

Trinucleotide repeat expansion in SCA17/TBP in white patients with Huntington's disease-like phenotype

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Huntington's disease (HD) is characterized by movement abnormalities and psychiatric symptoms. Prominent features include choreiform movements, dysarthria, ataxia, depression, dementia, and personality changes. The disease usually manifests during the third or fourth decade of life and progresses with dysphagia and subsequent cachexia causing death some 20 years later. Neuropathologically, the disease is characterized by atrophy of the caudate and putamen and, to a lesser extent, of the cortex, globus pallidum, thalamus, subthalamic region, and substantia nigra.¹

A CAG repeat expansion in the *HD* gene resulting in an expanded polyglutamine chain in the huntingtin protein was identified as the major cause of HD.² Phenocopies of HD have been described and designated as Huntington disease-like (HD-like). These disorders are genetically heterogeneous. In a consanguineous family of Saudi Arabian ancestry a juvenile-onset choreiform disease resembling HD was described, inherited as an autosomal recessive trait. The chromosomal mapping might point to 4p15.3, but still is controversial.^{3,4} In senile chorea, CAG repeat expansions in the *HD* gene have been excluded but a gene locus for this HD-like condition is not known.⁵ Several families have been reported with clinical features closely resembling HD and autosomal dominant inheritance. Among these, an early-onset non-progressive chorea with benign course has been associated with mutations in *TITF-1* mapped to chromosome 14q,⁶ and a progressive form has been described in a Swedish family, and has been designated as HDL-1 localizing to chromosome 20p.⁷ Moore and co-workers and Laplanche and co-workers identified a 192-nucleotide insertion in the prion-protein gene (*PRNP*) that segregated with this phenotype in the family of Xiang and in one French family.^{8,9} More recently, a second family of African-American ethnicity with HD-like features showed repeat expansion in a gene mapping to chromosome 16q23 and the locus was designated HDL-2.¹⁰ Subsequently, a CAG/CTG repeat expansion in the *junctophilin-3* gene was identified in this family and was shown to cosegregate with the disease in affected individuals.¹¹ As HDL-1 is reported only anecdotally and HDL-2 could not be demonstrated in a large number of HD-like samples of white ancestry,^{12,13} other loci are likely to contribute to the HD-like phenotype.

In addition to CAA/CAG repeat expansion in the *TBP/SCA17* gene resulting in an expanded polyglutamine chain leads to spinocerebellar ataxia type 17 (SCA17). Phenotypically, beside cerebellar signs, psychiatric disturbances such as psychosis, depression, and dementia may be the first symptoms of the disease. Moreover, within SCA17 families, affected members may present only with psychiatric symptoms while others show a cerebellar phenotype or dementia. Therefore, a remarkable overlap between SCA17 phenotypes and HD-like phenotypes exists.

To investigate whether a CAA/CAG repeat expansion in the *TBP/SCA17* gene may underlie the HD-like features in white patients, we analysed the CAA/CAG repeat in a group of 1712 patients who were referred to DNA laboratories in Germany

Key points

- Expansion of a CAA/CAG trinucleotide repeat in the TATA-binding protein (TBP/spinocerebellar ataxia 17, SCA17) has recently been thought to be involved in autosomal dominant cerebellar ataxias. SCA17 is a rare cause of dominant cerebellar ataxia in white subjects with particular interesting clinical features. Beside cerebellar signs, psychiatric disturbances such as psychosis, depression, and dementia may be the first symptoms of the disease. Moreover, within SCA17 families, affected members may present only with psychiatric symptoms while others show a cerebellar phenotype or dementia. Therefore, a remarkable overlap between SCA17 phenotypes and Huntington's disease-like (HD-like) phenotypes exists.
- To investigate whether a CAA/CAG repeat expansion in the *TBP/SCA17* gene may underlie the HD-like features in white patients we analysed the CAA/CAG repeat in a large group of 1712 patients who were referred for Huntington's disease (HD) testing to DNA laboratories in Germany and Austria. All patients were negative for expansions (had less than 36 CAG repeat units) in the *HD* gene, thus excluding HD as the cause of the symptoms.
- More than 45 CAA/CAG repeats in the *TBP/SCA17* gene were detected in nine independent patients. Their phenotypes were indistinguishable from HD although cerebellar ataxia was noticed in all (6) patients for whom clinical data were available.
- In conclusion, repeat expansion in the *TBP/SCA17* gene can be found in HD-like phenotypes. Particularly, the co-occurrence of psychiatric and cerebellar symptoms in addition to choreiform disturbances in different members of a pedigree suggest this etiology.

Abbreviations: ADCA, autosomal dominant cerebellar ataxia; HD, Huntington's disease; HD-like, Huntington's disease-like; *JPH3*, *Junctophilin-3* gene; PRNP, prion protein; SCA, spinocerebellar ataxia; TBP, TATA binding protein

Clinical features of HD-like patients with CAG/CAA repeat expansion in the SCA17/TBP gene (one patient has been described in detail elsewhere)¹⁶

Pat ID	Number of CAG/CAA repeats	Sex	Family history	Age at onset	Presenting symptom	Dementia	Psychiatric disturbances	Ataxia	Chorea
1	34/50	Male	AD	<45	Not reported	Not reported	Not reported	Not reported	Not reported
2	37/48	Female	Not reported	<68	Not reported	Not reported	Not reported	Not reported	Not reported
3	36/46	Female	AD	36	Not reported	Yes	No	Yes	Yes
4	35/46	Male	Sporadic	37	Psychiatric disturbances	Not reported	Yes	Yes	Yes
5	36/50	Male	AD	32	Dementia	Yes	Yes	Yes	Not reported
6	35/51	Female	AD	32	Focal dystonia	Yes	Yes	Yes	No
7	37/48	Male	AD	35?	Dementia	Yes	No	Yes	No
8	35/46	Male	AD	38	Dementia	Yes	No	Yes	Yes
9	40/52	Male	Not reported	50	Hyperkinesia	Not reported	Not reported	Not reported	Not reported

AD: autosomal dominant; "not reported" denotes that the clinical data accompanying the blood sample at the date of testing did not mention whether the clinical feature was present or not. As some DNA samples had been collected over 10 years ago, some patients were unavailable for a clinical update.

and Austria for testing the HD repeat expansion.¹⁴ All patients were referred by neurologists or psychiatrists. In this study we only included patients with fewer than 36 CAG repeat units in the HD-gene, thus excluding Huntington's disease as the genetic cause of the symptoms.

For SCA17, normal repeat numbers vary between 29 and 42. An intermediate range with reduced penetrance is assumed for 43–48 CAA/CAG repeats.¹⁵ In total we detected nine pathological CAA/CAG repeat expansions ranging from 46 to 52 repeats in the TBP/SCA17 gene in nine independent patients (table). From two patients clinical data were not accessible. Cognitive decline was reported as a prominent and early symptom in six patients. Two of these six patients had impressive cognitive impairment and PRNP gene mutations had previously been excluded. In five patients, ataxia in addition to choreiform movements had been observed prior to the exclusion of HD. Six patients had a family history of dementia, chorea, or ataxia and one patient was apparently sporadic.

Our findings are in accordance with a very recent report by Stevanin and co-workers (2003), who described repeat expansions in TBP/SCA17 gene in two sporadic French HD-like patients.¹⁷ Since at least 66% of our patients with pathological TBP/SCA17 repeats had positive family history, we therefore conclude that repeat expansions in the TBP/SCA17 gene are causative for HD-like symptoms in addition to the well-recognized spinocerebellar ataxia phenotype. As cerebellar ataxia is not a common sign in Huntington's disease,¹ this symptom should evoke special attention in patients with HD-like phenotype, eventually suggesting a TBP/SCA17 mutation. The TBP CAA/CAG repeat should also be tested in familial cases of HD-like symptoms with marked cognitive decline. In our large sample, CAA/CAG repeat expansions in the TBP/SCA17 gene represent a more common monogenic cause for a HD-like phenotype than HDL-1 and HDL-2, and should therefore be considered in testing white choreatic patients for whom the HD mutation has been excluded.

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