Gynecology and Obstetrics Clinical Medicine 1 (2021) 169–172

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Seizures as the first manifestation of chromosome 2q24.2-q24.3 in a two and a half years old girl: A case report

Wen-cheng Dai [a], Xue-xia Liu [b], Hui-jun Li [a], Gui-ning Song [b], Yan-hui Li [b], Cheng-ling Zhang [b], Lin Zhang [b,*]

[a] Prenatal Diagnose Center of Xinjiang Maternal and Child Health Hospital, Urumuqi, Xinjiang, 830000, China
[b] Prenatal Diagnose Center, People's Hospital of Peking University, Beijing, 100044, China

ARTICLE INFO

Keywords:
Seizure
Chromosome 2q22.2-q24.3
Microdeletion
Maternal origin

ABSTRACT

Background: Mutations and/or duplications in the chromosome 2q24.3 region are known to be responsible for various epilepsy phenotypes. However, microdeletion in childhood epilepsy is rarely reported.
Case presentation: A two-and-a-half-year-old girl with no history of hypocalcemia or seizures developed new symptoms of generalized tonic-clonic epilepsy. The clinical manifestations were growth retardation, prominent forehead, closed anterior fontanelle, and poor muscle tension. Peripheral blood, echocardiography, abdominal ultrasound, and electroencephalogram (EEG) examinations were all normal. No karyotype abnormality was found in the patient, but a single nucleotide polymorphism (SNP) array test detected that a 3.5 Mb single-copy microdeletion had occurred in the q24.2-q24.3 region on chromosome 2. Fluorescence in situ hybridization (FISH) tests revealed that the 2q24 fragment was inserted into the q11.2 region of the patient's chromosome 15, as well as that of her sister. In both cases, the patient's mother is the source carrier of the chromosome 15 insertion.
Conclusions: The deletion of the sodium channel gene cluster (SCN1A, SCN2A, and SCN3A), but not SCN1A haploinsufficiency alone, may contribute to complex infant epilepsy syndromes. However, the pathogenic mechanism still needs to be studied further.

1. Introduction

As a chronic brain dysfunction disease, epilepsy has an important impact on the development, cognition, and behavior of patients, and is a common disease of the nervous system in children.[1] The interactions between the brain development of children at different ages and various external factors make epilepsy heterogeneous. Due to the large size of chromosome 2, aberrations of its long arm often give rise to many specific phenotypes, such as developmental delay, growth retardation, microcephaly, severe behavioral disturbance, and dysmorphia of facial features.[2–4] Increasing evidence shows that the mutation, duplication, or microdeletion of the q24.3 region of chromosome 2 is associated with epilepsy syndromes.[5–9] In this region, sodium channel genes (*SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, and *SCN9A*) are clustered and might be responsible for epilepsy phenotypes.[10–12] However, the contribution of a specific *SCN* gene deletion to epilepsy is hard to evaluate due to the heterogeneous clinical features and common phenotypes. Therefore, the mechanism of epileptic seizures and the relationship between genotype and phenotype is currently unclear. In this study, we describe a two-and-a-half-year-old girl with clinical manifestations of growth retardation, prominent forehead, closed anterior fontanelle and poor muscle tension, but no history of hypocalcemia or seizures, who developed new symptoms of generalized tonic-clonic epilepsy. A single nucleotide polymorphism (SNP) array test detected a 3.5 Mb deletion on chromosome 2, specifically in the q24.2-q24.3 region, which encodes *FIGN*, *GRB14*, *COBLL1*, *SLC38A11*, *SCN2A*, *SCN3A*, *CSRNP3*, *GALNT3*, *TTC21B*, and *SCN1A*. A FISH test showed that this fragment of chromosome 2 was inserted into the q11.2 region of the patient's chromosome

* Corresponding author. Prenatal Diagnostic Center, People's Hospital of Peking University, Beijing, 100044, China.
E-mail address: zhanglinsun@sina.com (L. Zhang).

Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2021.04.002
Received 10 January 2021; Received in revised form 25 March 2021; Accepted 15 April 2021
Available online 17 July 2021

15, and that the patient's mother is the carrier of this chromosomal abnormality.

2. Material and methods

2.1. Case presentation

A two-and-a-half-year-old girl with an Apgar score of 10 and a weight of 3310 g at birth, developed new generalized tonic-clonic seizures. She had no history of hypocalcemia, seizures, psychiatric disorders, or obvious cognitive impairments. The clinical manifestations are growth retardation, prominent forehead, nasal sounds, and overfilled bridge of the nose, closed anterior fontanelle and poor muscle tension. Peripheral blood, echocardiogram, abdominal ultrasound, and electroencephalogram (EEG) examinations were all normal.

2.2. Chromosome G-band karyotype analysis

After obtaining the consent of the patient's parents, 3 mL of venous blood from the patient, her parents, and an unrelated fetus were collected separately, with heparin used for anticoagulation. From each of these samples,1 mL was taken, cultured in RPMI1640 medium, and Giemsa staining was performed according to conventional methods. The resultant chromosome karyotype was observed under an optical microscope.

2.3. 10× genome sequencing and SNP analysis

Genomic DNA was extracted from the peripheral blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instruction. Genome-wide copy number variation analysis was performed by using Affymetrix's CytoScan HD chip system platform, which contains more than 2.7 million probes, including 750,000 SNP typing probes and 1.95 million copy number probes. Clean reads were assembled and analyzed against database (http://sift.bii.a-star.edu.sg/), DGV (http://projects.tcag.ca/variation/), OMIM (http://omim.org/) and ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/). SNPs and INDELs were further analyzed using Chas3.0. The potentially pathogenic CNVs were verified by FISH test.

3. Results

3.1. Karyotype analysis

Peripheral blood analysis showed that the karyotypes of the patient, her parents, and the mother's second fetus (four months of age) are all 46, XXor 46, XY, as expected (Fig. 1a and 2a).

3.2. Overview of sequencing data and SNP analysis

A total of 1,107,148,416 reads were generated and 98.3% were mapped to the reference genome. SNP phasing results showed that the N50 phased block is 4,890,140 bp and the longest phase block is 23,522,905 bp. Further analysis revealed that a 3.55 Mb microdeletion was detected in the 2q24.2-q24.3 region, spanning nucleotides: 163,513,141–167,063,437 (Fig. 1b). After searching the UCSC genome database, it was found that the genes encoded by the missing fragment include *FIGN*, *GRB14*, *COBLL1*, *SLC38A11*, *SCN2A*, *SCN3A*, *CSRNP3*, *GALNT3*, *TTC21B*, and *SCN1A*. The chromosome karyotype of the fetus was normal (Fig. 2a), however, a 3.5 Mb duplication was detected on chromosome 2 (Fig. 2b). Further analysis suggests this duplication is potentially [also] pathological of induced seizures.

3.3. FISH test

To validate the result obtained via SNP analysis, FISH tests of the peripheral blood of the patient and her parents were performed using different probes. For the patient, a fragmentof chromosome 2 (2q24.2-q24.3) was found to have been inserted into the q12 region of chromosome 15, as detected by the probe RP11-119M1, which causes the abnormality of chromosome 15 (Fig. 3a). Additionally, the hybridization result showed that the mother was a carrier of abnormal chromosomes 15 and 2 (Fig. 3b), but no abnormality was found for her father (Fig. 3c). To further verify the reliability of the results, recombination probes were used for FISH test. Similarly, a fragment of chromosome 2 was detected on chromosome 15 of the patient by the probe RP11-119M14/15qter (Fig. 4b). Using the probe D15Z1/SNRPN/PML/RP11-119M14, the inserted fragment was localized in to the 15q11.2 region (chromosome 15) (Fig. 4c).

4. Discussion

SNP array tests can overcome the shortcomings of G-band staining technology by scanning the whole genome to detect small changes in chromosomes. Its high resolution and accuracy are conducive for the detection of microdeletions and/or microduplications, and also helpful for improving the detection of pathogenic variants. In this study, SNP array and FISH tests were used to explore the molecular mechanism of epilepsy in a two-year-old girl.

According to the UCSC human genome data, at least 10 genes are included in the deletion region of this patient, including three genes encoding sodium voltage-gated channel subunits (SCN1A, SCN2A, and SCN3A). An increasing number of studies show that abnormalities of *SCN* genes are associated with childhood epilepsy. Studies have shown that 70–80% of the genetic cause of epileptic phenotypes are the result of nonsense or missense mutations to SCN1A, with another few percent

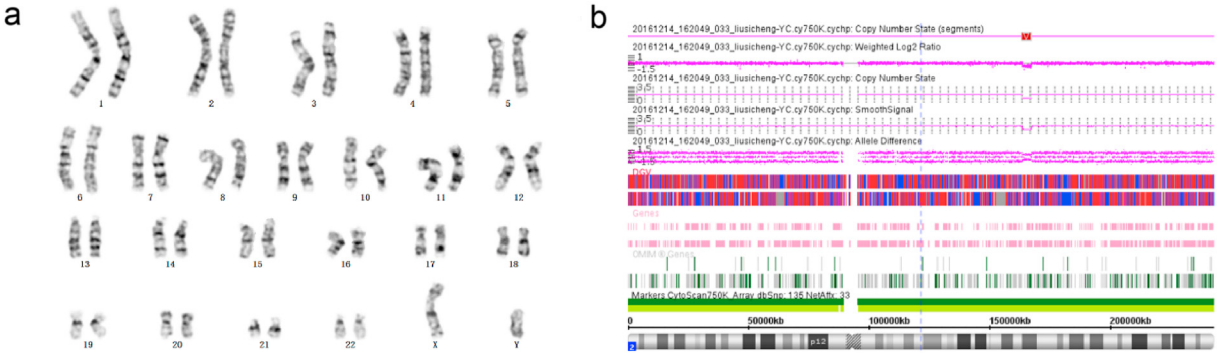

Fig. 1. Karyotypes of the patient and her parents, and SNP analysis of the patient a. All karyotypes are normal; b. A 3.5 Mb deletion in the region of 2q24.2-q24.3 (chromosome 2) was detected.

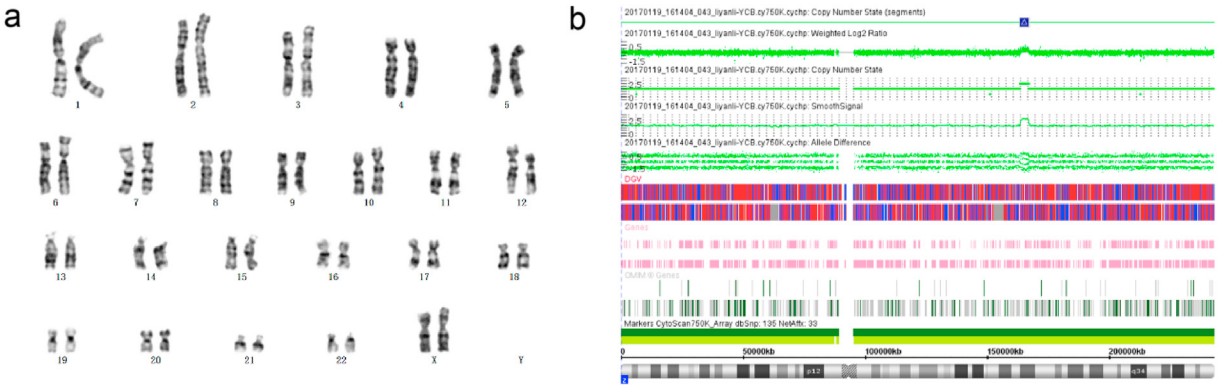

Fig. 2. Karyotypes of the patient's mother and the mother's second fetus, and SNP analysis of the fetus. a. Normal karyotype of the patient's mother (46, XX) and the fetus (46, XX); b. A 3.5 Mb microduplication was detected in the q24.2-q24.3 region of chromosome 2 of the fetus.

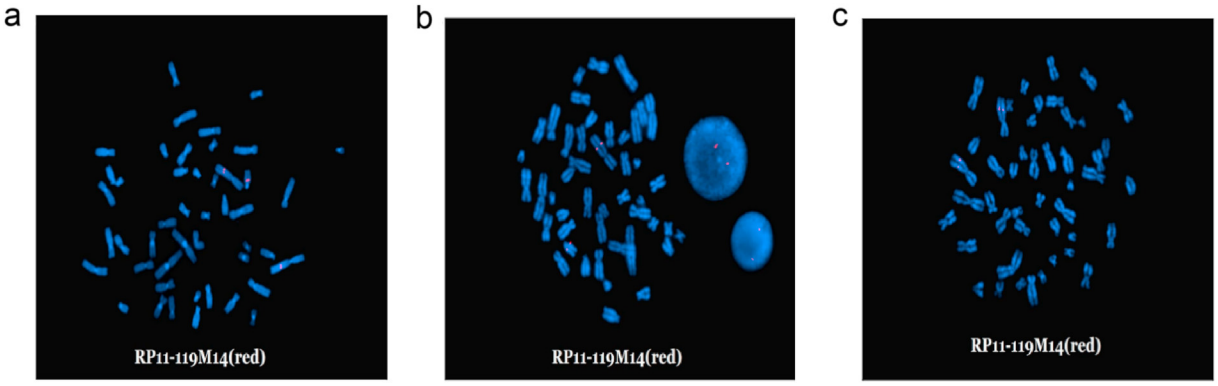

Fig. 3. FISH test of peripheral blood using the probe RP11-119M14. a. The results showed a q24.2-q24.3 fragment of chromosome 2 of the patient was inserted into the q12 region of chromosome 15, resulting in an abnormal chromosome 15; b. The hybridization result revealed that the mother is a carrier of abnormal chromosomes 15 and 2; c. The result of the patient's father is normal.

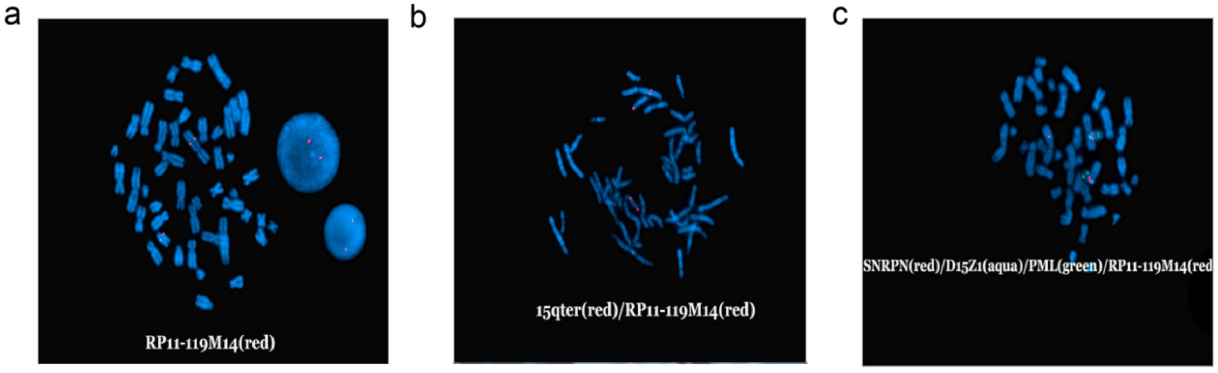

Fig. 4. FISH test of the pateint's peripheral blood using different probes. a. A fragment of chromosome 2 was found to be inserted into chromosome 15 (an acrocentric chromosome) of the patient's mother and detected by the probe RP11-119M14; b. A fragment of chromosome 2 had been inserted into a chromosome 15 of the patient and was detected by the probe RP11-119M14/15qter; c. A fragment of chromosome 2 was inserted into the q11.2 region of chromosome 15 and detected by the probe D15Z1/SNRPN/PML/RP11-119M14.

resulting from few fragmental deletions or duplications.[13–15] Therefore, mutations to SCN1A are responsible for the vast majority of cases of infant epilepsy. Previous study also revealed that in a small number of patients, the deletion or duplication of the *SCN1A* gene has been inherited from one of the parents.[16] This is consistent with our result that a fragment of 2q24.2-q24.3 (RP11-119M14) was inserted into chromosome 15 of the patient's mother. The duplication of this fragment in the fetus may be due to chimeric mutations in the germ cells of her mother.

Mutaions in *SCN2A* are thought to be associated with benign familial neonatal-infantile seizure (BFNIS), Dravet syndrome (DS), genetic epilepsy with febrile seizure plus (GEFS^{+}), and early onset epileptic encephalopathies (EOEE).[17–20] Mutations in *SCN3A* have also been detected in patients with epilepsy,[21,22] albeit less frequently. Unfortunately, clinical effects of this haploinsufficiency are not yet clear.

5. Conclusion

The deletion of the sodium channel gene cluster (SCN1A, SCN2A, and

SCN3A), but not SCN1A alone, may contribute to the complex infant epilepsy syndrome of a two-and-a-half-year-old girl. Due to limited reports on the number of 2q24.2-2q24.3 deletion/duplication cases, more data is needed to improve our understanding of epilepsy related thereto and its pathogenic mechanism.

Ethics approval and consent to participate

Ethics approval was obtained from the Research Review Board of Urumqi Maternal and Child Health Care Hospital. A written informed consent was obtained from the patient's parents to publish this case report and any relevant images. A copy of the written consent can be available for review by the Editor-in-Chief of this journal.

Consent for publication

The patient provided a written informed consent for publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contribution

Lin Zhang: Conceptualization and draft editing; Wen-cheng Dai: SNP array analysis, FISH test and draft preparation; Xue-xia Liu, Gui-ning Song AND Cheng-ling Zhang: data analysis and draft reviewing; Yan-hui Li: Clinical symptom analysis; DNA extraction and Karyotype analysis. All authors have read, revised and agree to the published version of the manuscript.

Acknowledgements

This work was supported by Natural Science Foundation of Xinjiang Uygur Autonomous Region [No.2018D01A50].

References

1. Berg AT. Epilepsy, cognition, and behavior: the clinical picture. *Epilepsia*. 2011; 52(Suppl 1):7–12. https://doi.org/10.1111/j.1528-1167.2010.02905.x.
2. Takatsuki S, Nakamura R, Haga Y, et al. Severe pulmonary emphysema in a girl with interstitial deletion of 2q24.2q24.3 including *itgb6*. *Am J Med Genet*. 2010;152A(4): 1020–1025. https://doi.org/10.1002/ajmg.a.33362.
3. Goeggel SB, Rieubland C, Courage C, et al. Duplication of the sodium channel gene cluster on 2q24 in children with early onset epilepsy. *Epilepsia*. 2012;53(12): 2128–2134. https://doi.org/10.1111/j.1528-1167.2012.03676.x.
4. Celle ME, Cuoco C, Porta S, et al. Interstitial 2q24.3 deletion including *SCN2A* and *SCN3A* genes in a patient with autistic features, psychomotor delay, microcephaly and no history of seizures. *Gene*. 2013;532(2):294–296. https://doi.org/10.1016/j.gene.2013.09.073.
5. Lim BC, Min BJ, Park WY, et al. A unique phenotype of 2q24.3-2q32.1 duplication: early infantile epileptic encephalopathy without mesomelic dysplasia. *J Child Neurol*. 2014;29(2):260–264. https://doi.org/10.1177/0883073813478659.
6. Zhao P, Mao B, Cai X, et al. 2q24 deletion in a 9-month old girl with anal atresia, hearing impairment, and hypotonia. *Int J Pediatr Otorhinolaryngol*. 2018. https://doi.org/10.1016/j.ijporl.2018.03.031.
7. Belengeanu V, Gamage TH, Farcas S, et al. A de novo 2.3 Mb deletion in 2q24. 2q24. 3 in a 20-month-old developmentally delayed girl. *Gene*. 2014;539(1):168–172. https://doi.org/10.1016/j.gene.2014.01.060.
8. Krepischi ACV, Knijnenburg J, Bertola DR, et al. Two distinct regions in 2q24. 2-q24. 3 associated with idiopathic epilepsy. *Epilepsia*. 2010;51(12):2457–2460. https://doi.org/10.1111/j.1528-1167.2010.02742.x.
9. Langer S, Geigl JB, Wagenstaller J, et al. Delineation of a 2q deletion in a girl with dysmorphic features and epilepsy. *Am J Med Genet*. 2006;140(7):764–768. https://doi.org/10.1002/ajmg.a.31141.
10. Mulley JC, Hodgson B, Mcmahon JM, et al. Role of the sodium channel *SCN9A*in genetic epilepsy with febrile seizures plus and Dravet syndrome. *Epilepsia*. 2013; 54(9). https://doi.org/10.1111/epi.12323.
11. Raymond G, Wohler E, Dinsmore C, et al. An interstitial duplication at 2q24.3 involving the *SCN1A, SCN2A, SCN3A* genes associated with infantile epilepsy. *Am J Med Genet A*. 2011;155A(4):920–923. https://doi.org/10.1002/ajmg.a.33929.
12. Vecchi M, Cassina M, Casarin A, et al. Infantile epilepsy associated with mosaic 2q24 duplication including *SCN2A* and *SCN3A*. *Seizure*. 2011;20(10):813–816. https://doi.org/10.1016/j.seizure.2011.07.008.
13. Wallace RH, Hodgson BL, Grinton BE, et al. Sodium channel alpha1-subunit mutations in severe myoclonic epilepsy of infancy and infantile spasms. *Neurology*. 2003;61:765–769. https://doi.org/10.1212/01.wnl.0000086379.71183.78.
14. Sharkia R, Hengel H, Schls L, et al. Parental mosaicism in another case of dravet syndrome caused by a novel scn1a deletion: a case report. *J Med Case Rep*. 2016; 10(1). https://doi.org/10.1186/s13256-016-0854-2.
15. Escayg AP, Macdonald BT, Meisler MH, et al. Mutations of *SCN1A*, encoding a neuronal sodium channel, in two families with GEFS+2. *Nat Genet*. 2000;24(4): 343–345. https://doi.org/10.1038/74159.
16. Wirrell EC, Lau L, Donner E, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a North American consensus panel. *Pediatr Neurol*. 2017;68:18. https://doi.org/10.1038/74159.
17. Shi X, Yasumoto S, Nakagawa E, et al. Missense mutation of the sodium channel gene *SCN2A* causes Dravet syndrome. *Brain Dev*. 2009;31(10):758–762. https://doi.org/10.1016/j.braindev.2009.08.009.
18. Shi X, Yasumoto S, Kurahashi H, et al. Clinical spectrum of *SCN2A* mutations. *Brain Dev*. 2012;34(7):541–545. https://doi.org/10.1016/j.braindev.2011.09.016.
19. Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. *Lancet*. 2002;360(9336):851–852. https://doi.org/10.1016/S0140-6736(02)09968-3.
20. Nakamura K, Kato M, Osaka H, et al. Clinical spectrum of *SCN2A*mutations expanding to Ohtahara syndrome. *Neurology*. 2013;81(11):992–998. https://doi.org/10.1212/WNL.0b013e3182a43e57.
21. Holland KD, Kearney JA, Glauser TA, et al. Mutation of sodium channel *SCN3A*in a patient with cryptogenic pediatric partial epilepsy. *Neurosci Lett*. 2008;433:65–70. https://doi.org/10.1016/j.neulet.2007.12.064.
22. Vanoye CG, Gurnett CA, Holland KD, et al. Novel *SCN3A* variants associated with focal epilepsy in children. *Neurobiol Dis*. 2014;62:313–322. https://doi.org/10.1016/j.nbd.2013.10.015.