Different studies assessing genetic and environmental aspects in migraine

Diferentes estudos abordando aspectos genéticos e ambientais na enxaqueca

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ABSTRACT

Recent advances in genetics have shown the importance of the genetic component on migraine. Studies on twins also point out to the importance of genetic migraine. On the other hand, epidemiological data identified environmental factors that are important in the genesis of migraine. Studies on familial hemiplegic migraine with or without aura will certainly bring new information and help understanding the real contribution of genetic and environmental factors to the genesis of migraine.

Keywords: Migraine/genetics; Epidemiological studies

RESUMO

Recentes avanços em análise genética da migrânea têm levado à identificação da forte influência de componentes genéticos na migrânea, como é o caso da migrânea hemiplégica familiar. Estudos em gêmeos também apontam para a importância do componente genético na migrânea. Por outro lado, estudos epidemiológicos vêm contribuindo para a identificação da contribuição dos fatores ambientais na gênese da migrânea, além dos fatores genéticos. Estudos sobre a migrânea hemiplégica familiar, da migrânea com e sem aura certamente trarão maiores esclarecimentos para que se possa entender a real contribuição dos fatores genéticos ou epidemiológicos na gênese da migrânea.

Descritores: Enxaqueca/genética; Estudos epidemiológicos

INTRODUCTION

Migraine is a common disease affecting approximately 15% of the Western population. The peak age of onset is 10-12 years in men and 14-16 years in women. The disease is typically characterized by recurrent attacks of disabling headaches and associated autonomic and focal neurological symptoms if aura is present[1].

As of 1988, migraine has been defined according to the criteria established by the Headache Classification Committee of the International Headache Society (IHS)[2]. The diagnostic criteria were revised in 2004 and the current classification for the most common subtypes of migraine is presented in Chart 1. Migraine is characterized by unilateral throbbing pain of moderate to severe intensity, aggravated by physical activity and lasting from 4 to 72 hours. The attacks are associated with nausea, vomiting, photophobia and phonophobia. Migraine with aura (MA) shares the same symptoms, but headache is usually preceded by attacks of focal neurological deficits (aura), including visual symptoms, hemiparesis, hemiparesthesia, and aphasia lasting less than 60 minutes[2]. Differently from what was previously thought, aura was reported to be associated not only to migraine but also to several other headache disorders, including cluster headache, hemicrania continua, and paroxysmal hemicranias, which may present accompanying visual, sensory or motor symptoms. The second edition of the International Classification of Headache Disorders[2] also included the possibility of typical aura with non-migrainous headache.

FAMILIAL HEMIPLEGIC MIGRAINE

In 1910, Clarke[3] described the familial hemiplegic migraine (FHM), which is a less common type of migraine. FHM attacks are characterized by motor aura symptoms consisting of typically unilateral motor weakness. The presence of coma, fever, prolonged hemiplegia and/or seizures can be observed in some patients[4]. FHM is a rare autosomal dominant form of MA providing a Mendelian model for migraine research.

The first FHM gene, CACNA1A, on chromosome 19p13, was identified by Ophoff et al.[5] in 1996. This gene encodes the Ca_v 2.1 protein, which is the pore-forming subunit of P/Q-type calcium channels. The CACNA1A gene is mutated in half of the pure FHM families and in all FHM cases with cerebellar signs who were studied[1].

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Chart 1. Diagnostic criteria for migraine with and without aura

Migraine without aura

A. At least 5 attacks fuifilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (*eg*, walking or climbing stairs)
D. During headache at least 1 of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia
E. Not attributed to another disorder

Migraine with aura

A. At least 2 attacks fulfilling criterion B
B. Migraine aura fulfilling criteria a–b
a. Aura consisting of at least of the following, but no motor weakness:
1. fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision)
2. fully reversible sensory sympoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbess)
3. fully reversible dysphasic speech disturbance
b. At least two of the following:
1. homonymous visual symptons and/or unilateral sensory symptom
2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. each symptom last ≥5 and ≤60 minutes
C. Not attributed to another disorder

A second gene responsible for pure FHM - ATP1A2 - was reported by De Fusco *et al.*[6], in 2003, on chromosome 1q23. The gene encodes the a2 subunit of sodium and potassium ATPase. These authors identified two missense mutations in two Italian families and several additional missense mutations in the ATP1A2 gene were later identified.

Recently, the third causative gene for FHM was discovered on chromosome 2q24.3. The SCN1A encodes the pore-forming subunit of neural-voltage-gated ($Na_v1.1$) sodium channels[7]. Studying three German families with common ancestry, the researchers identified a missense Gln489Lys mutation in the SCN1A gene. The identification of three genes related to FHM was very important to show the strong influence of genetic components in migraine.

Several studies have been performed to understand the contribution of both genetic and environmental factors for common forms of migraine. Some of the methodologies used by researchers will be presented in this report.

TWIN STUDIES

In the past two decades, several population-based twin studies have also supported a strong genetic component in migraine. Some investigations were performed before the introduction of the IHS criteria and have been criticized. The major problem is that samples are very small due to the small number of individuals available. However, all these studies indicated that genetic factors are a major contributor to the pathogenesis of migraine with aura (MA) or without aura (MO). This conclusion was reached when authors verified a higher concordance rate for migraine in monozygotic than in dizygotic twins.

A recent study performed by Svensson *et al.* (2003)[8] analyzed twins aged 42-81 years that were raised apart. The heritability of migraine was estimated at 38% for men and 48% for women. They concluded that genetic factors provide family resistance in migraine but environmental components make family members different.

In 2003, the GenomEUtwin consortium[9] was founded combining twins' registers and cohort studies from seven European countries and Australia. The studies focus on some chronic diseases and migraine. The project provides nearly 800 thousand twin pairs for study, and 30 thousand twin pairs are available for migraine studies.

Mulder *et al.* (2003)[10] studied 29717 twin pairs selected by the GenomEUtwin project and found that genetic heritability was the same between sexes, ranging from 34 to 57% in different cohorts.

EPIDEMIOLOGICAL STUDIES

Population-based studies are very important to understand the contributions of both genetic and environmental factors to migraine. In 1995, Russel *et al.*[11] observed a different pattern of familial risk for MA and MO. Comparing to the general population, the authors verified that first-degree relatives of probands with MO had a 1.9-fold higher risk of developing MO but only a 1.4-fold higher risk for MA.

Analyzing first-degree relatives of probands with MA, the risk of developing MA was nearly 4-fold higher, but no increased risk of MO was observed. These results showed that MA was determined by genetic components, whereas MO was caused by combination of both genetic and environmental factors.

CASE-CONTROL ASSOCIATION STUDIES

Association studies may help identify disease susceptibility genes without using any familial information. This type of studies tests if a particular allele occurs at higher frequency in affected individuals than in control individuals. This is an alternative method to assess the genetic background of migraine by studying case-control association designs to detect disease susceptibility genes on modest effect[12].

Numerous studies reported positive associations of candidate gene variants and migraine. Polymorphisms in the dopamine 2 receptor (DRD2), dopamine 4 receptor (DRD4), dopamine beta-hydroxylase (DBH) and insulin receptor (INSR) were implicated in susceptibility to migraine[13-14]. The functional significance of these susceptibility gene variants and the role they play in migraine pathophysiology are yet to be concluded.

The serotonin receptor 2C showed no association in a group of 275 migraine patients. No significant association was observed for the serotonin receptor 2A and serotonin transporter gene in migraineurs. Some studies did not confirm association of glutathione S-transferase variants, low-density lipoprotein receptor genes and MO[1].

An association study conducted by Kowa *et al*. (2000)[15] reported a positive association between the MTHFR C677T variant and migraine in a Japanese case-control cohort. The research indicated an increased risk of MA and MO in individuals with the homozygous T/T genotype. These results were confirmed by a Turkish study[16] and a third study also supported the association between C667T variant and migraine susceptibility[17].

Association studies are difficult to perform since publication biases, power problems, population admixtures and linkage disequilibrium within a gene could compromise their relevance.

GENOME WIDE-SCREEN

A well-defined approach to localizing genes responsible for monogenic inherited diseases is conventional linkage analysis. Genetic linkage reflects the fact that two loci near each other on the same chromosome are not inherited independently in families. The probability of a recombinational event (crossover) between two loci increases with distance. The closer loci are on the same chromosome, the more alleles at these loci tend to be inherited together.

In many linkage studies the relation between a disease locus and a number of marker loci from the same chromosomal region are investigated. Instead of testing each marker locus separately with the disease locus (two-point analysis), it is possible to use cumulative information by carrying out a multipoint linkage analysis, in which the relationship of three or more loci are analyzed simultaneously. Because these types of analyses are very complex, computer programs, such as the LINKAGE program package and the VITESSE algorithm, were developed to assist with the analysis.

The search for a gene starts by testing several polymorphic marker loci located in regions containing potential candidate genes. When evidence for linkage is not found, the search continues by a genome wide-screen that includes analysis of about 500 randomly distributed genetic markers resulting in exclusion of the major part of the total genome. Once linkage is found (lod score ≥ 3 between autosomal loci), additional genetic mapping can be applied in order to narrow down the responsible region[12].

Chart 2. Chromosome regions related to MA and/or MO by using linkage analysis

Loci identified	Disease	Families studied	Lod-Score	Research Group
4q21	MO	103	4.08	Bjornsson A et al.,2003
4q24	MA	50	4.45	Wessman M et al.,2002
6p12.2-21.1	MA, MO	1	5.78	Carlsson A et al.,2002
11q24	MA	43	5.6	Cader ZM et at.,2003
14q21.2-22.3	MO	1	5.25	Soragna D et at.,2003

Several linkage studies in FHM, MA and MO have been performed in the past years and some genes were found to be responsible for FHM1 (CACNA1A), FHM2 (ATP1A2) and FHM3 (SCN1A), as previously mentioned. Some linkage analyses were conducted to identify chromosome regions related to MA and/or MO and the loci found by these studies are presented in Chart 2.

FHM is a rare form of migraine that can provide insight into the more common forms of migraines for this disease seems to belong to a continuous migraine spectrum. The study of FHM, MA and MO are very important to understand how genetic and/or environmental components can contribute to migraine.

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