

Severe carbamazepine-induced drug reaction and whole genome analysis: case report

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Case report

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Abstract

Background Carbamazepine is an important treatment for epileptic disorders, bipolar disorder and trigeminal neuralgia. However, some patients would suffer from cutaneous adverse drug reactions (cADRs) after taking it. At present, the carbamazepine-induced drug reaction has a great relationship with genetic diversity. The present study reported a patient who presented with rash after starting carbamazepine, and a whole genome analysis was reported. Case presentation A 17-year-old girl was transferred to our Neurology Department with symptoms of painful neck and seizures. Skull computerized tomography (CT) revealed subarachnoid hemorrhage. Electroencephalogram (EEG) revealed sharp waves, spikes slow waves and sharp slow waves. The clinical diagnosis of subarachnoid hemorrhage and symptomatic epilepsy were made through a series of inspections. Carbamazepine was administered. The patient presented with rash at six days after starting carbamazepine, and presented with a striking clinical drug reaction. Hence, a whole genome analysis was carried out. And the Met1080Val mutation was found in the SCN4A gene (SCN4A: c.3238T>C|p.Met1080Val). Discussion The result revealed that the mutation of Met1080Val in the SCN4A gene was associated with the carbamazepine-induced drug reaction. However, this conclusion needs to be confirmed by a large number of clinical data and related functional mechanisms.

Background

Carbamazepine is an extensive prescription drug that is used not only as a first-line antiepileptic drug, but also for the treatment of trigeminal and bipolar disorders [1,2]. Although this is generally well-tolerated, up to 10% of patients would suffer from cutaneous adverse drug reactions (cADRs) [2]. These cADRs can be classified as light or heavy. Light cADRs include maculopapular eruption (MPE), while heavy cADRs include hypersensitivity syndrome (HSS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The morbidity rate of heavy cADRs are low, but the mortality rate can reach as high as 40% [3]. In the present study, a patient presented with carbamazepine-induced drug reaction, and a whole genome analysis was reported.

Case Presentation

A 17-year-old girl was admitted to the Intensive Care Unit of the Neurology Department due to painful neck with seizures. The patient had painful neck after waking up at noon, and she was not taken seriously at that time. However, she felt that the neck pain was aggravated and both limbs were weakened after washing her face. Hence, she sat down to rest. Shortly thereafter, the patient's friends reported that she had tonic-clonic movements with consciousness, with both arms flexed and both feet extended. The duration of movements was unknown. Furthermore, she felt headache accompanied by one episode of nausea and vomiting after awakening. The patient took no other medications, and had no other known allergies. Furthermore, there was no history of surgery, intracranial infection, or family history of seizures.

On examination, the patient's temperature was 37.7°C, blood pressure was 110/60 mmHg, pulse was 92 beats per minute, and respiratory rate was 18 breaths per minute. Furthermore, the detailed neurological examination revealed that the patient had low consciousness, and the remaining examination results were normal.

The skull computerized tomography (CT) revealed subarachnoid hemorrhage (Fig. 1). Digital subtraction angiography (DSA) exhibited poor development of the right transverse sinus in the venous phase, but no significant abnormal signs were seen in the remaining brain vessels (Fig. 2). Electroencephalogram (EEG) revealed sharp waves (120-150 μ V, 5 Hz), spikes slow waves and sharp slow waves (110-280 μ V, 2-3 Hz) (Fig. 3). The laboratory results revealed that the complete blood count, blood sedimentation rate, electrolytes, liver-function test, renal-function test, urine routine and stool routine were generally normal.

On the first day, carbamazepine was administered (50 mg, thrice daily) to prevent further convulsions. Then, the dose of carbamazepine was changed (100 mg, thrice daily) on the third day. On the second day, a lumbar puncture was performed. The analysis of the cerebrospinal fluid (CSF) revealed a red turbid fluid with a glucose level of 2.67 mmol/L (reference range: 2.5-3.9) and a total protein level of 0.30 g/L (reference range: 0.10-0.45), as well as 26,758 $\times 10^6$ red cells per liter (reference range: 0) and 14 white cells per liter (reference range: 0-8). The patient presented with a rash in the right thumb on the 6th day. Then, the patient presented with sore throat, especially after eating and drinking, and fever. Afterwards, the rash progressed to the arms, chest and back on the 13th day (Fig. 4a). The examination revealed that the patient's temperature was 37.7°C. The investigation reports revealed an elevated blood sedimentation rate. Carbamazepine was immediately stopped, and the patient was treated by topical antiallergic agents. However, within the next two days, the soreness of throat was aggravated with generalized rash all over the body, followed by hyperemic conjunctivae (Fig. 4b). Hence, the patient was started on tapering doses of steroids. The patient's skin symptoms and laboratory abnormalities started improving on the 24th day of hospitalization (Fig. 4c-d). The related inspections were completed, such as ultrasonic cardiogram (UCG) and brain magnetic resonance imaging (MRI). All inspections results were generally normal. The patient was discharged from hospital on the 30th day after admission.

The methods for the whole exome sequencing (WES) for exome capture, exon-enriched DNA library construction, sequencing, genotyping and variant analysis has been previously reported[4]. The DNA was extracted from blood using QIAamp DNA Kit (Qiagen). The integrity was confirmed by agarose gel electrophoresis. At the same time, the integrity was measured through Nanodrop and Qubit. The WES libraries were constructed using the built-in library process recommended by illumine, including DNA cleavage by ultrasound, end repair, 3'-end adenylation, indexed pair-end adaptors ligation, ligation products purification, and PCR amplification. Then, the samples were applied to the SeqCap EZ capture kit (Roche) for exome capture. After the PCR amplification, purification, library validation, normalization and pooling, the libraries were sequenced using an Illumina HiSeq Series Analyzer. Then, the sequencing fastq dates were mapped to the human genome (hg19) using the BWA software. The compared BAM files were generated to index using samtools software. The BAM files with the index were labeled with PCR repeat reads via the Picard software, and the GATK software was used for base quality recalibration

and INDEL re-mapping. The resulting BAM files were imported to the VARSCAN2 software to seek for germline mutations, and the fpfilter module of VARSCAN was applied to identify false-positive variations. The filtered mutations were annotated using the SNPEFF software. Finally, mutations that have been recorded in connection with the drug reaction were inquired. Met1080Val mutations in the SCN4A gene was found by whole genome analysis (SCN4A: c.3238T>C]p.Met1080Val) (Fig. 5).

Discussion And Conclusions

At present, the diagnosis of the carbamazepine-induced drug reaction mainly depends on the typical clinical manifestations. Genetic mutation screening can be used to determine whether known mutations have appeared, thereby reducing the incidence of drug reaction in the treatment process. In the present case, the main clinical manifestations were painful neck and seizures. Furthermore, the skull computerized tomography revealed subarachnoid hemorrhage, and the electroencephalogram revealed sharp waves, spikes slow waves and sharp slow waves. So the clinical diagnosis of subarachnoid hemorrhage and symptomatic epilepsy were made. Carbamazepine was administered. Then, the rash appeared and the range extended from the fingers to the whole body. The drug reaction gradually improved after stopping carbamazepine and taking topical antiallergic agents and steroids. It was considered that the drug reaction was caused by carbamazepine. The Met1080val mutation of the SCN4A gene was detected by whole genome analysis. Whole genome analysis can detect a variety of comprehensive mutations related to human diseases, such as single-nucleotide mutation, insertion-deletion, copy number variation and structural variation, at the whole genome level. Hence, human beings can fundamentally understand the causes of diseases, choose the correct treatment, and prevent diseases as early as possible.

At present, the mechanism of carbamazepine-induced drug reaction remains not fully understood. The hottest research is the relationship between genetic diversity and carbamazepine-induced drug reaction, particularly the HLA gene polymorphism. A large number of studies have reported that HLA-B*1502 and HLA-A*3101 alleles were importantly associated with the carbamazepine-induced drug reaction. The US FDA suggested that the HLA-B*1502 allele was highly associated with the outcome of carbamazepine-induced SJS and TEN in the Asian population, especially in the Han population. In addition, at least two studies have revealed that there was no such correlation among Caucasians [5]. Ozeki et al. conducted a study on the HLA-A*3101 allele and found that 60.7% of the patients had carbamazepine-induced cADRs in Japan, while only 12.5% were carbamazepine-tolerant controls. In addition, they implied that the HLA-A*3101 allele was a risk predictor of carbamazepine-induced cADRs with 60.7% sensitivity and specificity, which could reach 87.5% [6]. Other gene polymorphisms were also closely correlated to the carbamazepine-induced drug reaction. A logistic regression analysis with multiple clinical variables strongly suggested that the A-allele of the MRP2 single nucleotide polymorphism c.1249G>A was associated with the carbamazepine-induced neurological adverse drug reactions [7]. Alfirevic et al. found that HSP70 gene variants were associated with serious carbamazepine hypersensitivity reactions through analyzing 61 cases of carbamazepine allergy, 44 non-allergic patients, and 172 healthy controls [8]. With

the gradual application of precision medicine in clinical practice, more and more gene polymorphisms associated with carbamazepine-induced drug reaction have been found.

However, it is well-known that the mechanism of drug reaction is mainly associated with the drug-induced immune response. Drugs, as small molecules, belong to semi-antigens, which cannot cause immune response. The T-cell-mediated immune response be activated by combining with proteins or other vectors to form a complete antigen in vivo, or becoming a precursor substance with antigenic determinant after liver metabolism. In vitro, the drug-induced proliferation of peripheral blood mononuclear cells (PBMC) from patients allergic taking carbamazepine confirmed the involvement of drug-specific T-cells in drug allergies [9]. Wu et al. revealed that carbamazepine-specific CD4+, CD8+ and CD4+CD8+ T-cells were found in the peripheral circulation of five hypersensitive patients by using modified cloning methodologies [10]. Furthermore, the great majority of carbamazepine-specific clones express CD4+ T-cells and approximately 10% of clones express CD8+ T-cells [11,12]. The cells involved in carbamazepine-induced MPE immune response were mainly CD4+ T-cells [11]. While a large number of CD8+ T-cells were found in carbamazepine-induced TEN [13]. Therefore, the carbamazepine-induced drug reaction mediates immune response by activating CD4+ T-cells or CD8+ T-cells.

The SCN4A gene encodes the alpha subunit of the skeletal muscle sodium channel. The alpha subunit, which is a transmembrane glycoprotein, is mainly distributed in skeletal muscle, and is responsible for regulating the generation and transmission of skeletal muscle action potentials. The present literature reported that the SCN4A gene mutation mainly led to myotonic myopathies and periodic paralysis [PP]. Matthews et al. found that there were more than 20 SCN4A gene mutation sites associated with paramyotonia congenita (PMC) by summing up the HGMD database and the hotspot mutation regions were located in the 22th and 24th exon [14]. Furthermore, there was close relationship between paralysis periodica paramyotonica (PPP) and SCN4A mutations, such as Met1592Val, Arg1448Cys and so on [15,16]. Bugiardini et al. first reported that the variant c.215C>T (p.Pro72Leu) in the SCN4A gene was correlated to myotonic dystrophy type-2 (DM2) [17]. Previous studies had found that many SCN4A gene mutations were associated with hyperkalemic periodic paralysis (HyperKPP), such as Thr704Met, Ala1156Thr, Met1360Val, Ile1495Phe, Met1592Val and so on [18-22]. It was also revealed that Thr704Met, Met1592Val, Val-781-Ile and Arg675Gln mutations were correlated to normokalemic periodic paralysis (NormoKPP) in Chinese families, but there were no differences in the phenotype of these types of mutations and less reporting [23,24]. Similarly, hypokalemic periodic paralysis (HypoKPP) was closely associated with SCN4A mutations, such as R669H, R1135H, R1132Q, P1158S and so on [25-27]. Except for myotonic myopathies and periodic paralysis, SCN4A gene mutations can lead to other illness. Bergareche et al. performed whole exome sequencing analyses in a large Spanish family with essential tremor (ET), and found that the genetic variability of SCN4A was associated with the development of ET [28].

It is known that T-cell developing from immature CD4+CD8+ double-positive thymocyte to mature CD4 or CD8 single-positive stage requires proper T-cell receptor (TCR) signaling. Recent research has confirmed that proteins and miRNAs were correlated to specialized regulators of TCR signaling operating during

thymocyte development. A voltage-gated Na⁺ channel (VGSC) is one of important regulators during positive selection [29]. The VGSC offered a mechanism for the calcium signal, and responded to weak ligands in the ability of immature thymocyte [29,30], which enable CD4⁺T cells and CD8⁺T cells to mature and participate in the immune response. There were 11 genes (SCN1A–SCN11A) encoding a family of nine functionally expressed voltage-gated sodium channels in mammals [31]. It was speculated that SCN4A mutations would increase the activity of the calcium signal and proliferate the CD4⁺T cells and CD8⁺T cells, which would lead to the drug reaction.

The mechanism of carbamazepine-induced drug reaction remains unclear. The hottest research is the relationship between genetic diversity and drug reaction. The determination of whether the Met1080Val mutation of the SCN4A gene is associated with the carbamazepine-induced drug reaction still needs to be confirmed through a large number of clinical data and related functional mechanisms. It has important significance for patients to take carbamazepine.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publish

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Availability of data and material

All data containing relevant information to support the study findings are included in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HY analyzed the data, drafted the manuscript and review; JL acquired clinical data and drafted the manuscript; QZ, YL, MW, QC, YL and FH attended the cases, analyzed data and critically revised the manuscript; HW drafted and revised the manuscript critically, and gave final approval of the version to be published. All authors read and approved the final manuscript.

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Not Applicable

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Abbreviations

cADRs: cutaneous adverse drug reactions;

CT: computerized tomography;

EEG: Electroencephalogram;

MPE: maculopapular eruption;

HSS: hypersensitivity syndrome;

SJS: Stevens–Johnson syndrome;

TEN: toxic epidermal necrolysis;

DSA: Digital subtraction angiography;

CSF: cerebrospinal fluid;

UCG: ultrasonic cardiogram;

MRI: magnetic resonance imaging;

WES: whole exome sequencing;

PBMC: peripheral blood mononuclear cells;

PP: periodic paralysis;

PMC: paramyotonia congenita;

PPP: paralysis periodica paramyotonica;

DM2: myotonic dystrophy type-2;

HyperKPP: hyperkalemic periodic paralysis;

NormoKPP: normokalemic periodic paralysis;

HypoKPP: hypokalemic periodic paralysis;

ET: essential tremor;

TCR: T-cell receptor;

VGSC: voltage-gated Na⁺ channel;

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Figures

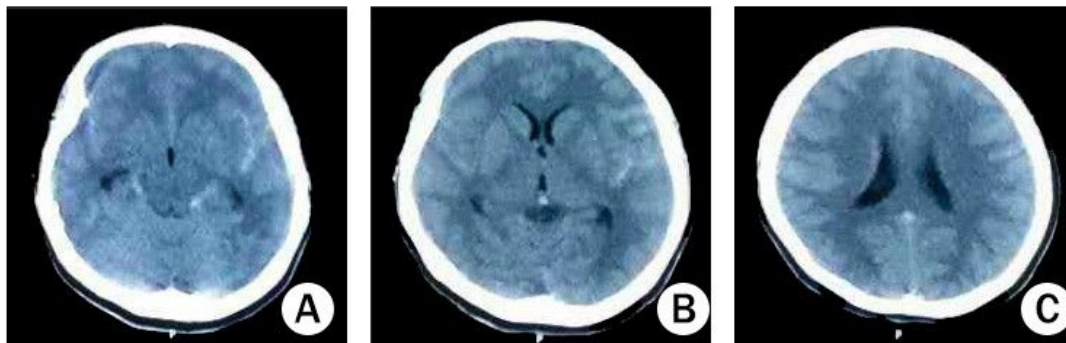


Figure 1

Skull computerized tomography. The skull CT showed subarachnoid hemorrhage.

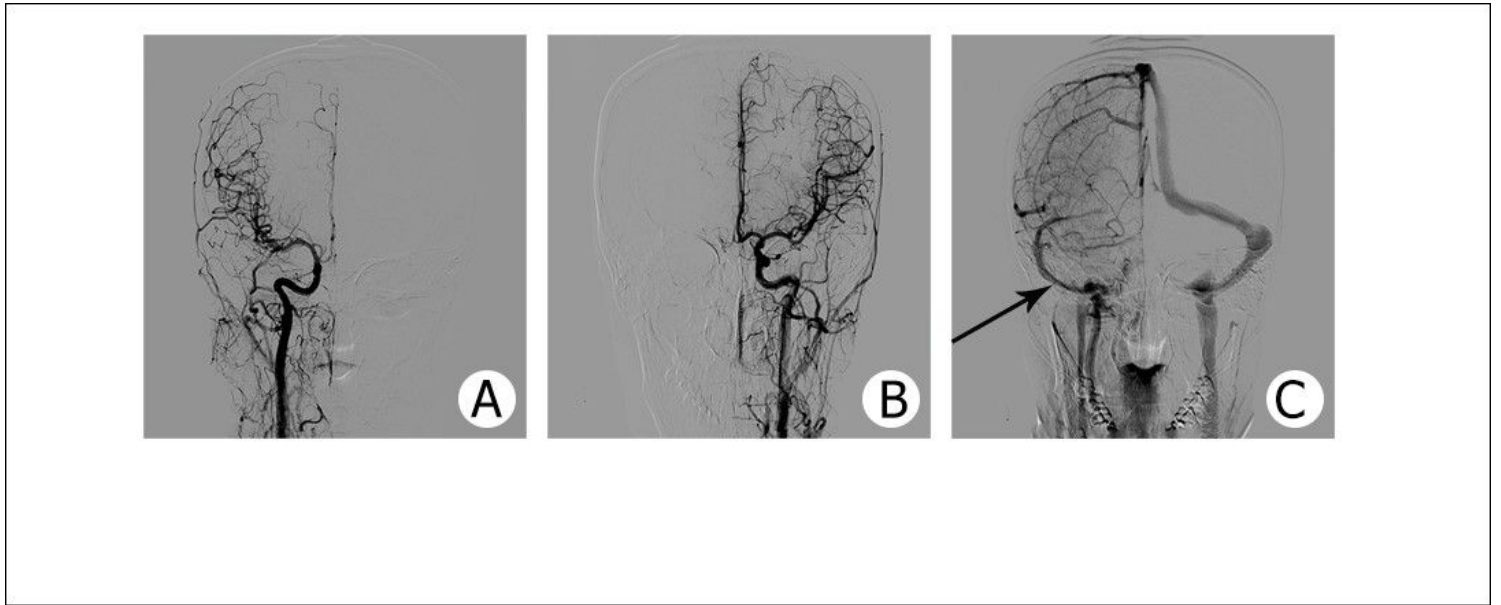


Figure 2

Digital subtraction angiography. a,b The DSA showed normal of bilateral internal carotid artery and its main branches. c Poor development of right transverse sinus in venous phase (black arrow).

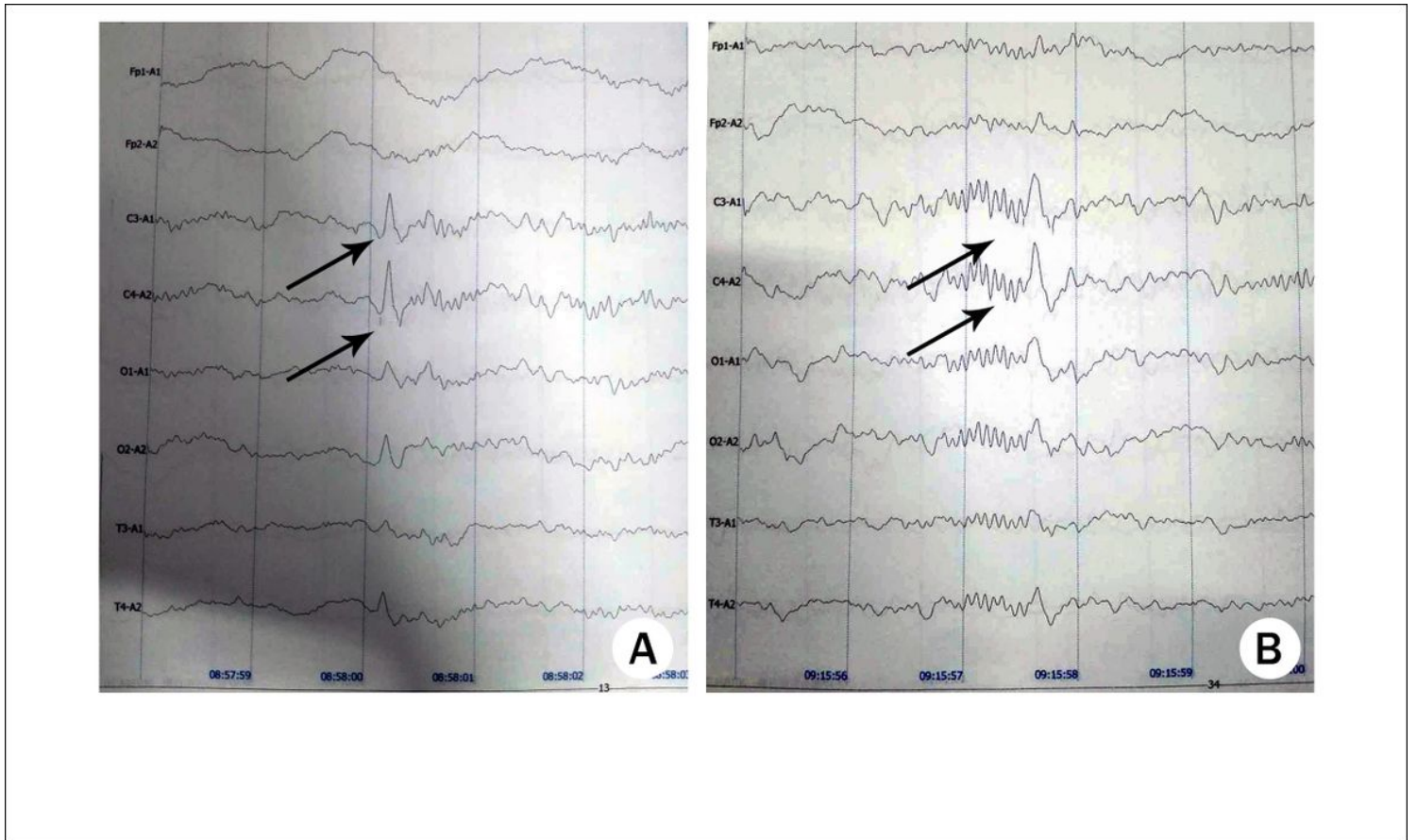


Figure 3

Electroencephalogram. a The EEG showed sharp waves (120-150 μ V, 5Hz) (black arrows). b Sharp slow waves (110-280 μ V, 2-3Hz) (black arrows).

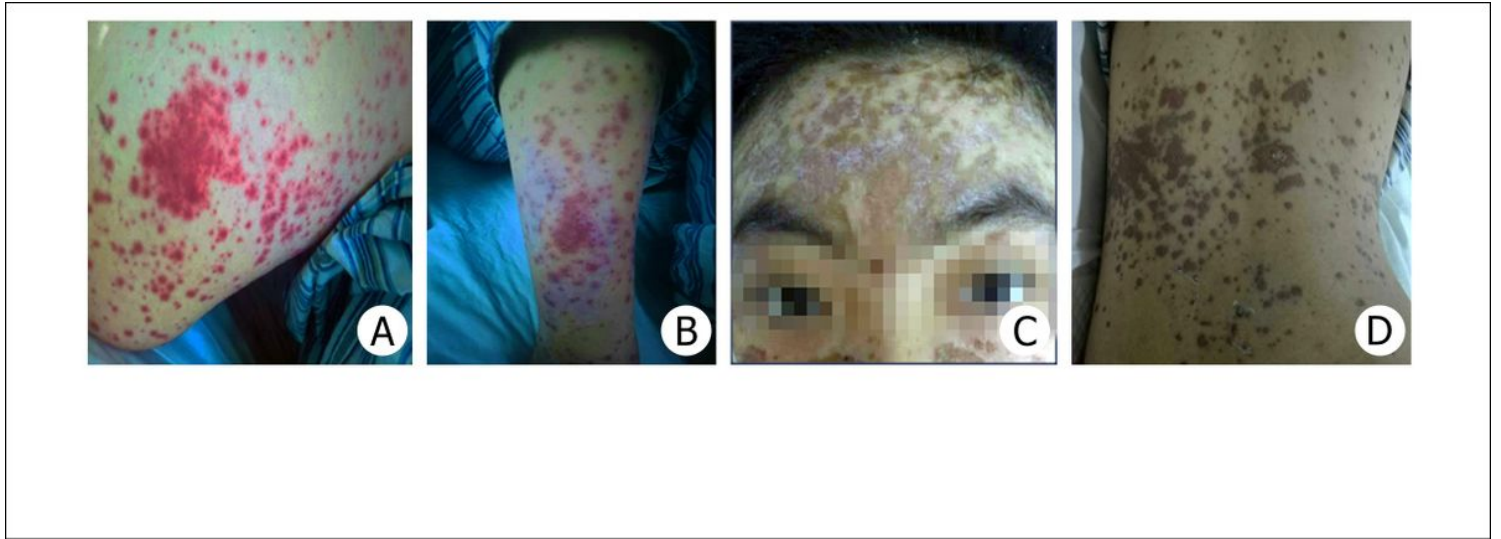


Figure 4

Rash of patient. a The rash of arm on the 13th days. b The rash of leg on the 15th days. c,d The rash of head-face and back on the 24th days.

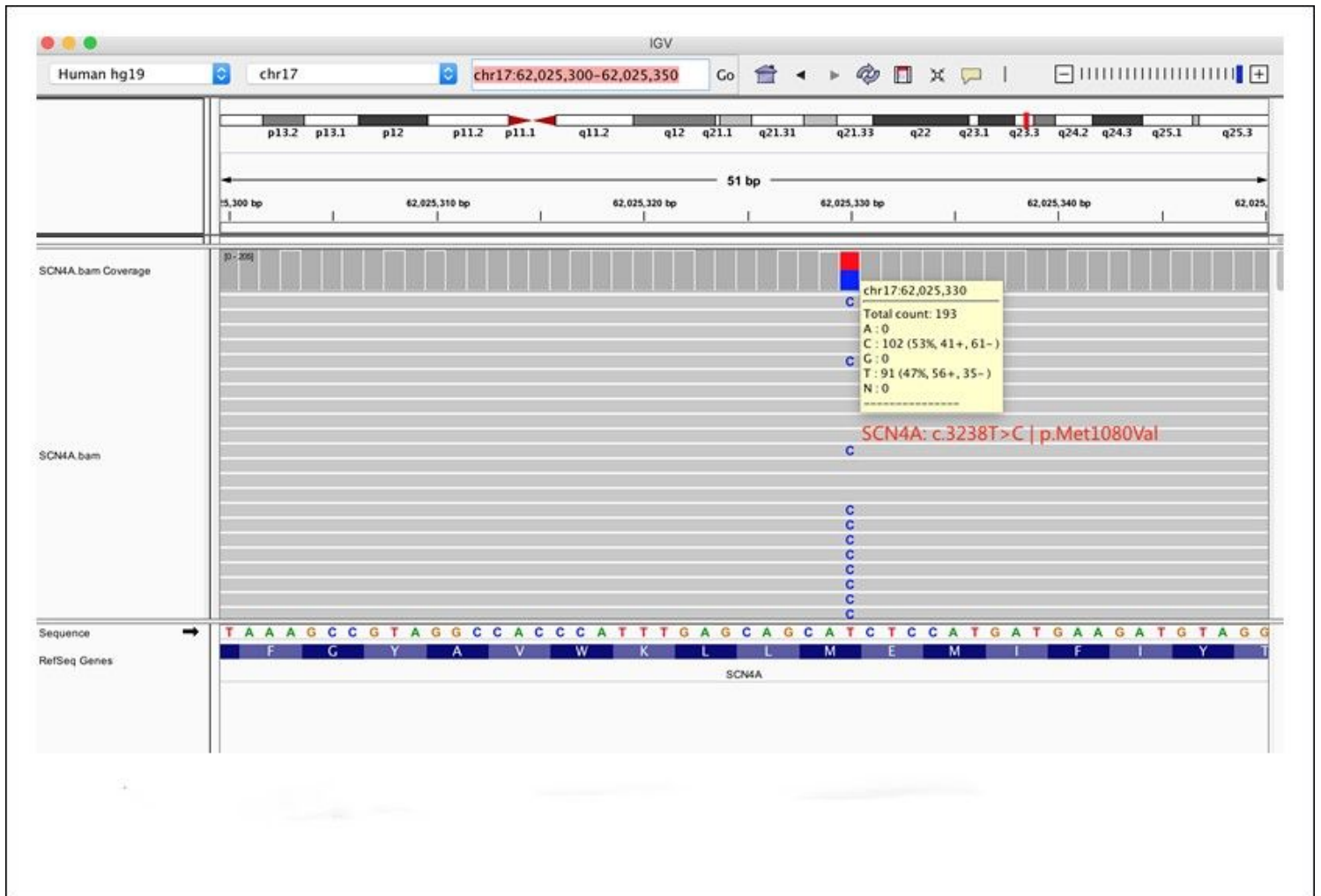


Figure 5

Whole genome analysis. The whole genome analysis showed Met1080Val mutations in SCN4A gene ((SCN4A: c.3238T>C|p.Met1080Val).

Supplementary Files

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