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·Minireview·

Migraine as a sex-conditioned inherited disorder: evidences from China and the world

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Abstract: Migraine is a complex and heterogeneous disorder. Although several genetic models has been proposed including autosomal-dominant/autosomal recessive, sex-linked, sex-limited, mitochondrial, and multi-gene, none of these models can well-explain the transmission of the disease. We hypothesied that migraine is a sex-conditioned inherited disorder (autosomal dominant in females and autosomal recessive in males). This hypothesis is supported by the evidence such as the locations of genes associated with familial hemiplegic migraine, possibly "typical" migraine as well (dominantly on chromosome 19p, 1q, and 2q), male:female ratio of prevalence (1:2-1:4), the mostly youth-onset, the provocation by the contraceptives, the induction by menstruation, and the self-limitation after menopause. Female sex-hormones appear to be the key contributor to a higher prevalence of migraine in female. Socio-environmental factors may also play an important role.
Keywords: epidemiology; genetics; migraine; familial hemiplegic migraine

1 Introduction

Migraine is manifested by disabling headache that is usually unilateral and frequently pulsatile in quality. It is often associated with vomiting, photo- and phonophobia, lassitude and malaise (migraine without aura)[1,2]. Additional transient focal neurological (aura) symptoms (migraine with aura) may occur in about 20% of patients. The frequency, duration and severity of the attacks vary substantially even in a single patient. Worldwide, up to 24% of females and 12% of males in the general population are affected by migraine[4]. However, the prevalence in China (including mainland, Hong Kong, Macao, and Taiwan) is less than 1% although the patient population is as large as ten millions. The heredity of migraine is not fully understood yet. For over 50 years, migraine has been thought to conform to autosomal transimission with a considerable genetic heterogeneity. Whether this transmission is autosomal dominant (AD) or autosomal recessive (AR) is not clear. In fact, neither of models can explain the varied genetic features of all affected families. In this paper, we summarized the evidence mainly from the research in Chinese population as well as the world and hypothesized that migraine is a sex-conditioned hereditary disorder (AD in the female and AR in male). We believe that this model may better describe the complex transmission of the disease.

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2 Migraine epidemiology in China

Migraine headache, along with vertigo and dizziness, account for 90% of the complaints of patients visited in general neurology clinic. Based on the literature published in the period 1961-1978, Goldstein and Chen found that the prevalence of adult migraine was 9.1% in male and16.1% in female[5]. Because there were no data available regarding the prevalence in China in that period, an area that accounts for 20%-25% of the entire world population, Bruyn made a conservative estimate of 1.5%-2.0%[6]. In 1982, an international neuroepidemiological investigationpartly sponsored by National Institutes of Health (NIH) and World Health Organization (WHO)[7] screened 63 195 Chinese citizens, in which 396 migraine cases (88 males and 308 females) were identified from six Chinese cities (Tab. 1). The prevalence was 0.63%. In

Tab. 1 Gender difference of migraine prevalence in China

	Male	Female	M:F
Wang WJ *et al.*, 1982 (six Chinese cities)	88/63195	308/63195	1:3.5
Gou SS *et al*., 1986 (Mainland China)	7547/1921369	30261/1916228	1:4.0

the same year, in a more extensive study in mainland China, Gou identified 37 808 migraineurs out of 3 837 597 participants, which had a similar prevalence (0.99%) as the one found in previous study (0.76% and 0.73% according to the standardization of the Chinese and World populations in 1982, respectively; Tab. 2)[8]. Subsequently, a study reported the prevalence of 1.0% in Hong Kong and 3% at Kimmen island of Taiwan[9]. Overall, the prevalence of migraine in China is 0.6%-1.0%, much lower than the rate of 10%-20% in Europe and the USA[4] (Fig. 1).

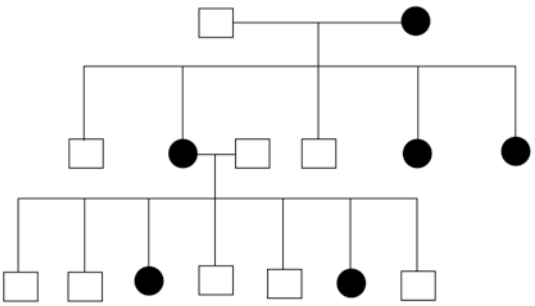

Fig. 1 A MoA pedigree in Anhui province of China. Note: The black represents migraineur; the square represents the male and the ball represents the female.

In addition to the estimate of prevalence, the 1982 neuroepidemiological investigation[7] showed a crude incidence rate of 0.027% (standardized rate: 0.021%). Gou *et al.* found 3 092 migraineurs in their study who had first attacks in that year[8]. They reported a slightly higher incidence rate of 0.0797% (0.0740% and 0.0658% according to the population standardization for China and the world, respectively).

Migraine attacks may occur at any age. The incidence grows steadily before the age of 40 years and then starts to decrease gradually from the peak stage. Most first attacks in females occur between the ages of 15 and 24 years and very few cases are found after the menopause. The highest incidence is found in females aged 25-39 years. The prevalence of migraine in females is much higher than in males, especially from 10 to 50 years of age.

Tab. 2 Primary epidemiological data: male to female ratio in provinces of China except for Taiwan, Hong Kong and Macao in 1986[8]

Province	Male	Female	M:F
1 Tibet (Xizang)	149/15880	489/15930	1:3.3
2 Hubei	364/54061	1554/51066	1:4.5
3 Hunan	349/53202	1551/51469	1:4.7
4 Ningxia	216/29206	1108/36408	1:4.1
5 Inner Monglia	169/29029	1154/37825	1:5.2
6 Shaanxi	514/86383	2425/78943	1:5.2
7 Gansu	571/86160	2399/78479	1:4.6
8 Xinjiang	189/44658	1442/48387	1:7.0
9 Qinghai	310/52390	1431/50192	1:4.8
10 Guizhou	184/48474	1271/45036	1:7.4
11 Guangxi	93/39867	1088/39523	1:11.8
12 Jiangxi	219/54920	1250/51221	1:6.1
13 Yunnan	1109/214842	4435/219258	1:3.9
14 Jilin	216/51048	972/50922	1:4.5
15 Anhui	160/53968	755/50308	1:5.1
16 Liaoning	248/73023	1021/73307	1:4.1
17 Heilongjiang	354/62917	580/60286	1:1.7
18 Guangdong with Hainan	211/89851	1128/87538	1:5.5
19 Henan	212/54617	554/49285	1:2.9
20 Tianjin	129/36142	396/37425	1:2.2
21 Shanxi	221/65968	562/83301	1:2.0
22 Sichuan with Chongqing	360/107797	485/105407	1:1.4
23 Beijing	153/50093	198/53703	1:1.2
24 Fujian	110/60773	310/61503	1:2.8
25 Hebei	120/56143	258/56040	1:2.2
26 Shanghai	168/102673	504/100391	1:3.1
27 Jiangsu	104/56635	242/55202	1:2.4
28 Shandong	204/105840	413/106108	1:2.0
29 Zhejiang	141/84809	286/81765	1:2.8
Total	7547/1921369	30261/1916228	1:4.0

3 Biological mechanisms

3.1 Vasospasm or cortical inhibition? Traditionally, migraine is thought to occur due to a spasm in one or more

cerebral arteries, which leads hyperperfusion. In this phase, atonic arteries, especially those extracranial ones, cause headache attacks[10]. Olesen demonstrated that no focal or generalized abnormalities of regional cerebral blood flow (rCBF) in the migraine without aura (MoA) were observed during attacks and rCBF did not differ during attacks, after treatment, and outside of attacks[11]. He emphasized the importance of calcium entry blockers, β-adrenoreceptor and engotamine in the control of the attacks. Migraine with aura (MA) is not caused by spasms in major cerebral arteries but a disorder spreading gradually in the cerebral cortex, possibly a spreading depression of Leao or a usual aura or permanent neurologic deficits. Van der Kamp studied interictal cortical excitability by magnetic stimulation in MA and familial hemiplegic migraine (FHM) patients and found that the level of excitability in migraine fluctuated and patients with FHM had a decreased interictal excitabilityon the affected side[11].

3.2 Hormone effect The peak incidence of migraine seen in young women is synchronized with the peak secretion of estrogen and it decreases with a self-limited tendency during the menopause[1,6]. Wang reported that in 17.2% of female migraineurs, the provocation factor was the menses period[6]. All the clinical phenomena and symptoms appear to be linked to female hormones, suggesting that estrogen fluctuation may be matched with the cycle of migraine. In addition, migraine attacks can be induced by oral contraceptives, which further supports this hypothesis. Nattero found that the deficiency of PGI_2 might be the classic feature of menstruation migraine[13]. PGI_2 is a strong vasodilator and an inhibitor of platelet aggregation. Together with TXA_2, a vasoconstrictor and platelet aggregator, they might be associated with the disorders of vasosystalic regulation in migraine.

3.3 Role of 5-HT in migraine Serotonin or 5-HT plays a major role in the pathogenesis of migraine. In humans, approximately 90% of total 5-HT is in the gut, 8% in blood platelets, and 2% in the nervous system, which suggests that the central nervous system regulates blood 5-HT release mainly by neuroendocrine pathway, and the high level of 5-HT in the gastrointestinal tract might be the cause of "vomiting" migraine. Danish specialists studied steroscopic electrical potentials of 5-HT by Magnetic Resonance Imaging and modern computer graphic techniques[12]. They identified 6 types of 5-HT conformations, mainly depending on the lateral radicals ($CH_2CH_2NH_2$). These 5-HT stero-conformations could be influenced by the local electrode ion densities and pH level. Seven distinct families of 5-HT receptors ($5\text{-}HT_1$ to $5\text{-}HT_7$) have been identified and each of these receptors has multiple subtypes (for example, $5\text{-}HT_1$ is divided into $5\text{-}HT_{1A}$ to $5\text{-}HT_{1F}$)[15].

The exact role of 5-HT in migraine is still controversial. Study findings demonstrated that typical migraine headache might be induced by m-CPP, a $5\text{-}HT_1$ receptor agonist, and low-dose resperpine was consistently involved in the mobilization of endogeneous 5-HT from both neuronal and non-neuronal sites. Such resperpine-induced headaches could be prevented by methysergid ($5\text{-}HT_2$ receptor antagonist)[17]. On the other hand, Ferrari[18] studied the metabolism of 5-HT by high-performance liquid chromatography and electrochemical methods and found that in addition to $5\text{-}HT_1$ receptor agonists, $5\text{-}HT_3$ receptor antagonists also demonstrated treatment effects on patients with acute stage of migraine. He also found that in MA and MoA migraineurs, serum 5-HT decreased in the interictal period but 5-HIAA increased during the intermittent time. While the patients' serum 5-HT increased (without MA), 5-HIAA decreased, and the activities of Phenolsulfotransferase M (PST-M) and monoamine oxidase (MAO) declined. Hanington[19] showed that platelet MAO levels increased as age increases, which could be an explanation of age-associated self-limitation of migraine attacks. Based on the fact that 5-HT gradually decreases after the climacteric, pharmacologic agents of 5-HT receptor agonists, such as eletriptan (a 5-HT1B/1D receptor agonist), are used to treat migraine.

4 Migraine genetics

4.1 Genetic models Migraine has been regarded as an inherited disorder for decades, characterized by gender difference but not sex-linked. Pedigree analysis found that 5 out of 7 generations, or 3 out of 5 generations were affected, indicating a positive rate of 50%-80%[1]. Precisely, the positive rate was 46% if the pedigrees included parents and sisters/brothers, or 55% if they included grandparents and grandparents-in-law[1]. The genetic risk seems to be the highest in patients with FHM and basoarterial migraine. The mode of inheritance of migraine is not clear. Wolff proposed an AR model. Allan (1933), Barolin (1970), and Walton (1978) believed an AD model[1]. Others hypothesized X-linked dominant or recessive, mitochondrial, and multi-gene transmissions.

However, none of these models explain the uneven sex ratio (M:F = 1:2-1:4) of migraine prevalence. In an elegant study, Ulrich *et al.* analyzed 31 MA families and found that both first and second-degree relatives outside the nuclear families were at significant lower risk of MA than expected[19]. Their results suggest that AD inheritance with or without reduced penetrance was unlikely, AR model was also unlikely because of the unequal sex distribution, mitochondrial and the X-linked transmissions were not possible, and female preponderance was too low to explain a sex-influenced inheritance. We observed a MoA pedigree in Anhui province of China, in which 6 MoA cases were identified. The transmission has following features: (1) consecutive attacks in all three generations; (2) all cases were females; (3) the prevalence was as high as 40%. This finding suggests an AD transmission in females of this family (Fig.1).

4.2 Genes associated with migraine Genetic factors are involved in migraine, most likely as part of a multifactorial mechanism[28]. FHM is a rare autosomal dominant subtype of migraine. One FHM gene has been identified on chromosome 19p13 in about 50% of the migraine families tested[20,21]. The second locus on chromosome 1q21-23 was found in French FHM[22], which is characterized by considerable heterogeneity, lower penetrance, and epileptic seizures that differs from the migraine linked to chromosome 19p13. Gardner *et al*. detected a new FHM locus that is on 1q31 in a German-native American family, featured with incomplete penetration and variable expressivity of the headache[23]. However, an attempt to identify the chromosomal locations of the candidate genes 5-HT_{1D} (1p36.3-34.3), 5-HT_{1B} (6p13), 5-HT_{2A} (13q14-21), 5-HT transporter (17q11.2-12), CACNLB1 (17q11.2-22) and FHM locus (19p13) was failed[24].The 11084 A to G base substitution was not confirmed to be the gene for the ND4 subunit of respiratory complex 1 as found in 25% of Japanese migraineurs[25] and the mutation of this gene was not associated with the migraine in Denmark. No differences or trends in allele or genotype frequencies of 5-HT_{2C} receptor gene were found in migraineurs[9]. Although a common complement C3 polyporphism has been found no association with migraine susceptibility, the dopamine D_2 receptor NcoI allele is associated with clinical susceptibility to MA and antagonists of the D_2 receptor have been reported to be effective in the treatment of acute migraine[26]. The polymorphism of endothelial nitric oxide synthase failed to be linked with migraine[27] .Guida proposed that FHM as well as episodic ataxia type 2 and spinocerebellar ataxia type 6 were genetic disorders caused by the mutation of CACNA1A gene, supported by their report of the first functional analysis of an EA2 phenotype associated new missense mutation found in exon 28 which was predicted to change a highly conserved phenylalanine residue to a serine at codon 1491 in the putative transmembrane segment S6 of domain III[28]. This hypothesis is also supported by the study conducted by Trettel *et al.*[30], which reported that the P/Q-type Ca^{2+} channel alpha (1A) subunit gene (CACNA1A) on the short arm of chromosome 19 between the markers D19S221 and D19S179 was associated with the three disorders. The FHM3 associated gene SCN1A, located on chromosome 2q24, encodes α1 subunit of the neuronal voltage-gated sodium channel Nav1.1[29]. More than 150 mutations in SCN1A have been found in families with generalized epilepsy or some rare epilepsy[30].

5 Discussion

Epidemiological evidence from studies on migraine in China and demonstrate that the first attacks usually occur during the youthful stage of life, a higher frequency of attacks is induced by menstruation, and migraine could be provoked by oral contraceptive use and is self-limited after the menopause. These features suggest that the fluctuation of female sex hormones is associated with the "natural" course of migraine. PG_{I2}/TX_{A2}, neuropeptides, 5-HT, and other sex-related biochemical mediators might also play substantial roles in the pain onset and maintenance of the disease.

Sex steroid hormones have an important influence on neuro-endocrine and behavioral function of brain [31] by modifying neuronal excitability. Unbalanced synthesis may lead to pathophysiological conditions such as migraine, epilepsy, depression, and anxiety. To explain the unequal gender distribution of migraine (F:M = 2:1-4:1), Wang first advanced the genetic hypothesis of a sex-conditioned model[32]. A classical example of a sex-conditioned inherited disorder is genetic baldness (GB), in which male heterozygotes are affected (AD) but female heterozygotes are not (AR). GB is associated with the high serum level of the male sex hormone (androgen). It is possible that migraine, the disease with a higher prevalence in females, is also a sex-conditioned inherited disorder associated with high serum level of the sex hormone (estrogen in this case). The fact that the locations of

genes associated with migraine are on chromosome 1q21-23, 2q24 and 19q13 suggest an autosomal transmission. However, this transmission is very likely influenced by genes in sex chromosome (sex-conditioned), resulting in unequal sex distribution of the disease. The sick homozygotes with either AR or AD transmission express the abnormal phenotype (migraine).

Sex-conditioned inheritance is not rare. In addition to GB and possibly migraine, it is also seen in other human diseases such as short-index-finger, Heberden nodes, and Aarskog's faciodigitogenital syndrome. Recently, some genes linked with the development of rheumatoid arthritis has been shown to be expressed in a sex-conditioned mode[35]. In addition, the cross-chromosome interaction similar to conditioned regulation can be seen in other disease such as Wilson disease[33,34], indicating an important role of chromosome-chromosome interaction in the development of genetic diseases.

It has to be pointed out that although migraine has been clearly linked with genetic factors, it is likely a multifactorial disorder. Other factors such as environments, stress and cultures may also contribute to the development of the disease. While the AD model only fits the transmission of FHM, our sex-conditioned hypothesis, which includes the mutifactorial components, explains all types of migraine well.

6 Conclusion

Migraine has been considered a "variable" hereditary disorder, characterized by gender difference[36]. However, none of the existing genetic models including AD/AR, sex-linked, sex-limited, mitochondrial and multi-gene model can explain the complex transmission of the disease. Recent discovery of mutations in neural calcium channels, mitochondrial DNA, serotonin receptors and transporter, dopamine receptors[37], the investigation of genetic prothrombotic risk factors, and the genetic linkage and association studies performed worldwide, represent the efforts to unveil the genetic basis of migraine. Although increasing genetic knowledge may help us clarify the role of certain genes in the development of migraine, it is unlikely to conclude that this disease is only determined by genetic causes. The complex and heterogeneous nature of the disorder[38] suggest the involvement of other elements such as socio-environmental factors[39,40].

This study proposed a sex-conditioned genetic model based on the published evidence from China as well as the world. We hypothesized that migraine transmission is autosomal-dominate in female and autosomal-recessive or "incomplete penetrance" in male. Nevertheless, although this model can better explain the complexity of migraine inheritance, it is still a scientific hypothesis. Further study is necessary to test its accuracy.

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偏头痛是从性性状式遗传疾患？来自中国以及世界的证据

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摘要：偏头痛是一种复杂的多样性疾患。尽管此前已提出包括常染色体显性/常染色体隐性, 伴性性状，限性性状，线粒体性及多基因性遗传模式，但均难以很好地解释该病的遗传性。笔者设想偏头痛为从性性状式(Sex-conditioned)遗传性疾患，即在男性患者为常染色体隐性遗传，在女性为常染色体显性遗传。支持此假设的证据有：家族性偏瘫性偏头痛以及其它一些经典的偏头痛疾病相关基因位于在常染色体 19p，1q 和 2q；男女性别比为 1:2-1:4；大多数在青年期前后发病；避孕药可以诱发；月经期好发；女性绝经期常自愈。女性性激素可能是该病在女性中高发的关键因素。此外，环境和人文经济因素亦可能具有重要作用。

关键词：流行病学；遗传学；偏头痛；家族性偏瘫性偏头痛