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Involuntary moaning in a Hispanic family with eight affected members

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ABSTRACT

Involuntary moaning has been reported in sporadic cases of neurodegenerative diseases. A five-generation Hispanic family with eight members exhibiting involuntary moaning, most of whom with isolated moaning in the absence of any additional neurological disorder carried a missense variant in the NEFH gene segregating in the family.

Involuntary moaning is characterized by low-tone, purposeless and inappropriate vocalizations. It has been reported in advanced stages of neurodegenerative disorders such as Parkinson's disease (PD), or progressive supranuclear palsy, neurometabolic and functional neurological disorders [1,2, Supplementary Table 1]. Although the etiology is largely unknown, it is thought to be caused by disinhibition of frontal subcortical neuronal circuits involved in the generation of non-verbal vocalizations or to be induced by drugs (L-dopa, neuroleptics) [1,2].

We here report a family of Hispanic ancestry and eight members exhibiting involuntary moaning. To date, only sporadic cases have been described in the literature. Because of its familial occurrence and segregation, we aimed to elucidate a presumably monogenic cause for the moaning phenotype in this family. Neurologic examinations were conducted in six family members, including five affected (Fig. 1A). In all affected members, moaning occurred intermittently at a variable daily frequency, lasted many seconds, was not related to pain, and was trigged by stress in one patient. Moaning occurred in different situations, e.g. at rest or while doing daily activities like cooking, watching TV, or using the computer or the cell phone. There was no specific context dependency or distractibility and moaning was not present during sleep. The index patient had an 8-year history of mild L-dopa-responsive PD without cognitive impairment. Moaning manifested during adolescence, more than 40 years prior to the diagnosis of PD. Her deceased mother, maternal grandfather, three sons, one daughter and one grandchild developed moaning during infancy or adolescence. None of them had parkinsonism or non-motor features suggestive of synucleinopathy or other neurological symptom or disorder, like akathisia or tics at the time of examination (age <50 years). Electromyography and motor and sensory nerve conduction studies of the four limbs were performed in the in the index patient and her daughter ruling out peripheral neuropathy.

To identify a possible genetic cause for the seemingly dominantly inherited moaning phenotype in this family, exome sequencing was carried out in three affected family members, that revealed a heterozygous missense variant (c.735C > G, p. Ile245Met; Fig. 1B) in the *Neurofilament Heavy Polypeptide* (*NEFH*) gene that segregated with the moaning phenotype (for details see Supplementary Table 2). Heterozygous mutations in *NEFH* gene are known to cause axonal Charcot-Marie-Tooth disease type 2CC (MIM #616924) and may be potentially related to PD [3], and amyotrophic lateral sclerosis [4].

Involuntary moaning has so far been predominantly described in patients with parkinsonism [1,2] (Supplementary Table 1), raising the question if there is a link between moaning and PD in the index patient who presents with both. In the previously reported cases of involuntary moaning and parkinsonism, moaning usually occurred in advanced stages of the disease in late adulthood and often appeared to correlate with cognitive impairment [1,2]. In contrast, in our patient, moaning manifested forty years prior to the onset of PD. In all affected members, the age at onset of moaning was in adolescence or infancy, none of the patients presented with cognitive impairment and the majority of individuals with moaning did not have PD. Of note, individuals in the two younger generations (age at examination: 35–48 years) had not yet reached the age at PD onset in the index patient (61 years) and may still develop PD. It is therefore unlikely that moaning and PD co-occur in the particular case based on a shared etiology and that moaning is a prodromal manifestation of PD, of which there is no evidence to date. Moaning has furthermore been reported in association with L-dopa or in cases of neuroleptic-induced tardive akathisia [1,2]. Since the index patient is the only one of the affected members taking L-dopa and the use of neuroleptic medication has not been reported, moaning seems unlikely to be induced by drugs in this family.

Assuming a possible monogenic cause for the moaning phenotype in this family, we identified a rare missense variant in the *NEFH* gene. As heterozygous mutations in this gene are known to cause axonal Charcot-Marie-Tooth disease type 2CC, two carriers were tested for neuropathy, which was not found. Thus, it remains elusive whether the *NEFH* variant is causative for the moaning in this family, which would add *NEFH* to the growing list of genes with pleiotropic disease manifestations. Thus, further genetic studies are warranted. Alternative to a monogenic cause in our family, moaning may possibly be explained by (poly)genic contributions, as has been discussed for several stereotypic behaviors including tics [5].

With the report of the first case of familial moaning in a large Hispanic family and our genetic findings, we hope to raise awareness amongst clinicians for this seemingly rare clinical presentation, since the clinical and genetic evaluation of further families with similar symptoms

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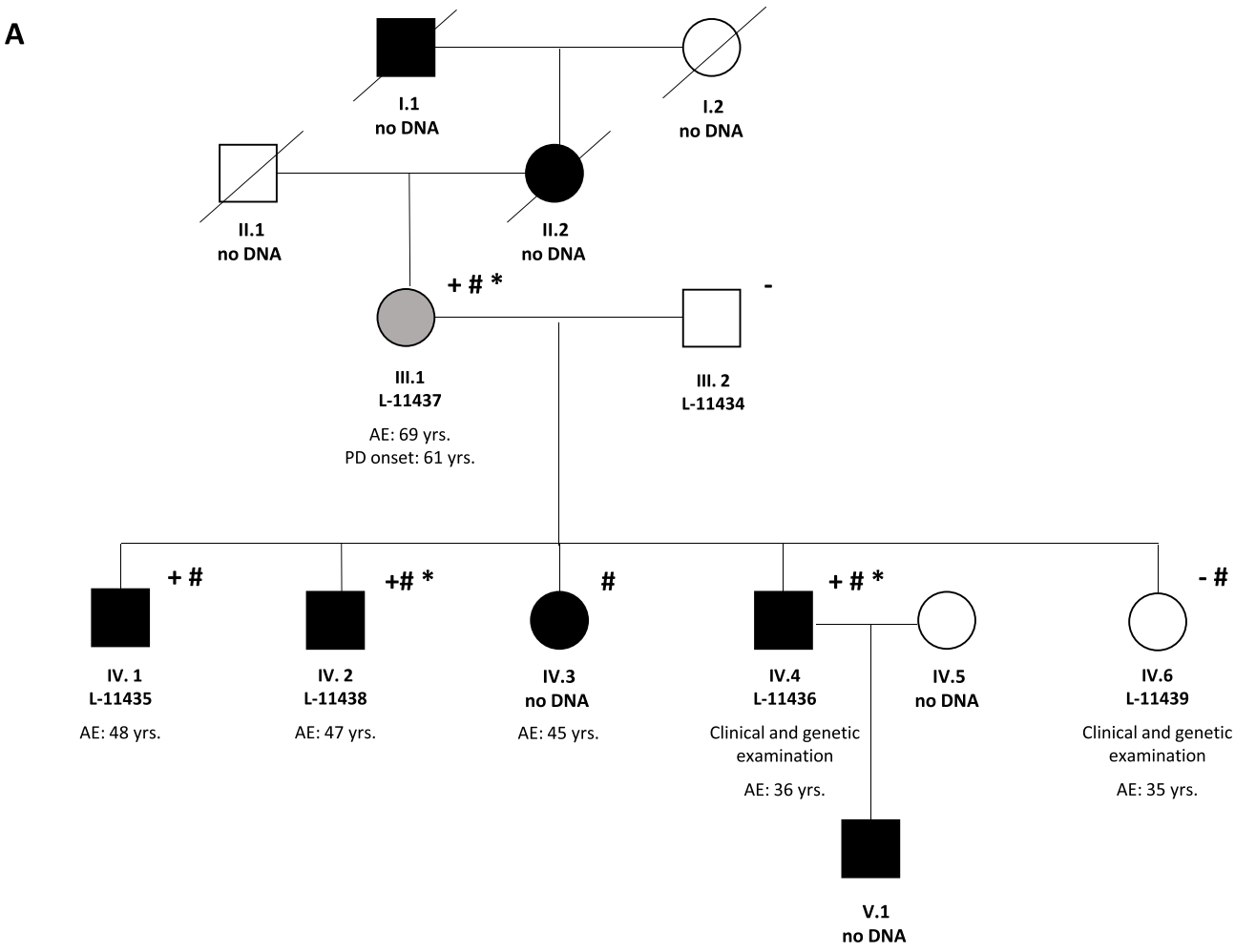

Fig. 1A. Segregating *NEFH* variant in a five-generation family with moaning. Family pedigree. Family members with moaning are indicated by black filled symbols, the index patient with moaning and Parkinson's disease (PD) is shown in gray, unaffected family members with an unfilled symbol. Deceased individuals are marked with a dash. A sample ID (L number) is given for individuals for whom DNA was available and segregation analysis by Sanger sequencing was conducted. The clinically examined individuals are indicated by a hash sign. The individuals with whom exome sequencing was performed are indicated by an asterisk sign. Mutational status for *NEFH* is indicated by a plus sign (=mutation present) or a minus sign (=mutation absent). For all the clinically examined individuals age at examination (AE) is provided.

B

Chr:Pos (hg19)	Gene	Variant (NM_021076)	Variant (NP_066554)	Mutation-Taster	CADD score v1.4	GnomAD frequency	GnomAD Z-score (missense) NEFH
22:29,876,986	*NEFH*	c.735C>G	p.Ile245Met	Disease-causing	22.4	0	0.52

Fig. 1B. Specifications of the identified candidate gene.

is crucial for the identification of possible underlying molecular mechanisms.

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Ethical statement

This study was approved by the local Institutional Review Board and informed consent was obtained. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Authors' contributions

All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.03.023.

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