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GENETICS

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Genetic risk factors in primary paediatric versus adult headache: complexities and problematics

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Abstract Numerous candidate genes for migraine have been proposed on the basis of their possible functional role in its pathogenesis. Genetic polymorphisms have been evaluated in association studies, some of which have been suggested to be susceptibility markers for adult migraine. To date, however, none of the identified polymorphisms in adult migraine susceptibility have been investigated in children, raising the possibility that they may not be necessarily involved in paediatric migraine susceptibility. This paper reviews studies of the genetic basis of migraine and summarises our experience in genetic association studies in primary paediatric headache susceptibility.

Key words Paediatric migraine • Susceptibility • Polymorphism • Endothelin type A receptor

Introduction

Recurring primary headaches, such as migraine or tension-type, are common during childhood (2.5%) and adolescence (15%) [1]. However, while ever increasing evidence shows that migraine is a complex neurovascular disorder with genetic factors playing a primary role in its aetiology, none of the genetic factors which have to date been shown to be linked to adult migraine susceptibility have been investigated in children, for whom primary headaches represent frequent causes for referral for neurologic assessment. In addition, while epidemiological, twin and family studies have revealed that approximately one-half of its variation is attributable to additive genes, with a negligible contribution of nonadditive genetic effects [2], the identification and validation of the underlying genetic risk factors poses enormous challenges even in adult migraine. The severity of migraine symptoms, such as the recurrence and duration of attacks and the age of onset, are variable among patients, thus rendering difficult both the definition of the appropriate phenotype as

well as the selection of the best population in which to investigate the genetic load. Furthermore, some individuals may, independently of the presence or absence of environmental influences or type of prophylactic therapy undertaken, remain attack-free despite their genetic load, while others will continue to suffer.

Given all this, the aim of the present paper is to provide a short overview of the current status of genetic susceptibility studies in migraine, herein including the problematics involved in their application in paediatric *vs*. adult settings.

Genetic factors contribute to migraine

Genetic epidemiological studies of migraine show both positive family history and increased disease risk in relatives of migraine probands [3], the likelihood of which increases when the age at onset in the proband is below 20 years [4]. However, while familiarity supports the importance of genetic factors in migraine susceptibility, it does not prove heritability as it does not exclude the influences of shared environmental factors and common lifestyles. The significantly higher pairwise concordance rate among monozygotic compared to dizygotic twin pairs better supports the importance of genetic factors with hereditability estimates of about 50% for migraine without aura and with aura [5]. In the case of tension-type headache, the genetic factor may have a major role in the aetiopathogenesis of chronic tension-type headache, whereas environmental influence is stronger in episodic tension-type headache [6].

Molecular studies of the genetic factors in adult migraine

Genome-wide scanning approaches have identified migraine susceptibility loci on chromosomes 1, 4, 6, 11, 14, 19 and X [7]. By investigating familial hemiplegic migraine (FHM), a rare Mendelian form of migraine with aura transmitted by autosomal dominance [8], the identification of migraine genes such as the calcium channel gene CACNA1A [9] and the $\alpha 2$ subunit of the Na+/K+ ATPase ATP1A2 gene [10, 11] was facilitated. In addition, given the major statistical power to detect several genes of small effect of the association studies by a candidate-gene approach, the relationship between migraine and candidate genes involved in pathogenic theories has been repeatedly investigated in adults [12]: unfortunately, the results have not often been replicated in subsequent, independent studies.

Do the genes identified in the adult migraine susceptibility explain susceptibility in children? Our experience

Given the increased familial risk in relatives of migraine probands, we have, among the genes shown to be associated to adult migraine liability, recently focused on whether the -231 G>A polymorphism in the endothelin 1 type A receptor (EDNRA) shown to strongly modulate the risk of adult migraine [13] contributes to paediatric migraine susceptibility. Results to date obtained, however, show that the -231 G>A polymorphism in the EDNRA gene is neither associated with primary juvenile headache nor significantly correlated with main clinical features characteristic of the headache pathology, thus suggesting the possibility of an age-related interaction of the EDNRA polymorphic variant on migraine liability and disease expression [14].

Worth noting is that the only other published study tackling the genetic aspects of juvenile migraine has, based on evidence suggestive of an association between migraine and prothrombotic genetic risk factors, considered the factor V Leiden mutation [15] due to its high prevalence in patients with stroke and history of migraine [16]. As in our experience, no difference in the prevalence of this mutation was found in children and adolescents with migraine with aura *vs*. controls.

Conclusive considerations

As migraine is characterised by wide phenotypic and, most likely, genotypic heterogeneity, the identification and validation of the genetic risk factors involved critically depends on the accuracy of the determination of the disease phenotype. However, although the recently revised International Headache Society criteria (ICHD-II) have incorporated many developmentally related sensitive changes allowing for broader applicability in juvenile patients [17], the lack of specific clinical and biological markers reduce the possibility to differentially classify paediatric patients and, hence, the chance to identify the genetic risk factors involved. This complexity, in addition, further increases when considering the likelihood, of effects of "modifying" genes, as well as of co-morbidity, including phenotypical heterochronia, together with the possibility that the expression of the disease may vary as a function of age. Thus, whilst the heterogeneous complex traits of migraine may, in part, account for the current discrepancies in genetic susceptibility studies conducted in adult and paediatric migraineurs, other factors including comorbidity of migraine with other age-related disorders sharing common similar pathways may be involved [18, 19], while environmental and individually related factors may interact to raise the disease expression.

In sum, although the identification and validation of the genetic risk factors in primary headache susceptibility introduce the possibility of identifying groups of patients who possess particular diagnostic or prognostic characteristics, it is particularly important to identify if and how these advances apply in different clinical settings, herein including the paediatric and adolescent settings, through the design of appropriate clinical trials. Only in this way it will be possible, at least on the basis of our attempts to identify genetic susceptibility markers in primary paediatric headache susceptibility based on those shown to be associated to adult migraine liability, to ensure that the resulting data are sufficiently robust in order to inform clinical decision making and to revise the available treatment strategies in primary headache disorders arising in either the paediatric or adult stage.

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