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# Clinical and genetic analysis of a family with two rare reflex epilepsies

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ABSTRACT

*Purpose:* To determine clinical phenotypes, evolution and genetic background of a large family with a combination of two *unusual* forms of reflex epilepsies.

*Method:* Phenotyping was performed in eighteen family members (10 F, 8 M) including standardized EEG recordings with intermittent photic stimulation (IPS). Genetic analyses (linkage scans, Whole Exome Sequencing (WES) and Functional studies) were performed using photoparoxysmal EEG responses (PPRs) as affection status.

*Results:* The proband suffered from speaking induced jaw-jerks and increasing limb jerks evoked by flickering sunlight since about 50 years of age. Three of her family members had the same phenotype. Generalized PPRs were found in seven members (six above 50 years of age) with myoclonus during the PPR.

*Evolution was typical*: Sensitivity to lights with migraine-like complaints around adolescence, followed by jerks evoked by lights and spontaneously with dropping of objects, and strong increase of light sensitivity and onset of talking induced jaw jerks around 50 years.

Linkage analysis showed suggestive evidence for linkage to four genomic regions. All photosensitive family members shared a heterozygous R129C mutation in the *SCNM1* gene that regulates splicing of voltage gated ion channels. Mutation screening of 134 unrelated PPR patients and 95 healthy controls, did not replicate these findings.

*Conclusion:* This family presents a combination of two rare reflex epilepsies. Genetic analysis favors four genomic regions and points to a shared *SCNM1* mutation that was not replicated in a general cohort of photosensitive subjects. Further genetic studies in families with similar combination of features are warranted.



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## 1. Introduction

Epileptic jaw jerks (orofacial myoclonus) provoked by reading is a rare, but known syndrome [1]. Isolated speaking-induced facial myoclonic jerks *without* provocation by reading and writing is even more special [1,2]. We describe a family with members who have both speaking induced jerks and reflex photosensitivity still active above 50 years of age; a phenotype that to our knowledge has never been reported.

Clinical photosensitivity and the photoparoxysmal EEG response (PPR), predominantly expressed around adolescence a female predominance. It is more common in patients with myoclonic forms of generalized epilepsies and seen in only 1% of non-epileptic controls [3,4]. A feature of PPR is the autosomal dominant segregation in families. Linkage and candidate gene studies have been performed for PPR but findings indicate that the epilepsy background of families determines which PPR locus is linked [5–8]. We describe an unique family to delineate its clinical expression and part of its genetic background.

## 2. Material and methods

### 2.1. Clinical assessments

The Dutch Caucasian family was ascertained through a single patient (II-2). After informed consent, eighteen family members (10 F, 8 M) were investigated, with medical history taking and obtainment of medical record data. Each subject underwent an EEG with standardized intermittent photic stimulation (IPS) using a Grass PS33 stimulator. Flash frequencies were given in trains of 5 s ranging from 2 to 60 Hz with clinical symptoms noted [9]. See Fig. 1 for pedigree.

### 2.2. Genetic analyses

Family members with PPR were classified as affected. The remaining family members were set as unknown. Linkage analysis, was performed using Merlin 1.1.2 and standard settings. WES of proband and II-1 was done to identify the gene mutation underlying the trait. Furthermore, European and Australian individual PPR–IGE samples and healthy control samples were analyzed for that particular gene mutation. Functional studies were done with a splicing assay based on a minigene construct [10] (see Fig. 3) that was analyzed using qPCR and different expressions were tested using *t*-test of dCt values of replicates.

## 3. Results

### 3.1. Summary (of evolution) of phenotypes (see Table 1)

We ascertained eighteen family members (10 F, 8 M):

Four had speaking evoked jaw jerks, jerks in the limbs provoked by light, and generalized PPRs. Another four had jerks provoked by flickering lights and generalized PPRs. Six of eight family members of above 50 years still showed PPR. Seven of these eight photosensitive members showed myoclonus during the PPR. MRI and background EEGs were normal in nearly all; mostly

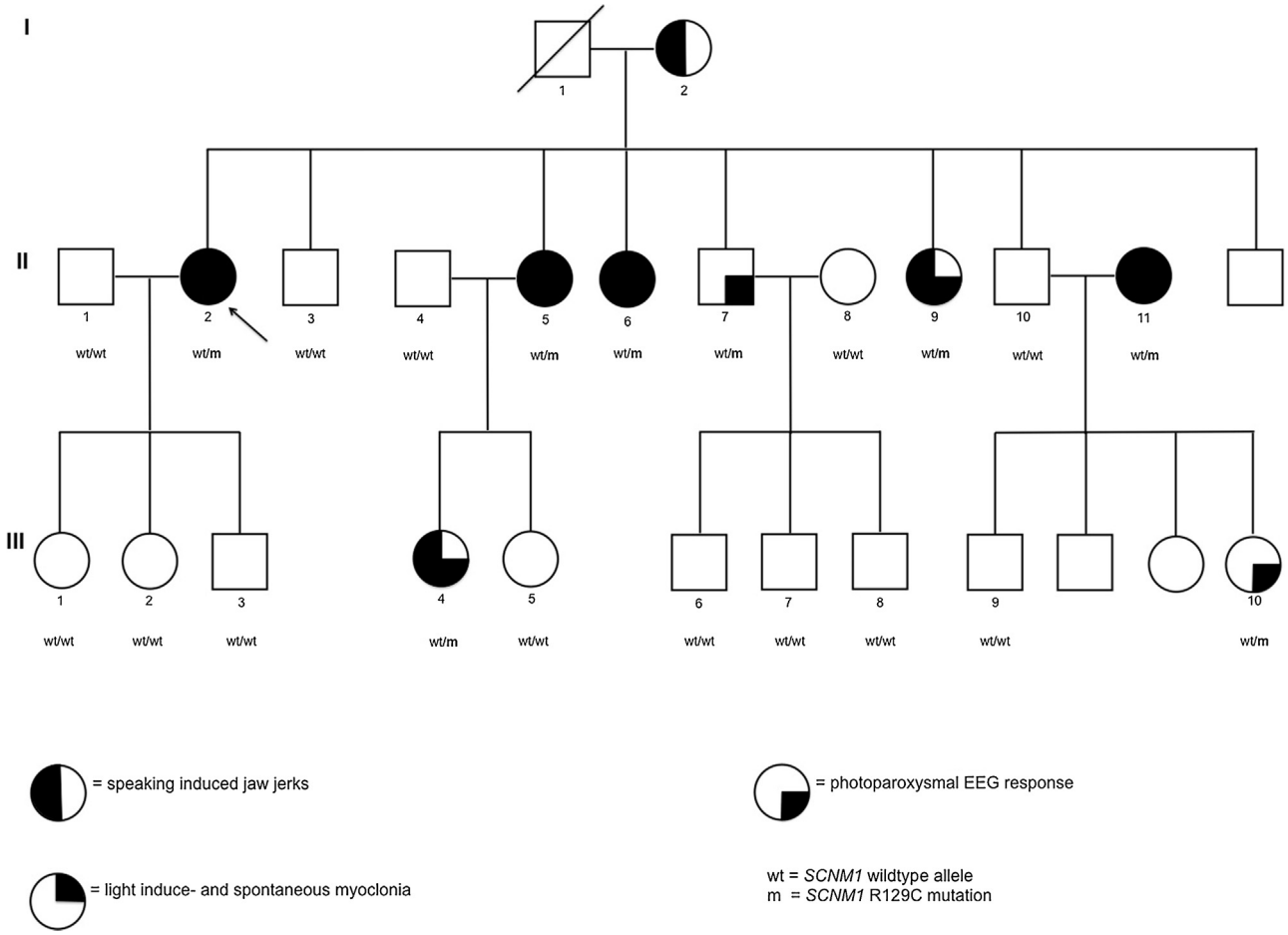


**Fig. 1.** Pedigree of the family with very rare combination of persistent photosensitivity and speaking induced jaw jerks.