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

Roberto Michelucci [a], Patrizia Pulitano [b], Carlo Di Bonaventura [c], Simona Binelli [d], Concetta Luisi [e], Elena Pasini [a,*], Salvatore Striano [f], Pasquale Striano [g], Giangennaro Coppola [h], Angela La Neve [e], Anna Teresa Giallonardo [c], Oriano Mecarelli [b], Elena Serioli [i], Emanuela Dazzo [i], Manuela Fanciulli [j], Carlo Nobile [i]

[a] IRCCS - Institute of Neurological Sciences of Bologna, Unit of Neurology, Bellaria Hospital, Bologna, Italy
[b] Department of Neurology and Psychiatry, University of Rome "Sapienza", Policlinico Umberto 1° Hospital, Roma, Italy
[c] Department of Neurological Sciences, University of Rome "Sapienza," Roma, Italy
[d] C. Besta Foundation Neurological Institute, Milano, Italy
[e] Neurology Clinic, University of Bari, Bari, Italy
[f] Department of Neurological Sciences, Federico II University, Napoli, Italy
[g] Muscular and Neurodegenerative Disease Unit, Institute "G. Gaslini," University of Genova, Italy
[h] Child and Adolescent Neuropsychiatry, Medical School, University of Salerno, Italy
[i] Section of Padua, Institute of Neurosciences, Consiglio Nazionale delle Ricerche, Padova, Italy
[j] Porto Conte Ricerche, Alghero, Italy

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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.

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

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 (LGI1) gene mutations [3,4]. Since then, however, it has become clear that a considerable proportion of families, more than 50%, does not carry any LGI1 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 LGI1 mutations [5].

Recently, heterozygous mutations of a second gene, reelin (RELN), have been detected in 7 previously unsolved (non-LGI1-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 LGI1-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%) LGI1 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 LGI1 and RELN mutations have been described in detail elsewhere [5,6]. In brief, probands' DNA samples were tested for LGI1 mutations by direct sequencing and LGI1-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 LGI1 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 LGI1 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 LGI1 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-conic 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

Table 1
Clinical and genetic details of LGI1 mutated families.

Clinical findings	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
N° patients (a/d)	3/0	4/0	4/0	3/1	6/1	2/2	5/2	3/2	4/1	6/2	2/0	3/1
Male/female	3/0	3/1	3/1	1/3	3/4	2/2	5/2	1/4	3/2	6/2	2/0	4/0
Age (years) at onset (range)	12 19	18–50	10 13	33–37	14–30	19–19	9 22	9 15	17–43	12 34	9–15	10–20
Seizure types												
- FS or SIC (n°)	3	3	2	2	5	1	5	3	3	6	1	4
- FSETCS (n°)	3	3	2	1	3	1	5	2	3	6	2	3
- TCSUO (n°)	0	1	2	2	2	3	2	2	2	2	0	0
- UEH (n°)												
Ictal symptoms												
- Auditory (n°)	–	3	2	1	5	1	4	3	3	5	1	1
- Aphasia (n°)	2	1	–	1	–	–	3	2	–	–	–	0
- Visual (n°)	–	–	–	–	–	–	1	–	–	–	2	3
- Other (n°)	1	1	–	1	2	1	4	3	1	1	–	–
Reflex seizures (n°)	–	3	–	–	1	–	2	–	1	–	–	–
Seizure free (n°/affected)	3/3	4/4	2/2	1/3	2/3	1/2	2/4	uk	2/4	0/5	2/2	2 3
EEG (n°)	3	3	2	1	4	2	5	4	2	3	2	3
- Ictal (findings n°)	–	–	–	lt se 1	–	–	–	–	–	–	–	–
- Interictal (findings n°)	bt sa 3	bt sa 3	n 2	lt ea 1	n 3, lt ea 1	n 2	n 3, bt ea 2	n 1,bt sa 1, lt ea 2	lt ea 2	bt sa 1, lbt ea 2	n 2	n 1,rt ea 1, lt ea 1
MRI (n°)	3	3	2	2	3	2	2	uk	2	2	2	2
- Normal (n°)	3	3	2	2	3	2	2		2	2	2	2
- Abnormal (findings n°)	–											
LGI1	1295 T>A	598 T>C	406 C>T	367 G>A	365 T>A	365 T>C	461 T>C	136 T>C	1138T>C	Deletion	1118T>C	856T>C

a/d = alive/deceased; FS = focal seizures; SIC = seizure with impaired consciousness; FSETCS = focal seizures evolving to tonic–clonic seizures; TCSUO = tonic–clonic seizures of unknown onset; UEH = unknown epilepsy history; lt = left; rt = right; bt = bilateral; n = normal; ea = epileptic activity; sa = slow activity.

over the temporal regions, involving the left side in 8 patients (53%), the right side in 3 (20%), and both sides in 1 (7%). In 3 patients (20%), EEGs were normal or showed aspecific abnormalities.

A conventional MRI scan was available in 12 patients. The exams were all normal in all patients and disclosed only minor abnormalities in 1 case (25%), consisting of mild temporal atrophy (n = 1).

3.1.2. LGI1 mutated families

The clinical findings of these 12 families have been reported in detail in previous papers [5,13] and are summarized in Tables 1–2. In brief, there were 57 patients (12 deceased) belonging to 12 families. Of these cases, however, 6 patients were quoted to have "epilepsy" but no additional clinical information was available and were therefore not included in the overall clinical description, which was limited to 51 affected individuals (10 deceased).

Age at onset ranged between 9 and 50 years (mean 17.7). Patients were classified as having genetic focal epilepsy (n = 39, 76%) or epilepsy with recurrent tonic–clonic seizures, undetermined whether focal or generalized, as the only seizure type (n = 13, 24%).

Among the 39 patients with idiopathic focal epilepsy, 1 (3%) had only focal seizures evolving to tonic–clonic seizures, 5 (12%) had only focal seizures with or without impairment of consciousness, and 33 (85%) had both focal seizures evolving to tonic–clonic seizures and focal seizures with or without impairment of consciousness. By adding those patients with tonic–clonic seizures undetermined whether focal

Table 2
Clinical and genetic details of RELN mutated families.

Clinical findings	F31	F33	F14	FIA	F15	PAC	CRR
N° patients (a/d)	5/0	5/1	4/3	3/1	2/0	2/0	2/0
Male/female	3/2	3/3	2/5	3/1	1/1	0/2	0/2
Age (years) at onset (range)	10–25	8–30	18–40	19–24	20–24	17–17	8–12
Seizure types							
- FS or SIC (n°)	4	3	3	3	2	2	2
- FSETCS (n°)	4	3	2	2	2	2	1
- TCSUO (n°)	0	1	4	0	0	0	0
- UEH (n°)	1	2	0	1	0	0	0
Ictal symptoms							
- Auditory (n°)	3	3	3	3	2	1	2
- Aphasia (n°)	1	–	–	2	–	2	–
- Visual (n°)	1	–	–	1	1	–	–
- Other (n°)	3	–	1	2	1	–	–
Reflex seizures (n°)	–	0.1	–	–	1	–	–
Seizure-free (n°/affected)	2/3	0/2	4/3	UK	1/1	1/1	1/1
EEG (n°)	4	3	4	UK	2	2	UK
- Ictal (findings n°)	–	–	–		–		
- Interictal (findings n°)	lt ea 3, lt sa 1	n 1, lt sa 2	n 4		rt ea 2	bt sa 1, rt ea 1	
MRI (n°)	3	2	3	UK	2	2	UK
- Normal (n°)	3	2	3		2	2	
- Abnormal (findings n°)	–	–	1		–	–	
REELIN	2392 C>A	2531 C>T	8347 G>T	2288 A>G	2168A>G	9526G>A	2015 C>T

a/d = alive/deceased; FS = focal seizures; SIC = seizure with impaired consciousness; FSETCS = focal seizures evolving to tonic–clonic seizure; TCSUO = tonic–clonic seizures of unknown onset; UEH = unknown epilepsy history; lt = left; rt = right; bt = bilateral; n = normal; ea = epileptic activity; sa = slow activity.

or generalized, a total of 47 patients (92%) suffered from convulsive seizures.

Auditory auras were observed in 29 cases (57%), occurring in isolation (n = 14, 27%) or preceding some kind of receptive aphasia (n = 7, 13%), vertigo (n = 5, 10%), visual hallucinations (n = 2, 4%), and déjà-vu (n = 2, 4%). In 2 patients the auditory symptoms followed a visual aura.

Other ictal symptoms not associated with auditory auras occurred in 10 patients (20%) and included visual symptoms (n = 4, 8%), aphasia (n = 2, 4%), déjà-vu (n = 3, 6%), and vertigo (n = 1, 2%).

Sudden noises and noisy environments could precipitate the seizures in 7 cases (13%) belonging to 4 families.

Seizure outcome was available for 33 patients, 21 of them (64%) being seizure-free since the first treatment and the remaining cases continuing to suffer from focal seizures, usually at a low frequency.

Routine and/or sleep deprivation EEGs were available in 31 out of the 45 living subjects and showed normal findings in 13 cases (42%) or interictal focal epileptiform/slow abnormalities (usually spikes or sharp waves) in 18 patients (58%) over the temporal regions, involving the left side in 7 patients (22%), the right side in 1 (3%), and both sides in 10 (32%). A conventional MRI scan was available in 25 patients and were normal in all cases.

3.1.3. Clinical comparison between RELN and LGI1 mutated families.

The clinical features of the patients belonging to the RELN and LGI1 mutated groups did not differ significantly as to age at onset (20.1 vs 17.7 years), frequency of auditory auras (71% vs 57%), ictal aphasic symptoms (21% vs 17%), occurrence of tonic–clonic seizures (88% vs 92%), and response to therapy (63% vs 64% of seizure freedom). Neuroradiological findings were substantially normal in both groups whereas EEGs showed a lower rate of normal recordings and higher rate of left temporal abnormalities in RELN group compared to the LGI1 group (20 vs 42% and 53 vs 22%, respectively), the latter difference being only mildly statistically significant (Table 3). The patients' descriptions of auditory auras in both groups is provided in Table 4.

3.2. Genetic findings

The genetic mutations segregating in these families have been reported elsewhere [5,6,13] and are given in Tables 1–2.

4. Discussion

In this paper we have described the clinical, EEG, and MRI findings of 7 ADLTE pedigrees associated with heterozygous RELN mutations, which had been reported in detail elsewhere by our group [5,6,13].

Table 3
Clinical comparison between RELN and LGI1 mutated families.

Features	LGI1 families (12)	RELN fam (7)	Fisher's exact test
N° pts (a/d)	51 (41/10)	24 (20/4)	
Age at onset (mean/range)	17,7 (9–50)	20.1 (8–40)	
Focal seizures, n°(%)	39 (76)	19 (79)	1
- Auditory	29 (57)	17 (71)	0.30
- Aphasic	9 (17)	5 (20)	1
- Visual	6 (12)	3 (12)	1
- Other	15 (29)	7 (29)	1
Tonic–clonic seizures n°(%)	47 (92)	21 (88)	0.6734
Reflex seizures n°(%)	7 (13)	2 (8%)	0.71
Seizure-free (%)	64	63	1
EEG, n°	31	15	
- Normal, n°(%)	13 (42)	3 (20)	0.19
- lt epil abn, n°(%)	7 (22)	8 (53)	0.05
- rt epil abn, n°(%)	1 (3)	3 (20)	0.09
- bt epil abn, n°(%)	10 (32)	1 (7)	0.07
MRI, n°	25	12	
- Abnormal, n°	0	1	0.32

a/d = alive/deceased; lt epil abn = left epileptiform abnormalities; rt epil abn = right epileptiform abnormalities; bt epil abn = bilateral epileptiform abnormalities.

Table 4
Comparison of auditory auras in both groups.

Type of auditory auras	LGI1 families	RELN families
Voices	1	2
Whistle/humming/swish	18	10
Music/chirping	1	1
Nonspecific sounds/rumors	5	2
Plugged ears	1	1
Increased/reduced sounds	1	1
Lateralized auras	4	0

By comparing these findings with those observed in families with LGI1 mutations, we did not observe any significant difference except for a left-sided preponderance of EEG abnormalities (53 vs 22%) in the RELN group. This difference, however, could relate to the low number of patients included and needs confirmation in larger series. Admittedly the lack of significant differences between the two groups may depend on the adoption of common and strict clinical criteria to select ADLTE families. Therefore, our findings do not exclude that LGI1 or RELN mutations may be found in families not exactly fitting these inclusion criteria. However, LGI1 mutations were not found in a vast cohort of families with familial mesial temporal lobe epilepsy [14] and RELN mutations have not been discovered so far in other familial focal epilepsies [6].

The clinical similarity between LGI1 and RELN mutated families suggests that mutations of both genes should be searched for when facing with a family showing an ADLTE phenotype, due to the lack of any clinical clue suggesting either RELN or LGI1 mutations. However, the use of multiple gene panels should help to solve the genetic diagnosis.

In addition, the clinical similarity between LGI1 and RELN pedigrees suggests that both genes may share similar mechanisms of action.

Reelin regulates the correct formation of laminated structures during embryonic development and modulates dendritic growth and synaptic plasticity at postnatal and adult stages [15]. LGI1, like Reelin, could serve different functions during brain development and adulthood [16]. Reelin and LGI1 have been shown to co-localize to distinct neurons in rat brain [6], suggesting that there may be a functional interplay between the two proteins in embryonic and postnatal life, which may be perturbed by mutations in either gene.

Homozygous RELN mutations have been reported to cause lissencephaly and cerebellar hypoplasia, a serious neuronal-migration recessive disorder presenting with epilepsy and severe cognitive defect, in three small consanguineous families [17,18]. The heterozygote individuals of these families, despite showing reduced reelin serum levels, had normal phenotypes, likely explained by a low penetrance of RELN mutations (estimated to be around 60%) [6] as well as by a mild clinical expression of these mutations, since auditory symptoms may remain unrecognized and undiagnosed for many years in some individuals. Alternatively, it could be hypothesized that additional genetic factors are needed to express the clinical phenotype.

Based on the neuroradiological findings of lissencephaly and cerebellar hypoplasia caused by homozygous RELN mutations, MRI of patients carrying heterozygous mutations could be expected to show even minor changes compatible with neuronal migration disorder. These signs have not been observed in our series but this may depend on a relatively low resolution power of the available MRI scans, which were not capable of detecting minor cortical malformations. It is therefore necessary to perform a study with a 3T MRI machine using advanced neuroimaging methods (volumetry, tensor diffusion imaging, etc), to exclude any sign of neuronal migration disorder.

Lastly in our series of 40 families with ADLTE, RELN heterozygous mutations and LGI1 mutations accounted for 17.5% and 30% of all pedigrees, respectively. Therefore, almost half of the families remains unsolved; moreover, the type of functional interaction between LGI1 and RELN are still largely unknown. Additional studies are required in the future to discover new ADLTE-associated genes and elucidate how their mutations lead to ADLTE.

5. Conclusions

ADLTE associated with *RELN* mutations shows a typical and homogeneous clinical picture, identical to that observed in LGI1 mutated families. *RELN* mutations account for about one-fifth of ADLTE pedigrees in Italy. Therefore the search for *RELN* mutations should become a routine procedure using multiple gene panels.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose.

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