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GRBT050-68 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 22:5

Chapter 68

Genetics of Tension-Type Headaches

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Tension-type headache is classified as infrequent, frequent, and chronic types with or without pericranial tenderness (1).

INFREQUENT EPISODIC TENSION-TYPE HEADACHE

The lifetime prevalence of infrequent episodic tension-type headache (ETTH) among 40-year-olds from the general population is 53%: 50% among women and 55% among men (7). The high prevalence causes a positive family history simply by chance in >92% of the families, if the proband has four first-degree relatives (parents, siblings, and children). One or both parents are affected by chance in >77% of the families. Thus, a positive family history does not necessarily suggest the importance of genetic factors. Due to the high prevalence, a genetic epidemiologic survey is not likely to elucidate the importance of genetic and environmental factors. Infrequent ETTH is most likely a heterogeneous disorder that can be caused by different mechanisms, and for that reason pathophysiologic studies may be helpful.

FREQUENT EPISODIC TENSION-TYPE HEADACHE

The lifetime prevalence of frequent ETTH headache among 40-year-olds from the general population is 20%: 31% among women and 13% among men (7). Thus, the gender ratio is different from that of infrequent ETTH and similar to that of chronic tension-type headache (3). This indicates that the subdivision of frequent ETTH and CTTH is arbitrary and not necessarily precise. The frequency cut-off point is not based on scientific evidence, so it is important to take that into consideration in future studies. A population-based twin study analyzed infrequent and frequent ETTH and found that the phenotypic variation consisted of 81% nonshared environmental effects and of 19% additive genetic effects (6). The twin population was selected among twin pairs where at least one twin had self-reported migraine or severe headache.

CHRONIC TENSION-TYPE HEADACHE

A genetic epidemiologic survey included 122 probands from a headache clinic (2). The first-degree relatives and spouses ages 18 years or above were interviewed by a neurologic resident. Table 68-1 shows CTTH assessed by proband report compared to the clinical interview. The observed agreement rate was 82% and kappa, the agreement rate corrected for chance agreement, was 48% (5). This indicates that a direct interview of all the participants is necessary in family studies of CTTH.

The familial occurrence was assessed by estimating the population relative risk (8).

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

A family aggregation is implied when this risk ratio significantly exceeds 1.

The 1-year period prevalence of CTTH is 3%: 5% among women and 2% among men (3). The lifetime prevalence has been estimated to be twice the 1-year period prevalence (5). As the prevalence of CTTH 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. Compared with the general population, first-degree relatives had a threefold increased risk of chronic tension-type headache, while spouses had no increased risk of chronic tension-type headache (2). The result suggests that genetic factors are important in CTTH. The gender of the proband did not influence the risk of CTTH among first-degree relatives. Neither were there

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GRBT050-68 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 22:5

TABLE 68-1 Sensitivity, Specificity, and Predictive Values of Chronic Tension-Type Headache Assessed by Proband Report Compared to the Clinical Interview

		Clinical Interview			
		Yes n (%)	*No n (%)*	*Total n (%)*	*Kappa 95% CL*
Proband report	Yes	48 (13)	43 (11)	91 (24)	0.48
	No	23 (6)	263 (70)	286 (77)	(0.37; 0.60)
	Total	71 (19)	306 (81)	377 (100)	
Sensitivity: 68% (48/71)			PVpos: 53% (48/91)		
Specificity: 86% (263/306)			PVneg: 92% (263/286)		

CL denotes confidence limits. From Russell MB, Ostergaard S, Bendtsen L, et al. Familial occurrence of chronic tension-type headache. Direct versus indirect information. *Cephalalgia* 1999;19:207–210, with permission.

any differences in the risk among parents, siblings, and children.

MODE OF INHERITANCE

A complex segregation analysis of the families mentioned above gave the sporadic model (i.e., no family resemblance, a poor fit compared with the multifactorial model) (4). None of the three models that incorporated a major locus (i.e., recessive, additive, and dominant major locus) explained the observed segregation pattern better than the multifactorial model. Thus, the complex segregation analysis supported that CTTH has a genetic cause, since the multifactorial model had a significantly better fit than the sporadic model. A complex segregation analysis cannot detect that one phenotype is caused by different genotypes (i.e., genetic heterogeneity). Thus, multifactorial inheritance may alternatively reflect genetic heterogeneity of CTTH.

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