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Genetics of Huntington's disease and related disorders

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Huntington's disease is the most frequent form of the hereditary choreas and has a multifaceted phenotype including cognitive and psychiatric impairment. The disorder is due to a dynamic mutation, which also influences the onset age of the disorder. Other genetic modifiers of the HD phenotypes have been suggested but often not confirmed by independent studies. Several syndromes with similar presentation have different genetic backgrounds, including the neuroacanthocytoses, mainly choreoacanthocytosis and MacLeod syndrome as a result of mutations in chorein and Kell protein, respectively, but also benign hereditary chorea, owing to mutations in *NKX-2-1*, and paroxysmal kinesigenic dyskinesia, as a result of recently found mutations in the proline-rich transmembrane protein 2, *PRRT2*. Chorea can also be a major feature in other neurogenetic disorders, including the spinocerebellar ataxias and also in neurometabolic disorders.

Introduction

Chorea is a prominent feature of Huntington's disease (HD), the most frequent cause of hereditary chorea; however the disease has a much more extended phenotype including cases with absent chorea at presentation. The gene involved in this disease was identified 20 years ago [1] and results on the search for genetic modifiers to explain the variable phenotype are being published. Our knowledge on the genetic background of other neurogenetic disorders, which can present with chorea, has also increased. This review presents a short summary of our present understanding of the genetic background of these disorders.

Huntington's disease

In a case of progressive cognitive and behavioural changes with hyperkinetic, choreatic involuntary movements starting at around 40 years old with a positive family history compatible with an autosomal dominant inheritance, the most probable diagnosis is HD. The mutation in the huntingtin (*HTT*; also named *IT15*) gene, located on chromosome 4p16, is an elongation of the CAG repeated element in exon 1 [1]. The age at onset is negatively correlated with the number of triplet repeats and this explains about 65% of its variance. However, this variability precludes the use of the number of triplet repeats to predict onset in the clinical setting. A large number of observations have allowed the delineation of the boundaries between normal and elevated triple-repeat numbers. The mean in normal subjects is around 17, and the range up to 27. People with HD have more than 36 repeats, but those with 36–39 have a less severe phenotype owing to a decreased penetrance of the mutation at these allele sizes. Repeat numbers can change from one to the next generation, explaining the frequent observation of a more severe phenotype in the next generations, the so-called anticipation effect. This is specifically relevant for carriers of triplet repeat numbers at the border of the above intervals, and people with alleles with 27–35 repeats could have children with higher repeat numbers now reaching the range associated with the disease [2]. Allelic instability with increase over generations has also been implicated in apparently sporadic cases. Such occurrences of HD in the absence of family history amount to about 8% of new cases [3]. Care must also be taken regarding laboratory quality control; indeed, in a comparison of several local laboratories with a single central one an analysis of the Registry Database collected by the European Huntington's Disease Network

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GLOSSARY

ADORA2A	adenosine A2a receptor
CO1	cytochrome c oxidase 1
DFFB	DNA fragmentation factor, 40 kDa, beta polypeptide
GluR6/GRIK2	glutamate receptor form A/glutamate receptor, ionotropic, kainate 2
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2b
HTT	huntingtin
JPH3	junctophilin-3
MAP3K5	mitogen-activated protein kinase kinase kinase 5
MAP2K6	mitogen-activated protein kinase kinase 6
NKX-2-1	NK2 homeobox 1
NRF1	nuclear respiratory factor 1
PGC1a	peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
TCERG1	transcription elongation regulator 1
TFAM	transcription factor A, mitochondrial
TITF1	thyroid nuclear actor 1
TP53	tumor protein p53
XK	X-linked Kx blood group

has demonstrated discrepancies, even some leading to a change in diagnostic category [4].

In a case with typical presentation with family history, at least among Caucasians, molecular diagnostic testing can be offered first line, avoiding additional costs of more-extensive investigations [5]. Of course this needs to be performed after thorough neurogenetic counselling, which should include the family. In a family with proven molecular diagnosis, carrier testing in presymptomatic cases might be offered during a careful, multidisciplinary, stepwise process during which the counselee's autonomy and her right to know or not is consciously recognised. The quality of the information must be of a high level and is best provided by someone with first-hand, profound knowledge of the disease. It must be given in understandable words adapted to the counselee for them to be able to make their own knowledge-based decision. Risks of presymptomatic carrier testing include suicide and depression, and they are increased in people with a history of psychiatric symptoms and unemployed status; by contrast, established and previously successful coping strategies are associated with a lower risk [6,7].

To minimise the risk of negative outcome during the presymptomatic testing, recommendations have been drawn up and recently revised [2]. After an initial session, time is given for further reflection, followed by a second session during which the test is performed after informed consent. The consellee has the freedom to change his mind about knowing his genetic status, or not, until the opening of the result. Follow-up sessions to assess coping are of high importance. The percentage of people at risk who ask for presymptomatic genetic testing is generally low with, for example, 5–20% in the UK [8]. This figure might change because the prevalence of the disorder has a tendency to increase [9] and if there is more availability of disease-modifying strategies in the future. Presymptomatic testing of minors has usually been rejected, but it is important that they can have access to appropriate genetic counselling and support if they wish [10]. Prenatal testing can be performed after chorionic villus sampling between week 11 and 13. Preimplantation genetic diagnosis is allowed in certain countries and can be performed in a non-disclosure way, so that the parents would not know their own genetic status. Both need to be performed after thorough consideration of the ethical issues raised.

Age of onset can vary widely and this is to be taken into consideration in the use of molecular genetic testing for the *HTT* gene and also for counselling and care management of the families [11]. In very early onset cases, a completely different phenotype linked to *HTT* gene mutation is found – closer to a developmental disorder [12]. Juvenile cases have a more akinetic phenotype than in adult cases to compare with other differential diagnoses. The probability of finding CAG in juvenile cases without family history is low [13], therefore testing in these patients should only be part of a comprehensive diagnostic investigation. By contrast, older people have a phenotype with mainly motor symptoms at onset, which can be undistinguishable from senile chorea. The diagnosis is often the first to be made in the family, associated dementia can be of the Alzheimer's type and death is related to other diseases of old age [14]. Although intermediate triplet numbers between 27 and 35 are not associated with definitive and typical HD, 5% of them have increased apathy and suicidal ideation, whereas their motor, cognitive and other behavioural scores are in the normal range [15].

The search for genetic modifiers

Other than the clear influence of the number of repeats in the longer allele on the age at onset, environmental or genetic reasons for HD phenotype variation are not well understood. Although the effect of the longer allele can already be seen in small groups of patients, larger numbers are needed to assess other aspects. In a cohort of more than 4000 patients the smaller allele had no effect on the age at onset, which is determined by the large allele in a fully dominant fashion [16].

Several studies have used a hypothesis-driven approach to search for other genetic modifiers in HD based on knowledge on molecular pathways. So far most of the studies have examined the association of single nucleotide polymorphisms (SNPs) with age of onset. However, age of onset is often difficult to establish and motor symptoms, which are fairly obvious, can wrongly be taken as the beginning of the phenotypic manifestation. Therefore, in Registry 3, the major study of the European Huntington's Disease Network (EHDN), a more comprehensive catalogue of symptoms that are historically present is being used. This will allow specific assessment of age at onset of different symptoms, which could be associated differentially with particular SNPs. So far, almost 30 studies have examined the association of SNPs with age at onset. They have studied genes coding proteins interacting with *HTT* (e.g. *TCERG1* and *HAP1*) or involved in neurotransmission (*GluR6/GRIK2*, *GRIN2A*, *GRIN2B*, *ADORA2A*), in energy metabolism (*PGC1a*, *CO1*, *NRF1* and *TFAM*), in stress response (*MAP3K5*, *MAP2K6*, *DFFB* and *TP53*) or in other processes [17]. Some of the findings have been further explored in replication studies, and only a few of them have been confirmed. For example association of *GRIN2A* and *GRIN2B* could not be replicated in a recent study [18].

Only a few genome-wide associations studies have been performed so far. A replication study confirmed only one of the loci