Chapter 86

# Genetics of Cluster Headaches

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Up until 10 years ago little evidence to support a genetic component to the etiology of cluster headache had been identified. More recently, a number of studies have indicated that genetic determinants are likely to be important in the etiology of cluster headache.

### *Cluster Headache and Migraine*

Cluster headache, migraine without aura, and migraine with aura are likely to be distinct headache disorders. Each is characterised by distinct clinical features (12,47). The prevalence of migraine is similar in cluster headache as is seen in the general population (31). Furthermore, brain activation occurs in different areas, namely the ipsilateral hypothalamic gray area in cluster headache and the contralateral side of the brainstem in migraine without aura (19,52).

### *Gender Ratio*

The ratio between men and women is 1.2:1 in familial cluster headache, but 4.4:1 in clinic populations (1,8,10,14, 15,18,28,29,31,49). The ratio in clinic populations has decreased in the last decades, possibly due to increased awareness that women also can suffer from cluster headache (8,18). A recent British study reported the ratio between men and women was 2.5:1 (1). The different gender ratio observed in familial cluster headache from that seen in clinic populations may suggest different etiologies.

## Genetic Studies

### *Twins*

The literature reports six concordant and two discordant monozygotic twin pairs and one concordant (unlike sex) and nine discordant (four same and five unlike sex) dizygotic twin pairs (3,7,25,33,37,38,45). The concordant twin pairs were all case reports, except for two twin pairs from clinic populations, while the discordant twin pairs were from a population-based twin study. Interpretation of the twin data should take into account the limited sample size and publication bias (21).

### *Positive Family History*

Probands from 12 clinic population-based studies from 1947 to 1985 reported that 47 first-degree relatives were affected in 1182 families (31). This suggests an increased family risk, even though the diagnosis may not have been confirmed in all families. More recently, an Italian and a Dutch survey with physician-confirmed diagnoses reported familial occurrence in 2.3% (5/222) and 4.1% (70/1720) of the families, respectively (20,51).

### *Genetic Epidemiologic Surveys*

Four genetic epidemiologic surveys provide more complete information about the relatives (10,14,15,28,29). Table 86-1 illustrates the risk to first- and second-degree relatives based upon a population prevalence of cluster headache of 1 per 500 inhabitants. The first-degree relatives had a five- to 18-fold increased risk of cluster headache compared to the general population. Second-degree relatives had a one- to threefold increased risk. Varying observations may, at least in part, be explained by methodologic differences. The French survey acquired a more comprehensive dataset, as all first-degree relatives were directly interviewed by a physician (10). A physician interviewed possibly affected relatives in the Danish survey (28,29). This causes the risk of cluster headache to be a minimum figure, as probands may fail to report about affected relatives. The American survey was based on probands reports only (14). This can cause either under- or overestimation of the risk of cluster headache depending on whether the probands misclassify their relatives more or less than they fail to report about the affected.

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**TABLE 86-1 Age and Gender Standardized Risk of Cluster Headache and Gender Standardized Risk Only***

| Country | Affected Relatives | No. of Affected Relatives | | Population Relative Risk Estimated (O/E) and 95% Confidence Intervals |
|---|---|---|---|---|
| | | Observed (O) | Expected (E) | |
| Denmark (29) | First-degree | 26 | 5.4 | 4.7 (3.1–6.9) |
| | Second-degree | 10 | 13.2 | 0.8 (0.4–1.4)* |
| USA (14) | First-degree | 41 | 2.7 | 15.2 (11.1–21.1)* |
| Italy (15) | First-degree | 39 | 3.0 | 13.1 (9.0–17.3) |
| | Second-degree | 18 | 6.7 | 2.7 (1.5–3.9)* |
| France (10) | First-degree | 22 | 1.3 | 17.6 (10.2–24.9)* |

The revised population relative risk calculations were made by Michael Bjørn Russell assuming that the prevalence of cluster headache is 200 per 100,000 inhabitants. (From *Lancet Neurology* 2004;3:279–283, with permission).
The risk was calculated according to the following equation (53):

$$\frac{\text{Prob (Relative is affected/Proband is affected)}}{\text{Prob (Random member of the population is affected)}}$$

The Danish probands reports were inaccurate, as the diagnosis of cluster headache was confirmed in only 57% while the remaining 43% had migraine (29). The Italian survey was based on probands reports, and possibly affected relatives were interviewed by a physician (15). Eleven of the 57 affected relatives had probable cluster headache. This is either an under- or overestimation of the risk of cluster headache, depending on whether the number of those with probable cluster headache is more or less than those affected not reported by the probands. The significantly increased familial risk strongly suggests that cluster headache has a genetic cause. Theoretically, a shared environment can produce relative risks of the magnitude observed for cluster headache only under extreme conditions (13).

### Clinical Heterogeneity

Clinical intra- and interfamilial variability of cluster headache were analyzed in 18 Danish families (30). Distinctive patterns of symptoms were found in three families. Two probands with chronic cluster headache each had a relative with episodic cluster headache, while a third proband had episodic cluster headache and his son had chronic cluster headache. The fact that cluster headache may change during the years and the different forms occur within the same family suggests a common etiology of episodic and chronic cluster headache (17,30,43). A Danish and a Swedish survey found that children have a significantly lower age at onset than parents ($p = 0.018$ and $p < 0.01$, respectively) (30,41). This may be anticipation, but the results can also be biased as only children with a relative early onset were included in the analysis. An American family with cluster headache in three generations is suggestive of anticipation, since the age at onset declined and symptoms got worse in each successive generation (43). A small number of people with otherwise typical cluster headache lack autonomic symptoms (9,22,26,30). A proband without autonomic symptoms had a second-degree relative with autonomic symptoms, suggesting a common etiology of cluster headache with and without autonomic symptoms (30). The clinical spectrum of cluster headache may be expanded, as persons with cluster headache sine headache have been reported (16,32). A man had only autonomic symptoms and no pain in the majority of attacks, but 6 years later he developed episodic cluster headache (32). A woman experienced only autonomic symptoms without headache, while her father had cluster headache without autonomic symptoms and her son had episodic cluster headache (16). After the son's cluster headache resolved, it was followed by a period with autonomic symptoms only at the same regular fashion as in the cluster period. Probable cluster headache is likely to add further to the clinical spectrum. Firstly, probable cluster headache occurs frequently in familial cluster headache (15). Secondly, some patients seem to experience only one cluster period (36,42). Thirdly, a pair of monozygotic twins initially described as discordant later became concordant for cluster headache (37,38). The cluster periods were very short in the beginning, and one of the twins experienced attacks of very short duration. Later, the pain characteristics changed to be typical episodic cluster headache (38). Atypical cluster headache, that is, severe unilateral headache with autonomic features that do not fulfil the International Classification of Headache Disorders criteria for migraine, cluster headache, probable cluster headache, paroxysmal hemicrania or SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) has recently been described in a Swedish survey (41). A total of 11 people from familial cluster headache

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families had a typical cluster headache. The majority of families had two or more affected with genuine cluster headache. This suggests that the clinical spectrum of cluster headache is broader than defined by the ICHD (47). Cluster headache has been associated with primary hyperlipidemia in one family and hemochromatosis in another family (24,44). This is likely to be a coincidental cooccurrence of two disorders. The twin studies and genetic epidemiologic survey included Caucasians only, but cluster headache has also been described in Africans, African-Americans, Japanese, and Chinese (6,46,48,51).

### Mode of Inheritance

A complex segregation analysis of cluster headache supports the segregation of an autosomal dominant gene acting with reduced penetrance (27). This model is favored by all parent offspring contributions that have been observed, namely from father to son, father to daughter, mother to son, and mother to daughter, and the almost equal ratio of men and women affected in familial cluster headache. Cluster headache has been observed across three generations (4,14,20,43,50). These findings do not exclude alternative modes of inheritance in some cluster headache families. Analysis of four large Italian kindred linked through marriage was interpreted to suggest autosomal recessive inheritance (5). This result is supported by no affected parents in 49% (44/90) of the Dutch and French families, although an autosomal dominant gene with reduced penetrance can produce the same pedigree pattern (10,27,50).

### Molecular Genetics

A point mutation in mitochondrial transfer RNA Leu(UUR) gene at nucleotide pair 3243 reported in a Japanese man with sporadic cluster headache but no family history of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) (35) was not replicated amongst Italian and German cohorts with cluster headache (2,34). Multiple deletions of mitochondrial DNA were identified in a Japanese man with probable cluster headache and chronic progressive external ophthalmoplegia (CPEO) (23). Two Swedish association studies of the CACNA1A, NOS1, NOS2A, and NOS3 genes found no linkage disequilibrium between cluster headache sufferers and controls (39,40). A Dutch haplotype study of a family with three affected and a subsequent mutation analysis of one affected excluded involvement of the CACNA1A gene in that family (11). At the time being, no molecular genetic clues have been identified for cluster headache.

### Future

Identification of a gene for cluster headache is difficult. Firstly, most families have few affected. Secondly, genetic heterogeneity is likely. Thirdly, the penetrance of the gene is likely to be low. Focus should be on ion channel and clock genes, due to the paroxysmal character and periodicity of cluster headache.

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