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PDE10A mutation in two sisters with a hyperkinetic movement disorder - Response to levodopa

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PDE10A (OMIM *610652, #616921, #616922) encodes phosphodiesterase 10A, which regulates the intracellular concentration of cAMP and cGMP in medium spiny neurons (MSNs) of the corpus striatum (for review [1]). Both recessive [2] and dominant mutations [3] in *PDE10A* have recently been found to cause an infantile/childhood-onset hyperkinetic movement disorder. In comparison to patients with dominant *PDE10A* mutations, the eight reported patients of two families with homozygous *PDE10A* mutations showed no striatal lesions on MRI but a more severe clinical presentation with a generalized hyperkinetic movement disorder characterized by limb and orofacial dyskinesia within the first six months of life, and mild cognitive impairment in some patients [2]. Here we describe two sisters with a novel homozygous *PDE10A* mutation, presenting with a generalized hyperkinetic movement disorder. This is the first report showing improved clinical outcome of levodopa therapy.

The two sisters of consanguineous healthy Afghan parents were affected by marked muscular hypotonia, ongoing motor restlessness, and hyperkinetic and choreatic movements (Video – segment 1). In the older sister, movement abnormalities and delay in motor development had first been noticed at the age of seven months. At age 6 years, when first presenting at our hospital, she was wheelchair-bound or moved by crawling. She could speak a few words and communicated with gestures as well. Furthermore, she had difficulties to thrive, microcephaly, underweight and small stature. She was reported to have shown repeated generalized seizures at the age of one year. Whereas MRI and MR spectroscopy performed at age 8 years did not show basalganglia abnormalities, bilateral mesial temporal sclerosis more prominent on the right side was detected (Fig. S1). Repeated electroencephalography (EEG) did not show abnormal findings. The younger 10-month-old sister showed inability to sit, axial hypotonia, difficulties to hold her head upright and problems to thrive; EEG, brain MRI and MR spectroscopy were normal.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.02.007.

Whole exome sequencing studies in rare disorders were approved by the local ethics committee (EK302/16) and the parents of the two girls provided written informed consent for whole exome sequencing and publication of the videos including online publication of the video material.

Whole exome sequencing (Illumina Nextera Rapid Capture Exome v.1.2, Illumina San Diego, CA, USA) in both sisters revealed a novel potentially deleterious homozygous missense mutation (NM_001130690.2:c.2024T > C, p.(Leu675Pro)), absent from public databases such as gnomAD, ExAC and 1000 Genomes Project, predicted to be damaging by several in silico prediction tools (PolyPhen-2: 1, SIFT: 0, CADD Phred score: 29,8 etc.), and affecting a highly conserved amino acid residue in *PDE10A* (Fig. 1C and Table S1). Subsequent segregation analysis in the family confirmed both parents and the unaffected brother as heterozygous carriers. (Fig. 1A). In the older sister no other rare homozygous variant that might explain the clinical finding of mesial temporal sclerosis could be identified.

Combined levodopa/decarboxylase inhibitor treatment was initiated and proved to be effective in both sisters leading to a reduction of chorea, hyperkinesia and motor restlessness (Video – segment 2). In the older sister therapy was started with 0,67/0,17 mg/kg/day levodopa/benserazide divided into two doses and augmented to 1/0,25 mg/kg/day levodopa/benserazide divided into three doses within three weeks. In the younger sister therapy was started with 0,63/0,16 mg/kg/day levodopa/carbidopa divided into two doses but had to be reduced to 0,25/0,06 mg/kg/day levodopa/carbidopa divided into two doses because of drowsiness. In both sisters a beneficial response was initially observed within two weeks after treatment had been started.

While reported bi-allelic *PDE10A* missense mutations led to reduced protein levels of PDE10A in the striatum and were localized in the GAF-A domain of PDE10A [2], autosomal dominant mutations resulted in reduction of enzymatic activity by altering the cAMP binding properties of PDE10A and were localized in the GAF-B domain [3]. In contrast, the mutation in our family is located in the catalytic domain of PDE10A (Fig. 1B), indicating that mutations in all domains of PDE10A are relevant for a hyperkinetic movement disorder.

Mesial temporal sclerosis has not previously been described in patients with *PDE10A* mutations. It represents the most common cause of temporal lobe epilepsy but can be found infrequently in patients without seizures [4]. While PDE10A expression is upregulated in patients with temporal lobe epilepsy [5], two different PDE10A inhibitors show opposing i.e. proconvulsant and anticonvulsant effects, respectively, in different animal models [5,6]. Mesial temporal sclerosis, importantly, was not present in the younger child and in the older girl it

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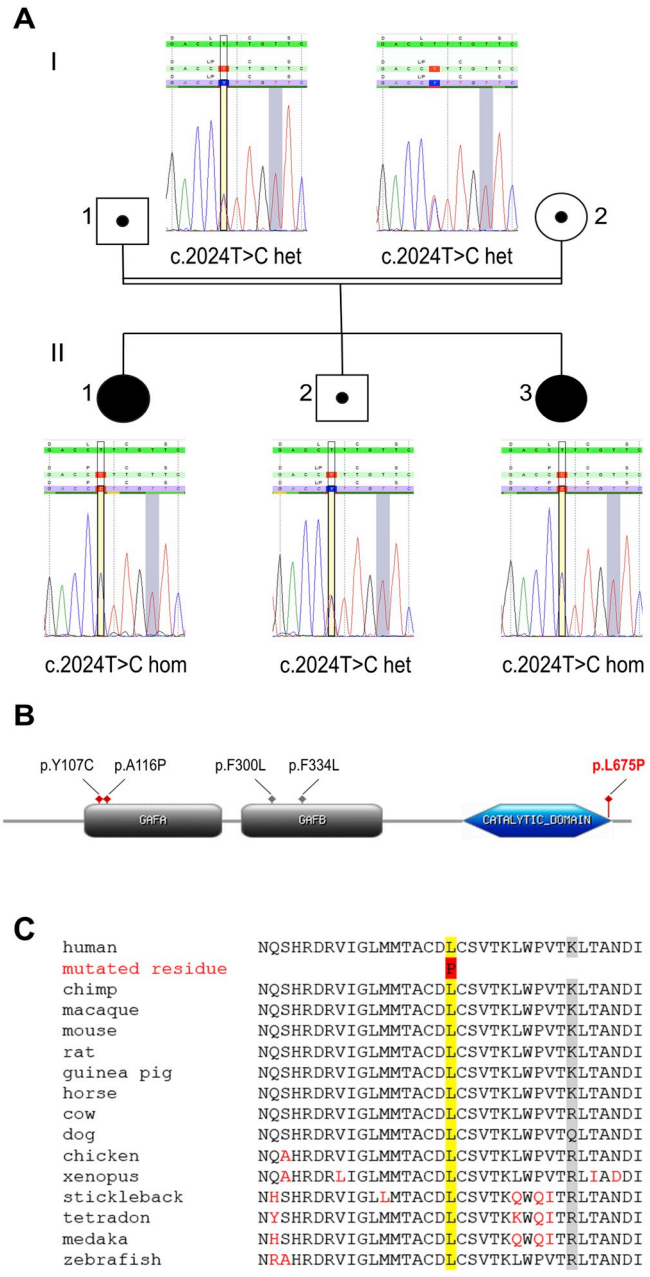

Fig. 1. Family tree and genetic studies (A) Pedigree of the family and segregation analysis by Sanger sequencing. **(B)** Schematic diagram of PDE10A. In contrast to the reported autosomal recessive mutations in the GAF-A domain (red) and the reported autosomal dominant mutations in the GAF-B domain (gray) the identified mutation in our family is located in the catalytic domain of PDE10A**. (C)** The affected amino acid is highly conserved across species. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was not associated with a severe epilepsy phenotype. Thus, its clinical relevance and its causal relation with the identified *PDE10A* mutation remains elusive at the moment, necessitating further studies of individuals with *PDE10A* mutations.

Diminished phosphodiesterase 10A activity in patients with *PDE10A* mutations predominantly affects striatal medium spiny neurons (MSNs). Other genetic causes of early-onset hyperkinetic movement disorders also involving striatal MSNs include benign hereditary chorea due to *TITF1* mutations [7], *de novo* or dominantly inherited mutations in adenylyl cyclase 5 (*ADCY5*) [8] and recessive mutations in phosphodiesterase 2A (*PDE2A*) [9]. While PDE10A and PDE2A regulate degradation of cAMP, ADCY5 catalyzes cAMP formation and pathogenic *ADCY5* mutations seem to increase cAMP synthesis [10]. This indicates that regulation of cAMP plays an important role in the pathophysiology of genetic hyperkinetic movement disorders [2,3]. For patients with benign hereditary chorea levodopa therapy has been shown to effectively reduce hyperkinetic movements [11] but to our knowledge has not been tested in patients with a hyperkinetic movement disorder due to mutations in phosphodiesterases. Combined levodopa/decarboxylase inhibitor therapy also showed effectiveness in both here reported children leading to a reduction of hyperkinetic symptoms. Interestingly Pde10a-knock-out mice and Pde10a-KI mice carrying a homozygous *PDE10A* mutation show a hypokinetic phenotype [2,12]. Furthermore, pharmacological inhibition of PDE10A seems to predominate in indirect pathway neurons (for review [1]). In contrast, the observed hyperkinetic phenotype in humans may suggest that *PDE10A* mutations predominantly affect D1 dopamine receptor-expressing MSN of the direct pathway and their promoting effect on motor function. However, even if it is well known that the activity of cAMP/PKA signaling is modulated by dopamine in basalganglia

circuits, complex regulation of cAMP in MSN in humans with *PDE10A* mutations and the effect of levodopa/decarboxylase inhibitor needs to be further elucidated.

Declarations of interest

None.

Ethics

Whole exome sequencing studies in rare disorders were approved by the local ethics committee, EK302/16 (Untersuchung der genetischen Grundlagen ungeklärter monogener Erkrankungen)". Written informed consent was provided by the patients' parents for publication of photographs and videos.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.007.

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