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LETTER TO THE EDITORS

Atypical parkinsonism with severely reduced striatal dopamine uptake associated with a 16p11.2 duplication syndrome

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Dear Sirs,

Copy number variants (CNVs) at the chromosome 16p11.2 are among the most frequent risk factors for neurodevelopmental and psychiatric conditions [1], such as autism spectrum disorder [2], schizophrenia [3] or intellectual impairment [4]. A link to parkinsonism has been discussed based on a single report of a child with an atypical combination of paroxysmal kinesiogenic dyskinesia (PKD) and parkinsonism carrying a 16p11.2 *microdeletion* [5]. Yet, confirmatory evidence from a second independent case with a 16p11.2 CNV as well as more direct evidence for nigrostriatal vulnerability is still missing. Moreover, it remains unclear whether parkinsonism might be associated only with 16p11.2 microdeletions or also with other 16p11.2 CNV types, as different 16p11.2 CNVs can be associated with different phenotypes [1]. We here show that parkinsonism and nigro-striatal vulnerability can be associated with a 16p11.2 *duplication*.

Case Report. A 69-year-old male with negative family history for neurological disease presented with mental retardation (IQ: 66) since early childhood and early-onset parkinsonism starting at age 35 years. Parkinsonism initially manifested with resting and postural tremor of the hands, later spreading to the lower extremities, face and chin. Right-sided rigidity and bradykinesia as well as reduced speech modulation, dysphagia and pseudohypersalivation were noticed at age 69 years (MDS-UPDRS III motor score: 27 points). Additionally, complicating left-sided spasticity was overt. Propranolol and levodopa had no therapeutic effect. Cerebral MRI showed slight frontal and parietal atrophy (Fig. 1c–e). Genome-wide array-based comparative genomic hybridization (Array-CGH) revealed a 544 kb 16p11.2 duplication (3 copies) including 29 genes (Supplement 1). Screening for additional genetic modifiers by NeuroChip array unravelled a N370S *GBA* variant, an established but weak risk variant for parkinsonism [5–7]. ^{123}I-Ioflupane-SPECT (FP-CIT; DaTSCAN™) showed highly reduced striatal dopamine transporter activity, particularly pronounced on the right side (Fig. 1).

Discussion. We here show that early-onset parkinsonism and nigrostriatal vulnerability can be associated with a 16p11.2 duplication. This finding provides the first confirmation of the link between parkinsonism and 16p11.2 CNVs, and demonstrates that it can also be associated with 16p11.2 *duplications*. Importantly, early-parkinsonism does not seem to present an isolated, distinct presentation but rather one end of a continuous gradual spectrum of 16p11.2 disease. Tremor, reduced agility and monotonic articulation are common frequent neurologic features in 16p11.2 duplication syndromes, as demonstrated by the largest study to date evaluating 110 carriers of 16p11.2 duplications [4]. This points to a general nigrostriatal vulnerability in 16p11.2 disease, with full-blown parkinsonism representing one end of this spectrum.

The N370S *GBA* variant observed here presents an only weak additional risk modifier as it is (i) relatively frequent in the general population (MAF: 0.2%), (ii) has a strongly reduced penetrance (5–10%) with a risk of 1% to show parkinsonism at age 65 (i.e. 90–95% of subjects with this variant do not show parkinsonism at all, thus the variant

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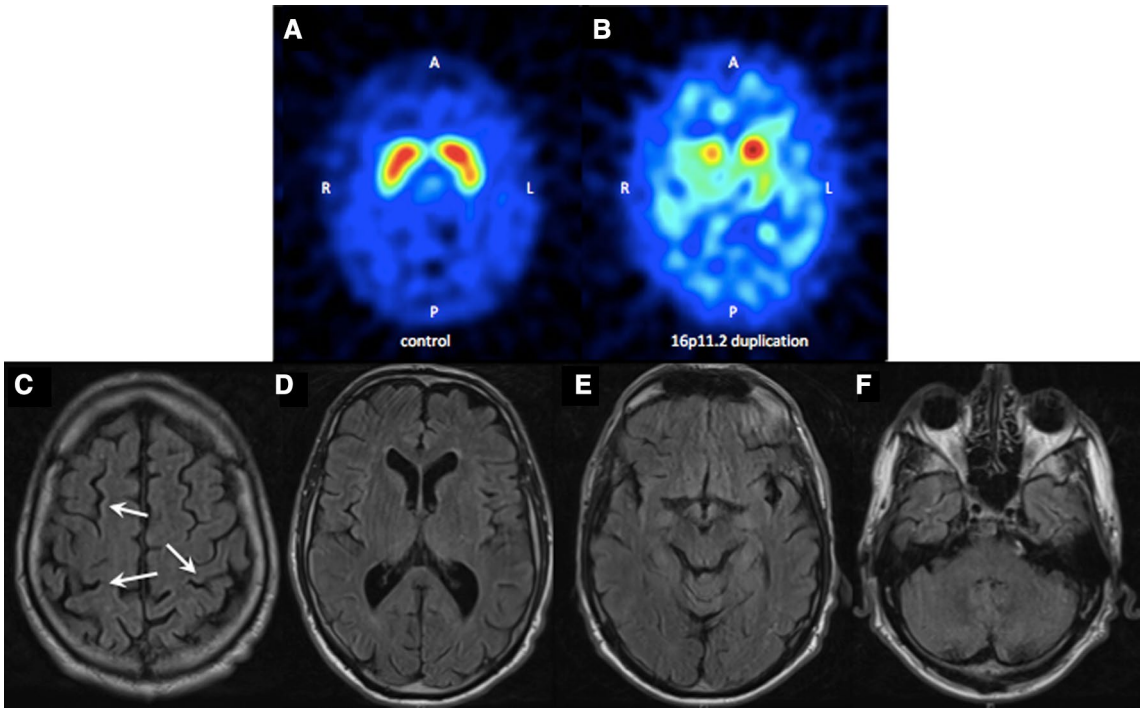

Fig. 1 123I-Ioflupane-SPECT (FP-CIT; DaTSCAN™) and MRI of the patient with 16p11.2 duplication syndrome: severely reduced dopamine transporter activity of the striatum, particularly pronounced on the right side (**b**) compared to an age-matched, healthy individual (**a**). Representative MRI sections demonstrating slight frontal and parietal atrophy, but no other structural abnormalities (**c**–**f**). *R* anterior, *P* posterior, *R* right, *L* left

alone cannot explain the occurrence of parkinsonism) [5], and (iii)—if parkinsonism occurs—manifests at an average age of 55 years, while the young onset of age 35 years in our patient is not well explained by this variant [5–7].

The exact gene (or combination of genes) responsible for causing parkinsonism within the 16p11.2 region still remains to be determined. Out of the 29 genes (Supplement 1), at least 3 genes in this region are involved in neuronal pathways: (i) *QPRT* encodes the QPRTase catabolising quinolinate, implicated in neurodegenerative processes; (ii) *DOC2A* is implicated in neurotransmitter release; and (iii) *SEZ6L2* plays a role in neuronal maturation and plasticity. Thus, further analyses of the 16p11.2 genomic region might reveal new genes conferring susceptibility to parkinsonism, which—if combined with other genetic modifier alleles (like the N370S *GBA* variant observed here)—might jointly give rise to (early-onset) parkinsonian phenotypes.

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Compliance with ethical standards

Conflicts of interest None to declare.

Ethical standards The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All individuals gave written informed consent prior to their inclusion in the present study.

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