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EDITORIAL

Genetic modifiers in Huntington's disease: fiction or fact?

Larissa Arning · Jörg T. Epplen

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Extensive evidence suggests that a significant proportion of variance in the age at onset (AO) of Huntington's disease (HD) arises from common genetic variations [1], including single nucleotide polymorphisms (SNPs). Such sequence variation and the resulting changes in protein structure and function could have an impact on various interacting metabolic networks by influencing gene expression. Such pathway interactions may influence the time when first characteristic extrapyramidal motor signs of chorea, bradykinesia, dystonia, or malcoordination become overt. Yet, the contributing variations individually might be neither necessary nor sufficient to affect the AO, in contrast to the classical *Huntingtin* (*HTT*) mutation itself, which leads in any case to the disease phenotype.

As early as 1993, it was proposed that variation within the normal allele of the *HTT* gene could have modifying effects on AO [2], and for two decades now, genetic modifiers in HD have been investigated (for review, see [3]). In this context, mostly the typical, hypothesis-driven, candidate-gene association studies have been performed, where genes are selected based on their known functions. The identification of SNPs associated with the AO might help to understand the biological mechanisms underlying the pathogenesis of HD and to define more personalized therapeutic approaches in the future.

To date, polymorphisms have been identified with significant associations to the AO of HD motor symptoms in more than two dozen different candidate genes implicated in various mechanisms, like dysregulation of energy metabolism, altered neurotransmitter receptor function, Huntingtin protein interactions, as well as the regulation of gene expression [3]. Some of these associations were replicated at least once, however, with varying results. For example, the association with the functional *BDNF* polymorphism V66M that influences intracellular trafficking and activity-dependent secretion of BDNF in the brain has most consistently failed to be replicated despite its highly plausible etiological relevance [3]. On the other hand, a polymorphism (rs7665116) in another biologically compelling candidate, *PPARGC1A*, has been replicated almost consistently [4–6]. However, there are recent speculations that this effect is a result of phenotypic (AO) and genotypic (MAF) stratification among European cohorts [7].

In this issue of Neurogenetics, Ramos et al. [8] again present results that fail to demonstrate a significant association between HD motor AO in a large European HD cohort and candidate polymorphisms in *N*-methyl D-aspartate receptor (NMDAR) subtype genes found previously to be associated in other HD populations (GRIN2A rs2650427 and GRIN2B rs1806201). Many lines of evidence support a role for NMDARs in mediating neuronal damage arising as a result of excessive activation of glutamate receptors by excitatory amino acids in the pathophysiology of HD. In HD patients, neurons expressing high levels of NMDARs are lost early in the striatum. Furthermore, in animal models, injection of NMDAR agonists into the striatum recapitulates the pattern of neuronal damage observed in HD. In addition, NMDAR function and expression are altered in several HD mouse models. Here, NR2B-containing NMDARs show increased surface expression, current, and toxicity in medium spiny neurons, and NR2B overexpression enhances striatal neuronal loss (for review, see [9, 10]). Genes coding for the NMDA receptor subtypes are therefore attractive candidate targets for modifier studies in HD.

The inability to replicate results gives rise to skepticism about the value of association study designs for the detection of genetic variation contributing to some of the variation in AO of HD motor manifestations. Attention has already been drawn to the problems that can, in theory, confound this approach in a fundamental way, e.g., through composition of the study cohort in terms of CAG distribution, or the genetic background related to ethnicity, or inadequate phenotyping (motor AO vs. psychiatric or cognitive AO), which is particularly aggravated when data are collected in different centers. Therefore, as is the case for all genetic association studies, the design is truly crucial in order to minimize or even eliminate sources of bias. Of course, this will not completely prevent false-positive results, but these precautions will keep

L. Arning (✉) · J. T. Epplen
Human Genetics, Ruhr University, 44780 Bochum, Germany
e-mail: larissa.arning@rub.de

them as rare as possible. However, for more frequently observed p values (p=0.05 to 0.01), replication probabilities will always be notably lower than one would hope, and failure to replicate in these situations does not really surprise [11].

Although after 20 years of research into candidate modifiers of HD, several variations with a possible effect on the AO have been identified, all of them seem to exert small effects explaining only a small percentage of the remaining heritable contribution to AO. Moreover, the vast majority of associations remain unexplained at a functional level so far. Nevertheless, this actual shortcoming should not lessen the value of modifier gene studies in providing novel clues to the complex pathogenesis of HD. Therefore, candidate–gene association findings together with future results of well-powered genome-wide association studies and human whole-genome or exome sequencing may be able to confirm a role for the genomic variations investigated so far and may also lead to the identification of novel and unexpected loci that affect AO variability in HD. After all, discovering any new molecular mechanisms or new pathways in HD is worth significant effort because the pathophysiology of this important neurological disease is still poorly understood.

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