



The clinical phenotype of autosomal dominant lateral temporal lobe epilepsy related to reelin mutations



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ABSTRACT

Objective: To describe the clinical phenotype of 7 families with Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE) related to Reelin (*RELN*) mutations comparing the data with those observed in 12 *LGI1*-mutated pedigrees belonging to our series.

Methods: Out of 40 Italian families with ADLTE, collected by epileptologists participating in a collaborative study of the Commission for Genetics of the Italian League against Epilepsy encompassing a 14-year period (2000–2014), 7 (17.5%) were found to harbor heterozygous *RELN* mutations. The whole series also included 12 (30%) *LGI1* mutated families and 21 (52.5%) non-mutated pedigrees. The clinical, neurophysiological, and neuroradiological findings of *RELN* and *LGI1* mutated families were analyzed.

Results: Out of 28 affected individuals belonging to 7 *RELN* mutated families, 24 had sufficient clinical data available for the study. In these patients, the epilepsy onset occurred at a mean age of 20 years, with focal seizures characterized by auditory auras in about 71% of the cases, associated in one-third of patients with aphasia, visual disturbances or other less common symptoms (vertigo or déjà-vu). Tonic-clonic seizures were reported by almost all patients (88%), preceded by typical aura in 67% of cases. Seizures were precipitated by environmental noises in 8% of patients and were completely or almost completely controlled by antiepileptic treatment in the vast majority of cases (96%). The interictal EEG recordings showed epileptiform abnormalities or focal slow waves in 80% of patients, localized over the temporal regions, with marked left predominance and conventional 1.5T MRI scans were not contributory. By comparing these findings with those observed in families with *LGI1* mutations, we did not observe significant differences except for a higher rate of left-sided EEG abnormalities in the *RELN* group.

Significance: Heterozygous *RELN* mutations cause a typical ADLTE syndrome, indistinguishable from that associated with *LGI1* mutations.

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1. Introduction

Autosomal dominant lateral temporal epilepsy (ADLTE) otherwise known as autosomal dominant partial epilepsy with auditory features (ADPEAF) is a genetic focal epileptic syndrome characterized by the onset at any age, but with preponderance in young adults, of focal seizures, either with or without impairment of consciousness or evolving to tonic-clonic seizures, with prominent auditory features or other

Abbreviations: RELN, reelin; *LGI1*, leucine-rich glioma inactivated 1; ADLTE, Autosomal Dominant Lateral Temporal lobe Epilepsy; ADPEAF, autosomal dominant partial epilepsy with auditory features.

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symptoms, such as aphasia, suggesting a lateral temporal onset [1,2]. The affected patients show normal neurological and cognitive status, normal conventional MRI, and belong to families where one or more members show a similar phenotype with evidence of autosomal dominant transmission. This condition has been associated with leucine-rich glioma inactivated 1 (*LGII*) gene mutations [3,4]. Since then, however, it has become clear that a considerable proportion of families, more than 50%, does not carry any *LGII* abnormality and remains genetically unsolved.

Following a collaborative study promoted by the Genetic Commission of the Italian League against Epilepsy, a large number of ADLTE families have been collected over the time and only one-third of them have been associated with *LGII* mutations [5].

Recently, heterozygous mutations of a second gene, reelin (*RELN*), have been detected in 7 previously unsolved (non-*LGII*-mutated) Italian ADLTE families through single nucleotide polymorphism-array linkage analysis and whole exome sequencing [6]. Interestingly, these ADLTE-related mutations significantly decreased serum levels of the secreted protein (reelin), suggesting an inhibitory effect of mutations on protein secretion.

To evaluate whether this new genetic basis (i.e. *RELN* heterozygous mutations) is associated with distinct clinical findings, we describe herein the clinical phenotype of such families comparing the data with those observed in 12 *LGII*-mutated pedigrees belonging to our series.

2. Material and methods

Seven *RELN* mutated families were discovered out of a series of 40 Italian families with ADLTE collected by epileptologists participating in a collaborative study of the Commission for Genetics of the Italian League against Epilepsy encompassing a 14-year period (2000–2014). The whole series also included 12 (30%) *LGII* mutated families and 21 (52.5%) non-mutated pedigrees.

The *RELN* mutated families were selected on the basis of the following criteria: presence of at least two family members concordant for unprovoked focal seizures with auditory auras or aphasic symptoms as first symptom, the absence of any known brain pathology, and normal neurological examination.

Each proband and affected individual were interviewed directly and examined by the referring clinician, either at the hospital or during a visit to the patient's home. The clinical interview included personal and family history, as well as details concerning the following features: age at onset of seizures, description of ictal semiology (obtained from the patient and an external observer), original patient's description of auras, types of stimuli if any triggering seizures, seizure occurrence in relation to the sleep–wake cycle, seizure frequency and response to treatment, and past and present therapy. Each affected individual also had a physical and neurologic examination. Medical records describing results of neurophysiologic, neuroimaging, and history data were collected whenever possible to supplement the clinical visits.

Routine and sleep (after afternoon nap) EEG studies as well as MRI scans were available in all the probands and the majority of affected individuals.

A genealogic tree was built for each pedigree, and overall data were reviewed by two epileptologists (RM, PS), who asked for additional information if needed, and who also analyzed original EEG and/or MRI findings if available.

After informed consent was obtained, blood samples were drawn from each proband and DNA was extracted using standard methods. The methods used to test *LGII* and *RELN* mutations have been described in detail elsewhere [5,6]. In brief, probands' DNA samples were tested for *LGII* mutations by direct sequencing and *LGII*-negative ADLTE families underwent either whole exome sequencing or targeted massive parallel sequencing to detect *RELN* mutations.

Because our study included published mutated families, we used the information from published pedigree figures. The 12 *LGII* mutated families have been described in detail elsewhere [2,5,7–13] whereas

the 7 pedigrees with *RELN* mutations have been reported limited only to the genetic findings [6].

Differences between the two sub-groups of families (harboring *RELN* and *LGII* mutations, respectively) in terms of clinical, neurophysiological and neuroradiological features were evaluated using the Fisher's exact test. Since this study included only retrospective/published clinical information, it did not require formal IRB approval.

3. Results

3.1. Clinical findings

We analyzed the clinical features of 7 *RELN* mutated families [6] and compared the results with those observed in 12 *LGII* mutated pedigrees [5,13]. The clinical, EEG, and neuroimaging findings of each family are reported in detail in Tables 1–2.

3.1.1. *RELN* mutated families

The 7 pedigrees included a total of 28 individuals (5 deceased) with seizures and/or epilepsy. Of these cases, one suffered from one single unprovoked seizure (of tonic–clonic type) and 3, belonging to two families, were quoted to have “epilepsy” but no additional clinical information was available. These patients were therefore not included in the overall clinical description, which was limited to 24 affected individuals (4 deceased).

The age of seizure onset ranged between 10 and 40 years, with a mean of 20.1 years.

Patients were classified as having genetic focal epilepsy ($n = 19$, 79%) or epilepsy with recurrent tonic–clonic seizures, undetermined whether focal or generalized, as the only seizure type ($n = 5$, 21%). All these 5 patients, however, were deceased and detailed information on clinical semiology, aside from a history of recurrent tonic–clonic seizures, was lacking.

Among the 19 patients with genetic focal epilepsy, 1 (5%) had only focal seizures evolving to tonic–clonic seizures, 3 (16%) had only focal seizures without impairment of consciousness, and 15 (79%) had both focal seizures evolving to tonic–clonic seizures and focal seizures with or without impairment of consciousness. Overall, focal seizures without impairment of consciousness were reported by 10 patients (41%), focal seizures with impairment of consciousness by 6 patients (25%) and focal seizures evolving to tonic–clonic seizures by 16 patients (67%). By adding those patients with tonic–clonic seizures undetermined whether focal or generalized, a total of 21 patients (88%) suffered from convulsive seizures.

Auras were reported by all the 19 patients with genetic focal epilepsy and allowed classifying seizures as focal.

Auditory auras were the most common type, being observed in 17 cases (71%) and occurring in isolation ($n = 11$, 46%) or preceding some kind of receptive aphasia ($n = 3$, 12%) and visual hallucinations ($n = 3$, 12%). Other symptoms following the auditory phenomena included vertigo, paroxysmal headache, déjà-vu, and epigastric discomfort.

Ictal aphasia without auditory symptoms occurred in the remaining 2 cases (8%).

Sudden noises and noisy environments could precipitate the seizures in 2 cases (8%) belonging to 2 families.

Seizures usually occurred at a low frequency, with tonic–clonic seizures being sporadic (1 to 3 times per year, either during wakefulness or sleep) and focal seizures with or without impairment of consciousness occurring at a variable frequency (ranging from a weekly to annual basis). Seizure outcome was available for 16 patients. Ten individuals (63%) were seizure-free for many years. Five patients (31%) continued to suffer from rare auditory auras and 1 patient (6%) still had many seizures per month. Interestingly, tonic-clonic seizures were completely controlled in all patients.

Routine and/or sleep deprivation EEGs were available in 15 out of 20 living subjects. The interictal recordings showed epileptiform abnormalities (usually spikes or sharp waves) or focal slow waves in 12 patients

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