is developed to achieve the statistical strength of randomized trials in an observational study, and is most often used in e.g., clinical drug trials where confounding factors can be randomized *a priori* to a trial. In Mendelian randomization the instrumental variable (randomizing factor) is assumed to be a casual factor for exposure only. This allows one to assess whether an association between exposure and outcome is bi- or uni-directional. The usability of such an approach using genetic variants with marginal risk is very much debated [10], however it holds the potential to formulate and test new hypotheses based on causality. Shi and colleagues used Mendelian randomization to test and provide evidence that maternal smoking around birth may be associated with increased risk of Rolandic epilepsy (odds ratio = 3•90, P = 0•0099). However, interpretation of the results should be done with caution, as the suggested associated gene *CHRNA5* is not statistically significant and smoking during pregnancy may well be confounded by factors not accounted for. Thus, replication studies are warranted to confirm this association. Although the results obtained in the study by Shi and colleagues are not of immediate clinical usefulness, they provide an important step towards understanding the genetic architecture of Rolandic epilepsy, which potentially could lead to clinically relevant prognostic markers in the future.

Declaration of Competing Interest

The authors report no competing interests.

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Authors' contribution

Both authors drafted and approved the final manuscript.

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