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CLINICAL REPORT

Complex cerebrovascular diseases in Roberts syndrome caused by novel biallelic *ESCO2* variations

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Abstract

Objective: Roberts syndrome (RBS), also known as Roberts-SC phocomelia syndrome, is a rare autosomal recessive developmental disorder caused by mutations in the *ESCO2* gene. Cardinal clinical manifestations are pre- and postnatal growth retardation and craniofacial and limb malformations. Here, we report RBS in a Chinese adolescent with novel biallelic *ESCO2* variations and complex cerebrovascular diseases.

Methods: Medical history, neurological examinations, neuroimaging, and pathology were collected in the proband and the family. Whole exome sequencing (WES) with copy number variation analysis was performed to screen for genetic variations.

Results: The clinical features of the proband were craniofacial and limb malformations together with complex cerebrovascular diseases. She suffered ischemic stroke at 6 years old and died of cerebellar hemorrhage secondary to an aneurysm at 13 years old. Besides, neuroimaging showed the triad of leukoencephalopathy, calcifications, and cysts. Brain histopathology revealed angiomatous changes and perivascular cysts suggesting chronic small cerebral vasculopathy. Whole exome sequencing (WES) identified novel biallelic variations in the *ESCO2* gene (c.1220A>T, p.H407L and c.1562delC, p.A521fs).

Conclusions: We describe complex cerebrovascular diseases in Roberts syndrome caused by novel *ESCO2* biallelic variations. This case expands not only the cerebral involvement in Roberts syndrome but also the disease spectrum of the neuroimaging triad with leukoencephalopathy, calcifications, and cysts.

KEYWORDS
calcifications, ESCO2, leukoencephalopathy, Roberts syndrome, stroke

1 | INTRODUCTION

Roberts syndrome (RBS), also known as Roberts-SC phocomelia syndrome (RBS OMIM#268300; SC phocomelia OMIM#269000), is a rare autosomal recessive developmental disorder caused by mutations in the cohesion regulator establishment of cohesion 1 homolog 2 (*ESCO2*) (Vega et al., 2005). It was first described in 1919

by John Roberts in affected siblings in a consanguineous Italian family. SC phocomelia was reported as a similar but milder disease by Herrmann et al in 1969. The two syndromes were united as RBS after the discovery that both disorders were due to *ESCO2* mutations (Maserati et al., 1991; Schule et al., 2005; Vega et al., 2010). Patients with RBS are characterized by symmetric hypomelia varying from tetraphocomelia to less severe limb abnormalities and craniofacial abnormalities (Maximo et al., 2021; Okpala et al., 2022; Schneeberger et al., 2020; Vega et al., 2010). Pre- and postnatal growth are delayed, as well as mild-to-severe mental retardation. The upper extremities are more affected than the lower extremities. Other limb abnormalities include oligodactyly with hypoplasia or thumb aplasia, clinodactyly, syndactyly, and flexion contractures of knees, ankles, wrists, or elbows. Craniofacial abnormalities include microcephaly, hypertelorism, hypoplastic nasal alae, malar hypoplasia, micrognathia, midfacial hemangioma, cleft lip/palate, ear malformation, down-slanting palpebral fissure, and corneal opacities. Neurological complications are rarely reported but include optic atrophy, stroke, arterial occlusion, cavernous hemangioma of the optic nerve, and Moyamoya disease (Afifi et al., 2016; Sezer et al., 2019; Vega et al., 2010).

Here, we report Roberts syndrome in a Chinese adolescent with novel biallelic *ESCO2* variations and complex cerebrovascular diseases.

2 | CLINICAL REPORT

2.1 | Case presentation

The proband (II-2) was a 13-year-old girl from a non-consanguineous Han Chinese family living in northern China. She was admitted to our hospital due to headache, dizziness, and vomiting for 2 days. She was full-term and normally delivered with a birth weight of 2.1 kg (<3 SD) and a circumference of 28.3 cm (<3 SD). At birth, facial and limb deformities were noted. Motor development was delayed and mental development was slightly delayed. She suffered from hemiparesis at 8 years old and was diagnosed with ischemic stroke at an outside university hospital. The recovery at that time was adequate, without major sequela. There was no history of hypertension or diabetes.

The proband's parents are healthy. Her elder brother (II-1) was born prematurely at 34 weeks. But he did not receive thorough prenatal examinations. Microcephaly, hypoplastic facial features, and tetraphocomelia were noted at birth. He died shortly after birth without postnatal cytogenetic testing. Her younger brother (II-1) was currently 1 year old without any notable physical and mental abnormalities (Figure 1a).

On physical examination, the proband was short with a height of 137 cm (<3 SD) and weight of 32 kg (<2 SD). Supine blood pressure was 160/96 mm Hg. Her speech was slurred but understandable. Craniofacial malformation

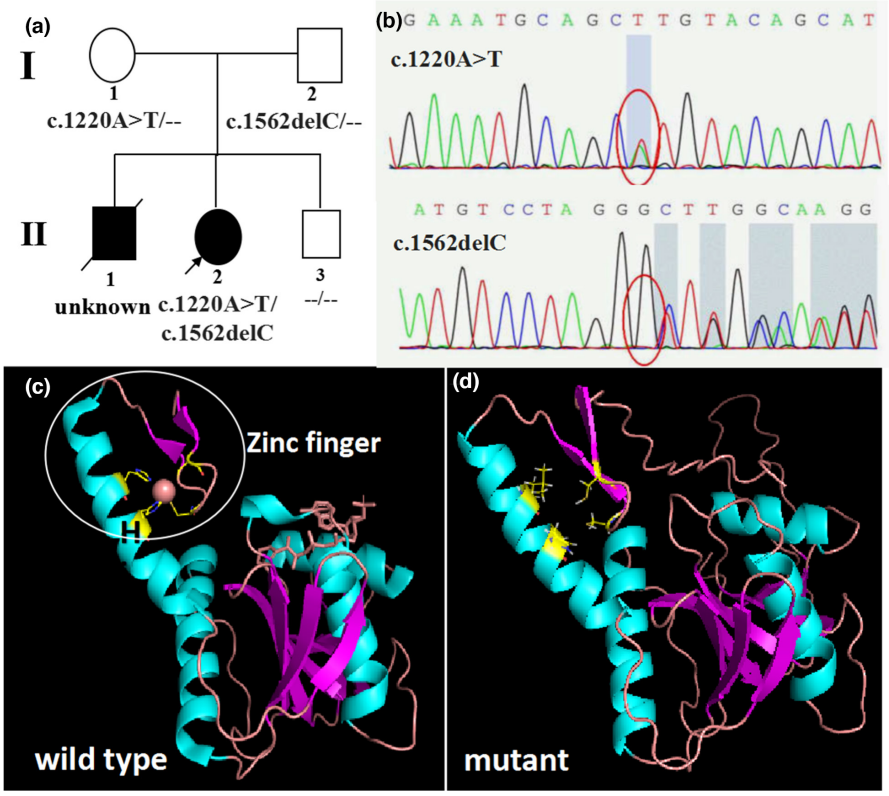

FIGURE 1 Genetic data of the Chinese family with RBS. (a) The family tree. (b) Sanger sequencing of the proband. (c, d) The wild type and mutated zinc finger structure of ESCO2 in mouse. The zinc finger consists of two β-strands and one α-helix, with the zinc ion wrapped in the center for the wild type. The four amino acid residues that directly interact with zinc ion are Cys386, Cys389, His404, and His408, constituting the C2H2 motif. The His407 residue in humans just corresponds to the His404 residue in mouse. The zinc finger formation will be affected when the His residue is mutated to Leu.

included telecanthus and cleft palate. The motion of shoulders, wrists, hips, knees, and ankles were in full range, but elbows were fixed. She could not extend the distal interphalangeal joints of her fingers and toes. Neurological examinations revealed intact cranial nerves, muscle strength of grade 4 (Medical Research Council Scale), brisk tendon reflexes, Babinsky sign, and meningeal irritation signs. Wechsler Children Intelligence Scale score was 65 (normal range 90–109).

The proband (II-2) underwent peripheral blood testing and radiological examinations. Peripheral blood tests included complete blood count, serum liver and renal function, electrolytes, glucose, antinuclear antibody profiles, thyroid and parathyroid hormones, vitamin B12, and folic acid levels. Radiographic analyses included brain and chest CT, brain MRI, and ultrasonography of the heart, abdomen, and urinary system.

Brain CT on admission showed cerebellar vermis hemorrhage, multicortical calcifications, and cavities (Figure 2). On MRI, hyperintensities in the cerebellar vermis were noted on T1WI images. Leukoencephalopathy and multilacuna or cysts were noted on T2WI and FLAIR

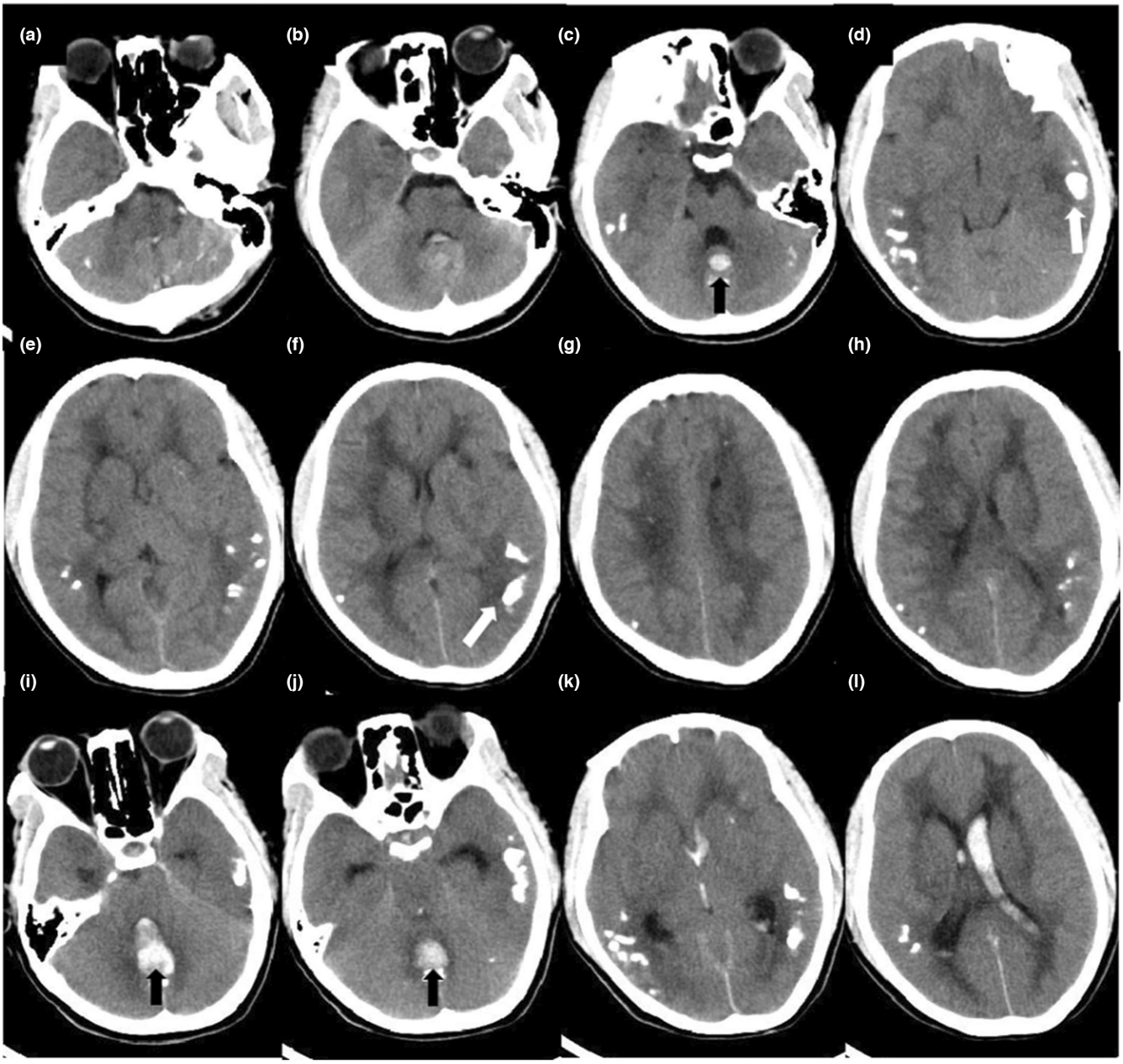

FIGURE 2 Brain CT showed cerebellar hemorrhage, white matter abnormalities, and calcifications. (a–h) First CT images on admission. (i–l) Second CT showed enlarged hemorrhage. White arrows indicate calcifications in the cortex. Black arrows indicate cerebellar vermis hemorrhage and hemorrhage breaking into ventricles.

images (Figure 3). The calcifications seen on CT were less evident on the T1WI and T2WI images. Aneurysms in posterior inferior cerebellar artery and anterior cerebral artery were displayed on 3D-TOF MRA. Cerebellar hemorrhage was secondary to the rupture of the aneurysm in posterior inferior cerebellar artery. She received anti-hypertensive agents. One day later, the patient suddenly became agitated with blood pressure elevating to 210/125 mm Hg. A few minutes later, she was in a coma and lost spontaneous breathing with bilaterally dilated pupils. Bolus mannitol was given intravenously and endotracheal intubation was administered. Subsequent brain CT showed enlarged cerebellar hemorrhage breaking into the lateral and fourth ventricles (Figure 2). She underwent emergent neurosurgery to clear the hematoma. Her condition did not improve and she died 12 days post the operation. Considering her critical condition, X-ray of her extremities was not performed, but adduction and flexion of the elbows due to humeroradial synostosis could be seen on chest CT.

As the proband underwent neurosurgery due to cerebellar hemorrhage, cerebellar tissue was taken for pathological examination. HE staining and special vascular wall staining including elastic fiber (for artery), Masson (for fibrinoid substance) and Congo red (for amyloid) were performed. Cerebellar tissue pathology revealed irregular angiomatous vessels with varying thicknesses and perivascular cysts (Figure 4). Some lumens were dilated and some were narrowed with thrombus. Inflammatory cells were infiltrated in the mesenchyma. Elastic fiber, Masson, and Congo red staining for vascular wall were all negative. Pathological findings support microangiopathic changes.

2.2 | Genetic investigations

Genomic DNA was obtained from peripheral blood in the proband (II-2) and three family members (I-1, I-2, and II-3). Whole exome sequencing (WES) with copy number variation (CNV) analysis was performed in the proband. Protein-coding exome enrichment was performed by xGen Exome Research Panel v1.0 (IDT). High-throughput sequencing was carried out by Illumina NovaSeq 6000 series sequencer (PE150). Genetic variants were filtered and annotated as previously described (Chen et al., 2022). The average sequencing depth was 229×, and the coverage rate was 99.81%. The coverage rate above 20× was 99.5%. CNV analysis was performed by CNV kit using WES data from the proband and reference samples. The reference panel was constructed from 30 samples in the same batch of WES experiments. NCBI RefSeq gene set, DGV, OMIM, and ClinVar databases were used to annotate the

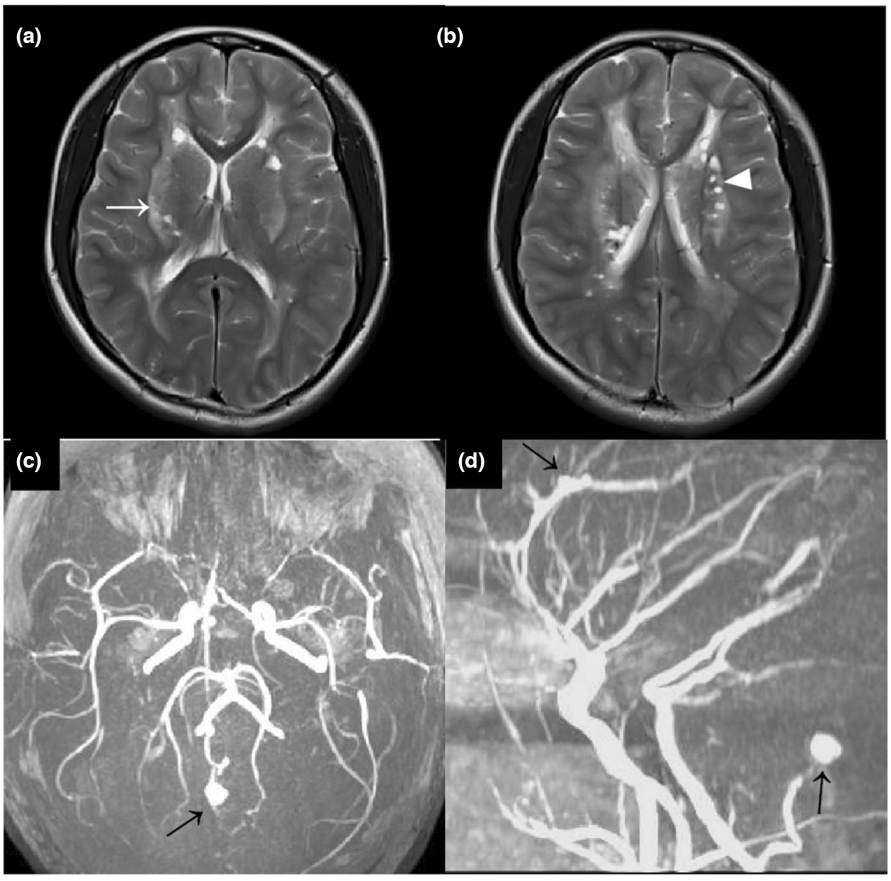

FIGURE 3 Brain MRI on admission. (a, b) Axial T2WI images. (c, d) MRA. Leukoencephalopathy (white arrow) was noted in the deep white matter and external capsule on T2WI images. Most of the lacuna or cysts (arrowhead) were located within the white matter lesions. Calcifications on CT were not evident on MRI. Aneurysms in posterior inferior cerebellar artery and anterior cerebral artery were seen on MRA (black arrows).

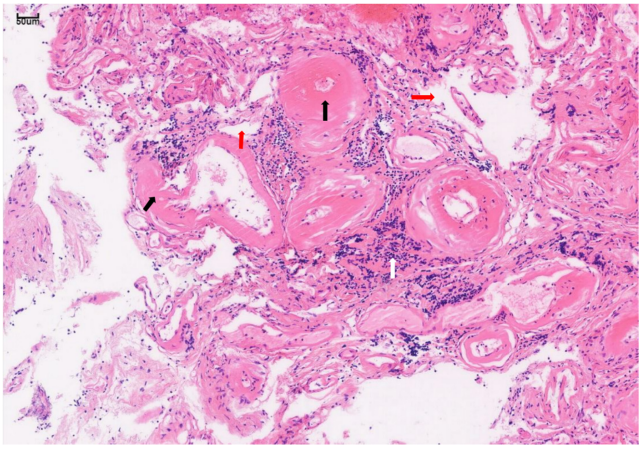

FIGURE 4 Cerebellar histological findings showing microangiopathy and cysts (HE). Proliferation of vessels was seen with varying wall thickness and lumen size (black arrows). Hyaline degeneration was found in some vessel walls. These indicate microvascular angiomatous changes. Perivascular cyst formation (red arrows). Inflammatory cells were infiltrated in mesenchyma (white arrows).

yielded CNVs. As the neuroimaging abnormalities indicated leukoencephalopathy with brain calcifications and cysts (LCC), the *SNORD118* gene was also screened using sanger sequencing.

3 | RESULTS

The proband harbored compound heterozygous variations: c.1220A>T (p.His407Leu) in exon 7 and c.1562delC (p.Ala521fs) in exon 10 of the *ESCO2* gene (NM_001017420, NP_001017420.1) (Figure 1b). The proband's father and mother carried the c.1220A>T and c.1562delC variations, respectively. His younger brother (II-3) did not carry any of the above variations. Both variations are not present in the normal controls in gnomeAD, ESP6500, ExAC, and 1000 Genomes Project databases, or HGMDpro and ClinVar databases. According to VarCards, an integrated functional prediction program, among the 23 prediction algorithms, 21 supported a deleterious effect for p.His407Leu. The REVEL score is 0.94 (damaging), the CADD score is 29.4 (damaging), and the ClinPred score is 0.999 (pathogenic). No clinically significant CNVs were found in the proband. We screened for leukoencephalopathy or calcification-related genes using WES data or sanger sequencing, but no meaningful variations were found.

The p.H407L variation is located in the C-terminal conserved zinc finger motif of *ESCO2*, while the p.A521fs variation is located within the acetyltransferase domain, leading to truncation. For p.H407L, protein stability prediction by DUET reveals decreased stability with the ΔΔG increase of 0.039 kcal/mol. The zinc finger structure of ESCO2 has been resolved in mouse (Accession number: 6sp0). It consists of two β-strands and one α-helix, with the zinc ion wrapped in the center (Figure 1c). The four amino acid residues directly interacting with the zinc ion are Cys386, Cys389, His404, and His408, constituting the C2H2 motif. The His407 residue in humans just corresponds to the His404 residue in mouse (Ajam et al., 2020). The zinc finger formation is affected when the His residue is mutated (Figure 1c,d). We speculate this His407Leu variation may affect the binding of ESCO2 to target DNA, which in turn affects the expression of the genes it regulates.

The proband's manifestations were consistent with RBS-SC phocomelia caused by mutations of *ESCO2*. Although the genetic data of proband's elder brother (II-1) were not available, current genetic data of the family supported the autosomal recessive inheritance model and genotype–phenotype segregation. According to ACMG/AMP 2015 guidelines, both variations were interpreted as likely pathogenic for c.1220A>T (PM1 + PM2 + PM3 + PP3 + PP4) and c.1562delC (PVS1 + PM2 + PM3 + PP4).

4 | DISCUSSION

RBS has rarely been reported in the Chinese population. One prior study (Zhu et al., 2022) provided detailed ultrasound characteristics for the prenatal diagnosis of RBS. Here, we report a juvenile patient of RBS in a non-consanguineous Chinese family.

Clinical presentation of this RBS case is unique in the central nervous system complications, with less severe craniofacial and limb malformations. The proband's elder brother had severe craniofacial and limb deformities and died shortly after premature birth. The intra-family phenotypic heterogeneity is common in Roberts syndrome.

The causative gene for RBS is the establishment of cohesion 1 homolog 2 (*ESCO2*) (Vega et al., 2005). *ESCO2* encodes for a 601-amino protein that targets the DNA-binding cohesin complex. ESCO2 belongs to the Ecol family of acetyltransferases involved in the establishment of sister chromatid cohesion during S phase and post-replicative sister chromatid cohesion induced by double-strand breaks. Loss of function of ESCO2 leads to faulty chromosomal cohesion and aberrant expression of genes that it regulates, which play a key role in RBS birth defects (Vega et al., 2010). Recent studies have highlighted the involvement of oxidative stress damage in this process. In normal cells following DNA damage, transiently generated reactive oxygen species (ROS) combine with ESCO2 to promote DNA repair. When ESCO2 is mutated, DNA repair is hampered. And ROS are further induced by DNA repair defects (Mfarej & Skibbens, 2020).

According to the HGMD database, 30 pathogenic mutations in *ESCO2* have been reported. The mutation spectrum includes missense/nonsense ($n=6$), splicing ($n=5$), small deletions ($n=12$), and small insertions ($n=7$). Most of the mutations cause frameshift effects, resulting in protein truncation or mRNA instability, which ultimately leads to loss of function of ESCO2. Cytogenetically, heterochromatin repulsion (HR) appears in all RBS-SC phocomelia probands and is closely linked with *ESCO2* mutations (Schule et al., 2005). There are no clear genotype–phenotype correlations. Another rare mild phenotype named Juberg–Hayward syndrome was also reported.

Cerebrovascular complications are rare in Roberts syndrome. One interesting finding in the current case is complex cerebrovascular diseases. At 6 years old, she experienced ischemic stroke. She died of cerebellar hemorrhage secondary to vascular defects at age of 13. Besides, neuroimaging in the proband showed the triad of leukoencephalopathy, calcifications, and cysts. In the literature, cerebrovascular diseases were reported in only a few Roberts patients with some case presentations being far back in time and not in detail (Van Den Berg & Francke, 1993). Spontaneous intracranial hemorrhage and multiple intracranial aneurysms were reported in a patient with Roberts syndrome in 2011 (Wang et al., 2011). Theoretically, as a developmental disease, neurovascular abnormalities in Roberts syndrome could occur just as other developmental defects. As in the current case, only a few mildly affected Roberts patients could survive into adulthood. Thus, cerebral abnormalities may not be comprehensively screened.

This neuroimaging triad should be differentiated from other diseases with similar neuroimaging, including leukoencephalopathy with brain calcifications and cysts (LCC), Coats plus syndrome, and Aicardi–Goutières syndrome (AGS). Calcifications in the current case were mainly cortical. In LCC, Coats plus, and AGS, calcifications are mainly located in the deep nuclei. Most of the cysts in the proband were located within white matter lesions. Several cysts had surrounding hyperintensities on the FLAIR-MRI sequence. Although she had ischemic stroke at 8 years old, we infer that most of the cysts are ischemic, but not due to chronic cerebral infarction. If these cysts were post-stroke changes, her motor function would be severely limited. In fact, in LCC, Coats plus syndrome, and AGS, most cysts are not classic epithelial cysts. In LCC, the cyst wall could have calcification and contrast enhancement, and in Coats plus syndrome, the cyst can have surrounding edema (Goncalves et al., 2020).

There is increasing evidence that Coats plus syndrome and LCC are pathologically alike. The primary pathological change seems to be an occlusive small cerebrovascular disease. Chronic ischemic necrosis of brain tissue leads to dystrophic calcification, which eventually forms cysts and leukoencephalopathy (Kleinschmidt-Demasters et al., 2009; Nagae-Poetscher et al., 2004; Paff et al., 2022). Therefore, the two diseases could be considered hereditary cerebral small vessel diseases (HCSVD). For this case, similar images of LCC, ischemic and hemorrhagic stroke, and brain histopathology also point to small cerebral vasculopathy.

LCC is an autosomal recessive disease resulting from *SNORD118* gene variations. *SNORD118* encodes U8 snoRNA, which is involved in the cleavage event during the maturation of the large ribosomal subunit 5.8S and 28SRNA (Mcfadden & Baserga, 2022). Coats plus syndrome is associated with variations in *CTC1*, *POT1* and *STN1*. The three proteins make up the conserved trimeric complex CST (CTC1-STN1-TEN1) which participates in controlling the length of telomeric 3′ G-overhangs, DNA replication, and DNA damage repair. For AGS, the mutated genes are mainly *TREX1* and *MASEH2b*. Disruption of TREX1 enzymes fails to maintain host immune tolerance to cytosolic self-DNAs and results in aberrant innate immune responses. Although the specific pathogenic mechanisms underlying these disorders are not completely understood, these genes, including *ESCO2* in RBS, are all involved in DNA replication, transcription, damage repair, and immune tolerance. This implies that the four diseases may share some common pathogenic mechanisms.

In conclusion, we describe complex cerebrovascular diseases in Roberts syndrome caused by novel *ESCO2* biallelic variations. This case expands not only the cerebral involvement in Roberts syndrome but also the disease spectrum of the neuroimaging triad with leukoencephalopathy, calcifications, and cysts.

AUTHOR CONTRIBUTIONS

Shuang He: conceptualization, investigation, and writing—original draft; Shuai Chen: methodology, formal analysis, and writing—original draft; Shu-Jian Li: investigation and conceptualization; Jie-Wen Zhang: supervision and writing—review & editing; and Xin-Liang Liang: Funding acquisition and writing–review. All authors critically reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data are available via contacting the corresponding author.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Zhengzhou University People's Hospital. Written informed consent for clinical and genetic findings was obtained from the proband's father.

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