J Headache Pain (2005) 6:234–236
DOI 10.1007/s10194-005-0194-x

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Genetics of cluster headache: an update

Published online: 20 July 2005

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Abstract Up to a few years ago, cluster headache (CH) was not thought to be an inherited disorder. However, several recent studies have suggested that genetic factors play a role in the disease. Genetic epidemiological surveys have shown that first-degree relatives of CH patients are more likely to have CH than the general population. CH has been reported in some concordant monozygotic twin pairs. At present, the type and the number of genes involved in the disease are still unclear. No mutation in the *CACNA1A* and *NOS* genes was found in CH patients. Recently, we have reported a significant association between the *HCRTR2* gene and the disease. The purpose of this review is to describe recent advances in the genetics of CH.

Key words Cluster headache • Genetics • Epidemiological surveys • CACNA1A • HCRTR2

Introduction

Cluster headache (CH) is a primary headache disorder characterised by attacks of severe unilateral, retro-orbital pain accompanied by restlessness and cranial autonomic symptoms, such as lacrimation or conjunctival injection. The signature feature of the disease is its periodicity and the patients present a striking unique diurnal and seasonal rhythmicity [1].

The aetiology of CH is still unknown. Up to a few years ago, CH was not thought to be an inherited disorder. However, several recent studies have suggested that genetic factors play an important role in the disease. In some families, the CH phenotype is inherited as an autosomal dominant trait [2, 3]. In comparison with the general population, both first- and second-degree relatives of CH patients have a significantly increased risk for the disease [4, 5]. Finally, some cases of monozygotic twin pairs concordant for CH have been reported in the literature [6]. At present, however, the type and the number of the genes involved in CH are still unclear. No mutation in *CACNA1A* and *NOS* genes has been found in CH patients. We have recently described a significant association between a *HCRTR2* gene polymorphism and the disease. The purpose of this review is to describe recent advances in the genetics of CH.

Familial studies

In 1974, Ekbom reported on three small families with multiple CH patients [7]. Since then, several families with CH in multiple generations have been described in the litera-

ture. A positive family history for the disease was found in 1.9%–20.0% of patients with CH, suggesting a role for genetic factors in the disease [8]. A recent study compared the clinical characteristics of patients with familial and non-familial CH [9]. The study did not show any significant differences in symptoms between the two CH groups, such as pain location, accompanying symptoms, duration and frequency of attacks, and active periods.

Anticipation (the tendency for some disorders to present at an earlier age in successive generations) has been described in some families with CH. At present, however, it is not clear if the anticipation observed in some families is a true phenomenon or a study bias. CH has been associated with primary hyperlipidaemia in one family and haemochromatosis in another family. This is likely to be the coincidental co-occurrence of two disorders.

Epidemiological surveys

Several genetic epidemiological surveys evaluated the disease risk of relatives of CH probands [4, 5]. First-degree relatives had a 5–18 times higher risk while second-degree relatives had a one to three times higher risk of CH than the general population. The different results can be partly explained by methodological differences. The increased familial risk of CH strongly suggests a genetic cause for the disease.

Twin studies

At present, CH has been reported in six concordant monozygotic twin pairs. This indicates the importance of genetic factors, although publication itself introduces selection bias. In a recent, large twin survey based on the Swedish Twin Registry and the Swedish Inpatient Registry, the two monozygotic and nine dizygotic twin pairs were all discordant for CH and had been discordant for 10–31 years [10]. The twin data support the importance of both genetic and environmental factors.

Segregation analysis

In families with multiple affected members, all types of disease transmission have been observed: from father to son, father to daughter, mother to son and mother to daughter.

A complex segregation analysis of CH suggested that an autosomal dominant gene has a role in some families with CH [11]. The penetrance is lower in women than in men. Multifactorial inheritance is the most likely explanation in the sporadic cases.

Molecular genetics of cluster headache

At present, no clear molecular genetic clues have been identified for CH. A study of a Japanese man with sporadic CH reported a mutation in mitochondrial transfer *RNAleu(UUR)* gene at nucleotide pair 3243 [12]. However, this mutation was not detected in Italian and German patients with CH [13, 14] and the involvement of mitochondrial genes in CH remains unproven. The paroxysmal character of CH suggests that ion-channel genes are candidate genes for the disease. Familial Hemiplegic Migraine, a rare subtype of migraine with aura, cosegregates with mutations in the *CACNA1A* gene, a gene that encodes for a P/Q type neuronal calcium channel [15]. A Swedish association found no linkage disequilibrium between polymorphisms of the *CACNA1A* gene and CH [16]. A Dutch haplotype study of a family with three affected members, followed by a subsequent mutation analysis of the gene, provided no data supporting a role for this gene in CH [17]. Nitric oxide has been implicated in the pathophysiology of CH. So, a Swedish association study investigated several polymorphisms of *NOS1*, *NOS2A* and *NOS3* genes and found no difference between CH patients and controls [18].

Observations of circadian biological changes and neuroendocrine disturbances have suggested a fundamental role for the hypothalamus in CH. Brain imaging studies with PET and voxel-based morphometry have identified the posterolateral hypothalamic grey matter as the key area for the basic defect in the disease [19]. Hypocretin-1 and -2 (also called orexin-A and -B) are newly discovered neuropeptides processed from a common precursor, preprohypocretin. Hypocretin-containing cells are located exclusively in the lateral hypothalamus, with widespread projections to the entire neuroaxis. We performed an association study between polymorphism of hypocretin/orexin pathway genes (HCRT, HCRTR1 and HCRTR2) and the disease in a large cohort of Italian CH patients. A highly significant association between the 1246 G>A polymorphism of the HCRTR2 gene and CH was found, suggesting that the HCTR2 gene or a linked locus significantly modulates the risk for CH [20].

Conclusion

Several epidemiological studies have clearly demonstrated that genetic factors play a role in CH. At present, however,

the type and the number of genes involved in the disease are still unclear. We have described the first significant association between CH and a polymorphism of the *HCRTR2* gene. Additional studies are needed to search for susceptibility genes for CH in this chromosomal region. Furthermore, considering the paroxysmal character and periodicity of the disease, ion-channel genes and clock genes may be analysed as candidate genes for cluster headache.

Acknowledgements The study was supported by grants from the Ministero dell'Università e della Ricerca Scientifica (MURST) and from the Regione Piemonte (Italy).

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