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RESEARCH REPORT

Association of Dopamine Receptor Gene Polymorphisms with the Clinical Course of Wilson Disease

T. Litwin · G. Gromadzka · J. Samochowiec · A. Grzywacz · A. Członkowski · A. Członkowska

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Abstract *Background:* Dopamine receptor D2 (*DRD2*) polymorphisms are proposed to be important factors in the presentation of neuropsychiatric symptoms in many disorders, including decreased striatum levels of dopamine D2 receptors in Wilson disease. The present study investigated the association between *DRD2* gene polymorphisms and clinical manifestation of Wilson disease.

Methods: Analyzing data from 97 symptomatic Wilson disease patients, we investigated the *DRD2* gene polymorphisms rs1800497, rs1799732, and rs12364283. We assessed the polymorphisms impact on the phenotypic presentation of the disease.

Results: Generally, the *DRD2* gene polymorphisms had no impact on the hepatic or neuropsychiatric clinical presentation of Wilson disease. However, rs1799732 deletion allele carriers with neuropsychiatric symptoms had earlier onset of WD symptoms by almost 6 years compared with individuals without this allele (22.5 vs. 28.3 years; $P < 0.05$). This unfavorable effect of the rs1799732 polymorphism was even more pronounced among adenosine triphosphatase 7B gene (*ATP7B)* p.H1069Q homozygous patients, in whom carriership of the deletion allele was related to earlier initial neuropsychiatric manifestation by 14 years (18.4 vs. 32.2 years; $P < 0.01$).

Conclusions: Genetic variation of *DRD2*, specifically the rs1799732 polymorphism, may produce an earlier clinical presentation of Wilson disease neuropsychiatric symptoms and signs that occur in the course of dopaminergic system impairment due to copper accumulation in the brain. We speculate that this effect may be due to the impact of *DRD2* polymorphism on dopamine D2 receptor density, but further studies are needed to understand the mechanisms of such phenotypic effects.

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T. Litwin (✉) · G. Gromadzka · A. Członkowski · A. Członkowska
Second Department of Neurology, Institute Psychiatry and Neurology, Sobieskiego 9 02 957, Warsaw, Poland
e-mail: tomlit@medprakt.pl

G. Gromadzka · A. Członkowski · A. Członkowska
Department of Experimental and Clinical Pharmacology, Medical University, Warsaw, Poland

J. Samochowiec · A. Grzywacz
Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland

Introduction

Wilson disease (WD) is an inherited copper metabolism disorder leading to copper accumulation in many tissues (mainly the liver and brain) with secondary damage to affected organs (Roberts and Schilsky 2008; Ala et al. 2007; Ferenci et al. 2003, 2007). WD is associated with a wide spectrum of symptoms (hepatic, neurological, psychiatric, and others) as well as great variability in clinical presentation and outcome (Roberts and Schilsky 2008; Ala et al. 2007; Ferenci et al. 2003, 2007; Schilsky et al. 1994). Although these differences remain largely unexplained, several factors are known to impact clinical presentation of WD, including gender (Schilsky et al. 1994; Litwin et al. 2012a) and genotype (Stapelbroek et al. 2004; Gromadzka et al. 2005, 2006). It is also suspected that WD presentation may be influenced by polymorphisms in the genes encoding prion-related protein, methylenetetrahydrofolate reductase, interleukin-1 receptor antagonist, and apolipoprotein-E

Table 1 *DRD2* polymorphisms and their possible clinical significance

Polymorphism	Possible clinical significance	Comment
rs1800497 *ANKK* TaqIA	The A1 allele frequency is higher in patients with neuroleptic malignant syndrome (Suzuki et al. 2001). The A1 allele is associated with tardive dyskinesia, Parkinson's disease (data are conflicting), and late onset hallucination induced by treatment with levodopa (Noble 2003; Makoff et al. 2000; Olivieri et al. 2000).	The A1 allele may be associated with decreased D2 receptors in striatum (Noble 2003).
rs1799732 −141 C Ins/Del	The Del allele frequency is higher in patients with neuroleptic malignant syndrome (mechanism not known; data conflicting) (Kishida et al. 2004; Farde et al. 1995). The Del allele is significantly associated with poorer antipsychotic drug response (Zhang et al. 2010).	Data are conflicting regarding the impact on D2 receptors density in striatum Deletion (Del+) may be associated with increased number of D2 receptors (Jonsson et al. 1999) or may have no impact on DRD2 density (Ritchie and Noble 2003).
rs12364283 DRD2 Ex8	*DRD2 Ex8* A/A genotype is associated with increased anxiety, depression, and suicide attempts after detoxification treatment in alcohol-dependent patients, with reduced response to dopamine D2 agonists (apomorphine) and to D2 antagonists (tiapride) (Samochowiec et al. 2000).	The E8A/A allele may be associated with reduced DRD2 expression (Samochowiec et al. 2000).

(Merle et al. 2006; Gromadzka et al. 2011a, b; Schiefermeier et al. 2000; Litwin et al. 2012b). Other genes like antioxidant-1 (Atox-1), copper metabolism gene *MURR1* domain containing proteins (COMMD), and X-linked inhibitor of apoptosis (XIAP) (Simon et al. 2008; Weiss et al. 2006; Burstein et al. 2005; Weiss et al. 2010) have also been suggested as WD modifiers. Nonetheless, phenotype-related differences in WD manifestation are still mainly unknown.

In WD, most of the neuropsychiatric symptoms are due to basal ganglia dysfunction secondary to copper accumulation (Magalhaes et al. 1994; Schlaug et al. 1994; Nyberg et al. 1982). Pathology studies in WD revealed reduced striatal dopamine and hydroxylase tyrosine levels (Vallone et al. 2000; Nyberg et al. 1982; Mousseau et al. 1993) and animal studies have indicated decreased dopamine receptor 2 (DRD2) during copper overloading (de Vries et al. 1986). Single photon emission computerized tomography (SPECT) and positron emission tomography (PET) studies have shown postsynaptic dopaminergic deficit (loss of D2 receptors in striatum) in WD patients (Oder et al. 1996; Westermark et al. 1995) as well as presynaptic nigrostratial dopaminergic damage (Jeon et al. 1998). WD patients also exhibit reduced bindings of dopamine ligands to dopamine receptors on lymphocytes probably due to dopamine receptors damage during copper intoxication (Członkowski and Członkowska 1984; Członkowska et al. 1987).

Polymorphisms in the *DRD2* gene and the related ankyrin repeat and protein kinase–containing protein (*ANKK*) gene – including *ANKK* TaqIA (rs1800497), *DRD2* PROM −141 C Ins/Del (rs1799732), and *DRD2* Ex8 (rs12364283) – impact the dopamine receptor D2 density in the striatum with a high clinical significance in the etiology of many neuropsychiatric disorders, especially involuntary movements (Table 1) (Wu et al. 2006; Noble 2003; Thompson et al. 1997; Kisihida et al. 2004; Suzuki et al. 2001; Tan et al. 2003; Zhang et al. 2010; Ritchie and Noble 2003; Farde and Nordstrom 1993; Farde et al. 1995, 1997; Tinsley et al. 2009).

We hypothesized that these polymorphisms may represent an important predicting factor for phenotypic manifestations of WD. The aim of the present study was to determine, in a large group of WD patients, the relationships among these three important DRD2-related single nucleotide polymorphisms (SNPs) and WD presentation.

Methods

We studied 97 WD symptomatic patients (42 men and 55 women) who had received a confirmed diagnosis from the Institute of Psychiatry and Neurology in Warsaw, Poland, between 1988 and 2010. This study was approved by the local ethics committee and informed consent was provided by all study subjects. The diagnoses were based on clinical symptoms, abnormal copper metabolism (decreased levels of serum ceruloplasmin and serum copper, and increased 24-h urine copper excretion), presence of the Kayser-Fleischer ring, and, in many cases, genetic examination. If the diagnosis was not certain, it was confirmed by measuring Cu-64 incorporation into ceruloplasmin after 24 and 48 h. None of the examined patients were treated with neuroleptics or drugs that could interfere with dopamine metabolism (dopamine agonists, levodopa),

Table 2 SNPs, primers, and PCR products

SNP ID	Position	Primer and sequence	PCR product	RE	DNA variant	Allele	Fragment size (bp)
rs1800497	11 q23.2	F: 5'-CTT GCC CTC TAG GAA GGA CAT	310	Taq1	T/C	T	310
	ANKK					C	180
		R: 5'-ACC TTC CTG AGT GTC ATC AAC C					130
rs1799732	11 q23.1	F: 5'-CAA CCC TGG CTT CTG AGT CC	207	MvaI	−141 ins/del	C	207
	Promoter	R: 5'-GAG CTG TAC CTC CTC GGC GAT C				–	177
rs1236428	11 q23.1	F: 5'-GCC TGT CCT CCC CGG CTC TG	349	Hpa II	A/G	A	349
	Ex 8	R: 5'-GGC AGT GAG GAG CAT GGA GCC AAC				G	282

as such treatment could produce neuropsychiatric manifestations, such as drug-induced movement disorders.

Symptomatic WD patients were defined as patients with clinical signs of WD at onset and/or diagnosis. The hepatic symptoms and signs were assessed based on a detailed questionnaire that included data on fatigue, weight loss, leg edema, jaundice, abdominal swelling, hematemesis, hemorrhages, and fulminant liver failure. Laboratory examinations included ultrasound examinations of the liver and spleen, gastroscopy, and assessments of aminotransferases, alkaline phosphatase, bilirubin, INR, and albumen that were available from medical history and records. The evaluation of neuropsychiatric symptoms and signs was also based on a detailed questionnaire addressing salivation, dysphagia, speech, writing and gait disturbances, involuntary movements, adynamia, epileptic seizures, mood disorders, anxiety, and cognitive impairment (Litwin et al. 2012a).

The age at WD symptom onset/diagnosis was assessed based on patient history, symptoms and signs of WD, and/or available medical documentation in addition to clinical and laboratory investigations.

WD genotyping was determined by polymerase chain reaction (PCR) as reported previously (Gromadzka et al. 2005, 2006) and was assessed according to *ATP7B* genotype (homozygous p.H1069Q/p.H1069Q, compound heterozygous p.H1069Q/other mutation, or negative for the p.H0169Q mutation). Polymorphisms were determined by PCR and restriction fragment length polymorphism analysis of *ANKK* TaqIA (rs1800497), *DRD2* PROM −141 C Ins/Del (rs1799732), and *DRD2* Ex8 (rs12364283) as previously described (Grandy et al. 1989; Hori et al. 2001; Samochowiec et al. 2000). Investigated SNPs, primers, and PCR products are presented in Table 2. One hundred (50 males and 50 females) unrelated, matched, healthy controls were used for SNP comparison and to check the Hardy–Weinberg equilibrium.

Due to the clinical significance of DRD2 in neuropsychiatric disorders, further analysis included a comparison of the distributions of the three polymorphisms between patients with and without neuropsychiatric symptoms and signs, and between patients with neuropsychiatric presentation and patients with dystonic symptoms (most severe neurologic presentation). All analyses of significance were repeated in the set of patients homozygous for the H1069Q mutation, a more homogenous WD patient group.

Statistical Analysis

All data were analyzed using Statistica version 9. The mean, range, percentage, and SD were noted for descriptive summary statistics. Quantitative variables were compared using the Mann–Whitney *U* test. Categorical variables were compared between groups using the chi-square test and Fisher's test; $P < 0.05$ was considered statistically significant. For the multiple comparisons, hypothesis testing was performed using the Bonferroni correction (the *P*-value divided by the total number of pairwise comparisons) to correct for the chance that in multiple comparisons the null hypothesis would be rejected by chance. For three polymorphisms, the level of significance was equal to 0.008.

Results

Polymorphisms and WD Clinical Manifestations

In our group of 97 symptomatic patients, 31 had both neuropsychiatric and hepatic manifestations at onset, 32 had only neurological, and 34 had only hepatic symptoms and signs. In total, 63 patients had neuropsychiatric symptoms; among them, 21 had dystonia.

In WD patients and control subjects, no significant deviation from the Hardy–Weinberg equilibrium form was found for *ANKK* TaqIA (rs1800497; WD patients, A1/A1 = 2, A1/A2 = 33, A2/A2 = 62; control subjects, A1/A1 = 3, A1/A2 = 28, A2/A2 = 69; chi-squared = 0.006, degrees of freedom (d.f). = 1, $P < 0.093$), *DRD2* PROM −141 C

Table 3 Distribution of neuropsychiatric and dystonia symptoms and signs in WD patients according to *DRD2* polymorphism

	ANKK TaqI (A1 allele)		*DRD2* PROM −141 C deletion		*DRD2* Ex 8 (A/A vs. A/G and G/G)	
Patients symptoms and signs:	**A1**	**A2**	**Del−**	**Del+**	**A/A**	**A/G and G/G**
	($n = 35$)	**($n = 62$)**	**($n = 83$)**	**($n = 14$)**	**($n = 54$)**	**($n = 43$)**
Not neuropsychiatric ($n = 34$)	14 (41 %)	20 (59 %)	31 (91 %)	3 (9 %)	20 (59 %)	14 (41 %)
Neuropsychiatric ($n = 63$)	21 (33 %)	42 (66 %)	52 (82 %)	11 (17 %)	34 (54 %)	29 (46 %)
Neuropsychiatric with dystonia ($n = 21$)	9 (43 %)	12 (57 %)	18 (86 %)	3 (14 %)	11 (52 %)	10 (48 %)
Neuropsychiatric without dystonia ($n = 42$)	12 (29 %)	30 (71 %)	34 (80 %)	8 (20 %)	23 (54 %)	19 (46 %)

Data do not sum to 100 % due to rounding errors. There were no statistically significant differences according to polymorphism or WD clinical form.

Table 4 Age of symptom onset in patients with presence/absence of neuropsychiatric signs and symptoms according to *DRD2* polymorphism

	ANKK Taq1 (A1 allele)		*DRD2* PROM −141 C deletion		*DRD2* Ex 8 (A/A vs. A/G and G/G)	
Clinical manifestation and age of symptoms and signs onset	**A1**	**A2**	**Del−**	**Del+**	**A/A**	**A/G and G/G**
	($n = 35$)	**($n = 62$)**	**($n = 83$)**	**($n = 14$)**	**($n = 54$)**	**($n = 43$)**
All WD patients 25.1 ± 8.7 ($n = 97$)	23.5 ± 7.6 ($n = 35$)	26.09 ± 9.3 ($n = 62$)	25.6 ± 8.9 ($n = 83$)	22.0 ± 7.0 ($n = 14$)	25.1 ± 8.1 ($n = 54$)	25.1 ± 9.3 ($n = 43$)
Not neuropsychiatric 21.2 ± 8.05 ($n = 34$)	20.5 ± 7.6 ($n = 14$)	21.6 ± 8.4 ($n = 20$)	21.2 ± 8.0 ($n = 31$)	20.3 ± 10.4 ($n = 3$)	19.5 ± 5.5 ($n = 20$)	22.4 ± 9.3 ($n = 14$)
Neuropsychiatric 27.3 ± 8.4 ($n = 63$)	25.5 ± 7.1 ($n = 21$)	28.2 ± 9.0 ($n = 42$)	28.3 ± 8.5 ($n = 52$)	22.5 ± 6.5[a] ($n = 11$)	26.3 ± 9.1 ($n = 34$)	28.4 ± 7.5 ($n = 29$)

[a] Significant difference in age at onset of symptoms ($P = 0.035$) between *DRD2* PROM −141 C del, Del + positive vs. negative patients.

Ins/Del (rs1799732; WD patients, Ins/Ins = 83, Ins/Del = 14, Del/Del = 0; control subjects Ins/Ins = 80, Ins/Del = 20, Del/Del = 0; chi-squared = 0.614, d.f. = 1, $P < 0.433$), and *DRD2* Ex8 (rs12364283; WD patients, A/G = 52, A/A = 40, G/G = 5; control subjects, A/G = 43, A/A = 52, G/G = 5; chi-squared = 1.234, d.f. = 1, $P < 0.266$). We did not detect an impact of these polymorphisms on the clinical manifestation of WD at onset (Table 3).

Polymorphisms and Age at First WD Symptom Onset

The mean age of all patients at the first signs of WD was 25.1 ± 8 years (range 7–57 years). We found a significant association only between rs1799732 polymorphism and age of onset of WD neuropsychiatric symptoms – carriers of the deletion (Del+) allele of the −141 C Ins/Del polymorphism presented earlier onset of WD neuropsychiatric signs by 6 years compared with Del − carriers (22.5 vs. 28.3 years; $P = 0.035$; Table 4).

Homozygous p.H1069Q Patients: Polymorphisms, Clinical manifestation, and Age of Symptom Onset

WD genotyping of 97 symptomatic WD patients revealed that 43 patients were homozygous for the p.H1069Q mutation, 36 patients were compound heterozygous, and 18 patients were negative for the p.H1069Q mutation. We did not detect an impact of polymorphisms on the clinical WD manifestation in p.H1069Q homozygous patients (Table 5). Due to the very small group of patients that were homozygous for p.H1069Q mutations in the dystonic group ($n = 3$), we did not assess these patients separately. However, among WD p.H1069Q patients, we detected a statistically significant effect of the *DRD2* −141 C Ins/Del polymorphism. In this homogenous group, Del + allele carriers presented earlier onset of any WD symptoms by 9 years (20.1 vs. 29.4 years; $P = 0.019$); furthermore, the subset of these patients with neuropsychiatic signs presented with symptom onset 14 years earlier (18.4 vs. 32.2 years; $P = 0.001$; Table 6).

Table 5 Distribution of neuropsychiatric symptoms and signs in WD patients according to *DRD2* polymorphism in 43 p.H1069Q homozygous patients

	ANKK Taq1 (A1 allele)		*DRD2* PROM −141 C deletion		*DRD2* Ex 8 (A/A vs. A/G and G/G)	
Clinical manifestation (symptoms and signs) ($n = 43$)	**A1 ($n = 16$)**	**A2 ($n = 27$)**	**Del− ($n = 36$)**	**Del+ ($n = 7$)**	**A/A ($n = 24$)**	**A/G and G/G ($n = 19$)**
Not neuropsychiatric ($n = 15$)	6 (40 %)	9 (60 %)	13 (86 %)	2 (13 %)	8 (53 %)	7 (46 %)
Neuropsychiatric ($n = 28$)	10 (35 %)	18 (65 %)	23 (82 %)	5 (18 %)	16 (57 %)	12 (42 %)

Data do not sum to 100 % due to rounding errors. There were no statistically significant differences according to polymorphism and WD clinical form.

Table 6 Age of symptom onset in all WD patients, and according to the presence/absence of neuropsychiatric symptoms and signs and to *DRD2* polymorphism in p.H1069Q homozygous patients

	ANKK Taq 1 (A1 allele)		*DRD2* PROM −141 C deletion		*DRD2* Ex 8 (A/A vs. A/G and G/G)	
Clinical manifestation and age of symptoms and signs onset (years)	**A1 ($n = 16$)**	**A2 ($n = 27$)**	**Del− ($n = 36$)**	**Del+ ($n = 7$)**	**A/A ($n = 24$)**	**A/G and G/G ($n = 19$)**
All WD patients ($n = 43$) 28.1 ± 9.2	25.5 ± 7.8 ($n = 16$)	29.2 ± 9.6 ($n = 27$)	29.4 ± 8.8 ($n = 36$)	20.1 ± 6.2[a] ($n = 7$)	27.8 ± 8.1 ($n = 24$)	27.9 ± 9.8 ($n = 19$)
Not neuropsychiatric ($n = 15$) 25.2 ± 7.6	22.6 ± 8.0 ($n = 6$)	27.0 ± 7.2 ($n = 9$)	25.3 ± 7.6 ($n = 13$)	24.5 ± 10.6 ($n = 2$)	27.6 ± 8.8 ($n = 8$)	22.5 ± 5.4 ($n = 7$)
Neuropsychiatric ($n = 28$) 29.7 ± 9.7	27.3 ± 7.5 ($n = 10$)	31.1 ± 10.7 ($n = 18$)	32.2 ± 8.8 ($n = 23$)	18.4 ± 4.0[b] ($n = 5$)	30.9 ± 7.3 ($n = 16$)	28.8 ± 11.3 ($n = 12$)

[a] Statistically significant difference ($P = 0.019$) in age at onset of symptoms between *DRD2* PROM −141 C del, Del + positive and negative patients (all WD patients).

[b] Statistically significant difference ($P = 0.001$) in age at onset of symptoms between *DRD2* PROM −141 C del, Del + positive and negative patients (patients with neuropsychiatric symptoms and signs).

Discussion

In the present investigation, we identified a significant impact of the *DRD2* PROM −141 C Ins/Del (rs1799732) polymorphism on WD clinical neuropsychiatric presentation. We were thus able to partially confirm our initial hypothesis that changes in dopaminergic neurotransmission due to *DRD2* polymorphism could be important for clinical neuropsychiatric manifestation. Carriers of the Del + allele of the −141 C Ins/Del polymorphism presented earlier onset of WD neuropsychiatric symptoms by almost 6 years compared with the Del variant. This unfavorable effect of the −141 C Ins/Del polymorphism was even more pronounced in WD p.H1069Q homozygous patients, as the Del + allele carriers presented earlier onset of any WD symptoms by nearly 9 years and neuropsychiatric symptoms by nearly 14 years. Our analysis suggests that the Del + effect was restricted to neuropsychiatric manifestation. Additionally, we did not find any correlation between WD manifestation and the two other studied polymorphisms *ANKK* TaqIA (rs1800497) and *DRD2* Ex8 (rs12364283). The p.H1069Q effect observed in our study could be explained by the fact that compared to other mutations, p.H1069Q *ATP7B* exerts a relatively mild effect on functions of ATPase 7B (Stapelbroek et al. 2004; Gromadzka et al. 2005) and it is possible that the WD phenotypes of patients possessing more severe *ATP7B* mutations are modulated by other factors to a lesser degree.

In WD, most neuropsychiatric symptoms are due to basal ganglia copper accumulation and the secondary damage to affected structures (dystonia, parkinsonism, and others) or prefrontal cortex disturbances (Magalhes et al. 1994; Schlaug et al. 1994; Nyberg et al. 1982; Oder et al. 1993; Seniow et al. 2002), as both of these areas involve the dopaminergic system (Vallone et al. 2000). Autopsies and radiological and laboratory investigations of WD cases have found reduced striatal dopamine and hydroxylase tyrosine levels (Nyberg et al. 1982), as well as reduced dopamine D2 receptor density (Oder et al. 1996; Schlaug et al. 1994). However, treatment with dopamine agonists or levodopa had no effect, probably due to the presence of both pre- and postsynaptic dopaminergic damage (Frankel et al. 1989; Jeon et al. 1998). The density of DRD2 postsynaptic receptors tends to increase during anti-copper treatment (Schlaug et al. 1994), suggesting that the

dopamine D2 receptor pathway may be critical to WD clinical presentation. Furthermore, *DRD2* polymorphisms are predictive of the dopamine receptor D2 density in the striatum (Noble 2003; Ritchie and Noble 2003), which may also affect WD neuropsychiatric manifestation.

Based on the previously reported clinical significance of the polymorphisms *ANKK* TaqIA and *DRD2* Ex8 (Table 1), we thought that the decreased DRD2 density in the striatum in TaqI A1 allele carriers or reduced expression of DRD2 in Ex8 A/A genotype may worsen dopaminergic neurotransmission leading to earlier onset of neuropsychiatric WD signs, but our data did not confirm this hypothesis. The *ANKK* TaqIA and *DRD2* Ex8 polymorphisms had no impact on WD clinical presentation. We also did not identify a relationship between dystonic manifestation of WD and *ANKK* TaqI or *DRD2* Ex8 polymorphisms as we had expected. This lack of a detected association may be due to our small patient sample, or there may be a different etiology of neuropsychiatric symptoms in WD via other mechanisms involving DRD2.

Previous reports of the clinical significance of the *DRD2* −141 C Ins/Del polymorphism have been conflicting (Table 1). According to some studies (Jonsson et al. 1999; Zhang et al. 2010) Del + carriers may have higher numbers of DRD2 receptors in the striatum. A decrease of postsynaptic DRD2 is usually observed during WD (Oder et al. 1996; Schlaug et al. 1994), and increase is observed during chelating treatment (Schlaug et al. 1994). According to these observations, we should have found a protective effect of the Del + allele on neuropsychiatric presentation (increased number of DRD2) in WD, but we did not. On the contrary, we found that the Del + genotype accelerated the onset of neuropsychiatric symptoms. This unfavorable effect of the Del + allele may be explained by other mechanisms – like changes in receptor affinity, changes in receptor structure, interactions with other genes or environmental factors, or D2 receptor hyposensitivity, leading to a decreased effect of dopaminergic transmission. Another possible mechanism with such an effect could be connected with the impact of the *DRD2* −141 C Ins/Del polymorphism on the number of presynaptic D2 receptors (Vallone et al. 2000). According to such a hypothesis, Del + allele carriers could present increased numbers of such receptors, thus providing WD patients with stimulation of D2 presynaptic receptors with low doses of dopamine, which could further reduce dopamine release and dopaminergic cell firing and finally reduce locomotor functions and lead to neuropsychiatric WD presentation (Vallone et al. 2000). Further studies to confirm such hypotheses are very important, because such information could help establish group of WD patients in whom treatment with higher dose of levodopa would be beneficial (Del + carriers). Future investigations of this topic should include assessment of DRD2 density in radiological studies.

Our study has a few limitations. The first is the small number of patients included and the further limited number of SNPs analyzed. However, it should be noted that WD is a rare disease, and the number of patients in our study is very similar to that in many other WD or *DRD2* gene polymorphism studies (Schiefermeier et al. 2000; Kishida et al. 2004). This is the first pilot study of *DRD2* gene polymorphism in WD, so we tried to assess the most important *DRD2* SNPs in neuropsychiatric disorders (especially movement disorders). Furthermore, data are conflicting regarding the impact of the *DRD2* −141 C Ins/Del polymorphism on DRD2 density; without more specific studies (PET), we cannot confirm the etiology of the impact of the Del + allele on WD neuropsychiatric presentation. In the present report, we can only hypothesize about the impact on DRD2 expression based on some previous studies (Zhang et al. 2010; Jonsson et al. 1999), but these possibilities should be further investigated especially in WD.

In summary, our findings suggest that the *DRD2* −141 C Ins/Del polymorphism affects WD neuropsychiatric presentation, probably through disruption of the balance of dopamine neurotransmission that makes these patients more sensitive to basal ganglia intoxication by copper accumulation. Further studies of *DRD2* SNPs with dopamine receptor imaging in WD patients are needed to better understand the mechanisms of such phenotypic effects.

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We have no relevant financial interest in the Submitted Publication material.

Conflict of Interest

The authors declare no potential conflict of interest relevant to this article.

Documentation of Author Roles

1. Anna Członkowska: research project – conception; manuscript preparation – review and critique
2. Grażyna Gromadzka: research project – execution; statistical analysis – review; manuscript critique review

3. Tomasz Litwin: research project – conception and organization, execution; statistical analysis – design, execution; manuscript preparation – writing of the first draft, review
4. Jerzy Samochowiec: DRD2 polymorphism analysis
5. Anna Grzywacz: DRD polymorphism analysis
6. Andrzej Członkowski: manuscript review and corrections

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