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Family-based association analysis of functional VNTR polymorphisms in the dopamine transporter gene in migraine with and without aura

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Summary. Because of the role of dopamine in triggering migraine attacks, genes of the dopamine system are candidates for involvement in migraine. We examined three VNTR polymorphisms in the dopamine transporter, the 5′UTR VNTR, the intron 8 VNTR and the intron 14 VNTR, in a sample of 205 family trios. We used the transmission disequilibirium test (TDT) to examine the transmission of these three markers and their haplotypes to offspring affected by migraine. We found no significant transmission distortion of any marker. Likewise haplotypes of the three markers did not show significant overall or individual association with migraine. Finally we examined migraine with and without aura, and likewise found no association between dopamine transporter VNTRs or their haplotypes and either classification of the disease. We conclude that functional genetic variation in the dopamine transporter does not act as a significant risk factor for migraine.

Keywords: Migraine; DAT; gene

Introduction

Genetic epidemiological twin studies demonstrated a significant heritability for migraine, with 61% of liability coming from additive genetic factors and 39% from non-shared environmental factors in migraine without aura (MO) (Gervil et al. 1999) and 65% additive genetic effects in migraine with aura (MA) (Ulrich et al. 1999). In these two subtypes of migraine a complex genetic pattern of inheritance has been suggested involving several susceptibility genes, most consistent with a polygenic-multifactorial model involving both genetic and environmental factors.

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The role for dopamine in the pathophysiology of migraine has been proposed (Peroutka 1997; Fanciullaci and Rosso 2000; Chen 2006), based on evidence that i) dopamine receptors are hypersensitive in migraine (Cerbo et al. 1997); ii) dopamine antagonists such as metoclopramide, prochlorperazine and haloperidol are active in the treatment of migraine attacks; iii) dopamine agonists such as bromocriptine are effective in prophylactic migraine treatment and iv) the density of dopamine D3 and D4 receptors seems to be increased on lymphocytes of migraineurs. However, a direct role for the dopamine system in migraine is still controversial, not least because evidence for involvement of the serotonin system is much stronger, even though not clear yet (Karwautz et al. 2007). There is substantial interaction between the dopamine and serotonin systems. Because of this and the evidence outlined above, involvement of the dopamine system in migraine is plausible and dopamine system genes are good candidate gene for aetiological involvement.

Up to now ten studies have examined dopamine receptor genes in migraine. The dopamine D1 receptor (DRD1) was examined in 2 studies, DRD2 in 8 studies, DRD3 in 3, DRD4 and DRD5 in 2 studies each, the dopamine beta hydroxylase gene (DBH) in 3 studies and the dopamine transporter gene (DAT) in 1 study. DRD1, DRD3, DRD5 and DAT were not associated with migraine in any study. DRD2 and the DRD2 'Ncol' polymorphism showed an association in 1 of 4 studies each and DBH in 2 of 3 studies.

In detail, Del Zompo et al. (1998) examined the dopamine D2 (DRD2), D3 (DRD3) and D4 (DRD4) receptor genes in family trios from Sardinia and found weak evidence for association with DRD2. Peroutka et al. (1997, 1998) analysed a DRD2 'NcoI' C to T silent polymorphism exon 6 of DRD2 and found a significantly increased incidence of MA in carriers of DRD2 NcoI C/C genotype, which Dichgans et al. (1998) failed to replicate. Lea et al. (2000) and Fernandez et al. (2006) examined the dopamine beta hydroxylase gene (DBH) and the DRD2 gene and found association between migraine and a DBH microsatellite marker, especially in migraine with aura. Maude et al. (2001) examined a 2 base pair deletion in the promoter of the DRD2 gene and found no association with migraine. Shepherd et al. (2002) examined polymorphisms in DRD1, DRD3 and DRD5 but found no association with migraine. Stochino et al. (2003) examined polymorphisms in the DRD1, DRD3, DRD5, DRD2, including the DRD2 'NcoI' C to T silent polymorphism, and found no association; Rebaudengo et al. (2004) likewise found no association between the DRD2 'NcoI' polymorphism and migraine or its clinical features. Mochi et al. (2003) examined three functional polymorphisms in dopaminergic genes: a 48-base-pair (bp) variable number of tandem repeats (VNTR) in DRD4, a 40-bp VNTR in the 5-untranslated region of the dopamine transporter (DAT) gene (5′UTR VNTR) and the same dinucleotide repeat in the DBH gene as Lea et al. (2003). They found no association except for a significantly different distribution of alleles for the DRD4 gene in migraine without aura (MO) compared to migraine with aura (MA) and control groups. However, Campos de Sousa et al. (2007) recently found the seven-repeat allele of the DRD4 VNTR being a protective factor for MO. Fernandez et al. (2006) examined two DBH polymorphisms, a functional insertion/deletion promote and a coding SNP A444G polymorphism and found an association with the insertion/deletion variant, but not with the SNP polymorphism.

In summary, a number of genes of the dopamine system have been tested for association with migraine; however these studies usually examined just one polymorphism per gene, and in most cases the studies were underpowered for analysis of a complex genetic disorder such as migraine, where susceptibility alleles are likely to confer a relative risk of less than 3, and thus would only be likely to detect the very strongest genetic effects.

In the present study, we used the transmission disequilibrium test (TDT) to examine three functional VNTR polymorphisms in the dopamine transporter gene DAT1. The gene encoding DAT1 (gene symbol SLC6A3) consists of 15 exons spanning 60 kb on chromosome 5p15.32 [MIM *126455] (Vandenbergh et al. 1992). Over one hundred studies have assessed possible associations between variants in the dopamine transporter and neuro-psychiatric disorders (for examples see Greenwood et al. 2006). However, the bulk of these studies examined only one polymorphism and have thus assessed only a portion of the phenotypic influence of genetic variation within the gene.

We analysed three VNTR polymorphisms, the intron 8 VNTR (int8), a VNTR in the 3′ untranslated region of the gene (3′ UTR-VNTR) (21), and a VNTR in intron 14 (Indel_14) (Greenwood and Kelsoe 2003), in a sample of 205 family trios each with a proband with childhood migraine. The TDT approach has several advantages over case-control studies, for instance the absence of stratification bias and the possibility of showing linkage in the presence of association. In addition the studies described above have not analysed children with well characterised MO and MA, and MOMA (comorbid migraine with and without aura). The three VNTR polymorphisms are responsible for significant functional variation in the DAT gene; indeed there are no common SNP polymorphisms thought to affect DAT function. Furthermore, linkage disequilibrium extends further for VNTRs than for SNPs, so the markers we have chosen may be more efficient at detecting the proxy effect of other polymorphisms in the DAT gene. Consequently in the present study we investigated the familial transmission of these polymorphisms of the DAT gene in a large sample of patients of both sexes with MO and MA.

Materials and methods

Subjects

We included 205 family trios, each with a patient with childhood migraine. Forty-eight percent were boys, and 52% girls. Age ranged from 6 to 19 years, with a mean of 10.8 ± 2.8 years. All patients had a clinical interview and a physical and neurological examination (Wöber-Bingöl et al. 1995). The diagnoses were established by one experienced child neurologist based on the criteria of the second edition of the International Classification of Headache Disorders (ICHD-II) (Headache Classification Subcommittee of the International Headache Society 2004).

The project was approved by the Ethics Committee of the Medical University of Vienna. We obtained informed written consent from all participants and parents and we kept data anonymous to ensure subject confidentiality.

DNA and genotyping

DNA was prepared using established methods from buccal swabs as described (Freeman et al. 1997; Plomin and Rutter 1998; Plomin and Crabbe 2000). The samples were taken by the subjects themselves and are either immediately left at the clinic or sent to our centre by mail. The samples were coded and anonymised before DNA extraction and storage at the SGDP molecular genetic laboratory of the Institute of Psychiatry. All markers are VNTRs and genotyping was performed by PCR followed by agarose gel electrophoresis and staining with ethidium bromide (Guindalini

et al. 2006). The 40-bp 3′ untranslated region VNTR (designated here as 3′UTR), and a VNTR in intron 8 (Int8) of the gene were selected for the investigation. In order to help estimate haplotype patterns of this region, we also selected a putatively functional 15 bp insertion/deletion polymorphism located in intron 14 of the gene (Indel_14; 26). The 37 bp VNTR is described as a 6.1 copies of a 37 bp repetitive element polymorphism and the Int8 also as 6.1 copies but of a 30 bp element in the Simple Repeat table of the Human Genome in the UCSC "Golden Path" database (http://genome.ucsc.edu; Gelfand et al. 2007). Alleles of the Int8 and Int_14 VNTRs were called according to their relative size (smallest = allele 1) whereas the coding system utilizing the range from 3 to 11 copies was applied for the 40 bp 3′UTR VNTR (Vandenberg et al. 1992).

Statistical analysis

Linkage disequilibrium between the VNTRs was estimated using the program GOLD (Slatkin and Excoffier 1996). The statistical association R^2 was used to measure LD between markers (Hill and Weir 1994). The program suite UNPHASED was used to test for association between the individual marker locus or haplotypes and the hypothetical disease locus (Dudbridge 2003). UNPHASED can be used for association analysis of multilocus haplotypes from unphased genotype data. Statistical analysis of family trios was performed using the TDTPHASE from UNPHASED. TDTPHASE performs TDT and HHRR analysis for nuclear families using the Transmission Disequilibrium Test (TDT); it is robust to families where genotypes are not available from both parents. Analysis was performed both for single marker and their haplotypes.

Power analysis

For 205 family trios with migraine analysed by the TDT (total sample of aura, non-aura) the sample has a non-centrality parameter (NCP) of 0.98 for a high risk allele with a frequency of 0.25 (modelled in the Intron 8 polymorphism) and genotypic relative risk of 1.5 for Aa and 3 for AA. This gives 77% power for $\alpha = 0.01$. If we use the less common haplotype of all three markers (with a frequency of 0.16) the NCP falls to 4.8 and power is 33% at $\alpha = 0.01$ and 57% at 0.05. Power calculation was performed using the GPC genetic power calculator (http://statgen.iop.kcl.ac.uk/gpc/index.html).

Table 1. *Single point analysis for overall migraine*

Allele	T	freq-T	NT	freq-NT	OR	%T	χ^2	*p*
DAT 3′ UTR VNTR								
1	2	0.01	0	0.00	1.00	100	2.78	0.10
3	91	0.25	88	0.25	−1.03	50.84	0.07	0.80
4	260	0.73	265	0.74	−0.98	49.52	0.18	0.67
5	4	0.01	4	0.01	−1.00	50	0.00	1.00
DAT Intron 8 VNTR								
2	71	0.20	63	0.18	1.00	52.99	0.59	0.44
3	279	0.79	284	0.81	0.87	49.56	0.22	0.64
4	0	0.00	1	0.00	0.00	0	1.39	0.24
6	2	0.01	4	0.01	0.44	33.33	0.69	0.41
DAT Intron 14								
1	334	0.93	330	0.91	1.00	50.3	0.30	0.58
2	27	0.07	31	0.09	0.86	46.55	0.30	0.58

DAT 3′ UTR VNTR: likelihood ratio test: null = −449.138; alternative = −447.703; LRS = 2.87049; DF = 3; $p = 0.41$. DAT Intron 8 VNTR, likelihood ratio test: null = −379.8; alternative = −378.5; LRS = 2.588; DF = 3; $p = 0.46$. DAT Intron 14, likelihood ratio test: null = −200.5; alternative = −200.3; LRS = 0.3002; DF = 1; $p = 0.58$.

Results

All three markers were in Hardy–Weinberg equilibrium (HWE) in the population, based on genotypes of unrelated parents: Int 8, F = −0.06, ns; Int 14, F = 0.030, ns; 3′UTR, F = −0.013, ns. HWE was calculated using the DeFinetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Allele frequencies in the unrelated control population were: 3′UTR VNTR, allele 1, 0.003; allele 2, 0.001; allele 3, 0.25; allele 4, 0.74; allele 5, 0.006; intron 8 VNTR, allele 2, 0.20; allele 3, 0.79; allele 4, 0.002, allele 6, 0.008; intron

Table 2. *Haplotype analysis for overall migraine*

Haplotype	T	freq-T	NT	freq-NT	OR	%T	χ^2	*p*
213	53.99	0.16	46.84	0.14	−1.15	53.55	0.59	0.44
313	36.01	0.10	37.16	0.11	−0.97	49.21	0.02	0.89
214	12.01	0.03	14.16	0.04	−0.85	45.89	0.18	0.67
314	212.00	0.61	208.80	0.60	−1.02	50.37	0.06	0.81
324	23.00	0.07	29.00	0.08	−0.79	44.23	0.75	0.39

Likelihood ratio test: null = −882.08; alternative = −877.30; LRS = 9.57; DF = 11; $p = 0.57$. Haplotype is in 5′–3′ order, DAT Intron 8; DAT Intron 14; DAT 3′ UTR VNTR.

Table 3. *Single point and haplotype analysis for MO*

Allele	T	freq-T	NT	freq-NT	OR	%T	χ^2	*p*
3′ UTR								
1	2	0.01	0	0	1	100	2.78	0.10
3	69	0.25	68	0.25	−1.02	50.36	0.01	0.92
4	197	0.73	199	0.73	−0.99	49.75	0.04	0.85
5	3	0.01	4	0.01	−0.75	42.86	0.15	0.70
Intron 8								
2	49	0.18	49	0.18	1.00	50	0	1
3	216	0.81	214	0.80	1.01	50.23	0.05	0.83
4	0	0.00	1	0.00	0.00	0	1.39	0.24
6	2	0.01	3	0.01	0.67	40	0.20	0.65
Intron 14								
1	253	0.92	256	0.93	1	49.71	0.24	0.63
2	22	0.08	19	0.07	1.172	53.66	0.24	0.63
Haplotype	T	freq-T	NT	freq-NT	OR	%T	χ^2	*p*
213	36	0.14	33.86	0.13	−1.06	51.53	0.07	0.79
313	32	0.12	30.14	0.12	−1.06	51.50	0.07	0.80
214	8	0.03	13.14	0.05	−0.61	37.85	1.31	0.25
314	159	0.61	157.90	0.60	−1.01	50.18	0.01	0.92
324	18	0.07	17	0.07	−1.06	51.43	0.03	0.86

Singlepoint: DAT 3′ UTR VNTR, LRS = 2.93; DF = 3; $p = 0.40$. DAT Intron 8 VNTR, likelihood ratio test: null = −286.9; alternative = −286.10; LRS = 1.60; DF = 3; $p = 0.66$. DAT Intron 14, LRS = 0.24; DF = 1; $p = 0.63$.

Haplotypes: likelihood ratio test: null = −676.04; alternative = −671.60; LRS = 8.88; DF = 11; $p = 0.63$. Haplotype is in 5′–3′ order, DAT Intron 8; DAT Intron 14; DAT 3′ UTR VNTR.

Table 4. *Single point and haplotype analysis for MA*

Allele	T	freq-T	NT	freq-NT	OR
3′ UTR					
3	22	0.26	20	0.23	1.00
4	63	0.73	66	0.77	0.87
5	1	0.01	0	0.00	−0.91
Intron 8					
2	22	0.26	14	0.16	1.00
3	63	0.74	70	0.82	0.57
Intron 14					
1	81	0.94	74	0.86	1.00
2	5	0.06	12	0.14	0.38

Haplotype	T	freq-T	NT	freq-NT	OR	%T	χ^2	*p*
213	18	0.21	12.99	0.15	1.00	58.08	1.00	0.32
313	4	0.05	7.01	0.08	0.41	36.33	0.90	0.34
214	4	0.05	1.01	0.01	2.86	79.83	1.96	0.16
314	53	0.62	50.99	0.60	0.75	50.97	0.10	0.75
324	5	0.06	12	0.14	0.30	29.41	3.29	0.07

Single point: DAT 3′ UTR VNTR likelihood ratio test: null = −99.39; alternative = −98.62; LRS = 1.55; DF = 2; $p = 0.46$. DAT Intron 8, likelihood ratio test: null = −92.28; alternative = −90.50; LRS = 3.55; DF = 2; $p = 0.17$; DAT Intron 14, likelihood ratio test: null = −55.47; alternative = −53.83; LRS = 3.29; DF = 1; $p = 0.07$.
Haplotypes: likelihood ratio test: null = −199.62; alternative = −194.96; LRS = 9.33377; DF = 6; $p = 0.16$. Haplotype is in 5′–3′ order, DAT Intron 8; DAT Intron 14; DAT 3′ UTR VNTR.

14 VNTR, allele 1, 0.90; allele 2, 0.10. Linkage disequilibrium (r^2 and D′) between the three markers was: int8-int14: Chi-squared = 5.36, $p = 0.06873$, $r^2 = 0$, D′ = 0.879; 3′UTR-int8: Chi-squared = 18.64, $p = 0.0009$, $r^2 = 0$, D′ = 0.29; 3′UTR-int14: Chi-squared 0.43, ns, $r^2 = 0.0$ D′ = 0.211. Haplotype frequencies were similar to other European populations. TDT analysis was performed both for the three single marker and their haplotypes, and the results of single marker analyses for migraine overall are shown in Table 1.

The results of the haplotypic TDT analysis for all migraine diagnoses are shown in Table 2.

The sample was also divided into migraine without aura (MO) and migraine with aura (MA). The total number of patients diagnosed with MO was 149, and 56 were diagnosed with MA. When we examined each individual marker and their haplotypes for MO and MA (Tables 3 and 4) we likewise saw no significant transmission distortion.

Discussion

In the present study we analysed three VNTR polymorphisms and their haplotypes, in 205 trios with childhood migraine diagnosed according to the ICHD-II. We used the family based association method, the transmission disequilibrium test (TDT), and also sub-classified migraine into types with and without aura (MA and MO). We found no significant transmission distortion of any marker, or their haplotypes. We also found no association with any of these markers with the subdiagnoses of MA or MO. In analysing three VNTR markers, we may have captured most of the functional genetic variation in this gene; the Int8 VNTR is functional and has an effect on expression of the DAT1 gene which is amplified by the effect transcriptional stimuli such as forskolin (Guindalini et al. 2006); the 3′UTR has been frequently associated with ADHD (Brookes et al. 2006) and although controversial several studies have observed a functional effect on expression (VanNess et al. 2005). It is not known whether the Indel_14 is functional.

There are two limitations of this study; firstly that we have not captured all genetic variation in the gene, as other markers which are not tagged by any of the three VNTRs exist, and our sample size means that we might not detect weak genetic effects (we have 98% power to detect relatives risks of Aa 1.5 and AA 3 for the Int8 polymorphism; for AA = 1.5 this power drops substantially). However given the robust published associations between these DAT1 VNTRs and complex disorders such as ADHD, and the highly conserved nature of the DAT1 gene, in that genetic variation in or around the coding regions is very rare (Grunhage et al. 2000) a main effect of other SNPs within the gene which we cannot detect using our markers seems unlikely. Given these caveats we conclude that the dopamine transporter does not play a major role in susceptibility to migraine.

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