

# Hemiconvulsion-Hemiplegia-Epilepsy syndrome with 5q33.3q34 microdeletion: causal or chance association

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## Case report

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# Abstract

## Background

Hemiconvulsion–hemiplegia–epilepsy (HHE) syndrome is a rare syndrome characterized by childhood onset partial motor convulsions, hemiplegia, and epilepsy in sequence. Exact pathogenesis is not clear.

## Case presentation:

We present a girl with global developmental delay with history and brain MRI consistent with the diagnosis of HHE syndrome. The cytogenetic microarray (CMA) showed 9.1 Mb deletion in 5q33.3q34 region. Along with HHE syndrome, the patient also had global developmental delay. Clinical phenotype of this microdeletion region has not been described in association with HHE syndrome in the literature. We compared the patient's phenotype with other patients in 5 previously published papers of a common region of deletion spanning 157501989–164166203. GABRA1, GABRB2, GABRG2, CYFIP2, THG1 are the important genes in the present deleted region, which may be responsible for the fever sensitivity and global developmental delay.

## Conclusions

This is the first case of HHE syndrome in which CMA showed a microdeletion of 5q33.3q34 region. This case report links HHE syndrome and global developmental delay to microdeletions of 5q33.3q34, which has never been reported in literature. Cause of HHE syndrome remains unexplained in present case and HHE may be a causal or chance co-occurrence.

## Background

The hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome was first described by Gastaut et al. [1]. It is a rare sequel of prolonged focal status epilepticus during childhood, which is characterized by childhood onset partial motor convulsions, hemiplegia, and epilepsy in sequence [2]. Exact pathogenesis is not clear. Here we describe a 3.5-year-old girl who presented to us with HHE syndrome and cytogenetic microarray (CMA) showed 9.1 Mb deletion in 5q33.3q34 region.

## Case Presentation

Our patient was born to a non-consanguineous couple. There was no family history of congenital metabolic errors or neuromuscular diseases. Antenatal and perinatal periods were uneventful and birth weight was 3.5 kg. Her motor and language development lagged behind that of children her age. She could sit at 9 months and walk at 2 years old. She could call "Papa" at 1 year old, and speak consecutive sentences with poor expression at 3 years old.

At the age of 3.5 years old, she had presented with a cluster of 3 febrile convulsions (38°C) within approximately 6 hours. At first, the convulsion was characterized by prolonged eyes stare, lip cyanosis, limbs stiffness and jitter, and loss of consciousness. The total duration of the episode was around 20 minutes and ceased by diazepam at the local hospital. After 5 minutes of remission, convulsion appeared again, with the same manifestation pattern, lasting for about 2 minutes and then self-reliving without medications. At the process of being transferred to our hospital, convulsions appeared again, characterized by mouth twitch, left arm and leg jitter, with fecal incontinence, which was successfully treated with diazepam. At the first admission to our unit, routine serological laboratory examinations showed elevated glutamic-pyruvic transaminase (102 U/L) and glutamic-oxalacetic transaminase (641 U/L). Cerebrospinal fluid (CSF) analysis were normal. Metabolic investigations were all normal and included a blood glucose, ammonia, lactate, blood gas analysis, plasma amino acids, and urine metabolic screen. Cranial magnetic resonance imaging (MRI) showed no significant abnormality (Fig. 1). Electroencephalography (EEG) showed asymmetric rhythm with slow and low amplitude electrical activity in the left hemisphere. In the first few days of hospitalization, she still had convulsions, mainly manifested as twitching of the mouth, which could be self-relieved. She was found to have a right hemiplegia. At the 5th day of admission, cranial MRI was rechecked and showed diffuse swelling of the left cerebral hemisphere (Fig. 1). Magnetic resonance angiography (MRA) showed multiple cerebral artery stenosis. Her karyotype at 550-band level was normal. Due to presence of global developmental delay and seizure we performed CMA (Affymetrix 2.7 M array) on DNA extracted from leukocytes. CMA report showed presence of 9.1 Mb deletion on chromosome 5q33.3q34 (CMA report-arr5q33.3q34 (155881647–164960115) X1) (Fig. 2).

At her age of 4 years and 2 months, she re-presented with a 3-hour convulsion with febrile (38.2°C), which presented as generalized tonic-clonic seizure for about 1 hour and then right-sided motor seizure for about 2 hours. The seizure stopped only after several doses of phenobarbitone, diazepam and midazolam. She had a prolonged right-sided hemiparesis. The right-sided hemiparesis persisted. During the hospitalization, she still had several focal seizures involving right side of body. Then she was given oxcarbazepine. Cranial computerized tomography (CT) scan revealed atrophy of the left cerebral hemisphere, widened sulci, and dilated lateral ventricles (Fig. 1). On the basis of characteristic history and brain MRI findings, diagnosis of HHE syndrome was made.

She still had repeated slight seizures even on oxcarbazepine, 1–3 times a day. One month after the last discharge, she re-presented with an afebrile right-sided motor seizure for 10 minutes. Then levetiracetam was added in combination with oxcarbazepine. 2018

On follow-up, at age 6 years 4 months, she had a residual right hemiparesis in her right hand. She still had cognitive delays, could understand commands and speak a small amount of language. She continued to have mild epileptic seizures with a combination of oxcarbazepine (36mg/kg/d) and levetiracetam (40mg/kg/d), presenting with body tremors 1–2 times a day.

## Discussion And Conclusions

We present a girl with global developmental delay with history and brain MRI consistent with the diagnosis of HHE syndrome. CMA analysis showed microdeletion on 5q33.3q34 region. Microdeletion of 5q33.3q34 region has not been described in association with HHE syndrome in the literature.

Five patients and the present patient showed a common region of deletion spanning 157501989–164166203 (Fig. 2). The genes located in the common shared region are GABRA1, GABRB2, GABRG2, GABRA6, IL12B, HMMR. Phenotypes of the 5 patients mainly included global developmental delay, intellectual disability and autistic behavior. Consistent with the previous reports, our patient had delayed speech and motor development. This is the first time to report a patient with HHE in this region of deletion. Along with the size of microdeletion, reduced penetrance, variable expressivity, and co-inheritance of various other copy number variants may be responsible for the observed clinical variability.

The involved region in present patient harbors few morbid genes including GABRA1, GABRB2, GABRG2, HAVCR2, ITK, CYFIP2, NIPAL4, THG1L, IL12B, HMMR. Out of these genes, the pathogenicity of GABRA1, GABRG2, GABRB2, CYFIP2, THG1L, has been described in relation to neurological diseases.

GABRA1, GABRB2, GABRG2 encode different subunits of functional GABA<sub>A</sub> receptors, which are heteropentameric, ligand-gated chloride ion channels that are activated by gamma-aminobutyric acid (GABA) to mediate both phasic synaptic transmission and tonic extrasynaptic inhibition in the brain. The mutations of GABRA1, GABRB2, GABRG2, through a possible mechanism of haploinsufficiency, cause an impairment of the GABA inhibitory function leading to a wide spectrum of epilepsy phenotypes [3]. The phenotypic spectrum among GABRA1, GABRB2, GABRG2 mutations was similar, ranging from febrile seizures, genetic (generalized) epilepsy with febrile seizures plus (GEFS+), idiopathic generalized epilepsy, to severe epileptic encephalopathies such as Dravet syndrome, infantile spasms, Lennox-Gastaut syndrome, etc. [4–10]. Fever sensitivity was observed in quiet a few patients carrying GABRA1, GABRB2, GABRG2 mutations [6,7,10]. Consistent with the characteristic of HHE syndrome that prolonged focal motor seizure usually occurs during the course of a febrile illness [2], the present patient's first two prolonged convulsions were both accompanied by fever. So, it is reasonable to speculate that the microdeletion here involving GABRA1, GABRB2, GABRG2 may play a role in the pathogenesis of HHE syndrome.

Besides, the morbid genes CYFIP2 and THG1L contribute to early infantile epileptic encephalopathy-65 (EIEE-65) and autosomal recessive spinocerebellar ataxia-28 (SCAR28) respectively [11, 12], which can lead to severe or mild psychomotor developmental delay, and may explain the presence of global developmental delay in present patient.

In addition to the genes associated with neurological diseases involved in the deletion region above, the HAVCR2 gene encodes a critical negative regulator in the immune system, acting as a negative checkpoint in peripheral tolerance and innate immune and inflammatory responses [13]. And it has been hypothesized that proteins involved in immune function, inflammation or thrombotic abnormalities participate in the pathogenesis of HHE [14].

This is the first case of HHE syndrome in which CMA showed a microdeletion of 5q33.3q34 region. This case report links HHE syndrome and global developmental delay to microdeletions of 5q33.3q34, which has never been reported in literature. Cause of HHE syndrome remains unexplained in present case and HHE may be a causal or chance co-occurrence. The function of many genes in this region is still not well established and their association with clinical phenotype cannot be explained. CMA analysis in more cases with HHE syndrome may help us in identifying pathogenic mechanism behind this rare condition.

## **List Of Abbreviations**

HHE: hemiconvulsion–hemiplegia–epilepsy; CMA: cytogenetic microarray; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; EEG: electroencephalography; MRA: magnetic resonance angiography; CT: computerized tomography; GABA: gamma-aminobutyric acid; GEFS+: genetic (generalized) epilepsy with febrile seizures plus; EIEE-65: early infantile epileptic encephalopathy-65; SCAR28: autosomal recessive spinocerebellar ataxia-28.

## **Declarations**

### **Ethical approval and consent to participate**

The study was approved by the Ethical Committee of Affiliated Hospital of Qingdao University. Written consent was obtained from the guardian of the child prior to data collection.

### **Consent for publication**

We obtained the written consent for publication from the guardian of the patient.

### **Availability of data and materials**

The datasets generated and analyzed during the current study are all shown in the manuscript.

### **Competing interests**

The authors declare no conflict of interest.

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### **Authors' contributions**

Jiao Xue: Conceptualization, Investigation, Validation, Writing-Original Draft; Zhenfeng Song, Zhi Yi: Formal analysis; Chengqing Yang: Validation; Fei Li: Visualization; Kaixuan Liu: EEG analysis; Ying Zhang: Supervision, Resources, Project administration. All authors critically reviewed the manuscript, participated in its revision and approved the final manuscript.

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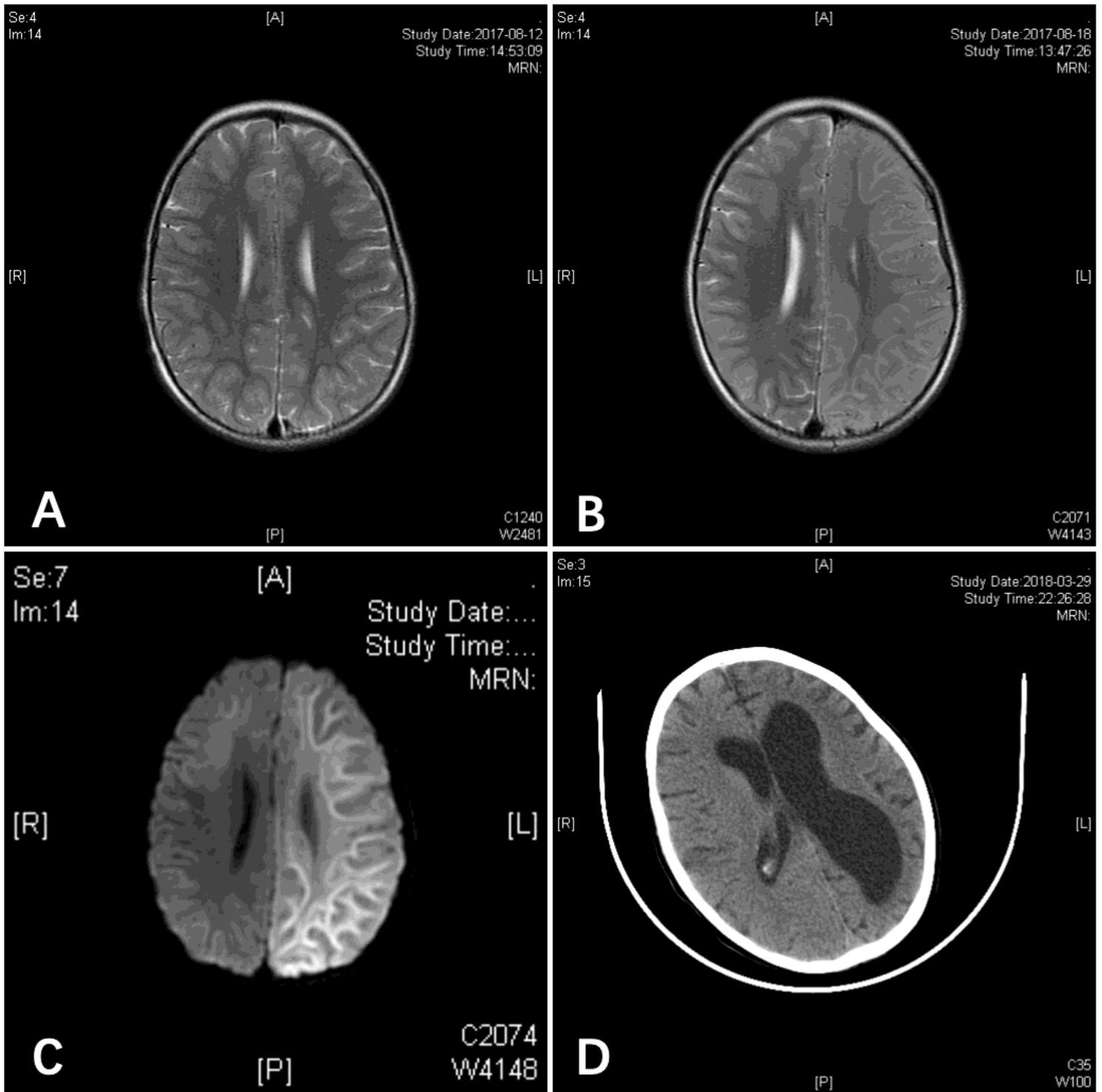
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## Figures



**Figure 1**

Summary of the MRI findings. Cranial MRI showed no significant abnormality at first (A), and then diffuse swelling of the left cerebral hemisphere (B-C). Cranial CT scan revealed atrophy of the left cerebral hemisphere, widened sulci, and dilated lateral ventricles several months later (D).



**Figure 2**

Cytogenetic microarray showing 9.1 Mb deletion on chromosome region 5q33.3q34. Deleted segments in five patients with deletion 5q33.3q34: they shared a common region from break points 157501989–164166203. It contains genes GABRA1, GABRB2, GABRG2, GABRA6, IL12B, HMMR.

## Supplementary Files

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