

NMDA receptor gene variations as modifiers in Huntington disease: a replication study

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Abstract

Several candidate modifier genes which, in addition to the pathogenic CAG repeat expansion, influence the age at onset (AO) in Huntington disease (HD) have already been described. The aim of this study was to replicate association of variations in the N-methyl D-aspartate receptor subtype genes *GRIN2A* and *GRIN2B* in the “REGISTRY” cohort from the European Huntington Disease Network (EHDN). The analyses did replicate the association reported between the *GRIN2A* rs2650427 variation and AO in the entire cohort. Yet, when subjects were stratified by AO subtypes, we found nominally significant evidence for an association of the *GRIN2A* rs1969060 variation and the *GRIN2B* rs1806201 variation. These findings further implicate the N-methyl D-aspartate receptor subtype genes as loci containing variation associated with AO in HD.

Introduction

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder characterised by motor disturbances, cognitive decline, and neuropsychiatric symptoms. It is caused by a CAG repeat expansion (>36 repeats) in exon 1 of the *HTT* gene. [1] The lengths of the expanded CAG tract is inversely related to the age at clinical onset of HD, accounting for more than half of the overall variance in age at onset (AO). [2] Despite this strong correlation, there remains considerable variation of over 40 years in AO in individuals with identical repeat lengths. Several candidate modifier genes of HD have already been described in independent studies. [3] [4] [5] [6] [7] [8] [9] In order to confirm the associations between modifier gene variations and AO, independent replication studies are compulsory. Here, we tested the primary hypothesis of an original study [4], that variations in the *NR2A* and *NR2B* glutamate receptor subunit genes (*GRIN2A*, *GRIN2B*) explain additional variance in AO for HD.

Methods

The study cohort comprised 1,211 individuals of European ancestry with HD collected by the EHDN “REGISTRY” study prior to October 14, 2008. “REGISTRY” is a multi-centre, multi-national observational study which aims to obtain natural history data on a wide spectrum of the European HD population (<http://www.euro-hd.net/html/registry>). [10] In order to test previously reported HD genetic modifiers in this cohort, HD patients with available data on age, sex, age at symptom onset, mutant CAG repeat size and body mass index (BMI) were included (initial $n = 1211$; $n = 1069$; 529 men and 540 women had a complete data set).

The expanded trinucleotide repeats ranged from 40 to 89 with a mean (\pm SD) of 45 ± 4.7 CAGs, and AO ranged from 6 to 74 years, with an onset (mean \pm SD) of 42 ± 11.8 years. AO was defined as the age at which, according to the rater, the first signs of HD appeared. Five hundred and thirty-eight patients first presented with motor disturbances (mean \pm SD motor AO = 43.4 ± 11.6 years), 241 with psychiatric problems (mean \pm SD psychiatric AO = 39.9 ± 10.8 years), and 112 with cognitive decline (mean \pm SD cognitive AO = 38.6 ± 13.1 years). For the remaining patients no specific symptoms were listed (mean \pm SD AO = 42.1 ± 11.8 years). Genotyping of three SNPs was conducted as described before. [4]

Results

None of the SNPs deviated from Hardy – Weinberg Equilibrium (HWE). Considering the earliest AO ($n = 1,069$), we did find evidence of association of the *GRIN2A* SNP rs2650427 (table 1). The R^2 statistic rose modestly (from 0.634 to 0.635) but significantly ($p = 0.028$) when *GRIN2A* genotypes were added to the regression model. The analysis did not, however, replicate the association reported between the SNP rs1969060 in intron 2 of the *GRIN2A* gene and SNP C2664T (rs1806201) in exon 12 of the *GRIN2B* gene (table 1); but when dividing the cohort according to the nature of the symptoms presented initially, both the *GRIN2B* C2664T and the *GRIN2A* rs1969060 polymorphisms explained a small but considerable amount of additional variance

in residual AO in the respective samples. Inclusion of the *GRIN2B* genotypes in the model for motor AO ($n = 538$) increased the R^2 statistic from 0.620 to 0.623 ($p=0.046$) and in the study of 241 patients with psychiatric AO, the R^2 statistic of the exponential regression rose from 0.515 to 0.523 with the *GRIN2A* rs1969060 genotypes included ($p=0.026$, table 1). Interestingly, the association of cognitive AO ($n = 112$) with the *GRIN2A* rs2650427 polymorphism shows the highest nominal significance as compared to the other models in the study (0.770 to 0.775, $p=0.014$). Yet, the results remain statistically significant when excluding the patients with CAGs over >70 ($n=4$).

Model	Genotypes	CAGmean \pm SD	earliest AO mean \pm SD	R ² *	P value
HD CAG 40-89 ($n=1069$)		44.97 \pm 4.7	41.87 \pm 11.8	0.634	<0.0005
+ <i>GRIN2B</i> C2664T (rs1806201)	CC ($n=560$)	44.94 \pm 4.8	42.13 \pm 12.1	0.634	0.541
	CT ($n=436$)	45.02 \pm 4.5	41.32 \pm 11.3	0.634	0.199
	TT ($n=73$)	44.86 \pm 4.6	43.14 \pm 11.9	0.634	0.196
	additive			0.634	0.973
+ <i>GRIN2A</i> rs1969060	TT ($n=745$)	44.83 \pm 4.5	42.00 \pm 11.9	0.634	0.160
	TC ($n=292$)	45.24 \pm 5.1	41.67 \pm 11.5	0.634	0.203
	CC ($n=32$)	45.75 \pm 4.2	40.66 \pm 11.5	0.634	0.645
	additive			0.634	0.172
+ <i>GRIN2A</i> rs2650427	CC ($n=374$)	44.99 \pm 4.0	41.40 \pm 11.9	0.634	0.125
	CT ($n=512$)	44.94 \pm 5.2	41.99 \pm 11.9	0.634	0.891
	TT ($n=183$)	42.51 \pm 4.2	43.14 \pm 10.9	0.635	0.031
	additive			0.635	0.028
Model	Genotypes	CAGmean \pm SD	motor AO mean \pm SD	R ² *	P value
HD CAG 40-77 ($n=538$)		44.72 \pm 4.0	43.39\pm11.6	0.620	<0.0005
+ <i>GRIN2B</i> C2664T (rs1806201)	CC ($n=274$)	44.52 \pm 3.8	44.41 \pm 11.8	0.622	0.099
	CT ($n=221$)	44.96 \pm 4.1	41.98 \pm 11.1	0.623	0.046
	TT ($n=43$)	44.77 \pm 4.9	44.07 \pm 12.4	0.620	0.560
	additive			0.621	0.296
+ <i>GRIN2A</i> rs1969060	TT ($n=373$)	44.51 \pm 3.6	43.79 \pm 11.5	0.620	0.824
	TC ($n=153$)	45.32 \pm 4.9	42.19 \pm 11.9	0.620	0.934
	CC ($n=12$)	43.75 \pm 2.5	46.25 \pm 9.5	0.620	0.658
	additive			0.620	0.744
+ <i>GRIN2A</i> rs2650427	CC ($n=181$)	44.15 \pm 3.8	41.99 \pm 11.8	0.620	0.362
	CT ($n=259$)	44.48 \pm 4.1	44.00 \pm 11.9	0.620	0.792
	TT ($n=98$)	44.60 \pm 4.2	44.34 \pm 10.4	0.621	0.143
	additive			0.621	0.158
Model	Genotypes	CAGmean \pm SD	psychiatric AO mean \pm SD	R ² *	P value
HD CAG 40-67 ($n=241$)		44.73 \pm 4.1	39.86\pm10.8	0.515	<0.0005
+ <i>GRIN2B</i> C2664T (rs1806201)	CC ($n=139$)	44.81 \pm 4.4	39.50 \pm 11.3	0.513	0.964
	CT ($n=90$)	44.74 \pm 3.8	39.79 \pm 10.5	0.514	0.607
	TT ($n=12$)	43.67 \pm 2.1	44.58 \pm 9.6	0.517	0.211
	additive			0.514	0.618
+ <i>GRIN2A</i> rs1969060	TT ($n=172$)	44.79 \pm 4.1	39.01 \pm 10.9	0.523	0.026
	TC ($n=63$)	44.01 \pm 3.7	42.78 \pm 9.8	0.523	0.033

	CC (n=6)	49.50±6.8	33.50±15.5	0.514	0.649
	additive			0.522	0.037
+ <i>GRIN2A</i> rs2650427	CC (n=83)	44.79±4.0	39.42±11.3	0.514	0.504
	CT (n=120)	44.24±3.8	40.90±10.5	0.514	0.702
	TT (n=38)	43.13±5.1	37.53±10.8	0.514	0.724
	additive			0.514	0.514
Model	Genotypes	CAGmean ± SD	cognitive AO mean ± SD	R ² *	P value
HD CAG 40-89 (n=112)		46.34±7.8	38.60±13.1	0.765	<0.0005
+ <i>GRIN2B</i> C2664T (rs1806201)	CC (n=54)	46.76±8.5	37.89±14.2	0.763	0.621
	CT (n=55)	45.74±7.1	39.73±11.9	0.763	0.530
	TT (n=3)	50.00±6.2	30.67±14.0	0.763	0.682
	additive			0.763	0.742
+ <i>GRIN2A</i> rs1969060	TT (n=74)	46.24±7.8	38.95±14.1	0.763	0.682
	TC (n=31)	46.74±8.5	37.68±11.4	0.763	0.799
	CC (n=7)	45.71±3.8	39.00±10.4	0.763	0.741
	additive			0.763	0.650
+ <i>GRIN2A</i> rs2650427	CC (n=40)	45.55±4.9	37.80±12.4	0.770	0.054
	CT (n=55)	47.67±10.0	36.87±13.2	0.763	0.742
	TT (n=17)	43.9±3.2	46.06±12.3	0.772	0.033
	additive			0.775	0.014

Table 1 The variability in AO attributable to the CAG repeat length was assessed by linear regression using the logarithmically transformed AO as the dependent variable and *GRIN* genotypes as independent variables. *R² illustrates the relative improvement of the regression model, when the genotypes are considered in addition to the CAG repeats.

In order to control the effect of sex-specific associations, we further analysed each combination of genotype with sex, but there was no trend towards significance. Moreover, on average, psychiatric and cognitive symptoms significantly predate clinical motor onset by 3.5 and 4.8 years ($p < 0.001$), thus confirming that affective and cognitive symptoms could be early manifestations of neuronal dysfunction.

Discussion

Of the three polymorphisms tested, *GRIN2A* rs2650427 showed the most consistent evidence of replication in the EHDN Registry study sample. This is in accordance with another replication study in the large set of kindreds from Venezuela, where *GRIN2A* variation also explained a small but considerable amount of additional variance in residual AO.[5]

Yet, the interpretation of the association of cognitive AO with the *GRIN2A* rs2650427 polymorphism should be considered with caution since the sample size of this subgroup (n=112) is too small to provide the statistical power required.

Unfortunately, none of the SNPs associated has been validated functionally and it is most likely that the polymorphisms analysed are not the functional variations, but represent markers in linkage disequilibrium with variations that modify the AO. Although, synonymous SNPs like *GRIN2B* rs1806201 might be pathogenetically relevant via influencing mRNA splicing, protein stability and structure.

The failure to replicate the sex-specific effect of rs1806201 suggests that the original observation may have been false positive, emphasizing the need for stringent statistical thresholds. On the other hand, since linkage disequilibrium is not uniform across populations, the mixed ancestry in the EHDN REGISTRY study sample could account for heterogeneous results. Inconsistent results may also occur because of difficulties in exact AO definitions. The data stresses the need for precise phenotyping in order to reduce heterogeneity, and to facilitate the discovery of clinically relevant biological pathways.

Although the associations replicated explain only a small fraction of the variance of AO, the observed correlations with HD phenotypes demonstrate that GRIN2A and GRIN2B remain promising candidate genes, worth to be studied further in more detail.

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Competing interests

The authors have declared that no competing interests exist.

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Ethics approval

This study was conducted with the approval of the local ethics committee of the different clinical centres.

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