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## Epilepsia Brief Communication

### **Inherited *RORB* pathogenic variants: overlap of photosensitive genetic generalized and occipital lobe epilepsy**

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**Summary:** 198/200 words

Variants in *RORB* have been reported in eight individuals with epilepsy, with phenotypes ranging from eyelid myoclonia with absence epilepsy to developmental and epileptic encephalopathies.

We identified novel *RORB* variants in 11 affected individuals from four families. One from whole genome sequencing and three from *RORB* screening of three epilepsy cohorts:

developmental and epileptic encephalopathies (n=1021), overlap of generalized and occipital epilepsy (n=84) and photosensitivity (n=123). Following interviews and review of medical records, individual's seizure and epilepsy syndromes were classified.

Three novel missense variants and one exon 3 deletion were predicted to be pathogenic by *in silico* tools, not found in population databases and located in key evolutionary conserved domains.

Median age of seizure onset was 3.5 years (0.5 to 10 years). Generalized, predominantly absence and myoclonic, and occipital seizures were seen in all families, often within the same individual (6/11). All individuals with epilepsy were photosensitive and 7/11 had cognitive abnormalities. EEGs showed generalized spike and wave and or polyspike and wave.

Here we show a striking *RORB* phenotype of overlap of photosensitive generalized and occipital epilepsy in both individuals and families. This is the first report of a gene associated with this overlap of epilepsy syndromes.

Key words: Retinoid-Related Orphan Receptor  $\beta$ , GGE, IPOE, Photosensitivity, Intellectual disability

### **Introduction:**

Copy number variants have provided critical insight into identification of genes causing human disease. One example in the epilepsies is the identification of *RORB*, encoding the retinoid-related orphan receptor  $\beta$ , which lies within the 9q21.13 microdeletion<sup>1</sup>. There is only a single study reporting patients with pathogenic variants in *RORB*<sup>2</sup>. The epilepsy phenotypes in this study varied from developmental and epileptic encephalopathies (DEEs) to photosensitive genetic generalized epilepsies, predominantly eyelid myoclonia with absence epilepsy associated with mild intellectual disability (ID)<sup>2</sup>.

*RORB* is present in immature neurons and is hypothesized to have a role in neuronal cell differentiation<sup>3</sup>. *RORB* has two differentially expressed isoforms, *ROR $\beta$ 1* and *ROR $\beta$ 2*, which differ only in their short N-terminal domains and are identical in the DNA-binding domain. *ROR $\beta$ 2* is expressed predominantly in the retina and pineal gland while *ROR $\beta$ 1* is also expressed in cortex, spinal cord, and the pituitary<sup>3</sup>. Despite relatively little knowledge about human disorders associated with *RORB* mutations, there has been considerable interest in *RORB* in murine models. Targeted knock out mouse models of both isoforms produce a

neurodevelopmental phenotype with visual and gait abnormalities, but seizures have not been observed<sup>4, 5</sup>.

In this study, we identified novel heterozygous *RORB* variants in eleven individuals from four families and describe the epilepsy phenotypes. Familial epilepsy with *RORB* variants is characterized by an overlap of photosensitive generalized and focal occipital epilepsy syndromes.

## **Methods:**

### ***Cohort***

Family A, with eight affected individuals, was referred for epilepsy genetic research and whole genome sequencing (WGS) was performed. Screening for *RORB* variants was performed in 1021 patients with DEE (family B and C identified), 84 individuals with an overlap of photosensitive GGE and occipital epilepsy either in the patient or their family (family D identified), and 123 individuals with photosensitive epilepsy (no variants identified).

### ***Phenotyping***

All available family members were interviewed using a standardized epilepsy questionnaire and seizure videos were reviewed<sup>6</sup>. Medical records, EEGs and neuroimaging were obtained. Seizures and epilepsy syndromes were diagnosed according to the 2017 International League Against Epilepsy classification<sup>7</sup>.

### ***Molecular***

Family A: WGS was performed on three individuals using an Illumina HiSeq X platform with a mean coverage of 30X. Reads were mapped against the human genome reference hg19. We selected coding variants with a frequency <0.0001 in population databases (1000 Genomes phase 3, and NHLBI GO Exome Sequencing Project [ESP], ExAC and gnomAD) and with an impact severity predicted by SnpEff of 'HIGH' or 'MED'.

Family B: 34 candidate genes including *RORB* were sequenced using molecular inversion probes targeting the coding exons and the intron-exon boundaries as previously described (>5bp)<sup>8</sup>.

Family C: An intragenic deletion in *RORB* was identified in family C by targeted oligonucleotide array comparative genomic hybridization (628 probes in *RORB*, average probe spacing 72 bp) to identify intragenic deletions and duplications.

Family D: Patients and families with overlap between photosensitive GGE and occipital lobe epilepsy were screened for *RORB* variants using Sanger sequencing with exon-specific primers (oligonucleotides available on request).

All variants were validated and segregation was performed with Sanger sequencing.

### ***Ethics***

Written informed consent was obtained from all patients and, in the case of minors or those with intellectual disability, their parents or legal guardians. The study was approved by the local ethics committees.

### **Results**

#### ***Phenotypes***

The four families included 14 individuals with *RORB* variants, of whom 11 had epilepsy, one had ID and two were unaffected (Figure A, Table 1). Clinical histories for all affected individuals are in the supplementary material.

Mean age of seizure onset was 3.5 years (range 6 months to 10 years). Age of onset varied according to the initial seizure type: 3 had seizures with myoclonic semiology at 6-9 months (myoclonic absence in 2, myoclonic in 1), 6 had absence seizures at 1-6 years and 2 had occipital seizures at 5 and 10 years.

Each family had some members with focal seizures and other members with generalized seizures, while 6 individuals had both seizure types. Generalized seizure types included absence (6/11), absence with eyelid myoclonia (2/11), myoclonic absence (2/11), infrequent GTCS (7/11) and myoclonic seizures (3/11). 7/11 individuals with *RORB* variants had occipital seizures; no other types of focal seizures occurred. Their seizures comprised of a visual hallucination of colored phenomena, such as colored vision, blotches, or formed visual images, sometimes followed by fear, eye deviation, loss of vision, nausea and loss of awareness. Seizures evolved to bilateral tonic-clonic seizures in only one individual. All seven were photosensitive.

Cognitive difficulties occurred in 7/11. These ranged from individuals who struggled at school and left early due to learning difficulties (4/11) to individuals with developmental delay in infancy resulting in mild (1/11) or severe (2/11) ID. The individuals with ID had seizure onset between 6 and 9 months and their mothers were on antiepileptic drugs (AED) during their pregnancy which may have impacted on their phenotype.

Nine patients showed generalized spike-wave (GSW) and/or polyspike-wave. Two individuals without GSW either did not have early EEGs or results of early EEGs were not available. Individual A-III-5 did not have an EEG until 8 years despite having well documented absence seizures from 2 years. A photoparoxysmal response on intermittent photic stimulation occurred in 10 individuals.

An overlap of generalized and occipital epilepsy syndromes occurred in all families. Absence epilepsy syndromes were the most common including childhood absence epilepsy (CAE) (3), juvenile absence epilepsy (JAE) (1), early onset absence epilepsy (EOAE) (2), epilepsy with myoclonic absence seizures (2) and eyelid myoclonia with absence epilepsy (EMAE). Idiopathic photosensitive occipital epilepsy (IPOE) was seen in four individuals. Occipital lobe epilepsy (OLE) occurred in three individuals without clear photosensitive induction of seizures, however, all had been photosensitive when they had absence seizures at a younger age (Table 1). Three individuals had a developmental and epileptic encephalopathy (DEE). Six individuals had both generalized and occipital epilepsies in a variety of combinations: CAE and IPOE (2), JAE and IPOE (1), EOAE and OLE (1), DEE and OLE (1) and EMAE & OLE (1).

In family B, the two children with DEE inherited their *RORB* variant from their father who had mild ID. He did not have a history of seizures but early history was not available. Information on his mother (B-I-2), who died prior to the study, was limited but she had learning difficulties and severe epilepsy with GTCS, absence seizures and episodes of nonconvulsive status epilepticus leaving her unable to care for her children. Her epilepsy worsened on carbamazepine and improved with sodium valproate.

There were two unaffected individuals that carried the familial *RORB* variant (A-II-4 and C-I-2). There was one individual (A-III-7) with a different phenotype with childhood focal impaired awareness seizures who did not carry the familial *RORB* variant (supplementary material).

**Molecular** (Table 1, Figure B, Supplemental Table):

Novel missense *RORB* variants were identified in families A, B and D and a deletion was found in family C. All missense variants were predicted to be damaging by *in-silico* prediction methods, evolutionarily conserved, and not reported in ExAC, gnomAD, ESP or dbSNP. The p.Ser37Arg variant in family A affects the DNA-binding domain, an area with a low missense tolerance ratio (Figure B). It is predicted to be destabilizing as arginine is

longer than serine with many possible rotamers that may interact with neighboring amino acids<sup>3</sup>. Variants in family B (p.Trp259Cys) and D (p.Ile388Phe) are likely involved in the regulation of ROR $\beta$  activity and in recruitment of coactivators<sup>3</sup>. The deletion in family C included all of exon 3 encoding the DNA binding domain; deletion of the 141-bp exon would be predicted to cause a frameshift and premature truncation of the protein, though additional studies would be required to confirm the effect on transcription. No other plausible variants were found.

### **Discussion:**

Here, we present eleven individuals from four families with inherited *RORB* variants showing an overlap of photosensitive GGE and occipital epilepsy. These phenotypes occurred both as separate syndromes in different family members and also together within single individuals. We delineate the co-occurrence of occipital epilepsy in *RORB* epilepsies, with the known association of photosensitive GGE and DEE published in the only study of *RORB* epilepsies to date. The previous study of a family and four sporadic individuals with *RORB* epilepsies reported a broad phenotypic spectrum encompassing GGE, predominantly eyelid myoclonia with absence epilepsy, and DEE. Individuals in the study had a cognitive profile ranging from learning disabilities to severe ID<sup>2</sup>. The phenotypes in these previously reported families are similar to what we have identified however they did not report any occipital epilepsies. Interestingly, eyelid myoclonia with absence epilepsy is a syndrome for which the occipital cortex is assumed to play a key role and may initiate the generalized epilepsy network.

Families with both generalized and occipital epilepsies occurring in different first- and second-degree members have been previously reported<sup>9-11</sup>. The finding of both generalized and focal epilepsy syndromes within a single individual is rare in common epilepsies, being reported in only 3.5% (39/1120) of individuals from 303 families<sup>9</sup>. It is considerably more frequent in families with photosensitive epilepsies; we found that 26% (21/82) of individuals with photosensitivity from 29 families had both generalized and focal epilepsy<sup>10</sup>.

*RORB* is expressed in layer IV cortical neurons and thalamic nuclei<sup>3</sup>. Both are integral to the thalamocortical network which underlies the generation of generalized spike-wave and generalized seizures. *RORB* is also expressed in the retina and necessary for the proliferation and differentiation of retinal cells<sup>3, 12</sup>. Although our patients did not show any visual abnormalities, all had clinical and/or electrical photosensitivity. A combination of

thalamocortical network and visual network abnormalities may be critical to bring together this fascinating overlap of photosensitive GGE and occipital epilepsy.

Monogenic diseases, such as *SCN1A* and *PCDH19*, often show a phenotypic spectrum within families. In our *RORB* families there is also a pattern where GGE and occipital phenotypes can be seen individually (occipital epilepsy:1 case, GGE:4 cases) or in combination (6 cases) in a single individual. A similar pattern of phenotypes is seen in Infantile Convulsions with Choreoathetosis Syndrome due to *PRRT2* pathogenic variants, where family members can have paroxysmal kinesigenic dyskinesia, infantile epilepsy, both or can even be unaffected<sup>13</sup>.

The seizure type of absence with eyelid myoclonia is associated with photosensitivity and can occur as the key feature of the epilepsy syndrome EMAE or be a part of a DEE. Genetic causes of the DEEs associated with absence with eyelid myoclonia include *CHD2*, *SYNGAP1* and *NEXMIF* (formally known as *KIAA2022*)<sup>14, 15</sup>. There has been little molecular success in identifying the genes causing an overlap between GGE and occipital epilepsy, with the GGE often considered to follow complex, or polygenic, inheritance<sup>9, 10</sup>. Conversely the overlap between generalized and occipital seizures in the DEE has been associated with a number of genes, such as *CLN6* and the CAG trinucleotide repeat in Huntington's disease<sup>16-18</sup>. Here, we expand the phenotype associated with *RORB* variants making it the first gene to be associated with the overlap of photosensitive GGE and IPOE.

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## Disclosure of Conflicts of Interest



Prof Sadleir is funded by the Health Research Council of New Zealand and Cure Kids New Zealand. She is a consultant for the Epilepsy Consortium and has received travel grants from Seqirus and Nutricia. She has received research grants from Zynerva.

Prof Mefford is funded by the NIH (National Institute of Neurological Disorders and Stroke).

Prof Scheffer serves on the editorial boards of *Neurology* and *Epileptic Disorders*, may accrue future revenue on a pending patent re: Therapeutic compound; has received speaker honoraria from Athena Diagnostics, UCB, GlaxoSmithKline, Eisai, and Transgenomics; has received scientific advisory board honoraria from Nutricia, UCB, and GlaxoSmithKline, has received funding for travel from Athena Diagnostics, UCB, and GlaxoSmithKline; and receives/has received research support from the National Health and Medical Research Council, Australian Research Council, National Institutes of Health, Health Research Council of New Zealand, March of Dimes, the Weizmann Institute, Citizens United for Research in Epilepsy, US Department of Defense, and the Perpetual Charitable Trustees.

The remaining authors have no conflicts of interest.

#### **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.

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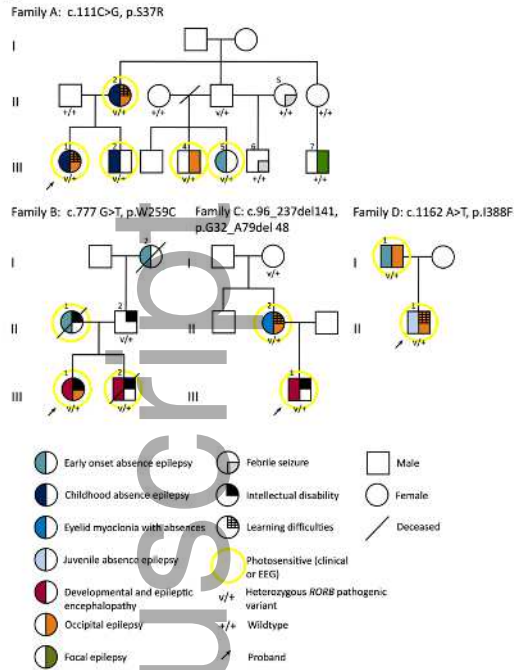
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	A					B		C		D	
<b>Case</b> (gender/age)	II - 2 (F/46y)	III - 1* (F/17y)	III - 2* (M/15y)	III-4 (M/18y)	III - 5 (F/14y)	III - 1* (F/18y)	III-2* (M/#11y)	II-2 (F/40y)	III-1* (M/11y)	I-1 (M/48y)	II-1 (M/20y)
<b>RORB Variant</b>	c.111C>G/p.Ser37Arg					c.777G>T/p.Trp259Cys		c.96_237del141/ p.Gly32_Ala79del48		c.1162A>T/p.Ile388Phe	
<b>Pathogenic predictions</b>	Sift - 0; Polyphen - 0.989; CADD - 25; GERP - 3.98					Sift - 0; Polyphen - 1; CADD - 34; GERP - 5.5999				Sift - 0.002; Polyphen - 0.943; CADD - 24.7; GERP - 5.73	
<b>Sz onset age</b> [offset]	5y: A	4y: A [7y]	6y: A	5y: Occipital Seizures [14y]	2y: A [10y]	9m: MA	9m: MA	3y: Absence with eyelid myoclonia	6m: M	12m: A [13y]	10y: Occipital Seizures
<b>Other Sz onset age</b>	10y: GTCS [31y]; 10y: Occipital Seizures	5y: Occipital Seizures [7y]	14y: GTCS	Nil	Nil	12m: FS [3.5y]; 9 y: GTCS; 22m: M; 15y: Occipital Seizures	16m: GTCS [20m]; 22m: M [11y]	19y: GTCS; 35y: Occipital Seizures	3y: A	18m: FS [18m]; 18 y: GTCS [23y]; 44y: Occipital Seizures [44y]	13y: EM [14y]; 13y: Absence status [13y]; 13y: GTCS [13y]
<b>Syndrome</b>	CAE + IPOE	CAE + IPOE	CAE	IPOE	EOAE	DEE - Epilepsy with myoclonic absences + Occipital Lobe Epilepsy	DEE - Epilepsy with myoclonic absences	EMAE + Occipital Lobe Epilepsy	DEE	EOAE + Occipital Lobe Epilepsy	JAE + IPOE
<b>Development (age DD noted)</b>	LD	LD	N	N	N	DD (9m), Mild ID,	DD (4m) Severe ID	DD (18m), LD	DD (birth) Severe ID	N	Learning difficulties

						12y - G-tube					
<b>Medication trials</b>	VPA, LTG, CBZ, TPM	VPA	VPA, ETX, LEV	VPA	Nil	CBZ, VPA, LTG, CLB, PB, ETX, LEV	CBZ, VPA, ETX, CLB, LTG, CZP	VPA, LTG	VPA, CLB, ETX, TPM, LEV, LTG	VPA, TPR, LTG	VPA, LEV
<b>Examination</b>	N	N	N	N	N	All growth parameter < 3 <sup>rd</sup> %	N	N	Mild hypertonia of limbs	N	N
<b>EEG</b>	15y: GSW, PSW, PPR; 40y: GSW	4y: GSW, PSW, PPR (sleep)	6y: GSW, PPR, OIRDA; 14y: GSW, PPR	8y & 9y: PPR, GSW, PSW, CPS	8y: PPR, CPS	1y & 5y: GSW, PPR	1y: GSW, PPR, 18m: GSW	8y: GSW, PPR, 19y: PPR	8m: GSW, PSW, PPR 15m: GSW	44 y: BD	13y: GSW, PPR 14y: Normal
<b>MRI</b>	N	Not done	N	N	Not done	Not done	N	Not done	N	N	N

F: Female, M: Male, y: Years old, #:age at death, \* AED exposure in utero ,A: Absence seizure, MA: Myoclonic absence seizures, M: Myoclonic seizures, GTCS: Generalised tonic clonic seizures, FS: Febrile seizure, CAE: childhood absence epilepsy, IPOE: Idiopathic photosensitive occipital lobe epilepsy, EOAE: Early onset absence epilepsy, DEE: Developmental and epileptic encephalopathy, EMAE: Eyelid-myoclonia with absence epilepsy, JAE: Juvenile absence epilepsy, LD: Learning difficulties, DD: Developmental delay, ID: Intellectual disability, G-tube: Gastrostomy tube, N: Normal, VPA: Sodium valproate, LTG: Lamotrigine, CBZ: Carbamazepine, TPM: Topiramate, ETX: Ethosuximide, LEV: Levetiracetam, PHT: Phenytoin, CLB: Clobazam, PB: Phenobarbital, CZP: Clonazepam, GSW: Generalised spike and wave, PSW: Polyspike and wave, PPR: Photo-paroxysmal response, OIRDA: Occipital intermittent rhythmic delta activity, CPS: Central parietal spikes, BD: Bitemporal delta

A



B



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