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Letter to the Editor

Analysis of the *TMEM230* gene in familial Parkinson's disease from south Italy

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Dear Editor,

To date, more than 20 genes have been reported as involved in familial Parkinson's disease (PD). Recently, Deng et al. reported c.422G > T (p.R141L) variant in the *TMEM230* gene in a large Canadian Mennonite family, in which another mutation (p.N855S) in the DNAJC13 gene had already been reported [1]. Moreover they found two other TMEM230 variants (p.Y92C and p.*184PGext*5) in 2 North American PD patients and one variant (p.*184Wext*5) in 9 PD patients from 7 Chinese families [2]. *TMEM230* encodes transmembrane protein 230, which belongs to the TMEM134/TMEM230 family, and it is involved in endocytosis and trafficking secretory/recycling vesicles. It is located on chromosome 20p13-p12.3 and contains five exons. Disease-linked mutations impair normal synaptic vesicle trafficking, and the presence of TMEM230 protein in alpha-synuclein-positive Lewy bodies and Lewy neurites in midbrain and neocortex sections from sporadic PD cases, gave supporting evidence for a role of this gene in PD pathology. However, in 15 published studies, only approximately 0.28% PD patients were mutated in the *TMEM230* gene [3].

In order to clarify the relationship between *TMEM230* and the PD population of southern Italy, we performed a mutational screening of this gene in 168 autosomal dominant familial PD patients, and a control group consisting of 500 subjects from the same geographical area. Autosomal dominant was defined by the presence of PD in at least one other first, second, or third degree relative. All subjects, both patients and controls, were recruited at the Institute of Neurology, Department of Medical Sciences, University of Magna Graecia, Catanzaro. The local ethics committee approved the study and informed consent was obtained from all participants. Genomic DNA was extracted from peripheral blood by a standard method. The presence of mutations of other genes involved in PD (*SNCA, LRRK2, VPS35, CHCHD2, DNAJC13, PARK2, PINK1* and *DJ1*) was previously excluded by sequencing analysis. All the 5 exons of *TMEM230* (NM_001009923) and intron-exon boundaries region were sequenced using an ABI 3500 Genetic Analyzed (Life Technologies, Carlsbad, CA, USA).

None of the three variants identified by Deng in TMEM230 was detected in our PD group. The screening highlighted the presence of four synonymous variants (rs186628284, rs6116651, rs763383477, rs6107576) with the same frequency in both population (PD cohort and control subjects) and the p.Ile125Met (c.375A > G, rs148033002) missense variant in a 64-years old woman (Supplementary Table 1). The patient (AAO: 39 years) who carries this variant in heterozygous state presented bradykinesia, rigidity and postural instability with a good response to levodopa treatment. Her family history was positive, with her mother and two sisters diagnosed with PD (Fig. 1). The genetic testing was extended to three sisters (II-3, II-4, II-5) of the proband and their mother (I-2), and it confirmed the segregation of the c.375A > G variant in the affected members of the family.

This variant was already described by Tejera-Parrado et al. [4], who identified it in a PD familial patient and a control from southern Spain. Then they concluded that p.Ile125Met is not related with the development of PD. Moreover, also Deng et al. [2] reported the rs148033002 in two PD cases and three house controls. However, the p.Ile125Met was not present in 500 healthy subjects from south Italy. A low MAF (0.001) was revealed by GnomAD, 1000 Genome database, dbSNPs and Exome Variants Server. The amino acidic alignment showed that the Isoleucine at position 125 is evolutionary conserved in Vertebrates (Fig. 1c). Functional prediction analysis by PolyPhen2, (http://genetics.bwh.harvard.edu/pph2/) and Mutation Taster, (http://www.mutationtaster.org/) revealed that p.Ile125Met variant can probably have a damaging role, while for PROVEAN (http://provean.jcvi.org/index.php) it is neutral. Therefore, these predictions, included the segregation of the variant with the disease in the family, may support the hypothesis that p.Ile125Met is a variant of susceptibility for the development of Parkinson's disease.

Before this study, our familial PD cohort (168) was examined for the entire coding region of the *DNAJC13* gene [5] and the family here reported with p.Ile125Met in *TMEM230* was negative for the screening. Further studies are needed to evaluate the role of both genes (*TMEM230* and *DNAJC13*) in the pathogenesis of Parkinson's disease.

Declaration of Competing Interest

The authors declare no financial or other conflict of interests.

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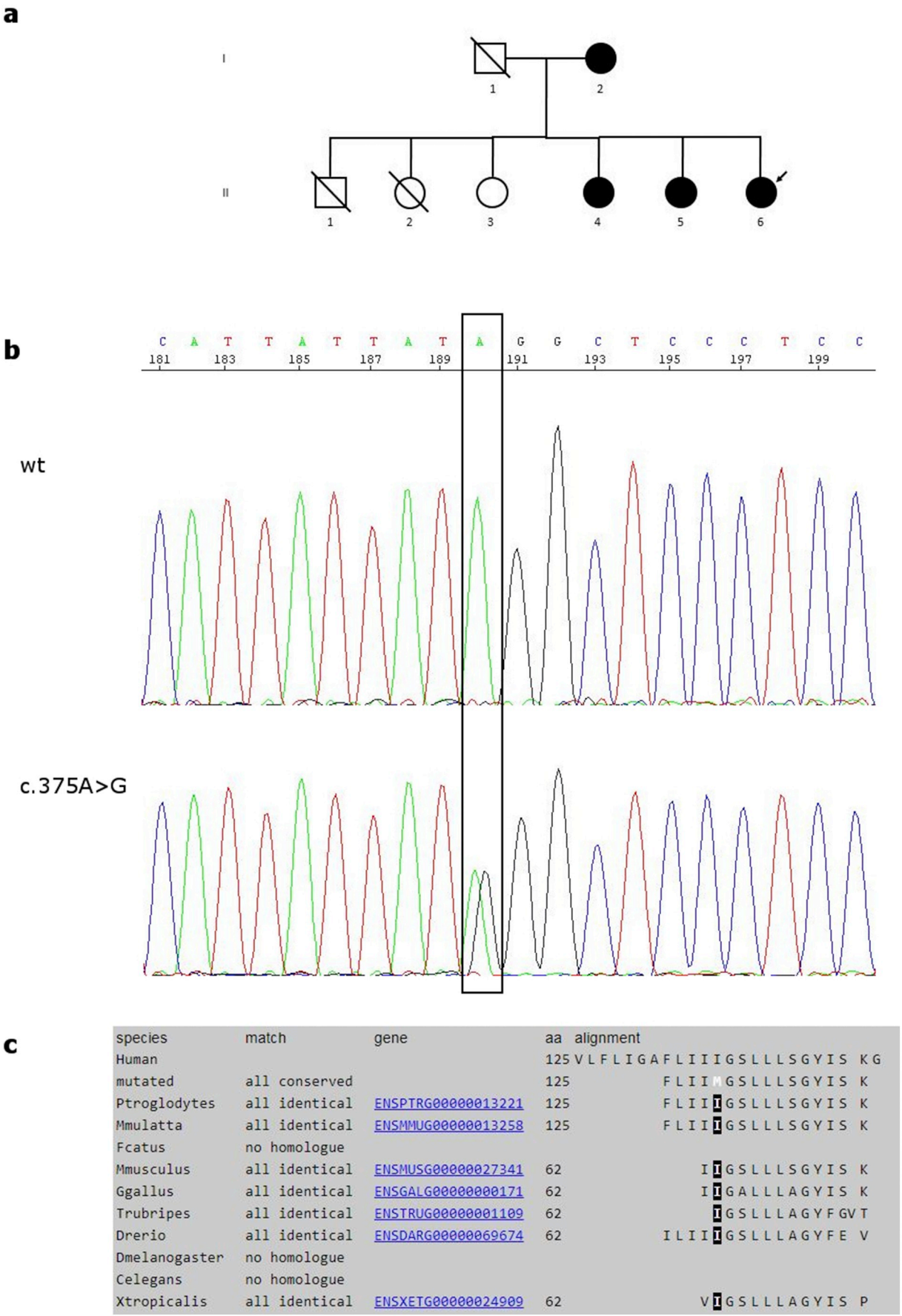

species	match	gene	aa	alignment
Human			125	V L F L I G A F L I I I G S L L L S G Y I S K G
mutated	all conserved		125	F L I I M G S L L L S G Y I S K
Ptroglodytes	all identical	ENSPTRG00000013221	125	F L I I I G S L L L S G Y I S K
Mmulatta	all identical	ENSMMUG00000013258	125	F L I I I G S L L L S G Y I S K
Fcatus	no homologue			
Mmusculus	all identical	ENSMUSG00000027341	62	I I G S L L L S G Y I S K
Ggallus	all identical	ENSGALG00000000171	62	I I G A L L L A G Y I S K
Trubripes	all identical	ENSTRUG00000001109	62	I G S L L L A G Y F G V T
Drerio	all identical	ENSDARG00000069674	62	I L I I I G S L L L A G Y F E V
Dmelanogaster	no homologue			
Celegans	no homologue			
Xtropicalis	all identical	ENSXETG00000024909	62	V I G S L L L A G Y I S P

Fig. 1. a) Pedigree of the patient carrying the c.375A > G (p.Ile125Met) variant in the TMEM230 gene; b) Electropherogram shows the wildtype sequence (above) and the c.375A > G variant in heterozygous state (below); c) Alignment of TMEM230 proteins shows high evolutionary conservation of Isoleucine 125.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.017.

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