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Genetics of tension-type headache

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Abstract The objective of this study was to investigate the importance of genetics in tension-type headache. A MEDLINE search from 1966 to December 2006 was performed for “tension-type headache and prevalence” and “tension-type headache and genetics”. The prevalence of tension-type headache varies from 11 to 93%, with a slight female preponderance. Co-occurrence of migraine increases the frequency of tension-type headache. A family study of chronic tension-type headache suggests that genetic factors are important. A twin study analysing tension-type headache in migraineurs found that genetic factors play a minor role in episodic tension-type headache. Another twin study analysing twin pairs without co-occurrence of migraine

showed a significantly higher concordance rate among monozygotic than same-gender dizygotic twin pairs with no or frequent episodic tension-type headache, while the difference was minor in twin pairs with infrequent episodic tension-type headache. Frequent episodic and chronic tension-type headache is caused by a combination of genetic and environmental factors, while infrequent episodic tension-type headache is caused primarily by environmental factors.

Keywords Genetics • Twins • Families • Tension-type headache • Migraine

Classification

The Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias and Facial Pain by the Headache Classification Committee of the International Headache Society provides operational diagnostic criteria for tension-type headache [1]. It divides tension-type headache into an episodic and a chronic form depending on whether the frequency is less than 15 days/month or 15 or more days/month for at least 6 months. This classifica-

tion was revised and renamed the International Classification of Headache Disorders (ICHD) in 2004 [2]. The ICHD is based on the same principles as the 1st edition, but the term “operational diagnostic criteria” has been replaced by “explicit diagnostic criteria”, as the term “operational” is not generally known. “Explicit” means “unambiguous, precise and with as little room for interpretation as possible”. The ICHD subdivides episodic tension-type headache into an infrequent form i.e., <1 day per month on average (<12 days per year), and a frequent

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form i.e., ≥ 1 and < 15 days/month for at least 3 months. The duration for chronic tension-type headache has been reduced from at least 6 months to > 3 months. Although the classifications by the International Headache Society provide very precise diagnostic rules, it is important to emphasise that the frequency cut-off point in tension-type headache is not based on scientific evidence, but is set arbitrarily. However, it is important to have some generally accepted rules and standards in order to be able to compare scientific results and provide the necessary information to be used for future revisions of the classification.

Epidemiology

Prevalence

Table 1 shows the prevalence of tension-type headache in the general population [3–14]. The prevalence varies considerably and is consistently found to be higher in Denmark than in other industrialised countries. Part of the difference is likely to be caused by different age groups and sampling methods.

Sex ratio

The different studies consistently showed a higher prevalence of tension-type headache among women than men [3–14].

Co-occurrence of tension-type headache and migraine

Tension-type headache and migraine are clinically distinct headache syndromes and defined so by the ICHD [1,2]. Tension-type headache is usually characterised by a mild pain intensity, normal or slightly reduced activities and no accompanying symptoms, while migraine is a more severe pain, causing reduced activity/bed rest and is accompanied by photo- and phonophobia, nausea and sometimes vomiting. Osmophobia, a symptom not included in the ICHD, is not experienced by those with tension-type headache, while it is experienced by 43% of those with migraine without aura and 39% of those with migraine with aura [15]. Patients often mentioned stress and mental tension as precipitating factors in both tension-type headache and migraine, while smoking and weather changes are mentioned more often as a precipitating factor in tension-type headache than in migraine [16]. Previous Danish epidemiological surveys of the general population based on interview by a physician do not show diagnostic overlap between tension-type headache and migraine, but a number of patients have co-occurrence of tension-type headache and migraine [5–7, 15, 17]. Table 2 shows that the prevalence of frequent episodic and chronic tension-type headache increases significantly in those with co-occurrence of tension-type headache and migraine as compared to those with exclusively tension-type headache [6]. This result was replicated in a large population-based twin study [7], while earlier population-based studies based on the 1st edition of the ICHD showed a similar tendency [18, 19].

Table 1 Prevalence of tension-type headache in the general population from industrialised countries (from [6], with permission)

Country	Study method	Number of participants	Age (year)	Time period prevalence	Tension-type headache		
					Men (%)	Women (%)	All (%)
Canada [3]	Telephone interview	2,737	> 15	Lifetime	21	37	29
Chile [4]	Questionnaire	1,385	> 14	Lifetime	18	35	27
Denmark [5]	Clinical interview and examination	740	25–64	Lifetime	69	88	78
				One year	63	86	74
				Point	9	16	12
Denmark [6]	Questionnaire	3,425	40	One year	77	91	84
Denmark [7]	Questionnaire	28,195	12–41	One year	79	93	86
Finland [8]	Clinical interview	200	> 15	One year	37	42	40
Germany [9]	Questionnaire	4,061	> 18	Lifetime	36	39	38
Norway [10]	Questionnaire	51,383	≥ 20	One year	22	30	26
Sweden [11]	Telephone lay interview	1,284	17–82	Lifetime	11	16	14
UK [12]	Questionnaire	727	Adults	Lifetime	29	35	32
UK [13]	Questionnaire	882	35–54	One year	42	61	52
USA [14]	Telephone interview	13,345	18–65	One year	38	45	41

Genetics

Family studies

The high prevalence of infrequent and frequent episodic tension-type headache causes a positive family history simply by chance in most families [6, 7]. Thus, genetic epidemiological survey is therefore not likely to elucidate the importance of genetic and environmental factors in the frequent subtypes of tension-type headache. A family study included 122 consecutive probands with chronic tension-type headache, 93 spouses and 377 first-degree relatives [19, 20]. The risk of familial occurrence was assessed by estimating the population relative risk of the

disease in specified groups of relatives [21]. The risk was calculated according to the following equation:

$$\frac{\text{Prob}(\text{relative is affected} \mid \text{proband is affected})}{\text{Prob}(\text{random member of the population is affected})}$$

A family aggregation is implied when this risk ratio significantly exceeds 1. As the prevalence of chronic tension-type headache depends on age and gender, the value of the denominator was adjusted according to the distribution of age and gender in the group of relatives studied. Table 3 shows the population relative risk of chronic ten-

Table 2 The one-year prevalence of tension-type headache in relation to migraine (from [6], with permission)

	Migraine	No migraine
<i>Men</i>	<i>N</i> =413 % (<i>n</i>)	<i>N</i> =2,128 % (<i>n</i>)
No tension-type headache	9.0 (37)	25.8 (548)
Infrequent episodic tension-type headache	38.0 (157)	53.5 (1,139)
Frequent episodic tension-type headache	49.6 (205)	20.0 (426)
Chronic tension-type headache	3.4 (14)	0.7 (15)
<i>Women</i>	<i>N</i> =256 % (<i>n</i>)	<i>N</i> =623 % (<i>n</i>)
No tension-type headache	3.9 (10)	10.4 (65)
Infrequent episodic tension-type headache	34.4 (88)	49.8 (310)
Frequent episodic tension-type headache	56.6 (145)	37.1 (231)
Chronic tension-type headache	5.1 (13)	2.7 (17)

Table 3 Gender standardised lifetime risk of chronic tension-type headache among first degree relatives and spouses of probands with chronic tension-type headache (data are from [17, 18])

	No. of affected first degree relatives		Population relative risk	
	Observed (O)	Expected (E)	Estimated (O/E)	95% CI
Parents	30	7.76	3.87	2.73–5.18
Siblings	18	8.38	2.14	1.31–3.27
Children	23	6.51	3.53	2.30–5.06
All first degree relatives	71	22.61	3.14	2.50–3.86
Spouses	4	4.85	0.82	0.23–2.68

CI, confidence intervals

Table 4 The number of concordant and discordant monozygotic (MZ) and same gender dizygotic (DZ) twin pairs with tension-type headache (from [26])

Tension-type headache	Men		Women		Total	
	MZ	DZ	MZ	DZ	MZ	DZ
No						
Number of pairs						
Concordant pairs	143	146	61	41	204	187
Discordant pairs	285	431	116	169	401	600
Concordance rate						
Probandwise	50	40	51	33	50	38
95% CI	(43–57)	(33–48)	(40–62)	(20–46)	(45–56)	(32–45)
<i>p</i> -values	<0.001		<0.001		<0.001	
Infrequent episodic						
Number of pairs						
Concordant pairs	630	757	674	642	1,304	1,399
Discordant pairs	413	539	377	519	790	1,058
Concordance rate						
Probandwise	75	74	78	71	77	73
95% CI	(73–78)	(71–76)	(76–81)	(68–74)	(75–79)	(71–74)
<i>p</i> -values	n.s.		<0.001		<0.001	
Frequent episodic						
Number of pairs						
Concordant pairs	40	20	148	119	188	139
Discordant pairs	153	188	297	401	450	589
Concordance rate						
Probandwise	34	18	50	37	46	32
95% CI	(21–48)	(2–34)	(43–57)	(29–45)	(39–52)	(25–39)
<i>p</i> -values	<0.001		<0.001		<0.001	
Chronic						
Number of pairs						
Concordant pairs	0	0	1	1	1	1
Discordant pairs	7	6	11	15	18	21
Concordance rate						
Probandwise	0	0	15	12	10	9
95% CI	(–)	(–)	(–52–83)	(–50–73)	(–47–67)	(–45–63)
<i>p</i> -values	–		n.s.		n.s.	
Migraine without aura						
Concordance rate						
Probandwise [27, 28]	29	15	50	37	43	31
95% CI	(3–55)	(–19–49)	(41–59)	(31–43)	(37–49)	(26–36)
Migraine with aura						
Concordance rate						
Probandwise [29, 30]	53	29	48	15	50	21
95% CI	(35–71)	(15–43)	(32–64)	(4–26)	(38–62)	(12–30)

sion-type headache among first-degree relatives and spouses [19, 20]. Compared with the general population, first-degree relatives had a significantly increased risk of chronic tension-type headache, while spouses had no increased risk of chronic tension-type headache. An

increased risk can be caused by both genetic and environmental factors. Probands and spouses in part share their environment but differ in genetic constitution. The data support the importance of genetic factors in chronic tension-type headache, as first-degree relatives had a signifi-

cantly increased risk of chronic tension-type headache, while spouses had no increased risk of chronic tension-type headache. A complex segregation analysis of chronic tension-type headache suggests multifactorial inheritance without generational differences [22]. The effect of co-occurrence of migraine was not investigated in the family study of chronic tension-type headache. Thus, the result might be biased due to the increased family risk of migraine without aura and migraine with aura [23].

Twin studies

A twin study of episodic tension-type headache concluded that environmental influence is of major importance for episodic tension-type headache and a genetic factor, if it exists, is minor [24]. This study was based on twin pairs selected for migraine features and the interrelation of tension-type headache and migraine was not addressed [25]. Infrequent and frequent episodic tension-type headache were analysed together as the first edition of the International Headache Society classification operated with episodic tension-type headache [1]. Although all twins were interviewed by physicians, the result is likely to be biased due to selection of twin pairs with co-occurrence of migraine. Another population-based twin study analysed twin pairs without co-occurrence of migraine

(Table 4) [26]. The probandwise concordance rates were significantly higher in monozygotic than same-gender dizygotic twin pairs with no or frequent episodic tension-type headache, while the difference was not significant in chronic tension-type headache due to small number of twin pairs. The concordance rates of infrequent episodic tension-type headache in monozygotic and same-gender dizygotic twin pairs were significantly different in women but not in men, although the difference was small in both genders. The difference in concordance rates in no and frequent episodic tension-type headache is similar to that of migraine without aura, while it was less than that of migraine with aura [27–30].

Conclusions and future studies

Infrequent episodic tension-type headache is primarily caused by environmental factors, while frequent episodic and chronic tension-type headache is caused partly by genetic factors. It is expected that identification of genetic markers will be difficult due to multifactorial inheritance. A road to success might be identification of large families with chronic tension-type headache without co-occurrence of migraine possibly caused by autosomal dominant inheritance.

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