Published in final edited form as:

N Engl J Med. 2018 April 26; 378(17): 1646–1648. doi:10.1056/NEJMc1714579.

Parental Mosaicism in "De Novo" Epileptic Encephalopathies

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

TO THE EDITOR

De novo disease-causing variants have been increasingly recognized in apparently sporadic, severe neurologic disorders in children, including developmental and epileptic encephalopathies[1] and autism.[2] Geneticists indicate that the risk of recurrence of these disorders in families with one affected child is approximately 1%; this accounts for the fact that one parent may have gonadal mosaicism.[2] In families with an affected child, the actual risk of recurrence may be as high as 50%.

Using single-molecule molecular inversion probes,[3] we investigated the frequency of low-level parental mosaicism in somatic tissue obtained from parents and their affected children with an apparently de novo pathogenic variant (according to American College of Medical Genetics and Genomics criteria[4]) in 1 of 33 genes known to cause developmental and epileptic encephalopathies. Of 154 consecutively ascertained family trios (consisting of a child and his or her biologic parents), 123 (79.9%) yielded a minimum of 200 discrete captures (i.e., molecules) (see the Supplementary Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org) in each parent; this coverage threshold provided 86.6% power to detect a 1% minor allele frequency (as calculated with the use of the binomial test). The variant was validated in each proband; paternity and maternity were genetically confirmed. Although ascertainment bias is possible, particularly in families with two affected children, genetic testing was commenced before the second affected child was born or before the child became clinically affected by the disorder. Three probands showed somatic mosaicism and so were excluded from the analysis.

We tested somatic tissue (blood or saliva) obtained from the parents in the remaining 120 families to infer gonadal mosaicism; of these, 10 parents (8.3%; 95% confidence interval, 3.4 to 13.3) had mosaicism for their child's pathogenic variant (6 fathers and 4 mothers; minor allele frequency, 1.4 to 30.6%; mean, 12.9%; median, 9.4%) (Table 1). The minor allele frequency was well below that traditionally detected by means of Sanger sequencing in 8 of these 10 parents. In the saliva and blood samples obtained from 8 of the 10 parents with mosaicism (Table 1), the mutant allele had a similar frequency. Pathogenic variants occurred in eight genes. These genes included *SCN1A* in 3 of 40 families with apparently de novo *SCN1A* mutations; these findings showing that approximately 10% of children with an apparently de novo SCN1A variant had a parent with mosaicism replicated those of another study.[5] In addition, one variant occurred in each of the following genes: *SCN8A, GNB1, SLC6A1, DNM1, KCNT1, CACNA1A*, and *KCNQ2*. Owing to the small sample size, we were unable to determine whether certain genes, such as those encoding ion channels, were more prone to mosaicism.

In 13 of 120 families, a second child had seizures or a neurodevelopmental abnormality. In 5 of these 13 families, the affected sibling had a phenotype concordant with that of the proband and shared the proband's mutation. However, parental mosaicism was detected in only 3 of these 5 families (these 3 families were captured in the 10 in which we observed parental mosaicism). Mosaicism in a parent of the other 2 families may have been below the level of detection by means of single-molecule molecular inversion probes or confined to

gonadal tissue (which we did not test). If so, we have underestimated the true frequency of mosaicism in the parents. Conversely, only 1 of 8 siblings with a milder (discordant) phenotype carried their sibling's mutation; mosaicism was detected in their father. Targeted high-coverage testing of parents who have a child with a developmental and epileptic encephalopathy due to an apparently de novo mutation may be helpful in counseling parents regarding the risk of recurrence.

A parental history of seizures was associated with an increased likelihood of parental mosaicism ($P = 0.03$ by Fisher's exact test). Of the 16 parents who had a history of seizures, 4 had mosaicism and 12 did not; however, only 6 of 104 families with unaffected parents carried a variant that was also present, in a mosaic pattern, in either the mother or father (Table 1, and Fig. S1 in the Supplementary Appendix). The level of mosaicism correlated broadly with the severity of disease in the 4 affected parents who were found to have mosaicism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Drs. Scheffer and Mefford contributed equally to this letter. Supported by grants from the National Institute of Neurological Disorders and Stroke (R01 NS069605, to Dr. Mefford), the National Health and Medical Research Council of Australia (to Drs. Berkovic and Scheffer), and the Health Research Council of New Zealand and Cure Kids New Zealand (to Drs. Sadleir and Scheffer), and by postdoctoral fellowships from the Lennox–Gastaut Syndrome Foundation and the American Epilepsy Society (to Dr. Myers) and from the Dravet Syndrome Foundation (to Dr. Muir).

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N Engl J Med. Author manuscript; available in PMC 2018 October 26.

Table 1

Parental Mosaicism in 8.3% of Parents Who Had a Child with a Diagnosis of an Apparently De Novo Monogenic Developmental and Epileptic Encephalopathy.[☆]

Family No.	Proband Phenotype	Mutation	Parent with Mosaicism	Sample Type, % Mosaicism	Phenotype of Parent with Mosaicism	No. of Affected Siblings	Phenotype of Affected Sibling, Mutation Status
1	Dravet syndrome	*SCN1A* p.R101W	Father	Blood, 29.6; saliva, 16.7	Unaffected	0	NA
2	Dravet syndrome	*SCN1A* p.S1516[☆]	Mother	Blood, 17.6	Febrile seizure	0	NA
3	Dravet syndrome	*SCN1A* p.I1483Mfs[☆]18	Father	Blood, 30.6; saliva, 24.1	Febrile seizure	1	Dravet syndrome, *SCN1A* heterozygote
4	Developmental and epileptic encephalopathy	*SCN8A* p.L1331V	Father	Blood, 12.0; saliva, 4.7	Febrile seizures plus[†]	1	Febrile seizures plus,[†] focal seizures, learning difficulties, *SCN8A* heterozygote
5	Developmental and epileptic encephalopathy	*KCNT1* p.R950Q	Father	Blood, 10.8; saliva, 14.0	Mild autosomal dominant nocturnal frontal lobe epilepsy	0	NA
6	Developmental and epileptic encephalopathy	*KCNQ2* p.V567D	Mother	Blood, 1.4; saliva, 1.5	Unaffected	0	NA
7	Epilepsy with myoclonic–atonic seizures	*SLC6A1* p.A334P	Mother	Blood, 8.0; saliva, 9.3	Unaffected	0	NA
8	Developmental and epileptic encephalopathy	*GNB1* p.A326T	Father	Blood, 7.8	Unaffected	0	NA
9	Developmental and epileptic encephalopathy	*CACNA1A* p.A713T	Mother	Blood, 6.4; saliva, 8.5	Unaffected	1	Developmental and epileptic encephalopathy, *CACNA1A* heterozygote
10	Developmental and epileptic encephalopathy	*DNM1* p.R237W	Father	Blood, 4.5; saliva, 4.1	Unaffected	1	Developmental and epileptic encephalopathy, *DNM1* heterozygote
11	Developmental and epileptic encephalopathy	*SYNGAP1* p.L150Vfs[☆]6	Inferred	ND	Unaffected	1	Developmental and epileptic encephalopathy, *SYNGAP1* heterozygote
12	Epilepsy with myoclonic–atonic seizures	*KIAA2022* p.R322[☆]	Inferred	ND	Unaffected	1	Epilepsy with myoclonic or atonic seizures, *KIAA2022* heterozygote

[☆]NA denotes not applicable, and ND not detected.

[†]Febrile seizures plus are febrile seizures that occur after the age when these seizures usually occur (3 months to 6 years) or when there are concurrent afebrile tonic–clonic seizures.