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Research Report

β-Defensin Genomic Copy Number Does Not Influence the Age of Onset in Huntington's Disease

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Abstract.
Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by the abnormal expansion of a CAG triplet repeat tract in the huntingtin gene. While the length of this CAG expansion is the major determinant of the age of onset (AO), other genetic factors have also been shown to play a modulatory role. Recent evidence suggests that neuroinflammation is a pivotal factor in the pathogenesis of HD, and that targeting this process may have important therapeutic ramifications. The human β-defensin 2 (hBD2) – encoded by *DEFB4* – is an antimicrobial peptide that exhibits inducible expression in astrocytes during inflammation and is an important regulator of innate and adaptive immune response. Therefore, *DEFB4* may contribute to the neuroinflammatory processes observed in HD.
Objective: In this study we tested the hypothesis that copy number variation (CNV) of the β-defensin region, including *DEFB4*, modifies the AO in HD.
Methods and results: We genotyped β-defensin CNV in 490 HD individuals using the paralogue ratio test and found no association between β-defensin CNV and onset of HD.
Conclusions: We conclude that it is unlikely that *DEFB4* plays a role in HD pathogenesis.

Keywords: Genetic modifier, copy number variation, inflammation

INTRODUCTION

Huntington's disease (HD) is a fatal neurodegenerative disorder characterized by motor dysfunction, severe psychiatric disturbances and cognitive decline, with a mean age of onset (AO) of ∼40 years [1]. The autosomal dominant mutation underlying the disease is a polymorphic CAG trinucleotide repeat expansion

[1]A full list of REGISTRY investigators is given as an appendix at the end of the manuscript.

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in the huntingtin (*HTT*) gene [2], which causes disease above the threshold of 36 repeats. Furthermore, the length of this repeat expansion accounts for up to 70% of the variability of AO with which it is inversely correlated [3–7]. Other genetic factors are very likely to explain a large proportion of the remaining variability of AO [8] and thus have the potential to modify AO in HD [9–22]. The identification of new genetic modifier loci furthers our understanding of the disease mechanisms and may ultimate facilitate the development of novel therapeutic interventions for HD.

In common with most age-associated neurodegenerative disorders [23–26], HD patients exhibit hallmarks of neuroinflammation, driven by microglia, reactive astrocytes and the innate immune system [27, 28], which are detectable in pre-manifest HD carriers up to 15 years before of the predicted onset [29]. Indeed, kynurenine 3-monoxygenase – an enzyme with microglia-specific expression in the central nervous system – is a leading candidate therapeutic target for HD [30–33]. The human β-defensin 2 (hBD2) protein – encoded by the gene *DEFB4* – is a member of a large family of antimicrobial cationic peptides, implicated in granulocyte activity, inflammatory body fluids and epithelial secretions [34]. hBD2 has chemoattractant activity and is an important mediator of both innate and adaptive immunity [35, 36], recruiting monocytes, T cells and dendritic cells [34]. Interestingly, the expression of hBD2 is stimulated in primary astrocytes in response to inflammatory stimuli such as LPS, IL-1β and TNF-α [37]. The inducible expression of hBD2 by cytokines, which are highly expressed in HD patients [38, 39], possibly following direct LPS-CD14/TLR interaction [36, 40, 41], suggests that *DEFB4* could be involved in the neuroinflammation succeeding reactive astrocytosis and therefore be implicated in HD pathology.

DEFB4 is located in the β-defensin cluster on chromosome 8p23, a region that, together with several other β-defensin genes, shows extensive copy number variation (CNV) as a block [42]. CNV is an alteration in the number of copies of a particular genetic region between different individuals, and can be a simple deletion or duplication, or a more complex multiallelic CNV. The β-defensin CNV is a multiallelic CNV where diploid copy number ranges from 2 to 8 copies in the population, but rare individuals with up to 12 copies have been identified by cytogenetic analysis [42, 43]. β-defensin copy number is correlated with both mRNA expression levels and levels of circulating hBD2 protein in serum [42, 44] and is associated with altered susceptibility to autoimmune and inflammatory diseases [45–47] and with HIV viral load [48]. In this study we are testing the hypothesis that β-defensin copy number, including the *DEFB4* gene, is associated with a variance in the AO in HD, where an increased copy number might lessen the age of onset of the disease.

MATERIALS AND METHODS

HD samples

The study cohort comprised 495 individuals of European ancestry with HD collected by the EHDN "REGISTRY" project. "REGISTRY" is a multi-centre, multi-national observational study which purposes to catalogue natural history data on a wide range of the European HD population (http://www.euro-hd.net/html/registry) [49]. Clinical data on age of onset, sex (263 men and 232 women), main symptom at onset and mutant CAG repeat size were provided.

The *HTT* gene CAG repeat length was analyzed by BioRep (BioRep, Milan, Italy) [50, 51]. When these data were not available from BioRep (90 samples), the CAG extent length estimated by the laboratory that collected the sample was considered. One sample carrying a 35 CAG repeat *HTT* allele, which by definition is not a disease allele, was included in the analysis due to ambiguity with the data provided by the collecting laboratory, where a 40 CAG repeat length mutation was identified. In our HD cohort the expanded trinucleotide repeats ranged from 36 to 67 with a mean (±SD) of 44 ± 4 CAGs, and AO ranged from 10 to 79 years, with a mean onset of 43 ± 11 (SD) years.

AO was defined as the age at which, according to the rater, the first sign(s) of HD appeared. Two-hundred and fifty eight patients were diagnosed by motor disturbances (mean ± SD motor AO = 44 ± 11 years), 114 with psychiatric disturbances (mean ± SD psychiatric AO = 39 ± 10 years), 44 with cognitive decline (mean ± SD cognitive AO = 41 ± 12 years), 5 with symptoms such as weight loss or insomnia, 1 with oculomotor deficits and the remaining 73 with mixed symptoms (mean ± SD cognitive AO = 44 ± 10 years).

DEFB4 genotyping

Genotyping of β-defensin CNV was conducted using a triplex paralogue ratio test (PRT), as previously published [52]. In this assay three parallel PCRs – two PRTs and one indel (insertion-deletion) PCR – are performed in duplicate in order to give six estimates of β-defensin copy number. The PCR products are analysed in a single fluorescent capillary electrophoresis

run and the resulting data are normalized against six controls samples of known copy number to level the variation between experimental PCRs. The same six controls samples were used in this study as in previous studies [52–54].

The β-defensin copy number is inferred from these six values using a maximum-likelihood approach [55], which also calculates a *p*-value that reflects the confidence in the inferred copy number compared to all the other copy number calls, with 99% of the samples having copy number call with $p < 0.05$ and among these 99% having copy number call with $p < 0.01$. Of the 495 samples tested, copy numbers with $p < 0.05$ were successfully obtained for 490.

Statistical analysis

Firstly, we analysed the β-defensin copy number distribution in the HD cohort dividing the cohort into three groups according to the age of onset: juvenile, AO $\leq$ 20 years; typical, AO between 20 and 50 years; late, AO $\geq$ 51 years [8]. We performed a one-way ANOVA to test whether there was any variation in β-defensin CNV distribution among each group, and all the groups and the European population without HD, analysed in a previous study [53].

Secondly, we constructed a generalized linear model using SPSS 20.0 (IBM Inc.), calculated using Type III statistics with Wald confidence intervals, with an identity link, assuming a normal distribution of the dependent variable. Log2 transformed AO of HD was the scalar dependent variable, CAG length as a scalar predictive variable and β-defensin copy number as an ordinal predictor variable. We also used a generalized linear model to investigate the effect of β-defensin copy number and CAG repeat length on the major estimated symptoms at the onset of HD (categorical dependent variable).

RESULTS

We determined the β-defensin copy number for 490 individuals from our HD cohort (Table 1). The distribution of β-defensin CNV in this cohort is not significantly different from the European population without HD (one-way ANOVA, $p = 0.91$). Furthermore, no AO class has a β-defensin CNV distribution that is significantly different from any other class or the European non-HD population (Fig. 1) [53].

We next constructed a generalized linear model to explore the effect of CAG repeat length and β-defensin copy number on AO. As expected, incorporating CAG length into the model improved the prediction of AO ($p < 5 \times 10^{-6}$, Table 2), but subsequent incorporation of β-defensin copy number into the model found no significant improvement in prediction of AO ($p = 0.41$, Table 2). Therefore we conclude that β-defensin copy number does not affect the AO of HD.

We found no significant correlation with any of the symptoms at the onset diagnosis and CAG length ($p = 0.76$) nor of copy number of β-defensin ($p = 0.85$).

DISCUSSION

HD is a monogenic disorder caused by an autosomal dominant mutation in the HD gene. Notwithstanding its relentless course, the wide temporal range of AO (ranging from 1 year to 85 years) of the motor symptoms and the several phenotypes associated to HD are not only explainable by the expanded CAG repeat in the HD gene. As previously shown in a study on Venezuelan families, the residual age of onset is highly heritable, suggesting the presence of other genetic factors involved in the mechanisms behind the disease [8].

To our knowledge, this is the first study that tests the potential role of an inflammatory mediator and

Table 1
β-defensin CNV genotypes in each AO class, in the HD cohort, and the European population

β-defensin copy number	Juvenile AO HD group	Typical AO HD group	Late AO HD group	HD cohort	European population
1	0	1	0	1	0
2	0	8	3	11	8
3	3	62	24	89	70
4	2	129	51	182	205
5	5	99	34	138	131
6	1	44	11	56	44
7	0	8	3	11	9
8	0	1	1	2	4
9	0	0	0	0	1
n	11	352	127	490	472

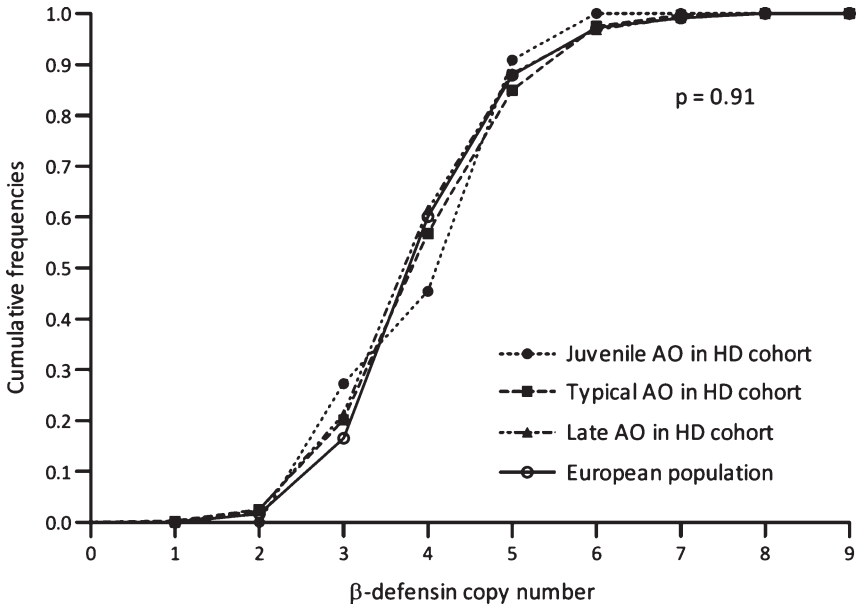

Fig. 1. Cumulative frequencies of β-defensin CNV genotypes in HD individuals with juvenile AO, typical AO, late AO and in the non-HD European population. The *p*-value is two-sided, calculated by one-way ANOVA.

Table 2
Effect of the β-defensin CNV on the age of onset in HD

	Mean (95%CI) (years)	*p*-value
Effect per extra CAG repeat	−2.17 (−2.36 to −1.98)	$<5 \times 10^{-6}$
Effect per extra copy of β-defensin	−0.28 (−0.96 to 0.4)	0.415

its CNV as a modifier of the age of onset in HD. CNV encompasses over 12% of the human genome [56] and is a significant contributor to genomic variation. CNVs have been investigated with regards to their functional impact on the full range of biology, from gene-expression studies to GWAS interrogating all the classes of human genetic diseases: Mendelian, complex, sporadic and infectious [57].

It is clear that β-defensin genomic copy number is not associated with modulation of HD pathogenesis and does not affect the age of onset of any sign. Notwithstanding, we cannot formally exclude the potential implication of single nucleotide polymorphisms within this region, considering that not only copy number change but also sequence variants can affect the expression of hBD2 [58].

Furthermore, the inducible expression of hBD2 in astrocytes driven by TNF-α and IL-β [37], which are both expressed in the striatum of HD brains [59], may not be copy number dependent. It is also possible that transcriptional and trafficking alterations in astrocytes due to mutant huntingtin [60, 61] might interfere with hBD2 expression or function, masking any possible modulation in the expression driven by its copy number. Thus, further studies are necessary to clarify the effects of β-defensin copy number on hBD2 expression in CNS tissues in both normal physiological and neurodegenerative milieus.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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