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Short communication

Expanding the phenotype of SCA19/22: Parkinsonism, cognitive impairment and epilepsy

Vincent Huin [a, b, *], Isabelle Strubi-Vuillaume [b], Kathy Dujardin [c, d], Marine Brion [d], Marie Delliaux [d], Delphine Dellacherie [e], Jean-Christophe Cuvellier [e], Jean-Marie Cuisset [e], Audrey Riquet [e], Caroline Moreau [c, d], Luc Defebvre [c, d], Bernard Sablonnière [a, b], David Devos [c, d, f]

[a] Univ. Lille, Inserm, CHU Lille, UMR-S 1172 - JPArc - Centre de Recherche Jean-Pierre AUBERT Neurosciences et Cancer, F-59000, Lille, France
[b] CHU Lille, Institut de Biochimie et Biologie moléculaire, Centre de Biologie Pathologie et Génétique, F-59000, Lille, France
[c] Univ. Lille, Inserm, CHU Lille, U1171 - Degenerative & vascular cognitive disorders, F-59000, Lille, France
[d] CHU Lille, Service de Neurologie et Pathologies du Mouvement, Hôpital Roger Salengro, F-59000, Lille, France
[e] CHU Lille, Service de Neuropédiatrie, Hôpital Roger Salengro, F-59000, Lille, France
[f] CHU Lille, Service de Pharmacologie médicale, Faculté de Médecine, F-59045, Lille, France

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ABSTRACT

Introduction: Spinocerebellar ataxia types 19 and 22 (SCA19/22) are rare conditions in which relatively isolated cerebellar involvement is frequently associated with cognitive impairment. Here, we report on new clinical features and provide details of the cognitive profile in two SCA19/22 families.
Methods: Two families displaying an autosomal-dominant form of cerebellar ataxia underwent clinical examinations and genetic testing.
Results: In addition to the classical clinical features of SCA, a wide spectrum of cognitive disorders (including visuospatial impairments) was observed. Eight patients had mild Parkinsonism, and five had epilepsy. Genetic testing showed that the *KCND3* mutation (c.679_681delTTC, p.F227del) was present in both families.
Conclusions: Our findings broaden the phenotypic spectrum of SCA19/22, and suggest that *KCND3* should be included in the list of candidate genes for epilepsy, Parkinsonism and cognitive impairment.

1. Introduction

Spinocerebellar ataxia types 19 and 22 (SCA19/22) are, rare inherited neurodegenerative disorders characterized by slowly progressing ataxia, frequent cognitive impairment, and signs of frontal lobe dysfunction [1,2]. Other neurological features observed in some (but not all) cases include postural head tremor, myoclonus, pyramidal signs and neuropathy [3]. SCA19 and SCA22 almost certainly correspond to the same disease, which is caused by loss-of-function mutations within the potassium voltage-gated channel subfamily D member 3 (*KCND3*) gene [4]. The *KCND3* gene encodes the voltage-gated potassium channel Kv4.3, which is known to be important for repolarization of the action potential in excitable cells [5]. In SCA19/22, mutations alter the channel's location and/or function. In turn, this alters the excitability of Purkinje neurons and leads to their neurodegeneration [6]. Here, we describe two novel SCA19/22 families and broaden the phenotypic spectrum to encompass mild Parkinsonism and epilepsy.

2. Methods

2.1. Clinical examination

Two unrelated French families displaying ataxia with an autosomal-dominant inheritance pattern were examined in the Department of Neurology at Lille University Medical Center (Fig. 1). All affected family members underwent a detailed clinical evaluation. During examination, Parkinsonism was defined with the classical association of rigidity and akinesia that can be associated with a rest tremor. The symptoms of four deceased family members

* Corresponding author. Inserm UMR-S 1172, JPArc, rue Polonovski, F-59045, Lille, France.
E-mail address: vincent.huin@inserm.fr (V. Huin).

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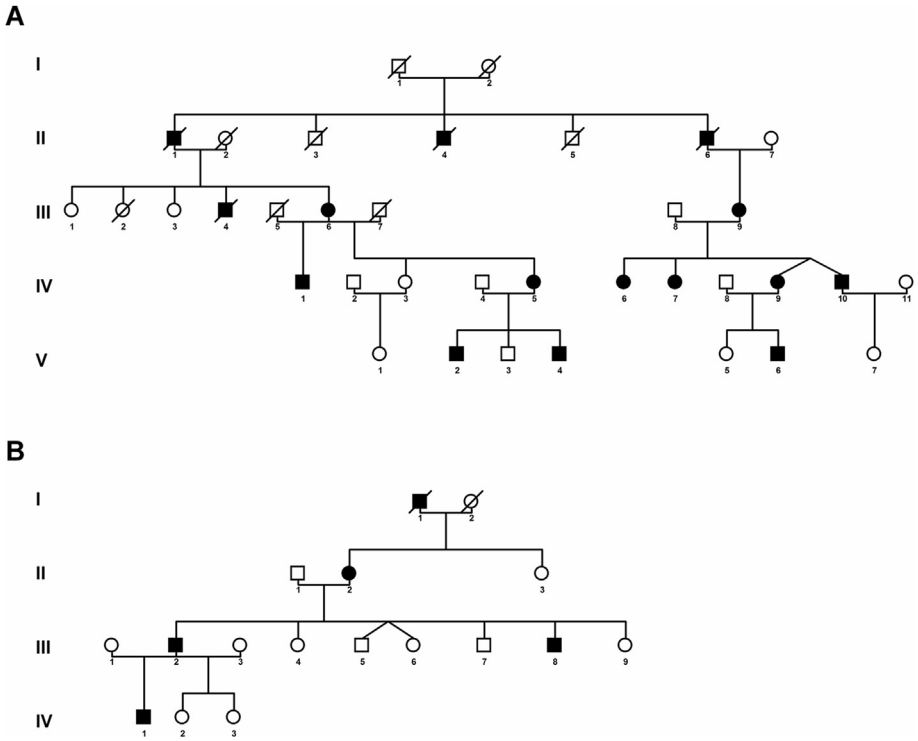

Fig. 1. Pedigrees of the two SCA19/22 families.
Circles denote females, and squares denote males. The arrows indicate the probands. Black filled symbols represent affected individuals./= deceased. *Genotyped individuals.

were also recorded. Repeat expansions in the SCA1, 2, 3, 6, 7, 8, 12, 17 genes and conventional mutations in the SCA13, 14, 21, 28 genes were ruled out. All individuals gave their written informed consent to participation in the study.

2.2. Cognitive and behavioral measures

Twelve affected individuals underwent a neuropsychological evaluation. Given that some individuals had trouble reading and writing (due to learning disabilities and ataxia), an adapted testing procedure was mainly focused on non-verbal tests. Overall cognition was assessed with the Montreal Cognitive Assessment (MoCA). Raven's colored progressive matrices (PM47) were used to assess abstract reasoning and non-verbal intelligence. Attention and working memory were assessed with the forward and backward Corsi block-tapping test. We used simple and choice reaction time tests to assess vigilance, inhibition and divided attention. Visuo-spatial learning and memory performance were tested with the 10/36 spatial recall test. Executive function was analyzed with the Tower of London test, with four difficulty levels: (i) "3N" items, where the goal can be achieved in a minimum of 3 moves, (ii) "5N" items, where the goal can be achieved with a minimum of 5 moves, and where initially no bead can be brought directly to its final destination, (iii) "5I+" items, where the goal can be achieved with a minimum of 5 moves, and one bead can be immediately moved into its final destination, (iv) "5I-" items, where the goal can be achieved with a minimum of 5 moves, and one bead can be immediately moved into its final destination but will immediately prevent the solution of the problem. Performance was assessed by the mean number of moves at each difficulty level. Given the individuals' ataxia, the test was not timed. A 15-item version of the Benton judgment of line orientation (BJLO) test was used to assess visuo-spatial abilities. Receptive language abilities were rated with the Token test. The Neuropsychiatric Inventory was administered to determine the presence and severity of behavioral disorders.

2.3. Molecular analysis

Genomic DNA was isolated from peripheral blood, according to standard procedures. Targeted, next-generation sequencing of 24 genes involved in dominant hereditary ataxia was performed in the probands and in one healthy sibling (Data S1). Variations were confirmed by Sanger sequencing. Repeat expansion in the SCA10 gene was ruled out using a fluorescent repeat-primed PCR assay [7].

3. Results

3.1. Clinical features

The probands were referred to our clinic for gait disorders, poor balance and dysarthria. The family medical history was suggestive of an inherited disease with autosomal-dominant transmission. Table 1A summarizes the clinical characteristics of the 16 affected patients.

Eleven patients (68.8% of the carriers) developed a classic SCA19/22 phenotype, i.e. slowly progressing cerebellar ataxia with predominant gait impairment (Video 1 and 2). Poor balance was the first symptom to be identified. As the disease progressed, the patients developed gait disorders, dysarthria, nystagmus and then dysphagia. The estimated mean age at ataxia onset was 23.1 years (range: 2–66). Mild Parkinsonism was observed in eight patients (50% of the carriers) (III-6, III-9, IV-5, IV-6, IV-9, V-2 in family A and II-2, III-2 in family B).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2017.09.014.

The phenotype was dominated by epilepsy in five younger patients (31.3%). In family A, the patients IV-10, V-2, V-4 and V-6 suffer from epilepsy with a mean age at epilepsy onset of 5.3 years

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