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Molecular variation within the dopamine receptor DRD2 gene in migraine

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Abstract Molecular genetics offers a novel approach to the understanding and management of migraine since the disorder is known to have a strong genetic component. In recent studies, polymorphisms in the genes for dopamine receptors have been evaluated. Both positive and negative association studies have been reported. In particular, these data suggest that activation of the DRD2 receptor plays a modifying role in the pathophysiology of migraine. As a result, existing data provide a molecular rationale for the documented efficacy of dopamine D2 receptor antagonists in the treatment of migraine. Therefore, at the present time, molecular genetic data provide support for the hypothesis that susceptibility to migraine may be modified, in part, by variations in dopamine DRD2 receptor function.

Key words Dopamine • Migraine • Genetics • DRD2

Introduction

A number of previous investigators have hypothesized a dopamine receptor hypersensitivity in migraine [1–11]. Migraineurs have exaggerated responses to the physiological effects of dopamine agonists such as bromocriptine, piribedil, and apomorphine. For example, apomorphine can induce a migraine headache, as well as the associated phenomenon of nausea and photophobia, in individuals with a history of migraine [9]. In addition, intracranial blood flow changes following apomorphine administration occur in migraineurs compared to control subjects [11]. Taken together, these data suggest that migraineurs have an altered responsivity to dopaminergic stimulation.

Molecular genetics offers a novel approach to the understanding and management of migraine since the disorder has a strong genetic component [12-15]. The hypothesis that activation of dopamine receptors may be involved in the pathophysiology of migraine in certain individuals is consistent with the clinical features of the disorder since many of the symptoms associated with migraine can be attributed to stimulation of dopamine receptors. For example, nausea and vomiting are common clinical features of migraine in which dopamine receptor stimulation is likely. Gastrokinetic changes, hypotension and other autonomic nervous system changes are additional migraine symptoms that are consistent with activation of dopaminergic neurotransmission.

The data summarized in the present review indicate that variations within dopamine receptor genes, particularly the DRD2 gene, may be the molecular basis for the increased sensitivity of a subset of migraineurs to the physiological effects of dopaminergic agonists.

NcoI polymorphism in the D2 dopamine receptor gene

The *Nco*I polymorphism in the gene encoding the D2 dopamine receptor (DRD2) was evaluated in a group of 250 unrelated individuals [16]. DRD2 was selected as a candidate gene in migraine since DRD2 antagonists are effective in the acute treatment of migraine and multiple investigators have reported alterations in dopaminergic neurotransmission in migraineurs.

Subjects were identified for this study directly by physician referral. Individuals were evaluated using the diagnostic criteria for migraine without aura (MO) and migraine with aura (MWA) established by the International Headache Society (IHS) [17]. The lifetime presence or absence was determined for each of the criteria in the IHS definition of migraine [17]. Interviews were conducted by physicians, nurses and/or trained interviewers. All interviewers were trained by the senior author in the use of the IHS criteria and all clinical data were reviewed by the senior author. Informed consent was obtained and DNA samples collected. All clinical data were obtained independently of the genotypic data. Control group individuals did not meet IHS criteria for migraine (based on direct interview) and were predominantly unaffected spouses of the individuals with migraine.

D2 Dopamine receptor *Nco*I allele frequencies in the overall dataset

In the dataset (n = 250 individuals), the DRD2 *Nco*I C allele frequency was 0.73 and the T allele frequency was 0.27. These values are similar to the DRD2 *Nco*I allele frequencies reported in Caucasians of northern or western European descent. In the overall dataset, 54% of individuals had the C/C genotype, 38% had the C/T genotype and 8% displayed the T/T genotype. The average age of the study participants was 52 ± 1 years. No significant differences in gene frequencies were found between males (n = 92) and females (n = 158).

D2 dopamine receptor *Nco*I A allele frequencies in control, MO and MWA groups

The DRD2 *Nco*I allele frequencies were determined in each subgroup of subjects. Similar DRD2 C allele frequencies were observed in both the control group (0.71; n = 121) and individuals with MO (0.70; n = 77). By contrast, individuals with MWA had a significantly greater frequency of the DRD2 C allele (0.84; n = 52) than the control individuals (Chi-square = 6.47; $p < 0.005$) or individuals with MO (Chi-square = 6.15; $p < 0.007$).

D2 dopamine receptor *Nco*I allele genotype distributions control, MO and MWA groups

An association of MWA and the DRD2 C allele was also apparent in an analysis of genotype distributions (Table 1). The C/C genotype in the dataset was significantly more frequent in individuals with MWA (69%) than in control individuals ($p < 0.007$) or individuals with MO ($p < 0.025$). Once again, no significant difference was observed in the genotypic distribution between the control group and individuals with MO. Finally, the incidence of MWA was determined in each genotypic subgroup. MWA was present in 27% of the C/C individuals, 16% of the C/T individuals and 5.2% of the T/T individuals.

Association of DRD2 *NcoI* alleles and neuropsychiatric disorders

A second study analyzed the possible association of DRD2 *Nco*I alleles with comorbid neuropsychiatric disorders [18]. Striking similarities exist between the epidemiological characteristics of migraine, anxiety and depression [19–29]. All three disorders afflict approximately 10%-25% of the general population at some point in life and are approximately twice as common in females as in males. Prophylactic medications for all three disorders have a subacute onset of action, requiring 3–6 weeks of therapy to measure clinical improvement. In epidemiological studies, a clinical diagnosis of migraine significantly increases the risk of comorbid anxiety and depression [19–29]. Taken together, these data suggest that a common metabolic variation may underlie comorbid migraine, anxiety and depression.

Frequency of neuropsychiatric disorders based on DRD2 *Nco*I genotypes

The incidences of the various clinical diagnoses based on DRD2 *Nco*I genotypes are provided in Table 2. A present or past history of MWA, anxiety disorders or major depression is present in 69% of the C/C individuals, 53% of the C/T individuals and 22% of the T/T individuals. The incidence of any of these neuropsychiatric diagnoses is significantly higher in the C/C individuals when compared to either the C/T individuals (Chi-square = 6.53; $p < 0.005$),

Table 1 Genotype distribution in control, migraine without aura and migraine with aura individuals (Modified from Peroutka et al. [16] with permission)[a]

Group	D2 dopamine receptor *Nco*I alleles, n (%)		
	C/C	C/T	T/T
Control	59 (49)	53 (44)	9 (7.4)
Migraine without aura	40 (52)	28 (36)	9 (12)
Migraine with aura	36 (69)[*,**]	15 (29)	1 (1.9)

[*] Chi-square = 6.16 ($p < 0.007$) vs. control group

[**] Chi-square = 3.83 ($p < 0.025$) vs. migraine without aura group

[a] A total of 250 individuals were studied

T/T individuals (Chi-square = 15.29; $p < 0.00005$), or the combined T/any group of individuals (Chi-square = 12.72; $p < 0.0002$).

The presence of an anxiety disorder is significantly more frequent in the C/C individuals than in either the C/T individuals (Chi-square = 3.87; $p < 0.02$), T/T individuals (Chi-square = 8.92; $p < 0.001$), or the combined T/any group of individuals (Chi-square = 7.20; $p < 0.004$). A similar pattern is seen with generalized anxiety disorder (GAD). Major depression, panic attacks, MWA and phobia are also all increased significantly in the C/C vs. T/any individuals (Table 2). Although both panic disorder and obsessive compulsive disorder (OCD) are more frequent in the C/C vs. T/any individuals, the difference does not reach statistical significance. However, OCD is more frequent in the C/C individuals than in the T/T individuals (Chi-square = 2.84; $p < 0.05$).

DRD2 *Nco*I allele frequencies in neuropsychiatric disorders

DRD2 *Nco*I allele frequencies were determined in individuals based on the presence or absence of neuropsychiatric disorders (Table 3) [18]. In individuals with MWA, anxiety disorders and/or major depression, the C allele frequency was 0.80 and the T allele frequency was 0.20. In individuals who have none of these neuropsychiatric disorders, the C allele frequency was 0.63 and the T allele frequency was 0.37. The difference in the DRD2 *Nco*I C allele frequencies between these two groups of individuals is highly significant (Chi-square = 17.13; $p < 0.00002$). These data are consistent with the allele frequencies reported in the general Caucasian population where the C allele frequency was reported to be 0.69 and the T allele frequency was reported to be 0.31 [22].

Table 2 Incidence of migraine with aura, anxiety disorders and major depression in the current database based on DRD2 *Nco*I genotypes (Modified from Peroutka et al. [18] with permission)

	C/C	C/T	T/T	Chi-square analysis	
	(n = 131)	(n = 93)	(n = 18)	C/C vs. T/any	*p* value
MWA, anxiety or depression	69%	53%	22%	12.72	0.0002
Any anxiety disorder	54%	41%	17%	7.20	0.004
Generalized anxiety disorder	23%	11%	11%	6.11	0.007
Major depression	45%	33%	17%	5.18	0.01
Panic attacks	38%	26%	17%	4.96	0.01
Migraine with aura	26%	17%	6%	4.09	0.02
Phobia	34%	27%	11%	2.60	0.05
Panic disorder	22%	16%	11%	1.45	n.s.
Obsessive compulsive disorder	14%	16%	0%	0.01	n.s.

n.s., not significant

Table 3 DRD2 *Nco*I allele frequencies in individuals with or without migraine with aura, anxiety disorders or major depression (Modified from Peroutka et al. [18] with permission)

	C	T	Chi-square	*p* value
MWA, anxiety or depression	0.80	0.20	17.13	0.00002
No MWA, anxiety or depression	0.63	0.37	–	–

*Nco*I C alleles and migraine

Dichgans et al. [30] reported no association between the *Nco*I allele frequencies and migraine in a German group of 47 patients with MA and 55 patients with MO. No control group was analyzed. The authors concluded that no association existed between the DRD2 *Nco*I C allele and MWA.

DRD2 intronic TG dinucleotide polymorphism

Del Zompo et al. [31] studied a clinical cohort consisting of 50 nuclear families from Sardinia. They identified a subgroup of patients with "dopaminergic migraine", defined by a relatively high frequency of yawning and nausea immediately before or during the painful phase of migraine attacks. A transmission disequilibrium test (TDT) was performed. The distribution of the TG dinucleotide intronic noncoding polymorphism in the DRD2 gene was significantly different ($p < 0.004$) in the 23 family units with dopaminergic migraine than in the 27 other migraine families. Specifically, allele 1 of the DRD2 gene was significantly more frequent in the patients with dopaminergic migraine ($p < 0.02$).

Conclusions

The major finding of these studies is that susceptibility to certain subtypes of migraine and neuropsychiatric disorders may be modified by DRD2 alleles. Specifically, the incidence of the clinical diagnoses of migraine, anxiety disorders and major depression has been associated with polymorphisms within the DRD2 gene in certain clinical databases. However, controversy exists as to whether these associations are present in other populations or clinical databases [30].

As demonstrated in the previously mentioned American clinical database studies, individuals with migraine, anxiety and/or depression display an increased frequency of the DRD2 *Nco*I C/C genotype compared to individuals with the C/T or T/T genotype. These data represent the first direct evidence to suggest that a specific genetic variant may, at least partially, underlie the well documented comorbidity of migraine, anxiety disorders and major depression [19–29].

In post-mortem brain samples, *Taq* A DRD2 alleles were associated with variations in the density of DRD2 binding sites [32]. No data exist at present on the effect of *Nco*I polymorphisms on DRD2 expression. Conceivably, intragenic nucleotide variations may result in functional variations in RNA stability or efficacy in transcription [33], thus resulting in alterations in the density of the expressed receptor protein. For example, recent data suggest that non-coding region variations within the 5-hydroxytryptamine transporter (5-HTT) gene may alter expression of the transporter [34]. Specifically, the transcriptional efficiency of the short variant of the 5-HTT gene is reduced compared to the long version of the gene [35]. In addition, intragenic nucleotide variations may also exist within a gene that could result in functional variations in splicing and/or RNA stability [33], thus resulting in alterations in the density of the expressed protein. In the case of monoamine oxidase A, for example, non-coding region variations have been shown to result in a 30-fold difference in enzymatic activity [36].

Alternatively, the DRD2 polymorphisms analyzed in the positive association studies may lie in linkage disequilibrium with a more directly causative mutation. However, a specific molecular variation within the DRD2 gene which could underlie functional variations in the expressed receptor protein remains unidentified [37]. Future studies are needed to more clearly define the possible functional significance of non-coding region variations within the DRD2 gene.

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