J Hum Genet (2008) 53:592–597
DOI 10.1007/s10038-008-0287-x

ORIGINAL ARTICLE

Positive association of the *FTSJ1* gene polymorphisms with nonsyndromic X-linked mental retardation in young Chinese male subjects

Ling Dai · Lianxi Xing · Pingyuan Gong · Kejin Zhang · Xiaocai Gao · Zijian Zheng · Jianping Zhou · Yale Guo · Shaoping Guo · Fuchang Zhang

Received: 21 January 2008 / Accepted: 16 March 2008 / Published online: 10 April 2008

Abstract To investigate the possible genetic association of nonsyndromic X-linked mental retardation (NS-XLMR) with *FTSJ1* gene polymorphisms, a case–control association study was performed focusing on the Chinese Han population in the Qinba mountain region. Three common single nucleotide polymorphisms (SNPs) (rs2268954, rs2070991, rs5905692) in the gene were selected and genotyped using the polymerase chain reaction single-strand confirmation polymorphism (PCR–SSCP) method. Pairwise linkage disequilibrium (LD) analysis showed that the three SNPs were in strong LD (all $D' > 0.8$). There were significant differences between cases and controls in allele frequency distribution of rs2268954 ($P = 0.036$), rs2070991 ($P = 0.043$), and rs5905692 ($P = 0.014$) and in the distributions of common haplotypes combined by these SNPs (global $P = 0.01236$) in male subjects. In female subjects, however, no positive results were found. Our results suggest a positive association between the genetic variants of the *FTSJ1* gene and NS-XLMR in young male subjects in the Chinese Han population in the Qinba region.

L. Dai · L. Xing · P. Gong · K. Zhang · X. Gao · F. Zhang (✉)
School of Life Science, Institute of Population and Health, Key Laboratory of Resource Biology and Biotechnology in Western China, Northwest University, Ministry of Education, 229 Tai Bai Road, Xi'an 710069, China
e-mail: zhfch@nwu.edu.cn

Z. Zheng
School of Public Management, Institute of Application Psychology, Northwest University, Xi'an 710069, China

J. Zhou · Y. Guo · S. Guo
Second Hospital, Xi'an Jiaotong University, Xi'an 710004, China

Keywords Non-syndromic X-linked mental retardation (NS-XLMR) · *FTSJ1* · Association study · Single nucleotide polymorphism (SNP) · Haplotype analysis

Introduction

X-linked gene defects have long been considered important causes of mental retardation on the basis of the observation that mental retardation is significantly more common in male subjects than in female subjects (Lehrke 1972, 1974). X-linked mental retardation (XLMR) is subdivided into syndromic (S-XLMR) and nonsyndromic (NS-XLMR) forms depending on whether further abnormalities (in addition to mental retardation) are found on physical examination, laboratory investigation, and brain imaging. NS-XLMR accounts for approximately two thirds of all cases, and as many as 100 different genes on the X chromosome may be involved in this condition (Gecz and Mulley 2000). Studying genes of NS-XLMR has been one of the hotspots in this field.

FTSJ1 is a human homolog of the *Escherichia coli* 2′-*O*-rRNA methyltransferase FtsJ/RrmJ gene (Ogura et al. 1991; Caldas et al. 2000) and is functionally unrelated to all previously identified NS-XLMR genes. It is located on chromosome Xp11.23 and harbors 13 exons, of which exons 2–9 encode a highly conserved FtsJ domain—*S*-adenosylmethionine (SAMe)-binding domain (Ramser et al. 2004). It is expressed widely in fetal tissue, including brain, lung, liver, and kidney. Remarkably, expression is highest in fetal brain. In the adult brain, it is expressed in amygdala, caudate nucleus, corpus callosum, hippocampus, and thalamus (Freude et al. 2004). Human FTSJ1 protein is presumed to function as a ribonucleic acid (RNA)

methyltransferase modifying untranslated RNAs and thereby plays a critical role in protein translation, that is, participate in gene expression regulation (Freude et al. 2004). According to Renieri et al. (2005), gene expression regulation is an important cellular process that is altered in patients with MR.

Different mutations in *FTSJ1* were found in family MRX44 (Hamel et al. 1999) and two other families when Freude et al. (2004) performed a systematic mutation screen of brain-expressed genes at Xp11. Northern blot hybridizations suggest that the phenotype in these families most likely results from functional loss of FTSJ1 protein due to these mutations. Ramser et al. (2004) also identified a splice-site mutation in the *FTSJ1* gene in a large Belgian family denominated as MRX9 (Willems et al. 1993). Reports about the association of the *FTSJ1* gene with NS-XLMR are all family-based studies using linkage analysis. Most of the mutations identified in the *FTSJ1* gene are single-site mutations (Freude et al. 2004; Ramser et al. 2004; Froyen et al. 2007). The patients of these families are all male subjects and are European. Association between *FTSJ1* gene variations and NS-XLMR in the Chinese Han population has not been reported. In this study, three SNPs were chosen as genetic markers, and a case–control study was conducted to investigate the association of the *FTSJ1* gene with NS-XLMR of children in the Qinba mountain region and whether there is a gender-specific effect of this gene.

Materials and methods

Subjects

All 556 Chinese Han subjects were recruited in the Qinba mountain region. There was a high prevalence of MR in this relatively isolated and mountainous area. The incidence ratio of 0- to 14-year-old children was about 3.19%(Guo et al. 2004). The epidemiological survey revealed family aggregation of MR in this region (Zhang et al. 2005, 2006), suggesting that genetic factors might play an important role in the etiology of MR. The intelligence of each child was screened using the Chinese Wechsler Young Children Scale of Intelligence (C-WYCSI) (Gong and Dai 1992) for 4- to 5-year-old children, and the Chinese Wechsler Intelligence Scale for Children (C-WISC) (Gong and Cai 1993) was used for 6- to 14-year-old children. The social disability (SD) scores were assessed using the adaptive scale for infants and children revised by Zuo et al. (1988). The children whose IQs were <70 combining SD scores of 8 or lower were classified as MR, and the children whose IQs were 70–79 with SD scores of 9 were classified as a borderline. The definition and the diagnosis criteria of MR and borderline were based on the *Chinese Classification of Mental Disorders, Second Revision* (CCMD-2-R; Psychiatry 1995) and the classification of mental and behavioral disorders from the World Health Organization (WHO) (T.W.H.Organization 1992). Subsequently, clinical examination and laboratory investigation were carried out by a group of psychologists, pediatricians, and neurologists to evaluate the children with an IQ < 80 and SD scores of 9 or lower. Cases of MR affected by pregnancy infection, toxicity, caecotrophy, birth asphyxia, cretinism, chromosomal syndrome, or other diseases such as nervous system diseases and metabolic diseases were excluded. Subjects who belonged to the genetic basis of NS-MR were included in the cases group. Controls came from the same areas and were randomly selected from families without history of MR, and there was a similar age and gender distribution to cases. In total, there were 118 cases of MR (56 boys and 62 girls), 116 borderline MR (52 boys and 64 girls), and 322 controls (167 boys and 155 girls) recruited for the study according to age, gender, and habitations.

All subjects were of the Chinese Han population and were randomly collected. Written informed consent was obtained from either the participant or the participant's guardian after the procedure had been fully explained. The protocol was reviewed and approved by the Ethical Committee of the National Human Genome Center.

Variants identification and genotyping

FTSJ1 spans ~10 kb in the human genome. According to the *LDView* (http://www.ensembl.org/Homo_sapiens/ldview), of the total six tagged single nucleotide polymorphisms (SNPs) within the *FTSJ1* gene, there are four tagged SNPs (rs2268954, rs2070991, rs7066831, and rs5905692) with minor allele frequency >5%. We tested allele frequencies in 48 individuals randomly chosen from subjects by using polymerase chain reaction single-strand confirmation polymorphism (PCR–SSCP) method. The rs7066831 was then excluded from the study because of no polymorphism. Finally, three tagged SNPs with minor allele frequency >5% (rs2268954, rs2070991, and rs5905692) were selected. The three tagged SNPs nearly cover the entire gene: rs2268954 in intron 1, rs2070991 in intron 8, and rs5905692 in intron 12. The PCR–SSCP method was used in genotyping the three SNPs, and the detailed information is described in Table 1.

Statistical analysis

Demographic data (including the age and gender) and alleles and genotype frequencies for the three SNPs were prepared using the SPSS 10.0 software (SPSS, Chicago, IL, USA) and Microsoft Visual Studio 6.0 package (Microsoft

Table 1 Single nucleotide polymorphisms (SNPs) of *FTSJ1* and their corresponding primers

SNPs	Primers	Allele
rs2268954	Forward: 5′-CCACCATAGCCCAACTA CTGA-3′	C\T
	Reverse: 5′-GGGATGGCAGAGTAAGCAAC-3′	
rs2070991	Forward: 5′-CGTAAGAATGGTCCAGCAGG-3′	A\G
	Reverse: 5′-ATCTCTGGGACGCCGACT-3′	
rs5905692	Forward: 5′-AGGTTTGGAGATAGAGCAG-3′	C\T
	Reverse: 5′-CCTGATTCTCTTCACCCT-3′	

Corporation, Washington, DC, USA). For each polymorphism, Hardy–Weinberg equilibrium (HWE) was tested using the Haploview program (http://www.broad.mit.edu/mpg/haploview/; Barrett et al. 2005). Differences in allele and genotype distributions were assessed by the Monte Carlo method with the CLUMP 2.3 with 10,000 simulations (Stephens et al. 2001). Haploview was also used to estimate pairwise linkage disequilibrium (LD) of all possible pairs of the three polymorphisms. Odds ratio (OR) and 95% confidence interval (CI) was measured with CI calculator (Newcombe 1998). Haplotypes were inferred by Bayesian methods (Stephens et al. 2001) and implemented in the UNPHASED package version 3.0.6 (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/; Dudbridge 2003). Statistical significance was defined as $P < 0.05$. Statistical power analysis was performed using the G*Power program (Erdfelder et al. 1996).

Results

We analyzed the rs2268954, rs2070991, and rs5905692 SNPs in 322 controls and 118 MR (MR) and 116 borderline MR (border) children. Genotype frequencies of all three markers showed no deviations from Hardy–Weinberg equilibrium (HWE). A breakdown comparison of *FTSJ1*, an X-linked gene, was conducted between cases and controls within different gender groups.

Single locus analysis

In the male group, results of single locus analysis using CLUMP showed that there were statistical differences in allele frequencies between cases and controls for all three SNPs. The T-allele frequency of rs2268954 was higher in cases (66.7%) than in controls (49.3%, $P = 0.036$, OR = 2.053, 95% CI 1.041–4.05). The G-allele frequency of rs2070991 was higher in cases (72.0%) than in controls (55.9%, $P = 0.043$, OR = 2.029, 95% CI 1.016–4.05). The C-allele frequency of rs5905692 was higher in cases (70.8%) than in controls (50.7%, $P = 0.014$, OR = 2.365, 95% CI 1.174–4.761). No differences of allele or genotype frequencies were observed among the compared groups (MR cases vs. controls, or borders vs. controls) at these three markers in the female group (Table 2).

Haplotype analysis

To identify the possible haplotypes for the three target SNPs, pairwise LD analysis was performed for each pair of the three SNPs. The D' value and r^2 value of each pair of SNPs demonstrated that the three SNPs were in strong LD (all $D' > 80\%$) (Table 3). Therefore, haplotype analysis was performed subsequently for haplotypes with probabilities >5%, which represented the majority of haplotype diversity.

In the analysis of the male group, there were significant differences between cases and controls in haplotypes T-G-C and C-A-T in rs2268954 (C/T), rs2070991 (A/G), and rs5905692 (C/T). The frequency of haplotype T-G-C was higher in cases (69.57%) than in controls (45.89%, $P = 0.0135$, OR = 2.191, 95% CI 1.127–4.261). At the same time, the frequency of haplotype C-A-T was lower in cases (28.26%) than in controls (45.89%, $P = 0.01202$, OR = 0.576, 95% CI 0.292–1.135). The global haplotype frequency also showed significant differences between cases and controls ($P = 0.01236$ from UNPHASED software). However, no differences of haplotype frequencies were observed between cases and controls at these three markers in the female group. All P values corresponding to haplotypes are shown in Table 4.

Power analysis

A power analysis was performed using the G*Power program, which is based on Cohen's method (Erdfelder et al. 1996). The sample size revealed >95% power for detecting significant association ($P < 0.05$), even if the tested variations had a weak to moderate gene effect (under a lower effect size index of 0.25).

Discussion

Three SNPs were selected in the *FTSJ1* gene, and a case–control study was performed to investigate the relationship between the *FTSJ1* gene and MR within our samples. Both single-locus and haplotype analyses showed a positive association between these three SNPs and NS-XLMR in the Chinese Han population of young male subjects of the Qinba mountain region in China.

Though the three markers (rs2268954, rs2070991, rs5905692) selected in this study are all in the intron region, they are in strong LD and nearly span the entire

Table 2 Genotype and allele frequencies of *FTSJ1* single nucleotide polymorphisms (SNPs)

SNPs	Allele (%)		*P* value (*df* = 1)	OR (95% CI)	Genotype (%)			*P* value (*df* = 2)
rs2268954	X^C	X^T			X^CX^C	X^CX^T	X^TX^T	
Female								
MR	44 (43.1)	58 (56.9)	0.576	1.138 (0.724–1.79)	8 (15.7)	28 (54.9)	15 (29.4)	0.279
Border	54 (46.6)	62 (53.4)	0.968	1.009 (0.656–1.55)	11 (19.0)	32 (55.2)	15 (25.8)	0.306
Controls	139 (46.3)	161 (53.7)			37 (24.7)	65 (43.3)	48 (32.0)	
Male								
MR[a]	16 (33.3)	32 (66.7)	**0.036**[c]	2.053 (1.041–4.05)				
Border[b]	24 (46.2)	28 (53.8)	0.575	1.198 (0.637–2.252)				
Controls	77 (50.7)	75 (49.3)						
SNPs	Allele (%)		*P* value (*df* = 1)	OR (95% CI)	Genotype (%)			*P* value (*df* = 2)
rs2070991	X^A	X^G			X^AX^A	X^AX^G	X^GX^G	
Female								
MR	38 (35.2)	70 (64.8)	0.102	1.459 (0.926–2.297)	6 (11.1)	26 (48.2)	22 (40.7)	0.184
Border	50 (40.3)	74 (59.7)	0.462	1.172 (0.768–1.789)	9 (14.5)	32 (51.6)	21 (33.9)	0.349
Controls	137 (44.2)	173 (55.8)			35 (24.7)	67 (43.3)	53 (32.0)	
Male								
MR	14 (28.0)	36 (72.0)	**0.043**[c]	2.029 (1.016–4.05)				
Border	21 (40.4)	31 (59.6)	0.638	1.165 (0.617–2.098)				
Controls	71 (44.1)	90 (55.9)						
SNPs	Allele (%)		*P* value (*df* = 1)	OR (95% CI)	Genotype (%)			*P* value (*df* = 2)
rs5905692	X^C	X^T			X^CX^C	X^CX^T	X^TX^T	
Female								
MR	56 (56.0)	44 (44.0)	0.489	1.174 (0.745–1.852)	14 (28.0)	28 (56.0)	8 (16.0)	0.177
Border	65 (55.0)	53 (45.0)	0.572	1.131 (0.737–1.736)	16 (27.1)	33 (55.9)	10 (17.0)	0.163
Controls	155 (52.0)	143 (48.0)			46 (30.9)	63 (42.3)	40 (26.8)	
Male								
MR	34 (70.8)	14 (29.2)	**0.014**[c]	2.365 (1.174–4.761)				
Border	31 (60.8)	20 (39.2)	0.211	1.509 (0.79–2.882)				
Controls	76 (50.7)	74 (49.3)						

OR odds ratio, *CI* confidence interval

[a] Mental retardation

[b] A borderline form of MR

[c] Bold indicates significantly associated statistic

Table 3 Pairwise linkage disequilibrium

SNP1	SNP2	Distance (kb)	D'	r^2
rs2268954	rs2070991	4.650	0.896	0.716
rs2268954	rs5905692	6.420	0.866	0.744
rs2070991	rs5905692	1.770	0.963	0.836

SNP single nucleotide polymorphisms

FTSJ1 gene. In general, a haplotype of closely located markers increases the power to detect association with the disease (Collins and Morton 1998). Therefore, though the biological functions of the three SNPs is obscure, they can still be used as a powerful tool to verify the association of *FTSJ1* and NS-XLMR. The three SNPs constructed effective haplotype block whose variants reflect, to a great degree, genetic covariance of the region they span. The common disease/common variant (CD/CV) hypothesis (Reich and Lander 2001; Smith and Lusis 2002) proposes that the genetic factors underlying common diseases could be common alleles in the population. Under this hypothesis and LD information, this study suggested that at least one susceptibility locus for NS-XLMR lies within, or very

Table 4 Estimated haplotype frequencies (rs2268954–rs2020991–rs5905692) and association significance

Haplotype	Frequency				*P* value		OR (95% CI)	
	Male		Female		Male	Female	Male	Female
	MR[a]	Controls	MR	Controls				
C/A/C	0	0	0	0.0104	/	/	/	/
C/A/T	0.2826	0.4589	0.3581	0.4207	**0.01202**[b]	0.3511	0.576 (0.292–1.135)	0.667 (0.422–1.054)
C/G/C	0.02174	0.0411	0.02254	0.02437	/	/	/	/
C/G/T	0	0.02055	0.06506	0.0105	/	/	/	/
T/A/T	0	0.02055	0.02238	0.02467	/	/	/	/
T/G/C	0.6957	0.4589	0.5209	0.489	**0.0135**[b]	0.3862	2.191 (1.127–4.261)	1.18 (0.766–1.818)
T/G/T	0	0	0.01103	0.02031	/	/	/	/
Global					**0.01236**[b]	0.3816		

OR odds ratio, *CI* confidence interval

All global *P* values with haplotype frequencies >0.05 were calculated using UNPHASED package version 3.0.6

[a] Mental retardation

[b] Bold font indicates significantly associated haplotypes and statistic

close to, the *FTSJ1* gene in young male subjects of the Qinba mountain region in China and that haplotype T-G-C might be a risk haplotype for NS-XLMR in the young male subjects.

FTSJ1 protein belongs to a large phylogenetically conserved family of RNA methyltransferases, and sequence conservation among all members of this protein family is high, especially in the functional domains (Bugl et al. 2000; Feder et al. 2003). Human FTSJ1 protein is presumed to function as an RNA methyltransferase for tRNA and/or for rRNA, possibly involved in the regulation of translation (Feder et al. 2003; Freude et al. 2004). So far, all mutations detected in the *FTSJ1* gene of NS-XLMR patients lead to partial or entire loss of functional domain of FTSJ1 protein (FtsJ domain) (Freude et al. 2004; Ramser et al. 2004), therefore impairing its capacity to bind SAMe. As is known, SAMe, which has the ability to cross the blood–brain barrier, serves as the sole methyl donor for methylation processes in the central nervous system. So far, low cerebrospinal fluid levels of SAMe have been observed in several neuropsychiatric and neurological disorders, including depression, brain ischemia, and dementia (Chishty et al. 2002). It is probable that mutations in *FTSJ1* lead to its encoded product's activity changing in some young NS-XLMR male subjects of the Qinba mountain region in China. The impairing of its capacity to bind SAMe can affect the methylation of transfer RNA (tRNA) and/or ribosomal RNA (rRNA) and result in an alteration in the normal pattern of gene expression in a small group of genes that maybe important for correct brain functioning in neuronal cells, thereby causing MR.

Particularly intriguing is the fact that a gender-related association was found in our case–control study, which is in accordance with the observation that NS-XLMR that arises from mutations in this gene occurs in male subjects only (Freude et al. 2004; Ramser et al. 2004; Froyen et al. 2007). There maybe two possible reasons for this phenomenon. *FTSJ1* is located on the X chromosome; therefore, mutations will not affect the function of the FTSJ1 protein of heterozygous female subjects. A second hypothesis is that the same X chromosome becomes inactivated in all cells in the obligate carrier in female subjects (Froyen et al. 2007). Further works needs to clarify the molecular mechanism of the gender-specific effect of *FTSJ1*.

In conclusion, this case–control study has shown a positive association of *FTSJ1* gene polymorphisms with NS-XLMR in young male subjects in the Chinese Han population of the Qinba mountain region in China. Further research is needed to validate whether this association still exists in the Chinese Han population of other regions.

Acknowledgments The authors sincerely thank all participants and researchers in this study. This work was supported by grants from the Tenth Five-Year Plan, National Tackle Problem Item (No.2001BA901A49), and Special Prophase Project on Basic Research of The National Department of Science and Technology (2007CB516702).

References

Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265

Bugl H, Fauman EB, Staker BL, Zheng F, Kushner SR, Saper MA, Bardwell JC, Jakob U (2000) RNA methylation under heat shock control. Mol Cell 6:349–360

Caldas T, Binet E, Bouloc P, Costa A, Desgres J, Richarme G (2000) The FtsJ/RrmJ heat shock protein of Escherichia coli is a 23 S ribosomal RNA methyltransferase. J Biol Chem 275:16414–16419

Chishty M, Reichel A, Abbott N, Begley D (2002) *S*-adenosylmethionine is substrate for carrier mediated transport at the blood–brain barrier in vitro. Brain Res 942:46–50

Collins A, Morton NE (1998) Mapping a disease locus by allelic association. Proc Natl Acad Sci USA 95:1741–1745

Dudbridge F (2003) Pedigree disequilibrium tests for multilocus haplotypes. Genet Epidemiol 25:115–121

Erdfelder E, Faul F, Buchner A (1996) GPOWER: a general power analysis program. Behav Res Methods Instrum Comput 28:1

Feder M, Pas J, Wyrwicz L, Bujnicki J (2003) Molecular phylogenetics of the RrmJ/fibrillarin superfamily of ribose2′-*O*-methyltransferases. Gene 302:129–138

Freude K, Hoffmann K, Jensen LR, Delatycki MB, des Portes V, Moser B, Hamel B, van Bokhoven H, Moraine C, Fryns JP, Chelly J, Gecz J, Lenzner S, Kalscheuer VM, Ropers HH (2004) Mutations in the FTSJ1 gene coding for a novel *S*-adenosylmethionine-binding protein cause nonsyndromic X-linked mental retardation. Am J Hum Genet 75:305–309

Froyen G, Bauters M, Boyle J, Van Esch H, Govaerts K, van Bokhoven H, Ropers HH, Moraine C, Chelly J, Fryns JP, Marynen P, Gecz J, Turner G (2007) Loss of SLC38A5 and FTSJ1 at Xp11.23 in three brothers with non-syndromic mental retardation due to a microdeletion in an unstable genomic region. Hum Genet 121:539–547

Gecz J, Mulley J (2000) Genes for cognitive function: developments on the X. Genome Res 10:157–163

Gong YX, Dai XY (1992) Chinese-Wechsler young children scale of intelligence (C-WYCSI). Map Press, Hunan

Gong YX, Cai TS (1993) Wechsler intelligence scale for children [Chinese revision (C-WISC)]. Map Press, Hunan

Guo TW, Zhang FC, Yang MS, Gao XC, Bian L, Duan SW, Zheng ZJ, Gao JJ, Wang H, Li RL, Feng GY, St Clair D, He L (2004) Positive association of the DIO2 (deiodinase type 2) gene with mental retardation in the iodine-deficient areas of China. J Med Genet 41:585–590

Hamel BC, Smits AP, van den Helm B, Smeets DF, Knoers NV, van Roosmalen T, Thoonen GH, Assman-Hulsmans CF, Ropers HH, Mariman EC, Kremer H (1999) Four families (MRX43, MRX44, MRX45, MRX52) with nonspecific X-linked mental retardation: clinical and psychometric data and results of linkage analysis. Am J Med Genet 85:290–304

Lehrke R (1972) A theory of X-linkage of major intellectual traits. Am J Ment Defic 76:611–619

Lehrke RG (1974) X-linked mental retardation and verbal disability. Birth Defects Orig Artic Ser 10:1–100

Newcombe RG (1998) Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 17:873–890

Ogura T, Tomoyasu T, Yuki T, Morimura S, Begg KJ, Donachie WD, Mori H, Niki H, Hiraga S (1991) Structure and function of the ftsH gene in *Escherichia coli*. Res Microbiol 142:279–282

Psychiatry CAo (1995) Chinese classification of mental disorders, 2nd revision. Southeast University Press, Nanking

Ramser J, Winnepenninckx B, Lenski C, Errijgers V, Platzer M, Schwartz CE, Meindl A, Kooy RF (2004) A splice site mutation in the methyltransferase gene FTSJ1 in Xp11.23 is associated with non-syndromic mental retardation in a large Belgian family (MRX9). J Med Genet 41:679–683

Reich DE, Lander ES (2001) On the allelic spectrum of human disease. Trends Genet 17:502–510

Renieri A, Pescucci C, Longo I, Ariani F, Mari F, Meloni I (2005) Non-syndromic X-linked mental retardation: from a molecular to a clinical point of view. J Cell Physiol 204:8–20

Smith DJ, Lusis AJ (2002) The allelic structure of common disease. Hum Mol Genet 11:2455–2461

Stephens M, Smith NJ, Donnelly P (2001) A new statistical method for haplotype reconstruction from population data. Am J Hum Genet 68:978–989

T.W.H.Organization (1992) The ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines. WHO, Geneva

Willems P, Vits L, Buntinx I, Raeymaekers P, Van Broeckhoven C, Ceulemans B (1993) Localization of a gene responsible for nonspecific mental retardation (MRX9) to the pericentromeric region of the X chromosome. Genomics 18:290–294

Zhang KJ, Zhang FC, Zheng ZJ, Gong PY, He G, Nan YP, Zhang R, Ma J (2005) An analysis of inheriting type of non-causing mental retardation children in Zhashui experimental station. J Northwest Univ 35:4

Zhang SM, Zhang FC, Gong PY, Zhang KJ, Yang XZ, He G, Li N (2006) The discussion of inheriting type of mental retardation in AnKang experimental station. J Northwest Univ 35:4

Zuo QH, Zhang ZX, Lei ZW (eds) (1988) Adaptive scale of infant and children. Medical University of China, Beijing, pp 9–69