JAMA Neurology | Review

Family History of Cluster Headache
A Systematic Review

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IMPORTANCE Genetic and environmental factors are thought to contribute to cluster headache, and cluster headache can affect multiple members of a family. A thorough understanding of its inheritance is critical to understanding the pathogenesis of this debilitating disease.

OBJECTIVE To systematically review family history rates and inheritance patterns of cluster headache.

EVIDENCE REVIEW A systematic review was performed in PubMed, Embase, and Cochrane Library. Search criteria were created by a librarian. Articles published between 1985 and 2016, after the publication date of a large review in 1985, were analyzed independently by 2 neurologists to identify family history rates and pedigrees. Pedigrees were analyzed by a genetic counselor.

FINDINGS A total of 1995 studies were found (1988 through the search criteria and 7 through other means). Forty articles met inclusion criteria: 22 large cohort studies, 1 twin-based study, and 17 case reports or small case series. Across the 22 large cohort studies, the positive family history rate of cluster headache varied between 0% and 22%, with a median of 8.2%. The largest 5 studies, of 1134, 785, 693, 609, and 500 probands each, had a positive family history in 18.0% (numerator not provided), 5.1% (40 of 785 cases), 10.0% (numerator not provided), 2.0% (12 of 609 cases), and 11.2% (56 of 500 cases), respectively. No meta-analysis was performed, given differences in methodologies. Separately, 1 twin-based study examined 37 twin pairs and reported a concordance rate of 5.4% (2 pairs). Finally, 67 pedigrees were identified. Most pedigrees (46 of 67 [69%]) were consistent with an autosomal dominant pattern, but 19 of 67 (28%) were consistent with an autosomal recessive inheritance pattern; 10 pedigrees of probable or atypical cluster headache were identified, and all were consistent with an autosomal dominant inheritance pattern. The sex ratio for cluster headache in identified pedigrees was 1.39 (103:74) in affected men and boys compared with affected women and girls, which is lower than that of the general cluster headache population.

CONCLUSIONS AND RELEVANCE Cluster headache is an inherited disorder in a subset of families and is associated with multiple hereditary patterns. There is an unexpectedly high preponderance of women and girls with familial cluster headache; genetic subanalyses limited to female participants are necessary to further explore this observation, because these data are otherwise masked by the higher numbers of male participants with cluster headache. Overall, this systematic review supports the notion that familial cluster headache is likely the result of multiple susceptibility genes as well as environmental factors.

JAMA Neurol. doi:10.1001/jamaneurol.2020.0682
Published online April 20, 2020.

Supplemental content

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Cluster headache is characterized by unilateral pain lasting 15 to 180 minutes that occurs up to 8 times per day, with bouts of headaches lasting for weeks to months punctuated by remission periods. Cluster headaches are associated with restlessness and ipsilateral cranial autonomic features.[1] Pain is severe and located maximally in the orbital, supraorbital, or temporal regions.

There have long been reports of hereditary factors in cluster headache, including physical features, such as facial structure, height, and eye color,[2,3] as well as linkage to human leukocyte antigens.[4-6] More recently, there has been extensive interest in identifying genetic risk factors for cluster headache, with several candidate genes proposed but none consistently verified as causal in multiple patient cohorts.[7,8]

Reports of familial cluster headache date back to at least the mid-20th century: a meta-analysis[9] of the rate of cluster headache between 1947 and 1985 and found 47 first-degree relatives affected in 1182 families. Historically, then, the rate of familial cluster headache was thought to be quite low (47 of 1182 participants [4.1%]), at least in first-degree relatives.

A comprehensive assessment of inheritance in cluster headache would complement recent studies of cluster headache genetics and epigenetics. The objectives of this systematic review are to (1) report on the rate of familial cluster headache and (2) provide the different possible inheritance patterns seen in pedigrees.

Key Points

Question What is the family history rate and inheritance pattern of cluster headache?

Findings In a systematic review of articles published between 1985 and 2016, which included 22 large cohort studies, cluster headache has a family history rate of 0% to 22%, with a median of 8.2%. A total of 67 pedigrees were identified, and the inheritance pattern of cluster headache was consistent with an autosomal dominant pattern in 69% of participants and an autosomal recessive pattern in 28%.

Meaning Per this systematic review, cluster headache is an inherited disorder in a subset of patients, and the pattern of inheritance could be the result of multiple susceptibility genes as well as environmental factors.

Methods

Eligibility Criteria

Inclusion criteria were established a priori and included all study types that reported both (1) a proband of any age with cluster headaches diagnosed by a neurologist and (2) any attempt to document the presence or absence of cluster headache in family members. Exclusion criteria specified non–English language articles, review articles or other articles that used previously reported data, and articles published before 1985. We chose 1985 as the starting date because an extensive review of family history, including a meta-analysis, has been reported on articles between 1947 and 1985.[9]

Information Sources and Search

An experienced librarian (A.T.) developed searches for PubMed, the Cochrane Library through Wiley, and Elsevier Embase. Guidelines for the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[10] were followed. The main search was constructed in PubMed using a combination of medical subject heading (MeSH) terms selected from core documents supplied by the neurologists (M.W.W. and M.J.B.) and through discussions between the authors. In general, search terms focused on (1) family, epidemiology, inheritance, or transmission and (2) cluster headache or trigeminal autonomic cephalalgia (PubMed search terms are in eTable 1 in the Supplement). These terms were then tested for relevancy, and the main search was finalized in PubMed on December 15, 2016. These search terms were then translated into the Cochrane Library on December 17, 2016, and Embase on December 22, 2016.

Study Selection

Screening was performed independently by 2 neurologists (M.W.W. and M.J.B.). In the screening step, we examined titles and abstracts in Rayyan[11] using our inclusion and exclusion criteria. In the eligibility step, we examined full-length articles for inclusion and exclusion criteria. At the end of each stage, disagreements were settled by discussion between the 2 neurologists. In all cases, a consensus was reached.

Data Collection Process, Data Items

Two authors (M.W.W. and M.J.B.) independently extracted data elements from each article. Data extracted included the authors' names, article title, journal name, publication year, country of authors, country of patients, family history rate of cluster headache, number of probands examined, twin study details, and presence of pedigrees. For quality assessment, these 2 authors independently assessed (1) the criteria for the diagnosis of cluster headache, (2) the method of diagnosis of cluster headache in the probands, and (3) the method of diagnosis of cluster headache in family members.

In the first part of the study, the family history rate of cluster headache was examined and defined as the percentage of probands who have a positive family history of cluster headache. In the second part of our study, pedigrees were analyzed. All articles with pedigrees were examined by a certified genetic counselor (K.J.Q.). Cases of probable cluster headache in 1 reference[12] and so-called atypical cluster headache in another[13] were analyzed in 2 ways: (1) relatives with probable or atypical cluster headache were considered negative for cluster headache and analyzed as if they were unaffected relatives and (2) relatives with probable or atypical cluster headache were considered positive for cluster headache and analyzed as if they were affected relatives. Both analyses are presented here.

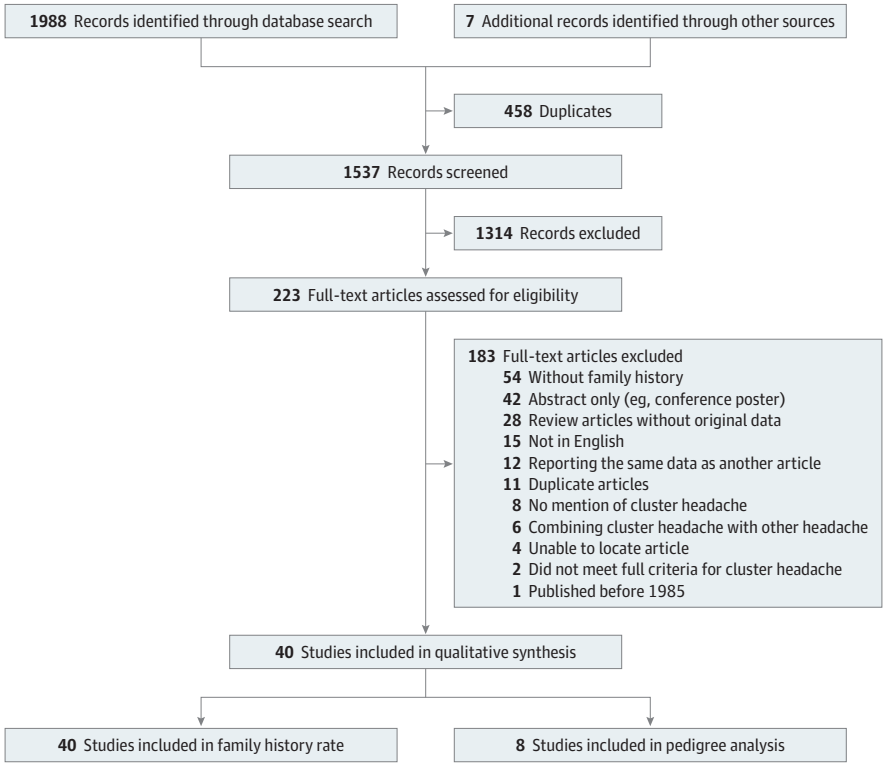
Summary Measures and Synthesis of Results

There were 2 summary measures: family history rate of cluster headache and inheritance pattern. No meta-analysis was performed given the significant differences in methods between studies, in particular the following: (1) the degrees of relatives examined (eg, first-degree relatives only vs first-degree and second-degree relatives), and (2) the method of diagnosis in relatives (ie, interviewing relatives vs obtaining a family history only from the proband).

Statistical Measures

Statistics were performed using JASP version 0.11.1 (University of Amsterdam; https://jasp-stats.org/). The Mann-Whitney *U* test was

Figure. Flow Diagram for Identification, Screening, Eligibility, and Inclusion



used to compare the familial cluster headache rates in different study characteristics. For calculations, categories were created as follows. Sources of participants were categorized as (1) clinics alone or (2) clinics and/or other methods. The number of participants examined was categorized as less than 500 or greater than or equal to 500 individuals. The degrees of relatives examined were categorized as first degree only or more than first degree. The criteria used to diagnose cluster headache were grouped by (1) International Classification of Headache Disorders 1 or International Headache Society Ad Hoc committee criteria or (2) other criteria.[14-17] The methods of diagnosis in the probands were categorized as in person alone or in person and/or another method. The methods of diagnosis in relatives were categorized as from proband alone or from proband and/or another method. A *P* value less than .05 was considered significant.

Results

Our search terms identified a total of 1988 articles prior to deduplication (553 in PubMed, 94 in Cochrane Library, and 1341 in Embase) (**Figure**). Through a general review of the literature, we found and included 7 additional articles[18-24] that were not identified by our search criteria. Ultimately, 40 articles were identified that met the predetermined eligibility criteria: 22 large cohort studies,[13,18-22,24-39] 1 twin-based study,[40] and 17 case reports and case series.[12,23,41-55] Large cohort studies were defined as studies that examined at least 20 patients with cluster headache for a possible family history of cluster headache, and case reports or case series were defined as studies with fewer than 10 patients with cluster headache; there were no studies that included between 10 and 20 patients. Also, within the final 40 articles, a total of 70 pedigrees were found[12,13,26,27,38,41,42,55]: 67 with relatives with a full diagnosis of cluster headache and 3 with relatives that had only probable or atypical cluster headache. In part 1 of our analysis, we examined the family history rates of the large cohort studies and the twin-based study. In part 2, we examined the pedigrees.

Our search criteria appeared to be reasonably inclusive: we identified 20 of 23 articles published after 1984 that were mentioned in 7 previous narrative reviews[9,56-61] on family history of cluster headache. Two of the 3 articles[19,24] that our search failed to identify were added to our analysis, while the third[62] was excluded because the data were incorporated into the previous meta-analysis from 1947 to 1985 by Russell.[9]

Part 1: Family History Rate

We identified 22 large cohort studies,[13,18-22,24-39] which examined participants from 14 countries on 3 continents (Asia, Europe, and North America) (**Table 1**). Most studies (17 of 22 [77%])[13,18-22,24-29,31-33,36,38] examined at least 100 participants. Recruitment came exclusively from patients seen in clinics in 16 of 22 studies[13,20-22,24,26,28,29,31-38] (72%), while 5 of 22 studies[18,19,25,30,39] (25%) recruited participants through other sources, such as national support groups, headache societies, or media postings (in websites, radio, or newspapers). Information on patient recruitment was not available in 1 of 22 studies[27] (5%). It should be noted that the largest study,[25] which included 1134 participants, was also the only large cohort study that did not use International

Table 1. Family History Rate of Cluster Headache[a]

Source	Year	Country[b]	Source of participants	Probands with family history of CH, No. (%)	Total probands examined, No.	Degrees of relatives who were investigated	Criteria used to diagnose CH	Method of diagnosis[c]	
								In probands	In relatives
Large cohort studies									
Bahra et al[18]	2002	United Kingdom	National support group, charity group, clinic	NR (5.0)	230	Part of first (parent or sibling)	ICHD1	In person or telephone	From probands
Bhargava et al[34]	2014	India	Clinic	0	30	Unknown	ICHD2	In person	From probands
Cruz et al[35]	2013	Portugal	Clinic	5 (20.8)[d]	22	First	ICHD2	By telephone	Telephone
Dong et al[29]	2013	China	Clinic	8 (6.7)	120	Unknown	ICHD2	In person	From probands
Donnet et al[36]	2007	France	Clinic	6 (5.5)	110	First and second	ICHD1 or ICHD2	In person	From probands
El Amrani et al[26]	2002	France	Clinic	20 (10.8)	186	First and second	ICHD1	In person or by telephone	In person or by telephone
Haane et al[39]	2013	The Netherlands	Media (website) and clinic	9 (12.5)	72	First and second	ICHD2[e]	Survey	From probands
Klapper et al[19]	2000	Global (online survey)	National support group and media (website)	NR (10.0)	693	Unknown	ICHD1	Survey	From probands
Kudrow and Kudrow[27]	1994	Not stated, presumed United States	Not stated	NR (8.7)	300	First	IHS Ad Hoc Committee and ICHD1	In person	From probands
Lademann et al[20]	2015	Germany	Clinic	NR (7.8)	434	Unknown	ICHD2 or ICHD3-beta	In person	From probands
Leone et al[33]	2001	Italy	Clinic	44 (20.0)	220	First and second	ICHD1	In person	In person, by telephone, or from probands
Lin et al[21]	2004	Taiwan	Clinic	6 (5.8)	104	Part of first degree (parent or sibling)	ICHD1	In person, by telephone, or by survey	From probands
Maytal et al[37]	1992	United States	Clinic	3 (8.6)	35	Parts of first and second (parent, grandparent, sibling)	ICHD1	In person	From probands
Montagna et al[38]	1998	Italy	Clinic	5 (2.3)	222	First and second in all families, third in 1 family	ICHD1	In person	Telephone
Rainero et al[32]	2008	Italy	Clinic	5 (4.6)	109	Unknown	ICHD2	In person	From probands
Riess et al[30]	1998	Canada	Media (newspaper and radio)	NR (22.0)	51	First	ICHD1	In person	From probands
Rozen and Fishman[25]	2012	United States	National support group and national headache society	NR (18.0)	1134	Unknown	Diagnosed by neurologist	Survey	From probands
Russell et al[31]	1996	Denmark	Clinic	25 (6.8)	366	First and second	ICHD1	By telephone or survey	Telephone
Sjöstrand et al[13]	2005	Sweden	Clinic	12 (2.0)	609	Unknown	ICHD2	In person	From probands, questionnaires, and/or personal interviews
Steinberg et al[22]	2018	Sweden	Clinic	56 (11.2)	500	First, second, and third	ICHD3-beta	Survey	From probands
Taga et al[28]	2015	Italy	Clinic	40 (5.1)	785	First	ICHD3-beta	In person	Chart reviews
Vikelis and Rapoport[24]	2016	Greece	Clinic	NR (17.5)	302	Unknown	ICHD3-beta	In person	From probands
Twin-based studies									
Ekbom, et al[40]	2006	Sweden	National registry	2 (5.4)	37	Twins only	ICHD2	By telephone	By telephone

Abbreviations: CH, cluster headache; ICHD, International Classification of Headache Disorders; IHS, International Headache Society; NR, not reported.

[a] References for the diagnosis of cluster headache include the ICHD editions 1,[63] 2,[36] 3-beta,[35] and 3[1] and IHS Ad Hoc Committee[37] criteria.

[b] For country of patients studied, *presumed* refers to articles in which the country of the patients was not specified, but the patients were personally seen in the clinic of the authors.

[c] In some cases, the method of diagnosis was not specifically mentioned; patients were presumed to be diagnosed in person if the study mentioned that the patient had a neurologic examination completed or a blood sample drawn.

[d] Of note, there is an intentional discrepancy in the value for percentage and the value for nominator and denominator for Cruz et al.[35] This study reported a positive family history in 20.8% (5 of 24 participants); however, 2 of the 24 patients had probable cluster headache and thus were excluded, and the study did not report if it was these patients who had a positive family history. Therefore, we report the original percentage of 20.8% (5 of 24 participants) instead of 22.7% (5 of 22 participants).

[e] For criteria used to diagnose cluster headache, this letter indicates that maximum attack duration and maximal attack frequency criteria were not examined.

Table 2. Systematic Review Results From Table 1, Grouped by Categories[a]

Characteristic	No. of studies	Family history rate of cluster headache, median (range), %
All population studies	22	8.2 (0-22)
Studies		
With diagnosis in the proband made exclusively by in-person interview	13	6.7 (0-22)
Performed at headache centers[a]	16	6.8 (2-22)
Limited to first-degree relatives	6	7.3 (5-22)
With interviews with relatives instead of relying on proband information	6	8.8 (2.0-20.8)
With inclusion of second-degree and/or third-degree relatives	8	9.7 (2.3-20)
With >500 participants	5	10 (2-18)

[a] Studies performed at headache centers.[13,18,20-22,24,26,28-33,36-38]

Table 3. Lack of Significant Differences Between Studies Based on Collection Characteristics[a]

Category	Comparison	*P* value
Study publication date	≤2004 vs >2004	.64
Sources of participants	Clinic vs nonclinic	.12
No. of probands examined	<500 vs ≥500	>.99
Degrees of relatives	First vs >first	.68
Criteria used to diagnose cluster headache	International Classification of Headache Disorders 1 vs other	.64
Methods of diagnosis		
In probands	In-person vs not in-person	.15
In relatives	Proband recall vs interview	.63

[a] Comparisons were performed using the Mann-Whitney *U* test for all categories. A *P* value less than .05 was considered significant.

Classification of Headache Disorders criteria to confirm the diagnosis. Probands were mostly diagnosed exclusively in person (13 of 22 studies[13,20,24,27-30,32-34,36-38] [59%]), while the remainder may have also been diagnosed by telephone or questionnaire. In most studies,[18-22,24,25,27,29,30,32,34,36,37,39] a diagnosis of cluster headache in the proband's relatives was made based on information reported only by the proband (15 of 22 studies [68%]), while in the remainder, relatives were diagnosed in person, by telephone, or by survey.

The family history rate of cluster headache in the 22 large cohort studies varied between 0% to 22%, with a median of 8.2% (the data were not normally distributed; therefore, we reported the median). The largest 5 studies, of 1134,[25] 785,[28] 693,[19] 609,[13] and 500 probands[22] each, had a positive family history in 18.0% (numerator not provided), 5.1% (40 of 785 cases), 10.0% (numerator not provided), 2.0% (12 of 609 cases), and 11.2% (56 of 500 cases), respectively. There was methodologic variability between studies, and we examined variables that might be important, such as direct in-person interviews, studies at headache centers, studies that interviewed more closely or more distantly related family members, studies that interviewed relatives directly, or studies with more than 500 probands (**Table 2**). Each subgroup had a median family history rate between 6.7% and 10.0% and a range similar to the entire cohort. There were no significant differences between the family history rates of cluster headache based on methodological differences in terms of the source of the patient cohorts, the number of probands examined, the degrees of relatives who were investigated, the criteria used to diagnose cluster headache, the study publication date, the method of diagnosis in the proband, or the method of diagnosis in the relatives (**Table 3**). Because of multiple differences in methodology between studies, no meta-analyses were performed.

In addition to the large cohort studies, we identified 1 population study[40] that exclusively examined twins using a national registry, which reported a concordance rate of 5.4% (2 of 37 twin pairs). The 2 concordant pairs were both monozygotic, and the 35 discordant pairs consisted of 10 monozygotic and 25 dizygotic sets of twins (with the same sex in 13 pairs and different sexes in 12 pairs).

We identified another 17 studies[12,23,41-55] that examined fewer than 10 probands with cluster headache each (eTable 2 in the Supplement). These studies were primarily case reports or case series and had methods similar to the larger studies. We deemed these studies too small or focused to be included in the aggregate calculation of family history rate of cluster headache. These studies are included here for completeness, should other researchers want to perform an analysis of all studies between 1985 and 2016 with a positive family history of cluster headache identified with our methodology.

Part 2: Pedigrees

A total of 71 pedigrees in 8 studies[12,13,26,27,38,41,42,55] were identified, with 1 pedigree[41] removed because it was a duplicate of a pedigree from another article.[42] Some of the studies[12,13] identified patients with probable cluster headache or atypical cluster headache (defined as cases that "did not fulfil the diagnostic criteria for CH [cluster headache], but had clinical symptoms with more resemblance to CH than to migraine or other trigeminal autonomic cephalgia syndromes"[13(p1068)]). Atypical cluster headache cases did not meet criteria either because the duration of their headache lasted for longer than 180 minutes or the frequency of headaches was less than every other day. In analysis A, we considered relatives with probable or atypical cluster headache to be unaffected relatives; in this analysis, there were 67 pedigrees.[12,13,26,27,38,41,42,55] In analysis B (eTable 3 in the Supplement), we reanalyzed the pedigrees considering both relatives with probable or atypical cluster headache and relatives with cluster headache to be affected individuals; in this analysis, there were an additional 3 pedigrees.[12,13]

Analysis A, Omitting Probable and Atypical Cluster Headache

Across 67 pedigrees (**Table 4**),[12,13,26,27,38,41,42,55] there were 177 affected and 788 unaffected individuals, with a sex ratio (affected men and boys divided by affected women and girls) of 1.39 (103:74). All 67 pedigrees were consistent with autosomal dominant or autosomal recessive patterns of inheritance. Autosomal dominant patterns were found in 46 of 67 pedigrees (69%) and autosomal recessive patterns in 19 of 67 (28%), with insufficient information to distinguish between autosomal dominant or autosomal recessive in the remaining 2 of 67 (3%).

Of the 46 autosomal dominant pedigrees,[13,26,27,38,41,55] 28 (61%) had insufficient information to exclude an X-linked pattern of inheritance, because there were no cases of male-to-male transmis-

Table 4. Hereditary Patterns in 67 Pedigrees of Cluster Headache[a]

Pedigree	Affected participants, No./total No.	
	Individuals	Generations
Autosomal dominant		
Bordini et al[12]		
2	2/18	2/4
3	2/10	2/3
El Amrani et al[26]		
1	3/14	3/4
5	3/19	2/4
9	3/12	3/3
Kudrow and Kudrow[27]		
K118	3/4	2/2
K119	3/9	¾
K120	3/7	3/3
K121	4/7	3/3
K122	4/6	2/2
Sjöstrand et al[13]		
2	2/9	2/3
9	4/17	3/3
Zarrilli et al[41]		
A	2/11	2/3
E	4/12	3/3
G	2/20	2/3
Autosomal dominant with incomplete penetrance		
El Amrani et al,[26] 16	3/14	2/3
Montagna et al[38]		
B	2/18	2/4
E	4/14	3/3
Autosomal dominant or in an X-linked pattern		
El Amrani et al[26]		
2	3/17	2/3
4	2/8	2/3
6	2/16	2/3
7	4/11	2/4
8	3/10	2/3
12	2/14	2/3
Kudrow and Kudrow[27]		
K100	2/9	2/3
K101	2/7	2/2
K103	2/5	2/3
K104	2/6	2/3
K105	2/7	2/3
K106	2/9	2/3
K110	2/11	2/3
K111	2/10	2/3
K112	2/7	2/3
K113	2/11	2/3
K114	3/10	3/4
K115	3/8	3/3
K116	3/7	2/3
K117	3/7	3/3
Sjöstrand et al,[13] 6	2/8	2/3
Autosomal dominant or X-linked with incomplete penetrance		
Haan et al[55]	3/26	2/5
Montagna et al,[38] A	3/18	2/5
Sjöstrand et al[13]		
1	3/12	2/3
5	3/13	2/3
Zarrilli et al,[41] B	3/22	2/4
Autosomal dominant, X-linked, or polygenic		
El Amrani et al,[26] 3	3/12	2/3
Autosomal dominant or X-linked with incomplete penetrance or polygenic		
Kudrow and Kudrow,[27] K123	5/22	3/4
Autosomal dominant with incomplete penetrance or autosomal recessive		
El Amrani et al,[26] 20	3/21	1/4
Zarrilli et al,[41] F	3/22	1/3
Autosomal recessive		
Bordini et al,[12] 1	2/21	1/3
El Amrani et al[26]		
10	2/11	1/3
11	2/9	1/3
13	2/20	1/4
14	2/13	1/3
15	2/8	1/2
17	2/14	1/3
18	2/15	1/3
19	2/15	1/3
Kudrow and Kudrow[27]		
K102	2/7	1/3
K107	2/4	1/2
K108	2/15	1/3
K109	2/5	1/2
Montagna et al[38]		
C	2/11	1/3
D	2/7	1/3
Sjöstrand et al,[13] 3	2/10	1/3
Zarrilli et al[41]		
C	2/24	1/4
D	3/18	1/3
Autosomal recessive or polygenic		
De Simone et al[42]	8/151	2/4

[a] Results were analyzed for the most likely inheritance pattern, although it should be noted that incomplete penetrance and multifactorial and/or polygenic inheritance patterns cannot be ruled out. In this analysis, we ignored the diagnosis of atypical cluster headache; relatives identified by the original studies as having atypical cluster headache were considered to be unaffected relatives. Numbers in the leftmost column refer to the figure numbers (for Bordini et al[12]) or pedigree number (for El Amrani et al,[26] Kudrow and Kudrow,[27] and Sjöstrand et al[13]). Letters in the leftmost column refer to pedigree letters (for Zarrilli et al[41] and Montagna et al[38])

sion of cluster headache within the families. Nine of 46 cases (20%) displayed incomplete penetrance.[13,26,27,38,41,55] Two of 46 autosomal dominant cases (4%) involved complex pedigrees that could

alternatively be explained by polygenic inheritance.[26,27] One pedigree depicts 2 parents with cluster headache whose child was also affected.[26] This could represent polygenic inheritance in which each parent carries the same susceptibility gene or different ones. Alternatively, this could be a case of autosomal dominant or X-linked inheritance in which 1 parent represents a sporadic phenocopy within the family. Neither parent had any additional known family history. The second pedigree[27] depicts 5 affected individuals from 2 independent families in which not all 5 affected individuals are blood related. Therefore, this family could represent a complex polygenic pattern of inheritance in which susceptibility genes are present in both intermarrying families. Alternatively, 1 or more of these individuals may represent a sporadic phenocopy within the pedigree.

Of the 19 autosomal recessive pedigrees, 1 (5%) involved a complex pedigree that could alternatively be explained by polygenic inheritance.[42] In this case, the pedigree depicts 8 affected individuals within a kindred group of 4 independent families from the Naples region of southern Italy that had intermarried.[42] For true autosomal recessive inheritance, all 4 families would be required to carry recessive mutations in the same gene. Such a high carrier frequency may be possible in some local populations. Alternatively, the affected individuals in this pedigree may be the result of multiple shared susceptibility genes, or 1 or more of these individuals may represent a sporadic phenocopy within the family. The remaining 2 families could be consistent with either an autosomal dominant pattern with incomplete penetrance or an autosomal recessive pattern of inheritance. For both of these families, autosomal recessive inheritance would require that 2 siblings each have children with a partner who is a carrier for a recessive mutation in the same causative gene (ie, the recessive gene is carried by 3 independent families).[26,41] Alternatively, an autosomal dominant mutation with incomplete penetrance could also explain the pattern of affected individuals observed in these families.

Analysis B Including Probable or Atypical Cluster Headache

Pedigree analyses were repeated to include cases of probable or atypical cluster headache as affected individuals in these families, thereby including 3 pedigrees that were previously excluded (full results in eTable 3 in the Supplement). All 10 pedigrees[12,13] were consistent with autosomal dominant patterns of inheritance. When incorporating these cases into the familial cluster headache pedigrees, 51 of 70 families (73%) had pedigrees consistent with an autosomal dominant pattern of inheritance, while 17 of 70 families (24%) had pedigrees consistent with an autosomal recessive pattern.

Discussion

In a systematic review of studies published between 1985 and 2016, the family history rate of cluster headache varied between 0% and 22%, with a median of 8.2%. When limiting our data to subgroups of studies that performed broader investigations—specifically subgroups with either more than 500 patients, second-degree and third-degree relatives, or direct interviews with relatives (Table 2)—the median was between 8.8% and 10%, with a range of 2% to 20.8%. Thus, the familial rate of cluster headache may be as common as 1 in 10 or even 1 in 5 individuals. In analyzing pedigrees, the most common inheritance pattern was autosomal dominant (69%), followed by autosomal recessive (28%). The inclusion of probable and atypical cluster headache diagnoses into the pedigree analysis did not substantially alter the distribution of inheritance patterns.

When comparing our results with a meta-analysis by Russell,[9] who found a family history rate of 4.1% (47 of 1182 individuals) for first degree-relatives in studies published between 1947 and 1985, every study of first-degree relatives between 1985 and 2016 found a higher rate of positive family history, ranging from 5% to 22% (Table 2). The difference in family history rate of first-degree relatives between these 2 periods is unclear but may reflect differences in clinical practice, patient awareness, or family dynamics.

The proportion of women with familial cluster headache was higher than expected in our data set. In the pedigrees with a positive family history of cluster headache, the sex ratio (affected men and boys divided by affected women and girls) is 1.39 (103:74), whereas in the general cluster headache literature, it is 4.3.[64] Some of the large cohort studies from Table 1 had similar sex ratios, of 2.3 (28 men and boys:12 women and girls),[28] 2.0 (4:2),[29] 2.0 (6:3),[30] 1.9 (17:9),[31] and 1.5 (12:8).[26] This difference suggests that factors predisposing men to develop sporadic cluster headache may be different than those that play a role in the pathogenesis of familial cluster headache. Additional investigation is needed to determine potential genetic and environmental factors involved in the sex ratio of cluster headache: the sex ratio in the general cluster headache population has decreased over the decades,[65] and recent studies of more than 1000 participants with cluster headache have found sex ratios of 2.6 (816:318),[25] 2.2 (1104:497),[66] and 1.3 (4356:3233).[67] There also may be systematic differences in sex between the data collected from researchers examining single families and researchers examining populations. Nevertheless, this finding warrants increased attention in future genetic analyses of cluster headache. As cluster headache is more common in men, data from male study participants have predominated genetic studies thus far and likely mask relevant data from female participants. One potential conclusion of this analysis is that women and girls are more similarly affected by cluster headache compared with men and boys in familial cluster headache. A subset analysis limited to female participants is required to explore why this apparent sex difference exists, and if so, whether inherited factors drive differential susceptibility to cluster headache between different sexes.

There are at least 2 potential explanations for a familial pattern of cluster headache: genetics and shared environmental factors. From a genetics standpoint, this systematic review supports the notion of complex genetic heterogeneity in cluster headache,[7,58,68,69] with the identification of multiple inheritance patterns in pedigrees. Possible susceptibility genes for cluster headache include the hypocretin/orexin receptor type 2 (*HCRTR2*),[32,70-74] alcohol dehydrogenase 4 (*ADH4*),[74-77] G protein beta 3 (*GNB3*),[77,78] pituitary adenylate cyclase-activating polypeptide type I receptor (*ADCYAP1R1*),[79,80] and membrane metalloendopeptidase (*MME*) genes.[79,80] We have limited data on genetic anticipation that was reported in 2 studies[13,81]; in both studies, there was a statistically significant difference of 9 years between the first generation and the second and/or third generations in 17 parent-child pairs[81] and 29 first-generation relatives with typical and atypical cluster headache vs 25 second-generation and third-generation relatives.[13] Future studies are needed to examine this genetic aspect of familial cluster headache.

In terms of shared environmental factors, there has been recent interest in the epigenetic mechanisms in cluster headache, with

reports on altered gene expression associated with inflammation,[6,82] circadian patterns,[83,84] and exposure to toxins, such as cadmium in tobacco.[85] All of these factors could be part of a shared environment. Tobacco use is of particular interest because it is seen at a much higher rate in patients with cluster headache than the general population,[25,86,87] and secondhand smoke exposure appears to be common in patients with cluster headache.[88] Environmental factors alone are unlikely to explain a strong familial aggregation,[59,89,90] as seen in some of the pedigrees, but familial cluster headache could be the result of multifactorial inheritance or the combination of both susceptibility genes as well as environmental factors. Our conclusions were based on 70 individual families; larger studies on cluster headache inheritance patterns are needed to explore this potentially multifactorial inheritance.

Limitations

This study has several limitations. First, in most of the studies, the diagnosis of cluster headache in family members was made indirectly, using information provided by the probands. There is an inherent verification bias, in that individual probands have varying abilities to distinguish cluster headache from other forms of headache in family members. Second, familial cluster headache may be underestimated in many studies because of a variety of factors, including an inability to contact certain family members (death and refusal to participate were both listed as reasons) and the fact that some studies only investigated first-degree relatives. Third, familial cluster headache may be overestimated in some studies because most did not report if their probands could have been related to each other. In 2 of our studies, there were reports of 6 affected patients from 4 families[21] and 12 affected patients from 5 families[13]; if multiple members of the same family all report a family history of cluster headache, it could overestimate the proportion with a positive family history. Finally, our search criteria failed to find 7 of the final 40 articles that reported a family history of cluster headache; these 7 articles were identified through other sources. Six of these 7 articles mentioned a family history of cluster headaches only in the results section. Because we first screened by title and abstract, it is possible that we missed other articles. A more comprehensive search might be performed in the future if the search is applied not only to the title and abstract but to the entire article.

Conclusions

In this systematic review, cluster headache had a family history rate of 0% to 22%, with a median of 8.2%. The inheritance pattern of cluster headache across 67 pedigrees was consistent with an autosomal dominant pattern in 69% and an autosomal recessive pattern in 28%. Future genetic studies of familial cluster headache should direct attention to sex differences and headache age at headache onset.

ARTICLE INFORMATION

Accepted for Publication: February 28, 2020.

Published Online: April 20, 2020. doi:10.1001/jamaneurol.2020.0682

Author Contributions: Dr Burish had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Burish.
Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Waung, Burish.
Administrative, technical, or material support: Taylor, Burish.
Supervision: Burish.

Conflict of Interest Disclosures: Dr Waung reported grants from the National Institutes of Health during the conduct of the study and personal fees from Biohaven outside the submitted work. Dr Qualmann reported serving as a contracted content consultant for My Gene Counsel LLC. Dr Burish reported grants from Will Erwin Headache Research Foundation during the conduct of the study and personal fees from *Continuum Journal* and Electrocore outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Waung received funding from the National Institutes of Health (grant K08 NS097632). Dr Burish received funding from the Will Erwin Headache Research Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the Texas Medical Center Library for assistance with search terms.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202

2. Graham JR. Cluster headache. *Headache*. 1972;11(4):175-185. doi:10.1111/j.1526-4610.1972.hed1104175.x

3. Kudrow L. *Cluster Headache*. Oxford University Press; 1980.

4. Martelletti P, Romiti A, Gallo MF, et al. HLA-B14 antigen in cluster headache. *Headache*. 1984;24(3):152-154. doi:10.1111/j.1526-4610.1984.hed2403152.x

5. Giacovazzo M, Martelletti P, Valeri M, Piazza A, Monaco PI, Casciani CU. Variations in the Leu7+ and LeuM3+ leukocyte subpopulations observed in cluster headache are dependent on HLA-DR antigens. *Headache*. 1987;27(1):35-38. doi:10.1111/j.1526-4610.1987.hed2701035.x

6. Sjöstrand C, Duvefelt K, Steinberg A, Remahl IN, Waldenlind E, Hillert J. Gene expression profiling in cluster headache: a pilot microarray study. *Headache*. 2006;46(10):1518-1534. doi:10.1111/j.1526-4610.2006.00611.x

7. Gibson KF, Santos AD, Lund N, Jensen R, Stylianou IM. Genetics of cluster headache. *Cephalalgia*. 2019;39(10):1298-1312. doi:10.1177/0333102418815503

8. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. *Nat Rev Dis Primers*. 2018;4:18006. doi:10.1038/nrdp.2018.6

9. Russell MB. Genetic epidemiology of migraine and cluster headache. *Cephalalgia*. 1997;17(6):683-701. doi:10.1046/j.1468-2982.1997.1706683.x

10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64. doi:10.7326/0003-4819-151-4-200908180-00135

11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. doi:10.1186/s13643-016-0384-4

12. Bordini CA, Arruda MA, Ciciarelli M, Daripa M, Martins Coelho J, Speciali JG. Cluster headache: report of seven cases in three families. *Funct Neurol*. 1997;12(5):277-282.

13. Sjöstrand C, Russell MBMB, Ekbom K, Hillert J, Waldenlind E. Familial cluster headache: is atypical cluster headache in family members part of the clinical spectrum? *Cephalalgia*. 2005;25(11):1068-1077. doi:10.1111/j.1468-2982.2005.00964.x

14. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808. doi:10.1177/0333102413485658

15. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9-160.

16. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial

neuralgias and facial pain. *Cephalalgia*. 1988;8(suppl 7):1-96.

17. AdHoc and Committee. Classification of headache. *JAMA*. 1962;179(9):717-718.

18. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology*. 2002;58(3):354-361. doi:10.1212/WNL.58.3.354

19. Klapper JA, Klapper A, Voss T. The misdiagnosis of cluster headache: a nonclinic, population-based, Internet survey. *Headache*. 2000;40(9):730-735. doi:10.1046/j.1526-4610.2000.00127.x

20. Lademann V, Jansen J-P, Evers S, Frese A. Evaluation of guideline-adherent treatment in cluster headache. *Cephalalgia*. 2016;36(8):760-764. doi:10.1177/0333102415612774

21. Lin K-H, Wang P-J, Fuh J-L, et al. Cluster headache in the Taiwanese—a clinic-based study. *Cephalalgia*. 2004;24(8):631-638. doi:10.1111/j.1468-2982.2003.00721.x

22. Steinberg A, Fourier C, Ran C, Waldenlind E, Sjöstrand C, Belin AC. Cluster headache—clinical pattern and a new severity scale in a Swedish cohort. *Cephalalgia*. 2018;38(7):1286-1295. doi:10.1177/0333102417731773

23. Stovner LJ, Hagen K, Waage A, Bjerve KS. Hereditary haemochromatosis in two cousins with cluster headache. *Cephalalgia*. 2002;22(4):317-319. doi:10.1046/j.1468-2982.2002.00367.x

24. Vikelis M, Rapoport AM. Cluster headache in Greece: an observational clinical and demographic study of 302 patients. *J Headache Pain*. 2016;17(1):88. doi:10.1186/s10194-016-0683-0

25. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012;52(1):99-113. doi:10.1111/j.1526-4610.2011.02028.x

26. El Amrani M, Ducros A, Boulan P, et al. Familial cluster headache: a series of 186 index patients. *Headache*. 2002;42(10):974-977. doi:10.1046/j.1526-4610.2002.02226.x

27. Kudrow L, Kudrow DB. Inheritance of cluster headache and its possible link to migraine. *Headache*. 1994;34(7):400-407. doi:10.1111/j.1526-4610.1994.hed3407400.x

28. Taga A, Russo M, Manzoni GC, Torelli P. Familial cluster headache in an Italian case series. *Neurol Sci*. 2015;36(suppl 1):141-143. doi:10.1007/s10072-015-2147-8

29. Dong Z, Di H, Dai W, et al. Clinical profile of cluster headaches in China—a clinic-based study. *J Headache Pain*. 2013;14(1):27. doi:10.1186/1129-2377-14-27

30. Riess CM, Becker WJ, Robertson M. Episodic cluster headache in a community: clinical features and treatment. *Can J Neurol Sci*. 1998;25(2):141-145. doi:10.1017/S0317167100033758

31. Russell MB, Andersson PG, Iselius L. Cluster headache is an inherited disorder in some families. *Headache*. 1996;36(10):608-612. doi:10.1046/j.1526-4610.1996.3610608.x

32. Rainero I, Gallone S, Rubino E, et al. Haplotype analysis confirms the association between the HCRTR2 gene and cluster headache. *Headache*. 2008;48(7):1108-1114. doi:10.1111/j.1526-4610.2008.01080.x

33. Leone M, Russell MB, Rigamonti A, et al. Increased familial risk of cluster headache. *Neurology*. 2001;56(9):1233-1236. doi:10.1212/WNL.56.9.1233

34. Bhargava A, Pujar GS, Banakar BF, Shubhakaran K, Kasundra G, Bhushan B. Study of cluster headache: a hospital-based study. *J Neurosci Rural Pract*. 2014;5(4):369-373. doi:10.4103/0976-3147.139987

35. Cruz S, Lemos C, Monteiro JMP. Familial aggregation of cluster headache. *Arq Neuropsiquiatr*. 2013;71(11):866-870. doi:10.1590/0004-282X20130170

36. Donnet A, Lanteri-Minet M, Guegan-Massardier E, et al; Société Française d'Etude des Migraines et Céphalées (SFEMC). Chronic cluster headache: a French clinical descriptive study. *J Neurol Neurosurg Psychiatry*. 2007;78(12):1354-1358. doi:10.1136/jnnp.2006.112037

37. Maytal J, Lipton RB, Solomon S, Shinnar S. Childhood onset cluster headaches. *Headache*. 1992;32(6):275-279. doi:10.1111/j.1526-4610.1992.hed3206275.x

38. Montagna P, Mochi M, Prologo G, et al. Heritability of cluster headache. *Eur J Neurol*. 1998;5(4):343-345. doi:10.1046/j.1468-1331.1998.540343.x

39. Haane DYP, Plaum A, Koehler PJ, Houben MPWA. High-flow oxygen therapy in cluster headache patients has no significant effect on nociception specific blink reflex parameters: a pilot study. *J Headache Pain*. 2016;17(1):7. doi:10.1186/s10194-016-0597-x

40. Ekbom K, Svensson DA, Pedersen NL, Waldenlind E. Lifetime prevalence and concordance risk of cluster headache in the Swedish twin population. *Neurology*. 2006;67(5):798-803. doi:10.1212/01.wnl.0000233786.72356.3e

41. Zarrilli F, Tomaiuolo R, Ceglia C, et al. Molecular analysis of cluster headache. *Clin J Pain*. 2015;31(1):52-57. doi:10.1097/AJP.0000000000000075

42. De Simone R, Fiorillo C, Bonuso S, Castaldo G. A cluster headache family with possible autosomal recessive inheritance. *Neurology*. 2003;61(4):578-579. doi:10.1212/01.WNL.0000078698.05379.FF

43. Havelius U, Milos P, Hindfelt B. Cluster headache in two sisters: pupillary response to phenylephrine and tyramine. *Headache*. 1996;36(7):448-451. doi:10.1046/j.1526-4610.1996.3607448.x

44. May A, Evans RW. The sexagenarian woman with new-onset cluster headaches. *Headache*. 2011;51(6):995-998. doi:10.1111/j.1526-4610.2011.01924.x

45. Roberge C, Bouchard J-P, Simard D, Gagné R. Cluster headache in twins. *Neurology*. 1992;42(6):1255-1256. doi:10.1212/WNL.42.6.1255-b

46. Schuh-Hofer S, Meisel A, Reuter U, Arnold G. Monozygotic twin sisters suffering from cluster headache and migraine without aura. *Neurology*. 2003;60(11):1864-1865. doi:10.1212/01.WNL.0000066050.07400.60

47. Siow HC, Young WB, Peres MFP, Rozen TD, Silberstein SD. Hemiplegic cluster. *Headache*. 2002;42(2):136-139. doi:10.1046/j.1526-4610.2002.02030.x

48. Sjaastad O, Shen JM, Stovner LJ, Elsås T. Cluster headache in identical twins. *Headache*. 1993;33(4):214-217. doi:10.1111/j.1526-4610.1993.hed33040214.x

49. Spierings EL, Vincent AJ. Familial cluster headache: occurrence in three generations. *Neurology*. 1992;42(7):1399-1400. doi:10.1212/WNL.42.7.1399

50. Aridon P, D'Andrea G, Rigamonti A, Leone M, Casari G, Bussone G. Elusive amines and cluster headache: mutational analysis of trace amine receptor cluster on chromosome 6q23. *Neurol Sci*. 2004;25(Suppl 3):S279-S280. doi:10.1007/s10072-004-0309-1

51. Couturier EG, Hering R, Steiner TJ. The first report of cluster headache in identical twins. *Neurology*. 1991;41(5):761. doi:10.1212/WNL.41.5.761

52. D'Amico D, Leone M, Moschiano F, Bussone G. Familial cluster headache: report of three families. *Headache*. 1996;36(1):41-43. doi:10.1046/j.1526-4610.1996.3601041.x

53. Fusco BM, Giacovazzo M. A case of MELAS syndrome with typical cluster headache attacks: is it a causal or coincindental association? *J Headache Pain*. 2002;3(1):51-53. doi:10.1007/s101940200017

54. Garg S, Kurup B. Episodic cluster headache: a rare diagnosis in children. *Indian Pediatr*. 2010;47(7):635-636.

55. Haan J, van Vliet JA, Kors EE, et al. No involvement of the calcium channel gene (*CACNA1A*) in a family with cluster headache. *Cephalalgia*. 2001;21(10):959-962. doi:10.1046/j.1468-2982.2001.00283.x

56. Ekbom K, Waldenlind E. Cluster headache: the history of the Cluster Club and a review of recent clinical research. *Funct Neurol*. 2004;19(2):73-81.

57. Russel M. Current status of genetic discoveries in cluster headache. *Ital J Neurol Sci*. 1999;20(2)(suppl):S7-S9. doi:10.1007/PL00015007

58. Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurol*. 2004;3(5):279-283. doi:10.1016/S1474-4422(04)00735-5

59. Russell MB. Genetics in primary headaches. *J Headache Pain*. 2007;8(3):190-195. doi:10.1007/s10194-007-0389-4

60. Sjöstrand C. Genetic aspects of cluster headache. *Expert Rev Neurother*. 2009;9(3):359-368. doi:10.1586/14737175.9.3.359

61. Vliet JA, Ferrari MD, Haan J. Genetic factors in cluster headache. *Expert Rev Neurother*. 2003;3(3):301-306. doi:10.1586/14737175.3.3.301

62. Andersson PG. Migraine in patients with cluster headache. *Cephalalgia*. 1985;5(1):11-16. doi:10.1046/j.1468-2982.1985.0501011.x

63. Haane DYP, de Ceuster LME, Geerlings RPJ, Dirkx THT, Koehler PJ. Cluster headache and oxygen: is it possible to predict which patients will be relieved? a prospective cross-sectional correlation study. *J Neurol*. 2013;260(10):2596-2605. doi:10.1007/s00415-013-7024-x

64. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia*. 2008;28(6):614-618. doi:10.1111/j.1468-2982.2008.01592.x

65. Manzoni GC. Gender ratio of cluster headache over the years: a possible role of changes in lifestyle. *Cephalalgia*. 1998;18(3):138-142. doi:10.1046/j.1468-2982.1998.1803138.x

66. Pearson SM, Burish MJ, Shapiro RE, Yan Y, Schor LI. Effectiveness of oxygen and other acute treatments for cluster headache: results from the Cluster Headache Questionnaire, an international Survey. *Headache*. 2019;59(2):235-249. doi:10.1111/head.13473

67. Choong CK, Ford JH, Nyhuis AW, et al. Clinical characteristics and treatment patterns among patients diagnosed with cluster headache in U.S. healthcare claims data. *Headache*. 2017;57(9):1359-1374. doi:10.1111/head.13127

68. Baumber L, Sjöstrand C, Leone M, et al. A genome-wide scan and *HCRTR2* candidate gene analysis in a European cluster headache cohort. *Neurology*. 2006;66(12):1888-1893. doi:10.1212/01.wnl.0000219765.95038.d7

69. Pinessi L, Rainero I, Rivoiro C, Rubino E, Gallone S. Genetics of cluster headache: an update. *J Headache Pain*. 2005;6(4):234-236. doi:10.1007/s10194-005-0194-x

70. Rainero I, Gallone S, Valfrè W, et al. A polymorphism of the hypocretin receptor 2 gene is associated with cluster headache. *Neurology*. 2004;63(7):1286-1288. doi:10.1212/01.WNL.0000142424.65251.DB

71. Schürks M, Kurth T, Geissler I, Tessmann G, Diener H-C, Rosskopf D. Cluster headache is associated with the *G1246A* polymorphism in the hypocretin receptor 2 gene. *Neurology*. 2006;66(12):1917-1919. doi:10.1212/01.wnl.0000215852.35329.34

72. Fourier C, Ran C, Steinberg A, Sjöstrand C, Waldenlind E, Belin AC. Analysis of *HCRTR2* gene variants and cluster headache in Sweden. *Headache*. 2019;59(3):410-417. doi:10.1111/head.13462

73. Weller CM, Wilbrink LA, Houwing-Duistermaat JJ, et al. Cluster headache and the hypocretin receptor 2 reconsidered: a genetic association study and meta-analysis. *Cephalalgia*. 2015;35(9):741-747. doi:10.1177/0333102414557839

74. Fan Z, Hou L, Wan D, Ao R, Zhao D, Yu S. Genetic association of *HCRTR2*, *ADH4* and *CLOCK* genes with cluster headache: a Chinese population-based case-control study. *J Headache Pain*. 2018;19(1):1. doi:10.1186/s10194-017-0831-1

75. Rainero I, Rubino E, Gallone S, et al. Cluster headache is associated with the alcohol dehydrogenase 4 (*ADH4*) gene. *Headache*. 2010;50(1):92-98. doi:10.1111/j.1526-4610.2009.01569.x

76. Fourier C, Ran C, Steinberg A, Sjöstrand C, Waldenlind E, Carmine Belin A. Screening of two *ADH4* variations in a Swedish cluster headache case-control material. *Headache*. 2016;56(5):835-840. doi:10.1111/head.12807

77. Papasavva M, Katsarou M-S, Vikelis M, et al. Analysis of *HCRTR2*, *GNB3*, and *ADH4* gene polymorphisms in a Southeastern European Caucasian cluster headache population. *J Mol Neurosci*. 2020;70(3):467-474. doi:10.1007/s12031-019-01439-0

78. Schürks M, Kurth T, Stude P, et al. G protein beta3 polymorphism and triptan response in cluster headache. *Clin Pharmacol Ther*. 2007;82(4):396-401. doi:10.1038/sj.clpt.6100159

79. Bacchelli E, Cainazzo MM, Cameli C, et al. A genome-wide analysis in cluster headache points to neprilysin and *PACAP* receptor gene variants. *J Headache Pain*. 2016;17(1):114. doi:10.1186/s10194-016-0705-y

80. Ran C, Fourier C, Michalska JM, et al. Screening of genetic variants in *ADCYAP1R1*, *MME* and 14q21 in a Swedish cluster headache cohort. *J Headache Pain*. 2017;18(1):88. doi:10.1186/s10194-017-0798-y

81. Russell MB, Andersson PG. Clinical intra- and interfamilial variability of cluster headache. *Eur J Neurol*. 1995;1(3):253-257. doi:10.1111/j.1468-1331.1995.tb00080.x

82. Steinberg A, Sjöstrand C, Sominanda A, Fogdell-Hahn A, Remahl AIMN. Interleukin-2 gene expression in different phases of episodic cluster headache—a pilot study. *Acta Neurol Scand*. 2011;124(2):130-134. doi:10.1111/j.1600-0404.2010.01434.x

83. Fourier C, Ran C, Zinnegger M, et al. A genetic *CLOCK* variant associated with cluster headache causing increased mRNA levels. *Cephalalgia*. 2018;38(3):496-502. doi:10.1177/0333102417698709

84. Costa M, Squassina A, Piras IS, et al. Preliminary transcriptome analysis in lymphoblasts from cluster headache and bipolar disorder patients implicates dysregulation of circadian and serotonergic genes. *J Mol Neurosci*. 2015;56(3):688-695. doi:10.1007/s12031-015-0567-9

85. Rozen TD. Linking cigarette smoking/tobacco exposure and cluster headache: a pathogenesis theory. *Headache*. 2018;58(7):1096-1112. doi:10.1111/head.13338

86. Rossi P, Allena M, Tassorelli C, et al. Illicit drug use in cluster headache patients and in the general population: a comparative cross-sectional survey. *Cephalalgia*. 2012;32(14):1031-1040. doi:10.1177/0333102412458190

87. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache: II, high tobacco and alcohol consumption in males. *Headache*. 1992;32(4):184-187. doi:10.1111/j.1526-4610.1992.hed3204184.x

88. Rozen TD. Cluster headache clinical phenotypes: tobacco nonexposed (never smoker and no parental secondary smoke exposure as a child) versus tobacco-exposed: results from the United States Cluster Headache Survey. *Headache*. 2018;58(5):688-699. doi:10.1111/head.13295

89. Khoury MJ, Beaty TH, Liang KY. Can familial aggregation of disease be explained by familial aggregation of environmental risk factors? *Am J Epidemiol*. 1988;127(3):674-683. doi:10.1093/oxfordjournals.aje.a114842

90. Guo SW. Familial aggregation of environmental risk factors and familial aggregation of disease. *Am J Epidemiol*. 2000;151(11):1121-1131. doi:10.1093/oxfordjournals.aje.a010156