

# Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance

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Microdeletion at chromosomal position 15q13.3 has been described in intellectual disability, autism spectrum disorders, schizophrenia and recently in idiopathic generalized epilepsy (IGE). Using independent IGE cohorts, we first aimed to confirm the association of 15q13.3 deletions and IGE. We then set out to determine the relative occurrence of sporadic and familial cases and to examine the likelihood of having seizures for individuals with the microdeletion in familial cases. The 15q13.3 microdeletion was identified in 7 of 539 (1.3%) unrelated cases of IGE using quantitative PCR or SNP arrays and confirmed by array comparative genomic hybridization analysis using probes specific to the 15q13.3 region. The inheritance of this lesion was tracked using family studies. Of the seven microdeletions identified in probands, three were *de novo*, two were transmitted from an unaffected parent and in two cases the parents were unavailable. Non-penetrance of the microdeletion was identified in 4/7 pedigrees and three pedigrees included other family members with IGE who lacked the 15q13.3 deletion. The odds ratio is 68 (95% confidence interval 29–181), indicating a pathogenic lesion predisposing to epilepsy with complex inheritance and incomplete penetrance for the IGE component of the phenotype in multiplex families.

## INTRODUCTION

Idiopathic generalized epilepsy (IGE) accounts for 20–30% of epilepsy in the general population. The disorder usually

follows complex inheritance although rare autosomal dominant families have been described (1). The mutations involved in the dominant forms confer very high risk to individuals who carry them but account for very little of the population risk.

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Candidate gene association studies and linkage studies across multiplex families to detect susceptibility regions have been reported, but their results have been disappointing (2–4).

Copy number variants (CNVs) are increasingly recognized as an important component of human genetic variation and a potentially significant contributor to disease risk. A recent study found a recurrent microdeletion at 15q13.3 present in 1% of IGE cases (5). This microdeletion was previously identified in intellectual disability (6) and then in schizophrenia (7,8) and autism (9,10). We aimed to confirm the initial finding in independent IGE cohorts and to examine the pattern of inheritance associated with 15q13.3 microdeletions. Specifically, we asked how this lesion was distributed across IGE subsyndromes and to what extent it was vertically transmitted in multiplex families. By an analysis of families associated with each of the index cases, we sought to resolve whether the microdeletion behaved as a highly penetrant mutation or conferred susceptibility for IGE with complex inheritance.

## RESULTS

### Detection of 15q13.3 microdeletions in IGE patients

We examined 539 patients diagnosed with an IGE syndrome according to the classification of the International League Against Epilepsy (11). All patients had at least two seizures, generalized spike wave on EEG and onset under 30 years of age. They did not have schizophrenia, autism or intellectual disability. The relatives of probands with a microdeletion underwent phenotyping including epilepsy syndrome, developmental history and outcome. The 293 Australian cases and the 246 mixed European cohort (from Turkey, Germany, Italy, Belgium, Netherlands, Denmark, Finland and Austria) were further divided into the IGE subsyndromes childhood absence epilepsy (CAE, 186 patients), juvenile absence epilepsy (JAE, 94 patients), juvenile myoclonic epilepsy (JME, 183 patients) and epilepsy with generalized tonic-clonic seizures alone (GTCSA, 76 patients) (Table 1). The country of origin and the number of subjects with each IGE subtype in the European cohort are shown in Table 2. The 494 Australian controls were drawn from anonymous blood donors and the 3283 German controls were from subjects with various common diseases (atopy  $n = 802$ , primary sclerosing cholangitis  $n = 253$ , sarcoidosis  $n = 602$ , ulcerous colitis  $n = 972$ ) and a cohort of individuals of high age ( $n = 654$ ), where epilepsies and other neurodevelopmental disorders are expected to occur at population frequencies.

In total, 405 IGE patients and 494 Australian controls were screened by quantitative PCR (qPCR), and 134 IGE patients and 3283 European controls were screened by Affymetrix Human SNP Array 6.0 to detect deletions and their reciprocal duplications. The micro-chromosomal abnormalities in the 15q13.3 region detected by these screening technologies were confirmed by array comparative genomic hybridization (CGH) using customized arrays covering the critical region (Fig. 1). Where copy number changes were identified, parents and first degree relatives where available were also screened by qPCR and array CGH. Six 15q13.3 microdele-

**Table 1.** Phenotypes of the extended EPICURE sample, gender breakdown

Phenotype	<i>n</i>	Male	Female
CAE	88	29	59
JAE	37	11	26
JME	79	19	60
EGTCS	42	19	23
Total	246	78	168

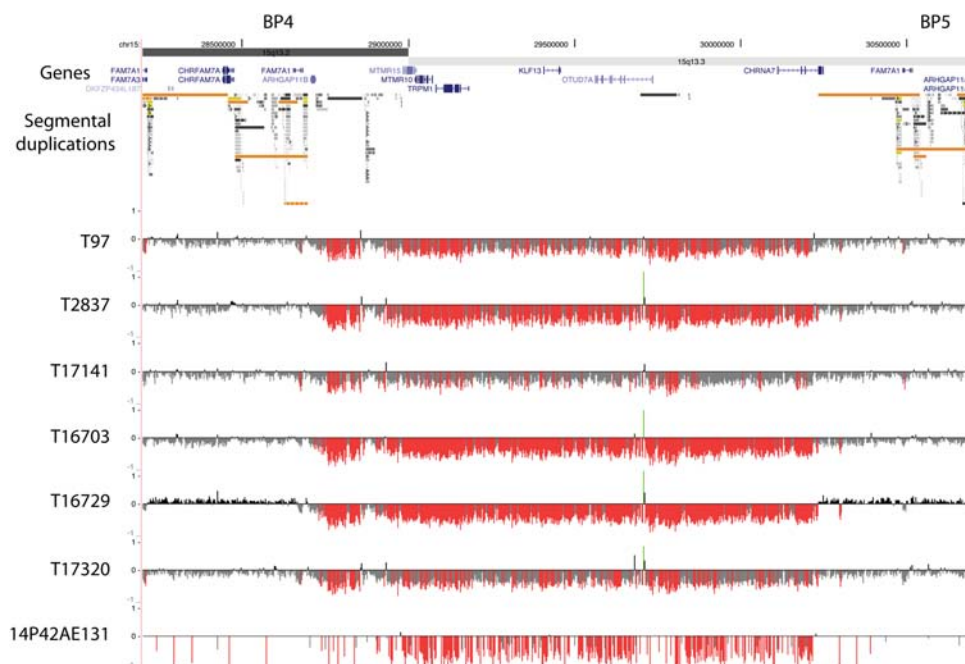
**Table 2.** Phenotypes of the extended EPICURE sample, country of origin

Country	Total	CAE	JAE	JME	EGTCS
Turkey	62	41	9	10	2
Germany	57	6	11	18	22
Italy	40	15	5	9	11
Belgium	35	12	4	15	4
Netherlands	28	8	3	17	
Denmark	12		2	8	2
Finland	10	6	3	1	
Austria	2			1	1
Total	246	88	37	79	42

tions were found in the Australian IGE cases (Families 2–6) and one microdeletion was found in a European (Turkish) IGE proband (Family 1), thus a total of seven microdeletions were found from a total of 539 IGE cases. The frequency of the 15q13.3 microdeletion in our IGE cohort was 1.3%. A microdeletion was found in three cases with the IGE subsyndrome JME, three cases with CAE (one with low normal intellect, one evolving to JME) and one with JAE. No deletions were identified in the 494 Australian or the 3283 European controls. The distribution of 15q13.3 microdeletions among IGE sub-syndromes appears random based on current ascertainment (Fisher's exact, all  $P > 0.4$ ). Association between the IGE phenotype and the 15q13.3 microdeletion was investigated using Fisher's exact test. In total, 15q13.3 microdeletions were identified in 7/539 cases with IGE and 0/3777 controls ( $P = 4.6 \times 10^{-7}$ ).

### Segregation analysis of the 15q13.3 microdeletions

The 15q13.3 microdeletions arose *de novo* in three probands (Fig. 2, Family 1, 2 and 5) as it was not present in either parent. Two probands inherited the microdeletion from an unaffected parent (Families 4 and 7) and the parental status was not able to be determined for two probands (Families 3 and 6). Parentage in Families 2, 4 and 5 was confirmed using eight highly polymorphic microsatellite markers. The microdeletion did not account for all the epilepsy risk in these families as there were both multiple affected individuals without 15q13.3 microdeletions and unaffected individuals with the deletion; this signifies segregation of the microdeletion as a susceptibility variant. Overall, wherever there was at least one relative carrying the microdeletion, apart from the proband, non-penetrance was demonstrated (four of seven cases) and in only one of four multiplex families did all affected members carry the microdeletion (Family 4). This finding presents a more accurate perspective than the impression given by the strong association detected with the 15q13.3 microdeletion in the case-control approach.



**Figure 1.** High-density oligonucleotide array CGH analysis of 15q13.3 microdeletions in patients with idiopathic generalized epilepsy. The 15q13.3 microdeletions were confirmed using high-density oligonucleotide array CGH (NCBI Build 36, chr15: 28 200 000–30 700 000 shown). The minimal deletion region lies between the segmental duplication clusters at breakpoints 4 (BP4) and 5 (BP5) and contains six RefSeq genes, shown in blue. Segmental duplications of increasing similarity (90–98%, 98–99% and >99%) are represented by grey/yellow/orange bars, respectively. For each individual, deviations of probe  $\log_2$  ratios from zero are depicted by grey/black lines, with those exceeding a threshold of 1.5 standard deviations from the mean probe ratio colored green and red to represent relative gains and losses, respectively.

## DISCUSSION

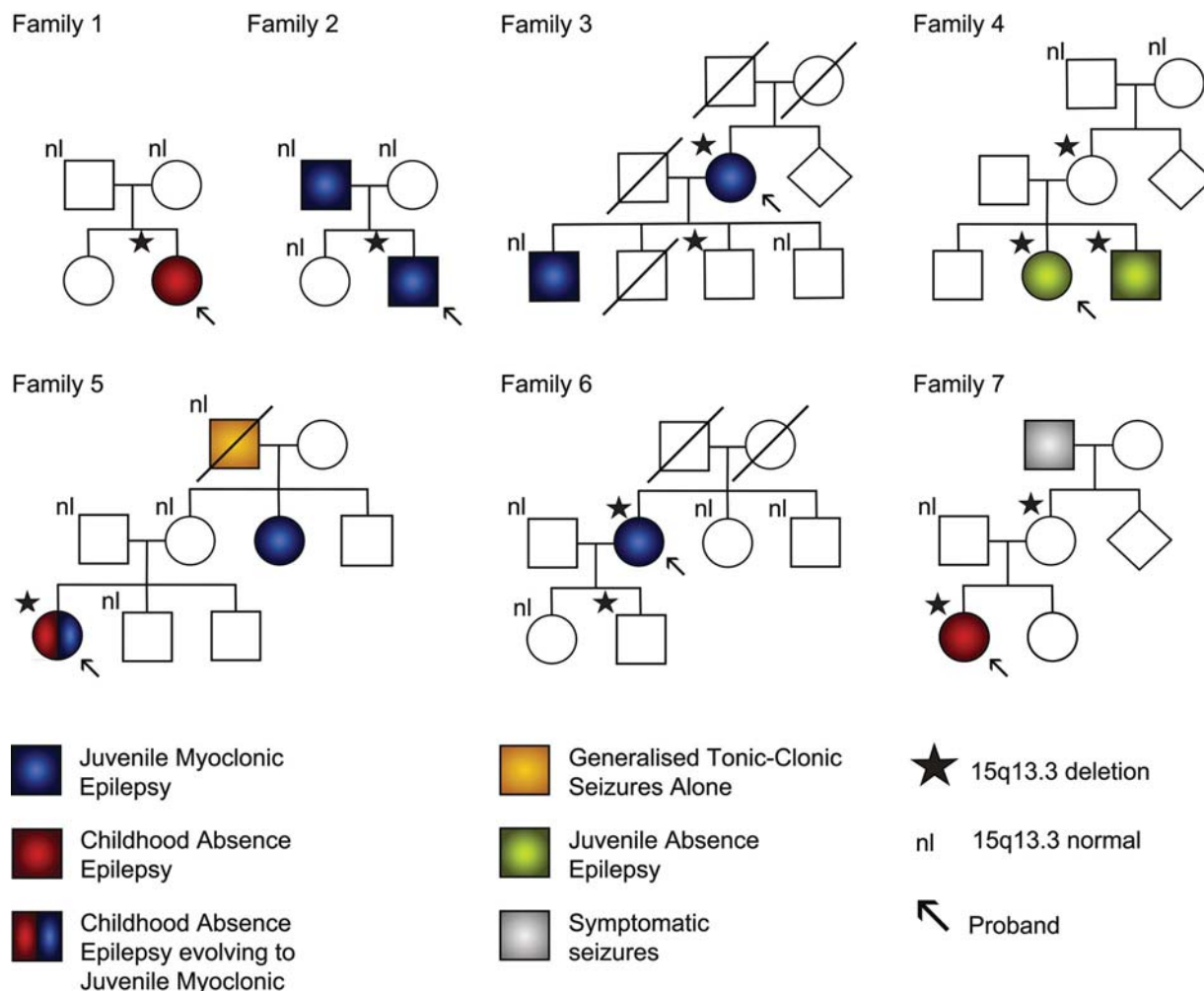
This study confirms in the independent cohorts examined that the 15q13.3 microdeletion is overrepresented among cases diagnosed with IGE and is present at frequencies of 1–2%. The frequencies in other non-epilepsy phenotypes associated with the 15q13.3 microdeletion are lower than in IGE, the highest being 0.3% in autism (9). IGE is thus the most frequent phenotype associated with the 15q13.3 microdeletion. A reliable estimate of the frequency of the microdeletion in the general population of 0.02% can be deduced from control cohorts in various previous publications investigating the 15q13.3 microdeletion, in which more than 50 000 controls have been genotyped in total (Table 3).

If our data are combined with a previous report (5) (19 of 1762 IGE cases), this gives an odds ratio of 68.2 for IGE susceptibility in subjects with the 15q13.3 microdeletion (95% confidence interval 28.5–181.2) (Table 4). In interpreting the odds ratio, the population risk of disease needs to be considered. The prevalence of IGE is relatively low with about 1 in 200 people (0.5%) developing it during their lifetime. The odds ratio is a measure of the increase in risk conveyed by a risk factor, in this case the 15q13.3 microdeletion. Although a 68-fold increase in risk appears very high, this would increase the risk for an individual with a 15q13.3 deletion from 1 in 200 to around 1 in 3. Although the upper end of the confidence interval for the odds ratio might be consistent with dominant inheritance, the likely value is suggestive of the complex inheritance demonstrated by the segregation in families.

The 15q13.3 microdeletions encompass seven genes including the  $\alpha 7$  nicotinic receptor subunit gene (*CHRNA7*).

This gene may play a role in epilepsy genetics as mutations in other members of the nicotinic receptor subunit gene family (*CHRNA2*, *CHRNA4* and *CHRNA7*) cause the familial idiopathic epilepsy autosomal dominant nocturnal frontal lobe epilepsy. Whether it is the loss of the *CHRNA7* gene alone, or the combined loss of several genes constituting a contiguous gene syndrome, or the alteration of regulatory mechanisms that contributes to the interplay of mechanisms causing IGE or other morbidities is yet to be determined (12). The 15q13.3 microdeletion can be non-penetrant where it segregates in families, as observed in this and a previous report (5). Moreover, the microdeletion is not necessarily present in all affected family members either, which is consistent with how the genetic architecture for the epilepsies with complex inheritance can be conceptualized (13).

Overall, although the 15q13.3 microdeletion shows a very strong association with IGE in case–control studies, it does not segregate as a dominant Mendelian allele in multiplex families. It behaves as a susceptibility component in a polygenic model where a combination of susceptibility alleles contributes to the phenotype in any one patient. While it is possible to formally predict using population data, the proportion of subjects with the microdeletion likely to develop IGE, such estimates of penetrance based on small numbers of cases are imprecise. Simple pedigree inspection of the few families so far known is equally instructive at this point (Fig. 2). Clearly, despite the high odds ratio associated with this susceptibility allele, once detected in a family, not all individuals with the microdeletion are affected clinically.



**Figure 2.** Family pedigrees of probands with 15q13.3 microdeletions showing only partial segregation with affected status. Family 1 is Turkish and Families 2–7 are Australian. Three microdeletions arose *de novo* in the proband in three families (1, 2 and 5), two were inherited (4 and 7) and in two families the parents of the proband were not available for study (3 and 6). Transmission of the microdeletion occurred in four families (3, 4, 6 and 7) and in all cases at least one unaffected individual carries the microdeletion. Four families have multiple individuals affected with IGE (2, 3, 4 and 5) and in one family (4) the microdeletion is present in all affected members of the family. Overall 8/12 subjects with the deletion are affected while 8/12 of those affected with IGE have the microdeletion. nl: signifies subjects who have been tested and who do not have the 15q13.3 microdeletion.

The 15q13.3 microdeletion in IGE is acting as a risk factor consistent with the common-disease, multiple rare-variant hypothesis of complex disease causation. Since the breakpoints map within segmental duplications that flank the critical region, non-allelic homologous recombination continues to create individuals with nearly identical genetic variation despite that variation being subject to selective pressure. The confirmed association of the 15q13.3 microdeletion with an IGE phenotype and other common brain disorders suggests that structural genomic variation represents an emerging entity contributing to human disorders with complex inheritance.

## MATERIALS AND METHODS

### Patient diagnoses

The 539 patients included in this study were diagnosed with IGE and its subsyndromes CAE, JAE, JME and epilepsy

with GTCSA according to the Commission on Classification and Terminology of the International League Against Epilepsy (1989). The 494 Australian controls were drawn from anonymous blood donors and the 3283 German controls were from subjects with various common diseases and a cohort of individuals of high age.

### Molecular genetic analyses

Genomic DNA was extracted from peripheral blood using the QIAamp DNA Blood Maxi Kit (Qiagen). Four hundred and five IGE patients and 494 controls were screened by quantitative PCR to detect deletions and their reciprocal duplications. The forward (5'-CCATCATACATTGCCTCCTTTCCAA-3') and reverse (5'-AGCATGATTCTGTCTGTAGGAGGAA-3') primers were designed to hybridize to intron 2 of *CHRNA7* and the TaqMan (Applied Biosystems) assay used the probe CACTCGCCTCAAATGT-FAM. CNV analysis of 134 Euro-

**Table 3.** 15q13.3 deletions in different cohorts

IGE	Origin	Total	15q13.3 del	Frequency
Controls	Australia <sup>a</sup>	293	6	0.02
	Turkey <sup>a</sup>	62	1	0.02
	Germany <sup>a</sup>	57	0	0
	Italy <sup>a</sup>	40	0	0
	Belgium <sup>a</sup>	35	0	0
	Netherlands <sup>a</sup>	28	0	0
	Denmark <sup>a</sup>	12	0	0
	Finland <sup>a</sup>	10	0	0
	Austria <sup>a</sup>	2	0	0
	Western Europe <sup>b</sup>	647	7	0.01
	Switzerland <sup>b</sup>	205	2	0.01
	USA <sup>b</sup>	133	1	0.01
	Northern Europe <sup>b</sup>	238	2	0.01
	This paper <sup>a</sup>	539	7	0.01
	Total	1762	19	0.01
	Australia <sup>a</sup>	494	0	0
	Germany <sup>a</sup>	3283	0	0
	Germany <sup>b</sup>	1202	0	0
	USA <sup>b</sup>	2497	0	0
	Iceland <sup>c</sup>	32 442	7	0.0002
	Scotland <sup>c</sup>	670	0	0
	Netherlands <sup>c</sup>	4039	1	0.0002
	Germany <sup>c</sup>	1034	0	0
	Denmark <sup>c</sup>	501	0	0
	Norway <sup>c</sup>	272	0	0
	Finland <sup>c</sup>	200	0	0
	UK <sup>c</sup>	96	0	0
	Italy <sup>c</sup>	91	0	0
	Scotland <sup>d</sup>	1097	0	0
	Ireland <sup>d</sup>	914	0	0
	Bulgaria <sup>d</sup>	646	0	0
	Sweden <sup>d</sup>	437	0	0
	Portugal <sup>d</sup>	200	0	0
	This paper <sup>a</sup>	3777	0	0
	Total	50 115	8	0.0002

<sup>a</sup>Current publication with samples not previously included in other studies.<sup>b</sup>Helbig *et al.* (5).<sup>c</sup>Stefansson *et al.* (8), German cohort minus 492 samples already included in footnote<sup>b</sup>.<sup>d</sup>International Schizophrenia Consortium (7).**Table 4.** Association results in current cohort and previous data

	Cases	Controls	OR (95% CI)	P-value
Current study	7/539	0/3777	Infinite (10.2–inf.)	$4.6 \times 10^{-7}$
Combined previous data	12/1223	8/46 338	57.3 (21.5–163.3)	$8.3 \times 10^{-15}$
All data combined	19/1762	8/50 115	68.2 (28.5–181.2)	$<2.2 \times 10^{-16}$

pean IGE patients and 3283 German controls were performed using the Affymetrix Genome-Wide Human SNP array 6.0. The microchromosomal abnormalities detected using these approaches were confirmed by array CGH using customized array CGH covering the critical region as previously reported (5).

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