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HFE mutations and transferrin C1/C2 polymorphism among Croatian patients with schizophrenia and schizoaffective disorder

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Abstract The aim of this study was to investigate the possible influence of hemochromatosis gene mutations (HFE-C282Y and H63D) and transferrin gene C2 variant (TF-C2) on susceptibility to schizophrenia and schizoaffective disorder and/or age at first hospital admission. Genotyping was performed in 176 Croatian patients and 171 non-psychiatric Croatian controls using PCR-RFLP analyses. Regarding the H63D mutation, allele and genotype frequencies reached boundary statistical significance. Other allele and genotype distributions were not significantly different between two groups. We also analyzed age at first hospital admission as a continuous variable using the non-parametric Mann–Whitney *U*-test and Kruskal–Wallis test, and multiple regression analysis. The results of these tests were negative. We concluded that investigated HFE mutations and TF-C2 variant are not high-risk genetic variants for schizophrenia/schizoaffective disorder in our population. Also our data do not support their impact on age at onset of the first psychotic symptoms.

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Introduction

Iron homeostasis is essential for numerous cellular processes, including tissue oxygenation and energy metabolism, in both the peripheral tissues and the brain. The iron sensing mechanisms in the peripheral tissues are well documented and involve membrane and cytosolic proteins, including hemochromatosis protein (HFE), transferrin (TF), transferrin receptors 1 and 2 (TfR1 and TfR2), hemojuvelin (HJV), iron regulatory factors (IRFs), and hepcidin [1–6]. The liver plays a primary regulatory role in maintaining iron homeostasis in the organism. However, the brain is an exception due to its separation from the systemic circulation by the blood–brain barrier and the possession of specific, insufficiently recognized iron regulatory mechanisms [6]. The expression patterns of *Hfe*, *Tf*, *TfR1*, and other genes encoding proteins with iron regulatory roles in different brain cell types and the exact mechanisms of iron distribution throughout the brain are not known [7–9].

Multidisciplinary evidence suggests that the pathogenesis of schizophrenia is related to the prenatal period of brain development [10]. Two large samples have implicated a disruption of iron homeostasis due to maternal iron deficiency during pregnancy in a 1.60–3.73 fold increased risk of schizophrenia and schizophrenia spectrum disorders in offspring [10, 11]. Irreversible effects have been suggested for iron deficiency during critical periods of early brain development [12–14]. In addition to causing fetal hypoxia during the period of high iron demand, iron status can influence different metabolic processes that are

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essential for proper brain development and function, such as the metabolism of specific long-chain *n*-3 fatty acids [13, 15, 16] that are abundant in the brain, the myelinization process [17], and different pathways of chemical communication between neurons [18, 19]. However, the roles of iron and other micronutrients during gestation and postnatal brain development have not yet been clearly elucidated [20, 21].

Mutations in the HFE generally affect the ability of the protein to prevent TF from binding its receptors, thereby increasing cellular iron uptake [3]. In homozygous adults, the HFE C282Y mutation is associated with hemochromatosis and iron accumulation in parenchymal tissues, including the brain. The effect of the HFE H63D mutation is milder, and it more effectively competes against the C282Y mutation to prevent TF-TfR1 binding and uptake. Transferrin is synthesized primarily in the liver, but a substantial amount is also produced in the brain. Through interaction with its receptors, brain TF may be involved in the management of iron in the brain [22]. The variant TF-C2 has been reported to have a lower binding affinity for iron [23]. Synergy between the HFE C282Y mutation and TF-C2 variant has been hypothesized to contribute to a higher level of cellular free iron and the production of free radicals associated with tissue damage in neurodegenerative diseases [24]. Therefore, the HFE C282Y mutation and TF-C2 variant have been investigated as risk factors for diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis. Results have been inconsistent for Alzheimer's disease [24–28], and no association was found between the HFE C282Y mutation and disease risk or clinical outcome in multiple sclerosis [29, 30]. However, in the Croatian and Slovenian sample of patients with multiple sclerosis, those who carried the mutant C282Y allele exhibited an earlier onset of disease symptoms [30].

We tested the hypothesis that HFE mutations (C282Y and H63D) and/or the TF-C2 variant contribute to disease risk in schizophrenia and influences the age at which psychotic symptoms first appear. To the best of our knowledge, this is the first report on the association between HFE mutations, a TF variant, and schizophrenia/schizoaffective disorder.

Subjects and methods

Subjects

This study was approved by the Ethics Committee of the University of Rijeka, School of Medicine. All subjects provided written informed consent prior to participation in the genetic analysis.

The test group included 176 Croatian patients (109 males and 67 females) who met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for schizophrenia ($N = 153$) or schizoaffective disorder ($N = 23$) using the structured clinical interview [31]. The diagnostic assessment was performed by experienced psychiatrists. The patients were recruited from the Department of Psychiatry, Clinical Medical Centre, Rijeka, Croatia ($N = 126$), and Psychiatric Hospital Rab, Croatia ($N = 50$) between 2007 and 2010. Eighty patients were already included in our recent investigation of genetic susceptibility to schizophrenia [32]. The mean patient age was 42.94 ± 11.74 years. The patients were consecutive. The exclusion criteria were drug abuse, traumatic head injury, or a history of neurological disorders. There were four patients with childhood-onset schizophrenia in our sample. Their clinical diagnoses have been reevaluated and confirmed in adulthood using above mentioned criteria.

The control group consisted of 171 healthy blood donors (69 males and 102 females) recruited from the same geographic area as the patients. The controls underwent no specific examination for psychiatric status. The practice of blood donation in Croatia includes providing a written statement about health status at every session. Therefore, blood donors are representative of the healthy general population between 18 and 60 years of age free of chronic diseases or regular medication.

Age of onset was obtained from medical records and determined as the patient's age at the time of their first hospital admission due to a psychotic episode at which the diagnosis of schizophrenia or schizoaffective disorder was used. Patients whose medical history was uncertain were excluded from the study. The median age of onset was 25 years (range, 12–57 years) when considering all patients. The median age of onset for male and female patients was 24.0 years (range, 12–57 years) and 27.0 years (range, 15–49 years), respectively.

Genotyping

Genomic DNA was extracted from whole blood using standard procedures. Genotyping was performed in the Molecular Genetics Laboratory (Department of Biology and Medical Genetics, School of Medicine, Rijeka) using PCR-RFLP-based methods as previously described [33, 34]. We selected 40 individuals at random to assess possible genotyping errors and observed no discordance.

Statistical analysis

Genotype and allele distributions between groups, as well as observed and expected genotype proportions under Hardy–Weinberg equilibrium, were compared by the

chi-square test. To analyze distributions of age at first admission in different allele and genotype categories, we used both non-parametric and parametric tests, specifically the Mann–Whitney *U*-test and Kruskal–Wallis test, and multiple regression analysis. Statistical analyses were carried out using Statistical software package for Windows 7.1 (StatSoft, Inc.). The statistical threshold for significant differences was set at $P = 0.05$.

Results

The distribution of allele and genotype frequencies is presented in Table 1. The H63D/wt genotype and H63D allele frequency trended towards greater representation ($P = 0.058$ and $P = 0.045$, respectively) and the C282Y allele frequency trended towards less representation ($P = 0.080$) among patients with schizophrenia or schizoaffective disorder compared to the non-psychiatric controls. Significant between group differences for C282Y/wt, TF-C1/C2 or combined H63D/TF-C2 genotypes were not found.

Compound heterozygotes (carriers of two different mutant alleles at a particular gene locus, one on each chromosome of a pair) H63D/C282Y were detected only in the control group, but the difference in frequencies between patients and controls was not significant.

We further analyzed the differences in median age at first hospital admission according to HFE or TF genotype using the Kruskal–Wallis test and according to the presence or absence of the allele or their combination using the Mann–Whitney *U*-test. No significant differences were found. The median ages of carriers of HFE mutations and the TF-C2 variant are provided in Table 2.

We also performed multiple regression analysis, and found no significant association between age distribution at first hospital admission, and HFE and TF genotypes as the predictor variables.

Chi-square goodness-of-fit tests for the HFE mutations and TF-C2 variant showed no deviation from Hardy–Weinberg equilibrium in the patient group or healthy controls.

Discussion

We have detected a higher frequency of H63D, and a lower frequency of C282Y mutation, in our test sample than in the controls. Regarding the H63D mutation the difference reached boundary statistical significance although our study had sufficient statistical power (92.8%) to detect a 2-fold increase or decrease in H63D frequency. The study had insufficient statistical power regarding the C282Y mutation (only 41.6% power to detect a 3.5-fold decrease in frequency), due to the low frequency of C282Y mutation carriers in the Croatian general population [35] and a small sample size. Control frequencies of HFE C282Y, H63D,

Table 1 HFE and TF genotype and allele frequencies in patients with schizophrenia/schizoaffective disorder and non-psychiatric controls

	Patients $N = 176$		Controls $N = 171$		Chi-square	*P*
	N	%	*N*	%		
H63D heterozygotes	55	31.3	34	20.2	5.68[a]	0.058
H63D homozygotes	5	2.8	4	2.4		
H63D-negative	116	65.9	130	77.4		
C282Y heterozygotes	3	1.7	7	4.2	1.08[a,b]	0.299
C282Y-negative	173	98.3	161	95.8		
H63D/wt-C282Y/wt	0	0	3	1.8	1.40[b]	0.236
TF-C2 heterozygotes	52	29.5	44	25.7	1.59	0.450
TF-C2 homozygotes	3	1.7	6	3.5		
TF-C2-negative	121	68.8	121	70.8		
H63D/TF-C2-positive	16	9.1	13	7.6	0.09[b,c]	0.759
H63D/TF-C2-negative	148	90.9	158	92.4		
Allele H63D	65	18.5	45	13.2	4.04[b]	0.045
Allele C282Y	3	0.9	10	2.9	3.06[b]	0.080
Allele TF-C2	58	16.5	56	16.4	0.01[b]	0.941

HFE hemochromatosis, *TF* transferrin

[a] Calculation based on 168 controls (three were compound heterozygotes)

[b] Yates-corrected chi-square

[c] No compound heterozygotes were positive for TF-C2

Table 2 Median age at first hospital admission according to combined HFE and TF genotypes

Genotype	*N*	Age at onset, years (range)
HFE wt/TFC1	74	25.0 (15–57)
HFE H63D/TFC1	44	26.0 (14–49)
HFE wt/TFC2	39	25.0 (12–43)
HFE H63D/TFC2	16	27.5 (17–45)
C282Y/TFC1	3	20.0 (19–37)

HFE hemochromatosis, *TF* transferrin

and TF-C2 were 2.9, 13.2, and 16.4, respectively, which is in agreement with earlier reports in the Croatian general population [35, 36]. Therefore, our results do not support either of the HFE mutations or the TF-C2 variant as high-risk genetic variants for schizophrenia/schizoaffective disorder. We also did not confirm the hypothesis that investigated mutations significantly influence age at first hospital admission.

However, the HFE H63D mutation, alone or in combination with other genetic factors involved in iron sensing and the regulation of iron metabolism, may play an important role in populations in which the HFE C282Y mutation is rare or absent, such as the majority of Asian, African, or indigenous Australian populations [37]. A protective role of the H63D mutation has recently been suggested in Alzheimer's disease susceptibility in the Basque population [26]. The H63D mutation, in contrast to the C282Y mutation, possibly exerts a beneficial impact on iron homeostasis in the brain, either alone or in synergy with other genetic polymorphisms. Through its effect on cellular iron uptake, the H63D mutation may protect against anemia in rural populations with poor dietary iron availability [26]. This possible effect of the H63D mutation on the management of iron in the developing brain might also be important in cases of maternal dietary iron deficiency during pregnancy. Unfortunately, we had no data on the iron status of our patients' mothers during pregnancy or the parental origin of the investigated genetic variants. One recent study confirmed that genetic factors significantly contribute to the age of psychotic symptom onset in individuals with schizophrenia [38]. The heritability of the age of psychosis onset was estimated to be 0.33, implying the effects of a large number of genetic loci, but also a large environmental contribution. Numerous studies have reported an association between genetic markers and the age of onset for schizophrenia [39–43]. In addition to the HFE and TF genes, other iron metabolism genes could modify the risk or age at disease onset in schizophrenia. For example, iron overload and hemochromatosis have been observed in the absence of HFE mutations [44] or associated with mutations within the TFR2 gene [45].

Our results need to be verified in larger samples of patients with schizophrenia, possibly in populations of Northern European origin and others in whom HFE mutations are present [46]. Larger samples are also necessary to investigate the possible effects of the HFE C282Y mutation or its synergy with the TF-C2 variant in schizophrenia spectrum disorders. Iron deficiency anemia is one of the most common nutrient deficiencies in pregnant women worldwide [18, 20], and studies have demonstrated an association between prenatal nutrition deficiency and an increased risk for schizophrenia; thus, prospective studies are needed on the interaction between maternal and/or offspring genotype and prenatal nutrition [47, 48].

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References

1. Muñoz M, García-Erce JA, Remacha AF (2011) Disorders of iron metabolism. Part 1: molecular basis of iron homeostasis. J Clin Pathol 64:287–296
2. Wallander ML, Leibold EA, Eisenstein RS (2006) Molecular control of vertebrate iron homeostasis by iron regulatory proteins. Biochim Biophys Acta 1763:668–689
3. Goswami T, Andrews NC (2006) Hereditry hemochromatosis protein, HFE, interaction with transferrin receptor 2 suggests a molecular mechanism for mammalian iron sensing. J Biol Chem 281:28494–28498
4. Weinzimer SA, Beers Gibson T, Collett-Solberg PF, Khare A, Liu B, Cohen P (2001) Transferrin is an insulin-like growth factor-binding protein-3 binding protein. J Clin Endocrinol Metab 86:1806–1813
5. Levy JE, Jin O, Fujiwara Y, Kuo F, Andrews N (1999) Transferrin receptor is necesarry for development of erythrocytes and the nervous system. Nat Genet 21:396–399
6. Wang SM, Fu LJ, Duan XL, Crooks DR, Yu P, Qian ZM, Di XJ, Li J, Rouault TA, Chang YZ (2010) Role of hepcidin in murine brain iron metabolism. Cell Mol Life Sci 67:123–133
7. Rouault TA, Cooperman S (2006) Brain iron metabolism. Semin Pediatr Neurol 13:142–148
8. Moos T, Rosengreen Nielsen T, Skjørringe T, Morgan EH (2007) Iron trafficing inside the brain. J Neurochem 103:1730–1740
9. Rouault TA, Zhang DL, Jeong SY (2009) Brain iron homeostasis, the choroid plexus, and localization of iron transport proteins. Metab Brain Dis 24:673–684
10. Insel BJ, Schaefer CA, McKeague IV, Susser ES, Brown AS (2008) Maternal iron deficiency and the risk of schizophrenia in offspring. Arch Gen Psychiatry 65:1136–1144
11. Sørensen HJ, Nielsen PR, Pedersen CB, Mortensen PB (2010) Association between prepartum maternal iron deficiency and offspring risk of schizophrenia: population-based cohort study with linkage of Danish national registers. Schizophr Bull [Epub ahead of print]
12. Beard J (2003) Iron deficiency alters brain development and functioning. J Nutr 133:1468S–1472S

13. Georgieff MK, Innis SM (2005) Controversial nutrients that potentially affect preterm neurodevelopment: essential fatty acids and iron. Pediatr Res 57:99R–103R
14. Georgieff MK (2008) The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. Biochem Soc Trans 36:1267–1271
15. Innis S (2007) Dietary (n-3) fatty acids and brain development. J Nutr 137:855–859
16. Rioux FM, Lindmark G, Hernell O (2006) Does inadequate maternal iron or DHA status have a negative impact on an infant's functional outcomes? Acta Pediatr 95:137–144
17. Connor JR, Pavlick G, Karli D, Menzies SL, Palmer C (1995) A histochemical study of iron-positive cells in the developing rat brain. J Comp Neurol 355:111–123
18. Lozoff B, Georgieff MK (2006) Iron deficiency and brain development. Semin Pediatr Neurol 13:158–165
19. Aguilar-Valles A, Flores C, Luheshi GN (2010) Prenatal inflammation-induced hypoferremia alters dopamine function in the adult offspring in rat: relevance for schizophrenia. PloS One 5:e10967
20. McCann JC, Ames BN (2007) An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr 85:931–945
21. Georgieff MK (2007) Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 85:614S–620S
22. Takeda A (2001) Significance of transferrin to iron delivery to the brain. J Health Sci 47:520–524
23. Wong CT, Saha N (1986) Effects of transferrin genetic phenotypes on total iron-binding capacity. Acta Haematol 75:215–218
24. Robson KJ, Lehmann DJ, Wimhurst VL, Livesey KJ, Combrinck M, Merryweather-Clarke AT, Warden DR, Smith AD (2004) Synergy between the C2 allele of transferrin and the C282Y allele of the haemochromatosis gene (HFE) as risk factors for developing Alzheimer's disease. J Med Genet 41:261–265
25. Berlin D, Chong G, Chertkow H, Bergman H, Phillips NA, Schipper HM (2004) Evaluation of HFE (hemochromatosis) mutations as genetic modifiers in sporadic AD and MCI. Neurobiol Aging 25:465–474
26. Blázquez L, De Juan D, Ruiz-Martínez J, Emparanza JI, Sáenz A, Otaegui D, Sistiaga A, Martínez-Lage P, Lamet I, Samaranch L, Buiza C, Etxerberria I, Arriola E, Cuadrado E, Urdaneta E, Yanguas J, López de Munain A (2007) Genes related to iron metabolism and susceptibility to Alzheimer's disease in Basque population. Neurobiol Aging 28:1941–1943
27. Lehmann DJ, Worwood M, Ellis R, Wimhurst VL, Merryweather-Clarke AT, Warden DR, Smith AD, Robson KJ (2006) Iron genes, iron load and risk of Alzheimer's disease. J Med Genet 43:e52
28. Namekata K, Imagawa M, Terashi A, Ohta S, Oyama F, Ihara Y (1997) Association of transferrin C2 allele with late-onset Alzheimer's disease. Hum Genet 101:126–129
29. Ramagopalan SV, Cukjati M, Cernilec M, DeLuca GC, Dyment DA, Degenhardt A, Sadovnick AD, Serbec VC, Ebers GC, Duquette P (2008) Mutations in the hemochromatosis gene and the clinical outcome of multiple sclerosis. J Neuroimmunol 203: 104–107
30. Ristić S, Lovrečič L, Brajenović-Milić B, Starčević-Čizmarević N, Jazbec SS, Sepčić J, Kapović M, Peterlin B (2005) Mutations in the hemochromatosis gene (HFE) and multiple sclerosis. Neurosci Lett 383:301–304
31. First MB, Spitzer RL, Gibbon M, Williams JBW (2002) Structured clinical interview for DSM-IV-TR Axis I disorders, research version, non-patient edition. (SCID-I/NP) New York: Biometrics Research, New York State Psychiatric Institute
32. Nadalin S, Rubeša G, Giacometti J, Vulin M, Tomljanović D, Vraneković J, Kapović M, Buretić-Tomljanović A (2008) BanI polymorphism of cytosolic phospholipase A2 gene is associated with age at onset in male patients with schizophrenia and schizoaffective disorder. Prostaglandins Leukot Essent Fatty Acids 78:351–360
33. Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ (1997) Global prevalence of putative haemochromatosis mutations. J Med Genet 34:275–278
34. Namekata K, Oyama F, Imagawa M, Ihara Y (1997) Human transferrin (Tf): a single mutation at codon 570 determines Tf C1 or C2 variant. Hum Genet 100:457–458
35. Ristić S, Makuc J, Starčević N, Logar N, Brajenović-Milić B, Stepec S, Pleša I, Kapović M, Milić S, Štimac D, Crnić-Martinović M, Peterlin B (2003) Hemochromatosis gene mutations in the Croatian and Slovenian populations. Clin Genet 64:444–446
36. Buretić-Tomljanović A, Vlastelić I, Radojčić Badovinac A, Starčević-Čizmarević N, Nadalin S, Ristić S (2009) The impact of hemochromatosis mutations and transferrin genotype on gonadotropin serum levels in infertile men. Fertil Steril 91:1793–1800
37. Gunel-Ozcan A, Murad Basar M, Kisa U, Ankarah HC (2009) Hereditary hemochromatosis gene (HFE) H63D mutation shows an association with abnormal sperm motility. Mol Biol Rep 36: 1709–1714
38. Hare E, Glahn DC, Dassori A, Raventos H, Nicolini H, Ontiveros A, Medina R, Mendoza R, Jerez A, Munoz R, Almasy L, Escamilla MA (2010) Heritability of age of onset of psychosis in schizophrenia. Am J Med Genet B 153B:298–302
39. Rasmussen HB, Timm S, Wang AG, Søeby K, Lublin H, Fenger M, Hemmingsen R, Werge T (2006) Association between the CCR5 32-bp deletion allele and late onset of schizophrenia. Am J Psychiatry 163:507–511
40. Kampman O, Anttila S, Illi A, Mattila KM, Rontu R, Leinonen E, Lehtimäki T (2004) Apolipoprotein E polymorphism is associated with age of onset in schizophrenia. J Hum Genet 49:355–359
41. Lee KY, Ahn YM, Joo E, Joo YH, Chang JS, Yoo HY, Kim YS (2006) Partial evidence of an association between epidermal growth factor A61G polymorphism and age at onset in male schizophrenia. Neurosci Res 56:356–362
42. Numata S, Ueno S, Iga J, Yamauchi K, Hongwei S, Ohta K, Kinouchi S, Shibuya-Tayoshi S, Tayoshi S, Aono M, Kameoka N, Sumitani S, Tomotake M, Kaneda Y, Taniguchi T, Ishimoto Y, Ohmori T (2006) Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism in schizophrenia is associated with age at onset and symptoms. Neurosci Lett 401:1–5
43. Zhang XY, Haile CN, Tan YL, Zuo LJ, Yang BZ, Cao LY, Zhou DF (2005) Tumor necrosis factor α polymorphism (−1031T/C) is associated with age of onset of schizophrenia. Mol Psychiatry 10:897–899
44. De Marco F, Liguori R, Giardina MG, D'Armiento M, Angelucci E, Lucariello A, Morante R, Cimino L, Galeota-Lanza A, Tarantino G, Ascione A, Budillon G, Vecchione R, Martinelli R, Matarazzo M, De Simone V (2004) High prevalence of non-HFE gene-associated haemochromatosis in patients from southern Italy. Clin Chem Lab Med 42:17–24
45. Lee PL, Barton JC (2006) Hemochromatosis and severe iron overload associated with compound heterozygosity for TFR2 R455Q and two novel mutations TFR2 R396X and G792R. Acta Hematol 115:102–105
46. Rochette J, Pointon JJ, Fisher CA, Perera G, Arambepola M, Arichchi DS, De Silva S, Vandwalle JL, Monti JP, Old JM, Merryweather-Clarke AT, Weatherall DJ, Robson KJ (1999) Multicentric origin of hemochromatosis gene (HFE) mutations. Am J Hum Genet 64:1056–1062

47. McGrath JJ, Burne TH, Féron F, Mackay-Sim A, Eyles DW (2010) Developmental vitamin D deficiency and risk of schizophrenia: a 10 year update. Schizophr Bull 36:1073–1078

48. McGrath J, Brown A, St Clair D (2011) Prevention and schizophrenia—the role of dietary factors. Schizophr Bull 37:272–283