ORIGINAL ARTICLE

Candidate glutamatergic and dopaminergic pathway gene variants do not influence Huntington's disease motor onset

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Abstract Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, cognitive, and behavioral disturbances. It is caused by the expansion of the *HTT* CAG repeat, which is the major determinant of age at onset (AO) of motor symptoms. Aberrant function of *N*-methyl-D-aspartate receptors and/or overexposure to dopamine has been suggested to cause significant neurotoxicity, contributing to HD pathogenesis. We used genetic association analysis in 1,628 HD patients to evaluate candidate polymorphisms in *N*-methyl-D-aspartate receptor subtype genes (*GRIN2A* rs4998386 and rs2650427, and *GRIN2B* rs1806201) and functional polymorphisms in genes in the dopamine

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pathway (*DAT1* 3′ UTR 40-bp variable number tandem repeat (VNTR), *DRD4* exon 3 48-bp VNTR, *DRD2* rs1800497, and *COMT* rs4608) as potential modifiers of the disease process. None of the seven polymorphisms tested was found to be associated with significant modification of motor AO, either in a dominant or additive model, after adjusting for ancestry. The results of this candidate-genetic study therefore do not provide strong evidence to support a modulatory role for these variations within glutamatergic and dopaminergic genes in the AO of HD motor manifestations.

Keywords Huntington's disease · Glutamate receptors · Dopamine pathway · Genetic modifiers

Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder, usually of adult onset, characterized by involuntary choreiform movements, cognitive impairment, and behavioral changes. HD is caused by the expansion of an unstable polymorphic CAG repeat in *HTT* [1]. Age at onset (AO) of diagnostic clinical symptoms is inversely correlated with the size of the expanded CAG repeat. It explains about 50–70 % of the variance in motor AO [2–4], while the remainder is highly heritable, strongly implying the existence of genetic factors that modulate the

rate of the pathogenic process that leads to onset of symptoms [5–7].

The neuropathological changes that comprise the pathological grading system for HD are found in the striatum, where there is a selective and progressive neuronal loss of medium spiny neurons (MSNs) [8, 9]. Glutamatergic and dopaminergic pathways are well known to regulate striatal neuronal function by interacting and modulating each other, suggesting that both glutamate and dopamine receptors may act coordinately in causing deregulation of calcium homeostasis [10–12] with consequent mitochondrial depolarization and caspase activation [13, 14]. Both pathways have been implicated in HD pathogenesis, suggesting that variation in function or expression of glutamate receptor subunits and/or dopamine pathway genes might modulate excitotoxic cell death, thereby modulating AO of symptoms. Indeed, polymorphisms within the genes that encode the NR2A and NR2B glutamate receptors (*GRIN2A* and *GRIN2B*) have been implicated in genetic studies with HD patients as potential modifiers of clinical AO [15–18].

Based upon these observations, the aim of the present study was to utilize common and multi-allele functional polymorphisms to test the possibility that genetic variation in genes of the glutamatergic (*GRIN2A* and *GRIN2B*) and dopaminergic (*COMT*, *DRD2*, *DRD4*, and *DAT1*) pathways may explain some of the variation in AO of HD motor manifestations, in a large and well-described cohort of 1,628 HD patients of European ancestry.

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Material and methods

Subjects We analyzed 1,628 DNA samples from HD patients participating in research from collaborating investigators (HD-MAPS), the HD observational study COHORT, the Harvard Tissue Resource Center Bank (McLean's Hospital, Belmont, MA) and the National Neurological Research Bank (VAMC Wadsworth Division, Los Angeles, CA). Our cohort comprises a well-described set of HD samples [19] with CAG repeat sizes ranging from 40 to 53 repeats, known motor AO, ancestry, and familial relationship.

Genotyping Repeat sizes of the *HTT* CAG alleles and *DAT1* and *DRD4* variable number tandem repeats (VNTRs) were determined using previously established polymerase chain reaction (PCR) amplification assays [20–22]. The size of the products was determined using the ABI PRISM 3730xl automated DNA Sequencer (Applied Biosystems, Foster City, CA) and GeneMapper version 3.7 software. Genotyping of the polymorphisms in *GRIN2A* (rs4998386 and rs2650427), *GRIN2B* (rs1806201), *COMT* (rs4680), and *DRD2* (rs1800497) was performed by real-time PCR using commercially available TaqMan Genotyping probes (Applied Biosystems, Foster City, CA) and carried out on the LightCycler® 480 (Roche Diagnostics, Mannheim), following the manufacturer's instructions.

Statistical analysis Multivariate analyses were conducted using generalized estimating equations (GEE) to assess the association of the different polymorphisms with residual HD motor onset, adjusting for familial component and ancestry. The weighted GEE was computed assuming an independent correlation structure and using the robust estimator of the variance to account for familial relationships. All statistical analyses were performed using PASW Statistics (version 18).

Results

Association with GRIN2A and GRIN2B The genetic evidence supporting a role for *GRIN2A* or *GRIN2B* in modulating AO of HD symptoms is equivocal. A candidate gene study with 167 German HD patients reported an association between AO and rs1969060 in *GRIN2A* and two polymorphisms in *GRIN2B* (rs1806201 and rs890) [17]. However, in a follow-up study, the same authors found that two other SNPs, rs8057394 and rs2650427, in *GRIN2A* had a stronger association with AO [16]. A subsequent study in 1,211 European HD individuals found an association of *GRIN2A* rs2650427, and when stratified by AO subtypes, they found a nominally significant association with rs1969060 (*GRIN2A*) and rs1806201 (*GRIN2B*) [15]. On the other hand, in a Venezuelan sample, no evidence was found for the *GRIN2B* polymorphisms, and a weak association was found for *GRIN2A* rs1969060 [18]. We attempted to replicate the apparent genetic association of the polymorphisms with the greatest evidence of association with HD AO, namely rs2650427 in *GRIN2A* and rs1806201 in *GRIN2B*, as well as an interesting *GRIN2A* polymorphism associated with decreased Parkinson's disease (PD) risk in conjunction with heavy coffee consumption (rs4998386) [23]. However, the results of association analysis for each polymorphism failed to demonstrate significant association with HD motor AO (Table 1).

Association with dopamine pathway genes Dopamine pathway genes have not previously been assessed as genetic HD AO modifiers. Therefore, we tested functional polymorphisms in *DRD2* and *DAT1* believed to affect neurotransmission primarily in the striatum, in addition to polymorphisms in *COMT* and *DRD4*, known to have an impact on the frontal cortex function. The Val158Met *COMT* polymorphism has been shown to affect, in a codominant mode, the activity level of the COMT enzyme that metabolizes dopamine [24–26]. The TaqIA polymorphism in the vicinity of *DRD2* is reported to be a genetic marker for D2 receptor density in the brain, with the minor allele being associated with a lower density of this receptor especially in the striatum [27–30]. However, the results of our genetic analysis failed to reveal significant evidence of association of the functional polymorphism in *DRD2* or in *COMT* with HD motor AO (Table 1).

We then evaluated the *DRD4* gene, as it has been suggested that different repeat sequences of the multi-allele 48-bp VNTR in *DRD4* may differentially affect the gene's expression and consequently alter D4 receptor density in the brain. The seven-repeat allele had a lower expression compared with two- and four-repeat alleles [31]. Given this observation, our analysis specifically tested the potential association of the seven-repeat allele with motor HD AO. The results demonstrated that the presence of this allele did not explain any variance of AO in our cohort of HD patients (Table 1).

We also assessed the *DAT1* gene by evaluating the multi-allele 40-bp VNTR polymorphism. This polymorphism was chosen because it has been reported that individuals with 10/10 repeats have lower dopamine transporter density than individuals with at least one copy of the nine-repeat allele who exhibit more effective dopamine removal at the synapse [32, 33]. However, despite evidence for biological effects, the results of our analysis did not reveal a significant association of the ten-repeat allele with HD motor AO (Table 1).

Discussion

The circuitry of the striatum, where MSNs are particularly vulnerable to the effects of the HD mutation [8, 9], has

Table 1 Multivariate correlation of the polymorphisms in the glutamatergic (*GRIN2A* and *GRIN2B*) and dopaminergic (*COMT*, *DRD2*, *DRD4*, and *DAT1*) pathway genes with residual age at motor onset

Gene	Polymorphism	Number of samples	Dominant model		Additive model	
			Standardized coefficient	p value[a]	Standardized coefficient	p value[a]
Glutamatergic pathway						
GRIN2A	rs4998386	1,585	0.087	0.108	0.074	0.144
	rs2650427	1,619	−0.014	0.739	0.004	0.878
GRIN2B	rs1806201	1,602	−0.056	0.164	−0.060	0.053
Dopaminergic pathway						
COMT	rs4680	1,620	−0.047	0.222	0.025	0.333
DRD2	rs1800497	1,625	0.051	0.196	0.035	0.326
DRD4	Exon 3 48-bp VNTR	1,527	−0.043	0.322	−0.035	0.322
DAT1	3′ UTR 40-bp VNTR	1,614	0.062	0.363	0.022	0.487

[a] p values were derived using GEE to account for familial relationships and ancestry

provided a rich source of candidate HD genetic modifiers. Aberrant function of *N*-methyl-D-aspartate receptors (NMDAR) and overexposure of MSNs to dopamine cause neurotoxicity [34–36], suggesting that variation in expression or function of glutamate receptor subunits and/or dopamine pathway genes could modulate excitotoxic death and thereby affect HD AO.

Association of AO with specific polymorphisms in *NR2A* and *NR2B*, encoding NMDAR subunits, has been previously reported [15–18]. However, in our sample of European ancestry, we found no definitive evidence of association for either of the two *GRIN2A* or for the *GRIN2B* SNPs that were tested with the residual AO after accounting for the effect of *HTT* CAG repeat length. One SNP, rs1806201 in *GRIN2B*, was close to nominal significance ($p=0.053$ in the additive model). Though this value would not survive correction for the multiple hypotheses tested in our study, it may be of interest for future modifier studies given the effects previously reported [15–17]. The lack of replication in our sample of the reported associations might be explained by different study designs, including the patient populations and definition of the phenotypic trait. We have previously shown that stringent sample selection and analysis criteria are critical factors in HD association studies. Indeed, genetic background related to ancestry [19] and non-normal distribution of CAG allele size [37] can have a profound confounding effect when testing for the effects of potential genetic modifiers.

Our test of the *GRIN2A* rs4998386 polymorphism that has been recently associated with decreased risk of developing PD in individuals who are heavy coffee drinkers [23] was an attempt to assess a neurodegenerative disease-associated risk allele that may interact with a common environmental factor. We did not find evidence of association of this particular SNP with AO of HD motor symptoms.

Though coffee consumption data are not available on our study subjects, this negative result is consistent with previous genetic findings showing that the *HTT* CAG repeat polymorphism is not a modifier of PD onset [38], strongly suggesting that the pathogenic process that culminates in HD manifestations may be distinct from the neurodegenerative disease process that leads to PD symptoms.

Genes in the dopamine pathway have not previously been evaluated as potential modifiers of the AO of overt motor symptoms in HD. We selected polymorphisms in four dopaminergic pathway genes that have been investigated in other neurological disorders because they are believed to affect neurotransmission by affecting the level of the enzyme that metabolizes dopamine, the density of dopamine receptors, and the activity of dopamine transporter. Our results did not reveal a significant modifying effect of any of the four polymorphisms, in *COMT*, *DRD2*, *DRD4*, or *DAT1*, on the onset of HD motor symptoms and therefore fail to support a role for these functional variants in the disease process that leads to the onset of neurological symptoms in HD.

In summary, the results of our study did not provide evidence for an association of DNA variants that affect the biology of particular genes in the glutaminergic pathway (*GRIN2A*, *GRIN2B*) or the dopaminergic pathway (*DRD2*, *DRD4*, *DAT1*, *COMT*) with the *HTT* CAG repeat length-dependent disease process that leads to the onset of clinical motor manifestations of HD. However, our study does not preclude the possibility that other DNA variants in these genes, or in other genes involved in these pathways, may act as genetic AO modifiers. Moreover, it is also possible that genes in the glutaminergic and dopaminergic pathways may serve to modify the rate of progression of the distinct processes that determine the rate of decline in the ~18-year period between the age at clinical diagnosis of HD and death, which is independent of the size of the *HTT* CAG repeat [39].

Ethical standards This study used only deidentified, previously collected DNA samples and phenotypic data in a manner approved by the Institutional Review Board of Partners HealthCare, Inc.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

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