Metab Brain Dis (2013) 28:447–453
DOI 10.1007/s11011-013-9399-x

ORIGINAL PAPER

Influence of *BDNF* polymorphisms on Wilson's disease susceptibility and clinical course

Dagmara Mirowska-Guzel · Tomasz Litwin · Grazyna Gromadzka · Andrzej Czlonkowski · Anna Czlonkowska

Received: 29 December 2012 / Accepted: 10 March 2013 / Published online: 22 March 2013

Abstract Susceptibility to Wilson's disease (WD) and its clinical manifestations are thought to be affected by genetic factors, including polymorphisms. The role of brain-derived neurotrophic factor (*BDNF*) in the pathogenesis of neurodegenerative diseases is now widely discussed. The aim of the present study was to evaluate the frequency of the *BDNF* Val66Met (G-196A) and C-270T polymorphisms in WD patients and in healthy controls, and to determine the role of these polymorphisms in the clinical characteristics of WD. We found that the *BDNF* Val/Val (−196 G/G) and −270 C/T genotypes occurred more frequently in WD patients than in healthy controls (66 % versus 45.5 %, p=0.0001, and 14 % versus 6 %, p=0.018, respectively). Similarly, symptomatic patients carried the *BDNF* Val/Val genotype more often than presymptomatic patients (75 % versus 53 %, p=0.0097). No association was detected between any of the determined polymorphisms and the dominant form of the disease or the age of onset for WD.

Keywords Brain-derived neurotrophic factor (*BDNF*) · Polymorphism · Wilson's disease · Disease susceptibility

Introduction

Wilson's disease (WD) is a rare inherited disease of copper metabolism that can lead to the accumulation of copper and damage to several organs. The main symptoms are liver failure and neuropsychiatric manifestations; symptomatology and age at symptom onset are thought to vary greatly among patients. Genetic variability, including gene mutations and polymorphisms, may underlie this variability. Mutation of *ATP7B* has been shown to affect disease manifestation (Gromadzka et al. 2006), but polymorphisms in, for example, the methyltetrahydrofolate reductase gene (Gromadzka et al. 2011), some cytokine genes (Gromadzka et al. 2011), and the apolipoprotein gene (Schiefermeier et al. 2000; Litwin et al. 2012) may be essential for the clinical characteristics of WD. Other genes, such as those encoding antioxidant-1, copper metabolism gene MURR1 domain-containing protein, and X-linked inhibitor of apoptosis have also been investigated, but with conflicting results (reviewed by Litwin et al. 2013).

Although WD is recognized as a neurodegenerative disease, previous studies of the pathogenesis of some neurodegenerative disorders revealed increased expression of pro-inflammatory cytokines in the brains of experimental animals and of patients. The inflammatory process is considered to be one step in neuronal degeneration (Frank-Cannon et al. 2009). The role of neurotrophins, including polymorphisms in brain-derived neurotrophic factor (*BDNF*), is now discussed widely with regard to susceptibility to neurodegeneration and to the courses of various neurological diseases, such as Parkinson's disease (Gao et al. 2010), Alzheimer's disease (Laske et al. 2006), and Huntington's disease (Albrech et al. 2005; Koshikawa et al. 2006). The effects of polymorphisms have also been explored in multiple sclerosis (Mirowska-Guzel et al. 2008; Mero et al. 2012), a disease in which neurodegeneration is thought to be secondary to autoimmunity.

The best-known *BDNF* polymorphism is G-196A, which results in a change of valine to methionine at codon 66 (Val66Met). The Met allele is associated with impaired intracellular trafficking and activity-dependent secretion of *BDNF* in neurons (Egan et al. 2003; Chen et al. 2004). A second

D. Mirowska-Guzel · G. Gromadzka · A. Czlonkowski · A. Czlonkowska
Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, 00-927 Warsaw, Poland

D. Mirowska-Guzel · T. Litwin · G. Gromadzka · A. Czlonkowska (✉)
2nd Department of Neurology, Institute of Psychiatry and Neurology, Sobieskiego 9, 02-957 Warsaw, Poland
e-mail: czlonkow@ipin.edu.pl

polymorphism, C-270T, occurs in the 5′-noncoding region of *BDNF*; functionality of this polymorphism is suspected, but has not been fully elucidated (Szczepankiewicz et al. 2005). Although at present the *BDNF* C-270T polymorphism is not known to cause changes in *BDNF*, the T allele is thought to affect the translation efficacy of *BDNF* (Kunugi et al. 2001). No data are currently available on the impact of *BDNF* genetic variants on WD susceptibility and symptomatology.

The aim of the present study was to compare the frequency of the *BDNF* Val66Met (G-196A) and C-270T polymorphisms in WD patients and in healthy controls, and to determine the role of these polymorphisms in the clinical characteristics of WD in terms of the clinically dominant form, its symptomatology, and age at onset in a large patient population.

Materials and methods

Patients and controls

We studied 414 patients diagnosed with WD at the Institute of Psychiatry and Neurology in Warsaw, Poland, between 1970 and 2010. A total of 145 healthy volunteers served as a control group. This study was approved by the local ethics committee, and informed consent was provided by all subjects included in the study. Patient diagnoses were based on clinical symptoms, abnormal copper metabolism (decreased serum ceruloplasmin and serum copper, increased 24-h urinary copper excretion), and the presence of the Kayser-Fleischer ring; many diagnoses were confirmed by genetic examination (Gromadzka et al. 2011). Clinical and family data, as well as physical, neurological, laboratory, brain magnetic resonance, and liver examination data were collected if available.

Patients with WD were divided into two groups according to the presence of clinical symptoms: presymptomatic and symptomatic. The presymptomatic group consisted of patients without clinical symptoms or signs of WD (usually siblings of the index case), and these patients were only included in the overall *BDNF* polymorphism distribution. The symptomatic group consisted of patients with clinical signs of WD at onset.

The clinical form of WD was established based on the presence and intensity of individual signs of WD at diagnosis. In symptomatic patients, a predominant symptoms scoring system at diagnosis was used as described in previous studies (Merle et al. 2007; Litwin et al. 2012). The assessment of hepatic signs and symptoms was based on a detailed questionnaire that included data on fatigue, weight loss, leg edema, jaundice, abdominal swelling, hematemesis, hemorrhaging, fulminant liver failure, and laboratory examinations (e.g., ultrasound, liver and spleen assessment, and measurement of aminotransferases, bilirubin, international normalized ratio for blood coagulation, and albumin) available from medical history and records. The evaluation of neuropsychiatric symptoms and signs was also based on a detailed questionnaire and included data on salivation, dysphagia, speech, writing and gait disturbances, involuntary movements, adynamia, epileptic seizures, mood disorders, anxiety, and cognitive impairment. Neurological symptoms at diagnosis were classified (i.e., rigidity-tremor, tremor, dystonic, rigidity) by a system used in our department since 1960 and described by Marsden (1987). Age at the onset of WD symptoms and at diagnosis was assessed based on patient history, symptoms and signs of WD, and/or available medical documentation, as well as the results of clinical and laboratory investigations.

BDNF polymorphisms

Genomic DNA was isolated using Tri-Reagent (Sigma, Poland). *BDNF* Val66Met (G-196A) and C-270T genotyping was performed by polymerase chain reaction restriction fragment length polymorphism analysis as described previously (Riemenschneider et al. 2002; Neves-Pereira et al. 2002). *ATP7B* genotyping was performed by polymerase chain reaction restriction fragment length polymorphism analysis and/or direct *ATP7B* gene sequencing as described previously (Gromadzka et al. 2006).

Statistical analysis

Statistical analyses were carried out with STATISTICA PL (version 10.0) provided by StatSoft® (2012, Poland). Genotype and allele frequencies were compared with the chi-squared test. The Bonferroni correction for multiple comparisons was used as needed. The Mann–Whitney *U* test was used for comparisons of two independent groups. Results of multiple logistic regression are expressed as an adjusted odds ratio (OR) and a 95 % confidence interval (95 % CI). Significance was set at $p \leq 0.05$.

Results

Patient demographics and clinical characteristics

A total of 414 patients (220 women and 194 men) were enrolled in the study (Table 1). The control group consisted of 145 healthy sex- (83 females and 62 males) and age- (mean±standard deviation, 40.09±10.19 years) matched volunteers.

BDNF Val66Met and C-270T polymorphisms and WD susceptibility

No significant differences were found in the *BDNF* allele and genotype distributions between male and female

patients and healthy volunteers (data not shown). However, significant differences were detected in the distributions of Val66Met and C-270T alleles and genotypes between WD patients and healthy volunteers, even when Bonferroni correction for multiple comparisons was applied. None of the control subjects carried the *BDNF* Met/Met genotype; thus, in the patient group the Met/Met genotype was combined with the Val/Met genotype for statistical purposes (Table 2).

In logistic regression analysis, the *BDNF* Val/Val and −270 C/T genotypes were more frequent in patients with WD than in controls (p=0.0001, OR 2.26, 95 % CI 1.54–3.33, and p=0.046, OR 2.12, 95 % CI 1.01–4.45, respectively). *BDNF* Val/Val and −270 C/T occurred together in 10 % of WD patients and in 4 % of healthy controls (p=0.001, OR 1.69, 95 % CI 1.53–1.86).

BDNF polymorphisms and course of WD

No differences were found in the distributions of the *BDNF* Val66Met and −270 C/T genotypes between patients with predominant neurological-psychiatric disease and patients with the hepatic form of the disease at diagnosis. The *BDNF* Val/Val genotype was detected in 68 % of WD patients with a neuropsychiatric form of the disease and in 68 % of patients with the dominant hepatic form. The *BDNF* −270 C/C genotype was detected in 84 % and 85 % of WD patients with the neuropsychiatric and hepatic forms of the disease, respectively. No difference was identified in the age of onset between patients with different *BDNF* variants, including comparisons within and between sex groups and patients with different dominant neurological symptoms of the disease (tremor-rigidity, rigidity, tremor, dystonia; Table 3).

The *BDNF* Val/Val genotype occurred more frequently in symptomatic patients than in presymptomatic patients. This difference became even more evident when only patients homozygous for *ATP7B* p.H1069Q were considered (Table 4). In this group of patients the *BDNF* Val/Val genotype occurred more frequently in symptomatic patients than in presymptomatic patients (logistic regression analysis p=0.01, OR 2.71, 95 % CI 1.23–5.96).

Discussion

WD is a copper metabolism disorder that results in the formation of unstable ceruloplasmin, which is rapidly degraded. The disorder results in copper accumulation in hepatocytes (Mercer 2001). Excess copper is taken up by extrahepatic tissues, including the brain and the cornea limbus. Copper accumulation leads to the clinical manifestation of WD.

Though classically considered to be involved in the pathogenesis of neurodegenerative and psychiatric disorders, *BDNF* has been found outside of the central nervous system, in muscle, heart, gonads, and in systemic circulation (Matthews et al. 2009; Nakahashi et al. 2000). Increasing evidence has demonstrated a function of *BDNF* outside the brain, especially in metabolic health (Golden et al. 2010; Pedersen 2009). The role of peripherally circulating *BDNF* in WD is not known. The involvement of *BDNF* in oxidative processes and systemic low-grade inflammatory states may at least partly underlie *BDNF*'s contribution to the pathogenesis of neurodegenerative diseases with primary hepatic pathology, although this hypothesis requires verification. Elevated plasma *BDNF* levels in cardiovascular disease have been speculated to represent a compensatory response to underlying disease processes (Golden et al. 2010); a similar protective effect may be exerted in WD by increased *BDNF* levels controlled by genetic mechanisms.

To the best of our knowledge, the present study is the first to investigate *BDNF* polymorphisms with regard to WD susceptibility and the course of the disease. The distribution of *BDNF* genotypes in WD patients was similar to those described previously: 66 % for *BDNF* Val/Val in the current study, as compared to 65.4 % in Alzheimer's disease (Ventriglia et al. 2002), 64 % in Huntington's disease (Mai et al. 2006), 62.9 % in cervical dystonia (Groen et al. 2012), and 60 % in multiple sclerosis (Mirowska-Guzel et al. 2008). In the case of the *BDNF* C-270T polymorphism, the C/C genotype was noted in 88.2 % of Alzheimer's disease patients (Kunugi et al. 2001) and 68 % of multiple sclerosis patients (Mirowska-Guzel et al. 2008), versus 86 % of WD patients in the current study. The distributions of these variants are considered to be stable in diseases of primary neurodegenerative pathology and in healthy volunteers. However, these previous studies were performed in ethnically diverse populations with central nervous system diseases with different underlying pathogenesis processes, at least in terms of primary or secondary neurodegeneration.

Here we have determined that the *BDNF* Val66Met and C-270T polymorphisms are associated with WD, acting both independently and together. The *BDNF* Val/Val genotype occurs more often in WD patients than in controls, but the Met allele is thought to be involved in the *BDNF* impairment typical of neurodegenerative diseases. It is unclear why the *BDNF* Val/Val genotype occurs more frequently in WD patients than in healthy controls. Although the Met allele is traditionally thought to result in decreased secretion of the peptide (Egan et al. 2003), increased secretion of *BDNF* in the presence of the Met allele was shown in an animal study (Lang et al. 2005). The protective role of the Met allele on working memory performance was detected in multiple sclerosis patients (Zivadinov et al. 2007) and in Parkinson's disease patients (Foltynie et al. 2005), and was evident in imaging-genetic studies of multiple

Table 1 Wilson's disease patient demographics and clinical characteristics

	All patients (n=414)	Women (n=220)	Men (n=194)	Test statistics
Age at qualification for the study [a]	40.90±12.98	40.60±13.30	41.24±12.66	p=0.49*
Age at first symptoms [a]	27.18±9.38	27.51±9.82	26.83±8.92	p=0.93*
Age at diagnosis [a]	28.45±9.86	28.57±10.12	28.31±9.58	p=0.96*
Symptomatic, n (%)	338 (82)	174 (79)	164 (84.5)	Chi^2=2.04, df=1, p=0.15**
Presymptomatic, n (%)	76 (18)	46 (21)	30 (15.5)	
Neuropsychiatric form, n (%)	194 (57)	84 (48)	110 (65)	Chi^2=12.20, df=1, p=0.0005**
Hepatic form, n (%)	145 (43)	90 (52)	54 (33)	
Neurological symptoms, n (% of all patients):	224 (54)	105 (48)	119 (61)	Chi^2=7.69, df=1, p=0.0055**
Discrete, n (%)	20 (9)	12 (11)	8 (7)	Chi^2=1.33, df=1, p=0.25**
Rigidity-tremor, n (%)	60 (27)	24 (23)	36 (31.5)	Chi^2=1.56, df=1, p=0.21**
Rigidity, n (%)	15 (7)	4 (4)	11 (10)	Chi^2=2.64, df=1, p=0.10**
Tremor, n (%)	101 (46)	53 (50)	48 (42)	Chi^2=2.32, df=1, p=0.13**
Dystonia, n (%)	28 (13)	12 (11)	16 (14)	Chi^2=0.21, df=1, p=0.65**

[a] Data are presented in years as mean and standard deviation

*p value from the Mann–Whitney U test comparing women and men

**Chi-squared test comparing women and men

sclerosis patients (Cerasa et al. 2010). One explanation is that the pro-*BDNF* produced in the brains of Val/Val carriers potentially interferes with the mature form of *BDNF*, and may even inhibit *BDNF* maturation. Furthermore, mature *BDNF* promotes cell survival by activating tropomyosin-related kinase receptor B, whereas pro-*BDNF* preferentially binds to the $p75^{NTR}$ receptor and induces cell apoptosis (Beattie et al. 2002; Lee et al. 2001). As we did not measure the *BDNF* concentration, we are unable to examine possible correlations between either of the assessed polymorphisms and serum *BDNF* levels.

In the present study, no difference was found in the distribution of any of the investigated alleles and genotypes between patients with two different forms of the disease at diagnosis (hepatic or neurological). In addition, neither *BDNF* polymorphism was associated with any neurological symptoms typical of the disease (tremor, rigidity, dystonia) or with age of disease onset in patients with different neurological symptoms. Considering the age of disease onset, our observations were

Table 2 Frequency of *BDNF* Val66Met and C-270T alleles and genotypes in Wilson's disease patients versus healthy controls

	Wilson's disease patients n=414 (%)	Healthy controls n=145 (%)	Test statistics[a]
BDNF Val66Met			
Allele frequency			
Val	674 (81)	211 (73)	Chi^2=9.72, df=1, p=0.018, (p=0.036**)
Met	154 (19)	79 (27)	
Genotype frequency			
Val/Val	274 (66)	66 (45.5)	Chi^2=19.25, df=1, p=0.0001, (p=0.0002**)
Val/Met+Met/Met	140 (34)	79 (54.5)	
BDNF C-270T			
Allele frequency			
C	772 (93 %)	281 (97 %)	Chi^2=5.25, df=1 p=0.022, (p=0.044**)
T	56 (7 %)	9 (3 %)	
Genotype frequency			
C/C	358 (86 %)	136 (94 %)	Chi^2=5.60, df=1 p=0.018, (p=0.036**)
C/T	56 (14 %)	9 (6 %)	

[a] Chi-squared test

[b] Bonferroni correction

Table 3 Distribution of *BDNF* Val66Met and C-270T genotypes in Polish patients with Wilson's disease with respect to the dominant neurological form of the disease

Wilson's disease patients	*BDNF* Val/Val (*n*=274)	*BDNF* Val/Met + Met/Met (*n*=140)	*p*-value	*BDNF* C/C (*n*=358)	*BDNF* C/T (*n*=56)	*p*-value
Age at onset [a]	26.65±9.51	26.79±9.83	0.77*	26.85±9.76	25.83±8.67	0.57*
Age at diagnosis [a]	28.53±9.51	28.28±10.58	0.68*	28.47±10.07	28.30±8.56	0.93*
Dominant neurological form, *n* (%):						
Rigidity-tremor (*n*=60)	40 (67)	20 (33)	0.93**	48 (80)	12 (20)	0.11**
Rigidity (*n*=15)	12 (80)	3 (20)	0.25**	13 (87)	2 (13)	0.98**
Tremor (*n*=101)	69 (68)	32 (32)	0.60**	90 (89)	11 (11)	0.37**
Dystonia (*n*=28)	20 (71)	8 (29)	0.54**	24 (86)	4 (14)	0.90**

[a] Data are presented in years as mean and standard deviation

*Mann–Whitney *U* test for age comparisons between carriers of different *BDNF* Val66Met and C-270T genotypes

**Chi-squared test for distribution of WD forms between different *BDNF* Val66Met and C-270T genotypes

similar to those previously made in patients with cervical dystonia (Groen et al. 2012); no associations were noted between the *BDNF* Val66Met polymorphism and age of onset, but a higher frequency of bilateral postural arm tremor was observed in patients with the *BDNF* Val/Val genotype. In contrast, we did not uncover any association between the *BDNF* Val66Met and C-270T polymorphisms and tremor in WD. Although *BDNF* is known to be widely distributed in the mammalian brain, significant differences may exist in its localization and distribution, especially in neurodegenerative disorders. In Huntington's disease, reduced expression of *BDNF* occurred in the putamen and caudate compared to controls, but expression was preserved in the temporal cortex, parietal cortex, and hippocampus (Ferrer et al. 2000). No such studies have been performed with WD patients, and thus we cannot be certain whether any differences exist in *BDNF* expression in various brain structures in WD patients.

An interesting finding is the significant difference in the distribution of *BDNF* Val/Val between symptomatic and presymptomatic WD patients. The more evident difference in *ATP7B* p.H0169Q homozygotes can be explained by the homogeneity of our population of WD patients. The *BDNF* Val allele may exert a protective role, but this hypothesis requires verification by long-term observation of our group of patients.

Table 4 Distribution of *BDNF* Val66Met and C-270T genotypes in symptomatic and presymptomatic Wilson's disease patients harboring the *ATP7B* 1069 HQ/HQ genotype

	Symptomatic *n*=153 (%)	Presymptomatic *n*=34 (%)	Test statistics*
BDNF Val66Met			
Allele frequency			
Val	262 (86)	51 (75)	Chi^2=4.60, df=1, *p*=0.032
Met	44 (14)	17 (25)	
Genotype frequency			
Val/Val	115 (75)	18 (53)	Chi^2=6.69, df=1, *p*=0.0097
Val/Met+Met/Met	38 (26)	16 (47)	
BDNF C-270T			
Allele frequency			
C	284 (93)	64 (94)	Chi^2=0.01, df=1, *p*=0.9046**
T	22 (7)	4 (6)	
Genotype frequency			
C/C	131 (86)	30 (88)	Chi^2=0.02, df=1, *p*=0.9009**
C/T	22 (14)	4 (12)	

*Chi-squared test

**Yates correction for fewer than five samples

In conclusion, the results of the present study suggest that genetically determined *BDNF* functions may be related to the occurrence of WD but not with its course or symptomatology. However, large variations in the age of onset and clinical manifestation of WD make this hypothesis difficult to investigate. The other major limitation of the current study is due to this study's ability to detect only the association of two particular *BDNF* polymorphisms with WD, similar to many other studies; however, these relationships are difficult to explain on a molecular level. We cannot exclude the possibility that the observed effect is due to another gene located near *BDNF* on the chromosome, as pathogenic mutations in a neighboring gene causing or modifying WD could be overlooked by this study design. To validate the present results, further studies are needed to elucidate the role and mechanism of *BDNF* action in WD susceptibility and disease course.

Acknowledgments We thank Ms. Marzena Zdan for her excellent technical support.

Conflict of interest The authors declare no conflicts of interest.

References

Albrech J, Lopez M, Badenas C, Carrasco JL, Mila M, Munoz E, Canals JM (2005) Association between BDNF Val66Met polymorphism and age of onset in Huntington disease. Neurology 65:964–965

Beattie MS, Harrington AW, Lee R, Kim JY, Boyce SL, Longo FM, Bresnahan JC, Hempstead BM, Yoon SO (2002) ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. Neuron 36:375–386

Cerasa A, Tongiorgi E, Fera F, Gioia MC, Valentino P, Liguori M, Manna I, Zito G, Passamonti L, Nistico R, Quattrone A (2010) The effect of BDNF Val66Met polymorphism on brain function in controls and patients with multiple sclerosis: an imaging-genetic study. Behav Brain Res 207:377–386

Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, Lee FS (2004) Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. J Neurosci 24:4401–411

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolchana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269

Ferrer I, Goutan E, Marin C, Rey MJ, Ribalta T (2000) Brain-derived neurotrophic factor in Huntington disease. Brain Res 866:257–261

Foltynie T, Lewis SG, Goldberg TE, Balckwell AD, Kolachana BS, Weinberger DR, Robbins TW, Barker RA (2005) The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. J Neurol 252:833–838

Frank-Cannon TC, Alto LT, McAlpine FE, Tansey MG (2009) Does neuroinflammation fan the flame in neurodegenerative diseases? Mol Neurodegener 4:47

Gao L, Diaz-Corrales FJ, Carrillo F, Diaz-Martin J, Caceres-Redondo MT, Carballo M, Palomino A, Lopez-Barneo J, Mir P (2010) Brain-derived neurotrophic factor G-196A polymorphism and clinical features in Parkinson's disease. Acta Neurol Scand 122:41–45

Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, Egan JM, Driscoll I, Ferrucci L, Martin B, Mattson MP (2010) Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from Baltimore longitudinal study of aging. PLoS One 5(e10099):1–9

Groen JL, Ritz K, Velseboer DC, Aramideh M, van Hilten JJ, Boon AJW, van de Warrenburg BP, Baas F, Tijssen MA (2012) Association of BDNF Met66Met polymorphism with arm tremor in cervical dystonia. Mov Disord 27:796–797

Gromadzka G, Schmidt H, Genschel J, Bochow B, Rodo M, Tarnacka B (2006) The p.H1069Q mutation in ATP7B and biochemical parameters of copper metabolism and clinical manifestation of Wilson's disease. Mov Disord 21:245–248

Gromadzka G, Rudnicka M, Chabik G, Przybyłkowski A, Członkowska A (2011) Genetic variability in the methylenetetrahydrofolate reductase gene (MTHFR) affects clinical expression of Wilson's disease. J Hepatol 55:913–919

Koshikawa S, Li JL, Gillis T, Hakky MM, Warby S, Hayden M, MacDonald ME, Myers RH, Guzella JF (2006) Brain-derived neurotrophic factor does not influence age at neurologic onset of Huntington's disease. Neurobiol Dis 24:280–285

Kunugi H, Ueki A, Otsuka M, Isse K, Hirasawa H, Kato N, Nabika T, Kobayashi S, Nanko S (2001) A novel polymorphism of the brain-derived neurotrophic factor (BDNF) gene associated with late-onset Alzheimer's disease. Mol Psychiatry 6:83–86

Lang UE, Hellweg R, Sander T, Galliant J (2005) The Met allele of the BDNF Val66Met polymorphism is associated with increased BDNF serum concentration. Mol Psychiatry 14:120–22

Laske C, Stansky E, Leyhe T, Eschweiler GW, Wittorf A, Richartz E, Bartels M, Buchkremer G, Schott K (2006) Stage-dependent BDNF serum concentration in Alzheimer's disease. J Neural Transm 113:1217–1224

Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294:1945–1948

Litwin T, Gromadzka G, Czlonkowska A (2012) Apolipoprotein E gene (APOE) genotype in Wilson's disease: Impact on clinical presentation. Parkinsonism Relat Disord 18:367–369

Litwin T, Gromadzka G, Samochowiec J, Grzywacz A, Członkowski A, Członkowska A (2013) Association of dopamine receptor gene polymorphisms with the clinical course of Wilson disease. JIMD Rep 8:73–80

Mai M, Akkad AD, Wieczorek S, Saft C, Andrich J, Kraus PH, Epplen JT, Arning L (2006) No association between polymorphisms in the BDNF gene and age at onset in Huntington disease. BMC Med Genet 7:79

Marsden CD (1987) Wilson's disease. Q J Med 65:959–966

Matthews VB, Astrom MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, Akerström T, Yfanti C, Broholm C, Mortensen OH, Penkowa M, Hojman P, Zankari A, Watt MJ, Bruunsgaard H, Pedersen BK, Febbraio MA (2009) Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia 52:1409–1418

Mercer JF (2001) The molecular basis of copper-transport diseases. Trends Mol Med 7:64–69

Merle U, Schaefer M, Ferenci P, Stremmel W (2007) Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. Gut 56:1115–1120

Mero IL, Samestad C, Lie BA, Lorentzen AL, Sandvik L, Landro NI, Aarseth JH, Myhr KM, Celius EG, Harbo HF (2012) Polymorphisms of the BDNF gene show neither association with multiple sclerosis susceptibility nor clinical course. J Neuroimmunol 244:107–110

Mirowska-Guzel D, Mach A, Gromadzka G, Czlonkowski A, Czlonkowska A (2008) G-196A and C720T BDNF gene polymorphisms and susceptibility to multiple sclerosis. J Neuroimmunol 193:170–172

Nakahashi T, Fujimara H, Altar CA, Li J, Kobayashi J (2000) Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. FEBS Lett 470:113–117

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL (2002) The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from family-based association study. Am J Hum Genet 71:651–655

Pedersen BK (2009) The diseasome of physical inactivity—and the role of myokines in muscle-fat cross talk. J Physiol 587:5559–5568

Riemenschneider M, Schwarz S, Wagenpfeil S, Diehl J, Müller U, Förstl H, Kurz A (2002) A polymorphism of the brain-derived neurotrophic factor (BDNF) is associated with Alzheimer's disease in patients lacking the apolipoprotein E ε4 allele. Mol Psychiatry 7:782–785

Schiefermeier M, Kolleger H, Madl C, Polli C, Oder W, Kühn H, Berr F, Ferenci P (2000) The impact of apolipoprotein E genotypes on age at onset of symptoms and phenotypic expression in Wilson's disease. Brain 123:585–590

Szczepankiewicz A, Skibinska M, Czerski PM, Kapelski P, Leszczynska-Rodziewicz A, Słopień A, Dmitrzak-Weglarz M, Rybakowski F, Rybakowski J, Hauser J (2005) No association of the brain-derived neurotrophic factor (BDNF) gene C-270T polymorphism with schizophrenia. Schizophr Res 76:187–193

Ventriglia M, Bocchio Chiavetto L, Benussi L, Binetti G, Zanetti O, Riva MA, Gennarelli M (2002) Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. Mol Psychiatry 7:136–137

Zivadinov R, Weinstock-Guttman B, Benedict R, Tamaño-Blanco M, Hussein S, Abdelrahman N, Durfee J, Ramanathan N (2007) Preservation of gray matter volume in multiple sclerosis patients with the Met allele of the rs6265 (Val66Met) SNP of brain-derived neurotrophic factor. Hum Mol Genet 16:2659–2668