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Molecular cytogenetic characterization of isolated recurrent 4q35.2 microduplication in Chinese population: a seven-year single-center retrospective study

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Abstract

Background With the extensive use of chromosomal microarray analysis (CMA), an increasing number of variants of uncertain significance (VOUS) have been detected. The objective of the present study was to elucidate the pathogenicity and clinical variability associated with isolated recurrent 4q35.2 microduplications within the Chinese population.

Methods The present study involved 14 cases of isolated recurrent 4q35.2 microduplication (including 12 fetuses and 2 cases of pediatric patients) out of 5,188 subjects who sought genetic consultation at our hospital and received CMA detection. WES technology was subsequently utilized to identify additional sequence variants in a patient with multiple clinical anomalies.

Results All 14 cases exhibited isolated recurrent 4q35.2 microduplications spanning a 1.0-Mb region encompassing the *ZFP42* gene. Among the 12 fetuses, 11 displayed normal clinical features, while one was born with renal duplication and hydronephrosis. Additionally, in the two pediatric patients, WES was performed for Case 1, who presented with congenital cataracts, severe intellectual disability, and seizures. This patient inherited the 4q35.2 microduplication from his phenotypically normal mother. WES identified a novel NM_000276:c.2042G>T (p.G681V) variant in the *OCRL* gene, which is associated with Lowe syndrome and may account for the observed phenotypic variability within this family.

Conclusion A series of 14 cases with isolated recurrent 4q35.2 microduplications were investigated, highlighting a potential association with increased susceptibility to renal abnormalities. Further, the present findings may expand the mutation spectrum of the *OCRL* gene associated with Lowe syndrome and provide valuable insights for the genetic etiological diagnosis of patients with unexplained copy number variants.

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Keywords Whole exome sequencing, Chromosomal microarray analysis, Phenotypical diversity, 4q35.2 microduplication, Lowe syndrome

Introduction

Partial trisomy 4q is a relatively rare syndrome. The first documented case of this condition was reported in 1971 by Hoehn et al. [1]. The clinical features of partial 4q microduplication syndrome are typically characterized by developmental delay, intellectual disability, microcephaly, facial dysmorphism, congenital heart defects and renal malformations [2–4]. Notably, there is a scarcity of research on pure 4q35.2 microduplication at present. A previous study conducted by Zaki et al. [5] reported bilateral calcification of basal ganglia in a patient with duplication of both 11q13.1q22.1 and 4q35.2. This finding suggests that the 4q35.2 microduplication may contribute to susceptibility to basal ganglia calcification. At the same time, a recent study conducted by Bogs et al. [6] indicated that duplication or triplication of 4q35.2 may increase susceptibility to the development of renal, ear, and diaphragmatic anomalies. Nevertheless, the recurrent 4q35.2 microduplication encompassing a 1.0-Mb segment that includes the *ZFP42* gene is classified as a variant of uncertain significance (VOUS). Currently, there are no studies linking the *ZEP42* gene specifically to a particular disease.

As chromosomal microarray analysis (CMA) technology advances and becomes more widely utilized, the identification of VOUS is likely to increase [7–9]. In addition, whole exome sequencing (WES) technology has also been employed in revealing the phenotypical variability of VOUS, including the variants of Xp22.31, 1q12.1 and 16p11.2 microdeletions/microduplications [10–12]. However, to date, there has been no study investigating the genetic etiology of 4q35.2 microduplications with variable phenotypes.

The aim of the present study was to investigate the genotype-phenotype correlations of isolated recurrent 1.0-Mb 4q35.2 microduplications in 14 cases within the Chinese population. Moreover, WES was employed to identify supplementary sequence variants in a patient with recurrent 4q35.2 microduplication, who displayed phenotypic variability within the family.

Materials and methods

Subjects

The present study encompassed a total of 5,014 prenatal amniotic fluid samples and 174 peripheral blood samples from individuals who underwent CMA from September 2017 to April 2023 at Quanzhou Women's and Children's Hospital, China. Among the described individuals, 14 unrelated subjects who harbored isolated recurrent 4q35.2 microduplication were enrolled, including 12

fetuses and two pediatric patients. Additionally, one pediatric patient with congenital cataracts, severe intellectual disability and seizures was further subject to WES detection. Informed consent was obtained from all the subjects. The study protocol was approved by the Ethics Committee of the aforementioned hospital (2020 No.12).

Karyotype analysis

Approximately 30 ml of amniotic fluid or 2 ml of peripheral blood was collected from pregnant women or pediatric patients for karyotype analysis. Chromosomes were prepared using the Sinochrome Chromprep II automatic chromosome harvesting system (Shanghai Lechen Biotechnology Co., Ltd.) following the karyotype operation procedure established by the Prenatal Diagnosis Department of our hospital [13, 14]. Nomenclature and diagnosis of the karyotypes were performed according to the International System for Human Cytogenomic Nomenclature (ISCN 2020).

Chromosomal microarray analysis

The QIAamp DNA blood Kit (QIAGEN, Germany) was used for DNA extraction from amniotic fluid and peripheral blood in the samples. SNP array detection was performed using the AffymetrixCytoScan™ 750 K chip according to the Affymetrix CytoScan Assay User Guide (<http://www.thermofisher.com>), as described previously [14]. To assess the genome-wide variation in each sample, Chromosome Analysis Suite (ChAS) v4.0 software was used to analyze the fluorescence signals. Copy number variants were interpreted using databases such as DGV, OMIM, DECIPHER, and PubMed. These variants were classified as pathogenic, likely pathogenic, VOUS, likely benign, or benign according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) [15].

Whole exome sequencing and data analysis

The extracted DNA was further subjected to WES analysis. DNA quantification was performed using the Qubit dsDNA HS Assay (Invitrogen, Carlsbad, CA, USA). Approximate mean fragment length of 150–200 bp was sheared using the Covaris LE220 (Covaris, Woburn, MA, USA). Sheared DNA was used for library preparation of targeted regions by means of the SureSelect whole-exome capture kit (Agilent). The Illumina DNA Standards and Primer Premix Kit (Kapa Biosystems, Boston, MA, USA) was subsequently used for the quantification of sequencing libraries. Paired-end libraries were sequenced using

the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA) with 150 bp paired-end reads.

Data analysis encompassed variant calling, annotation, and screening. Minor allele frequencies for all known variants were queried using the dbSNP, 1000 Genomes Project, Exome Aggregation Consortium, and Exome Variant Server databases. To assess the potential pathogenicity of the detected mutations, the OMIM, ClinVar, Human Gene Mutation Database, and SwissVar databases were utilized. Additionally, SIFT, MutationTaster, PolyPhen2, PROVEAN, Human Splicing Finder, MetaSVM, GERP++_RS, and MaxEntScan were employed to predict the biological impact of amino acid substitutions or indels. Variants were classified according to the ACMG guidelines [16] as pathogenic, likely pathogenic, VOUS, likely benign or benign. Candidate variants were selected after combining the clinical information of proband and the aforementioned information, placing emphasis on *de*

novo variants, compound heterozygote, homozygote and hemizygote. Sanger sequencing was performed for further verification of the variants detected using WES.

Results

Sample information

In the present study, a total of 14 unrelated subjects who harbored isolated recurrent 4q35.2 microduplication were enrolled, including 12 fetuses and two pediatric patients. As detailed in Table 1, among the 12 pregnancies included in the present study, only one case (Case 4) showed structural ultrasound anomalies, specifically renal duplication and hydronephrosis. Five other cases exhibited ultrasonic soft markers, while the remaining six cases had normal ultrasound findings but presented with other high-risk factors, including advanced maternal age, a history of poor pregnancy outcomes, high-risk results from non-invasive prenatal testing, or serological

Table 1 Results of karyotype and chromosomal microarray analysis of the enrolled subjects

Cases	Specimen	Ultrasound findings	Karyotype	CMA	Origin	Follow-up results
Case 1	PB	/	46,XY	arr[GRCh37] 4q35.2(187,912,524_188,944,075)x3,1.0 Mb	Maternal	Global developmental delay, severe intellectual disability, congenital cataract, seizures, short stature
Case 2	PB	/	46,XX	arr[GRCh37] 4q35.2(187,933,402_188,944,075)x3,1.0 Mb	/	Uterus duplex and unilateral renal agenesis, mild intellectual disability
Case 3	AF	Increased nuchal translucency	46,XN	arr[GRCh37] 4q35.2(187,929,331_188,943,890)x3,1.0 Mb	Maternal	Born with normal phenotype
Case 4	AF	Fetal left renal duplication and hydronephrosis	46,XN	arr[GRCh37] 4q35.2(187,900,881_188,943,890)x3,1.0 Mb	/	Born with left renal duplication and hydronephrosis
Case 5	AF	Fetal hyperechoic bowel	46,XN	arr[GRCh37] 4q35.2(187,929,331_188,943,890)x3,1.0 Mb	/	Born with normal phenotype
Case 6	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,907,094_188,943,890)x3,1.0 Mb	Paternal	Born with normal phenotype
Case 7	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,912,583_188,943,890)x3,1.0 Mb	Paternal	Born with normal phenotype
Case 8	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,907,095_188,943,890)x3,1.0 Mb	/	Born with normal phenotype
Case 9	AF	Nasal bone absence/hypoplasia	46,XN	arr[GRCh37] 4q35.2(187,929,332_188,938,377)x3,1.0 Mb	/	Born with normal phenotype
Case 10	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,929,332_188,943,890)x3,1.0 Mb	/	Born with normal phenotype
Case 11	AF	Fetal hyperechoic bowel and renal pelvis dilation	46,XN	arr[GRCh37] 4q35.2(187,929,332_188,943,890)x3,1.0 Mb	/	Born with normal phenotype
Case 12	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,933,402_188,943890)x4,1.0 Mb	/	Born with normal phenotype
Case 13	AF	Normal	46,XN	arr[GRCh37] 4q35.2(187,933,402_188,943,890)x3,1.0 Mb	/	Born with normal phenotype
Case 14	AF	Fetal cardiac hyperechogenicity, hyperechoic bowel and renal pelvis dilation	46,XN	arr[GRCh37] 4q35.2(187,942,663_188,943,890)x3,1.0 Mb	/	Born with normal phenotype

PB: peripheral blood, AF: amniotic fluid, CMA: chromosomal microarray analysis

prenatal screening. Moreover, two pediatric patients were enrolled, in Case 1 several clinical features, including developmental delay, intellectual disability, congenital cataracts, short stature, and other congenital abnormalities were observed. Case 2 displayed clinical features including uterus duplex, unilateral renal agenesis, and mild intellectual disability.

Karyotype analysis results

Among the enrolled 14 cases with isolated recurrent 4q35.2 microduplication, karyotype analysis did not reveal any obvious chromosomal abnormalities.

Chromosomal microarray analysis results

A recurrent 1.0-Mb 4q35.2 microduplication encompassing the *ZFP42* gene was identified in all 14 enrolled cases. According to the Database of Genomic Variants, some CNVs that include the 4q35.2 microduplication were also detected in the present study [17, 18]. The DECIPHER database revealed that some cases with similar duplication fragments exhibited clinical phenotypes such as intellectual disability, language developmental delay, autism, and short stature (DECIPHER ID: 411617, VOUS; 300341, VOUS; 285401, VOUS; 294172, VOUS; 272963, /). Meanwhile, other cases containing the *ZFP42* gene were interpreted as likely benign/benign in the database (DECIPHER ID: 288944, 287945, 270613, 289815, 290193). According to the ACMG guidelines, these recurrent 4q35.2 microduplications observed in the study were interpreted as VOUS.

In addition, parental CNV verification was conducted in four cases. Among these cases, two CNVs were inherited from the fathers, and two were inherited from the mothers. Notably, all parents exhibited normal clinical features.

Whole exome sequencing detection results

WES was conducted to further investigate a pediatric patient with isolated recurrent 4q35.2 microduplication and multiple abnormal features. As shown in Fig. 1, a novel hemizygous variant of NM_000276: c.2042G>T(p.G681V) in the *OCRL* gene on the X chromosome was observed in Case 1, which was inherited from his mother and further verified by Sanger sequencing (Fig. 1D). No frequency was reported in the databases of dbSNP, 1000 genomes, gnomAD, Clinvar, ExAC and PubMed. Moreover, several prediction software tools, namely Polyphen2_HDIV (1.0), Polyphen2_HVAR (1.0), MutationTaster (1.0), PROVEAN (-8.59), MetaSVM (0.181), SIFT (0.002) and GERP++_RS (6.16), indicated that the novel variant was harmful. As indicated in the InterPro database, the p.G681V variant is located in the RhoGAP domain of the *OCRL* protein (<https://www.ebi.ac.uk/interpro/>). Structural simulations of the *OCRL* protein

revealed that, in the wild-type protein, the glycine at position 681 forms hydrogen bonds with threonine at position 644. Yet, in the mutant protein with valine at position 681, these bonds are instead formed with cysteine at position 679, potentially altering the tertiary structure of the *OCRL* protein (Fig. 2). The *OCRL* gene variant was classified as a VOUS (PM2_supporting, PP3, PP4), according to the ACMG guidelines. Unfortunately, Case 2 and Case 4, who also presented with clinical abnormalities, declined to undergo further WES detection.

Pregnancy outcome follow-up results

Further follow-up on pregnancy outcomes revealed that all 12 fetuses with isolated recurrent 1.0 Mb 4q35.2 microduplication continued their pregnancies. As shown in Tables 1 and 11 fetuses were born with normal appearances and exhibited normal clinical features during six-month follow-up assessments. However, in Case 4, the fetus was born with left renal duplication and hydronephrosis, consistent with the prenatal ultrasound findings. A surgical procedure was performed to remove the duplicated left kidney shortly after birth. Currently, no additional clinical anomalies have been observed in this case.

Discussion

To the present knowledge, there are fewer than 10 clinical studies available in the literature on 4q35.2 microduplication, with research specifically focusing on isolated 4q35.2 microduplication being even more limited [5, 6, 19]. The phenotypical diversity associated with 4q35.2 microduplication has been documented in prior research and various databases. Nonetheless, the presence of unexplained variable features adds complexity to clinical consultations and highlights the need for further research and investigation in order to better understand and manage this condition. WES has emerged as a valuable technology for identifying the genetic etiology of uncertain CNVs [10–13]. The sequence variants detected through WES may provide insights into the clinical variability observed in patients with unexplained CNVs [20]. In the present study, 14 cases of isolated recurrent 4q35.2 microduplication with 1.0-Mb segment containing the *ZFP42* gene were presented in a Chinese cohort. These cases also exhibited variable phenotypes. In addition, WES technology was conducted to find additional sequence variants which may be responsible for the variable clinical phenotypes observed in patients with isolated recurrent 4q35.2 microduplication.

In the present study, two pediatric patients with isolated recurrent 4q35.2 microduplication were identified, both of whom exhibited multiple clinical abnormalities that could not be fully explained by the 4q35.2 microduplication alone. Consequently, WES was performed for Case 1. A novel hemizygous variant of c.2042G>T

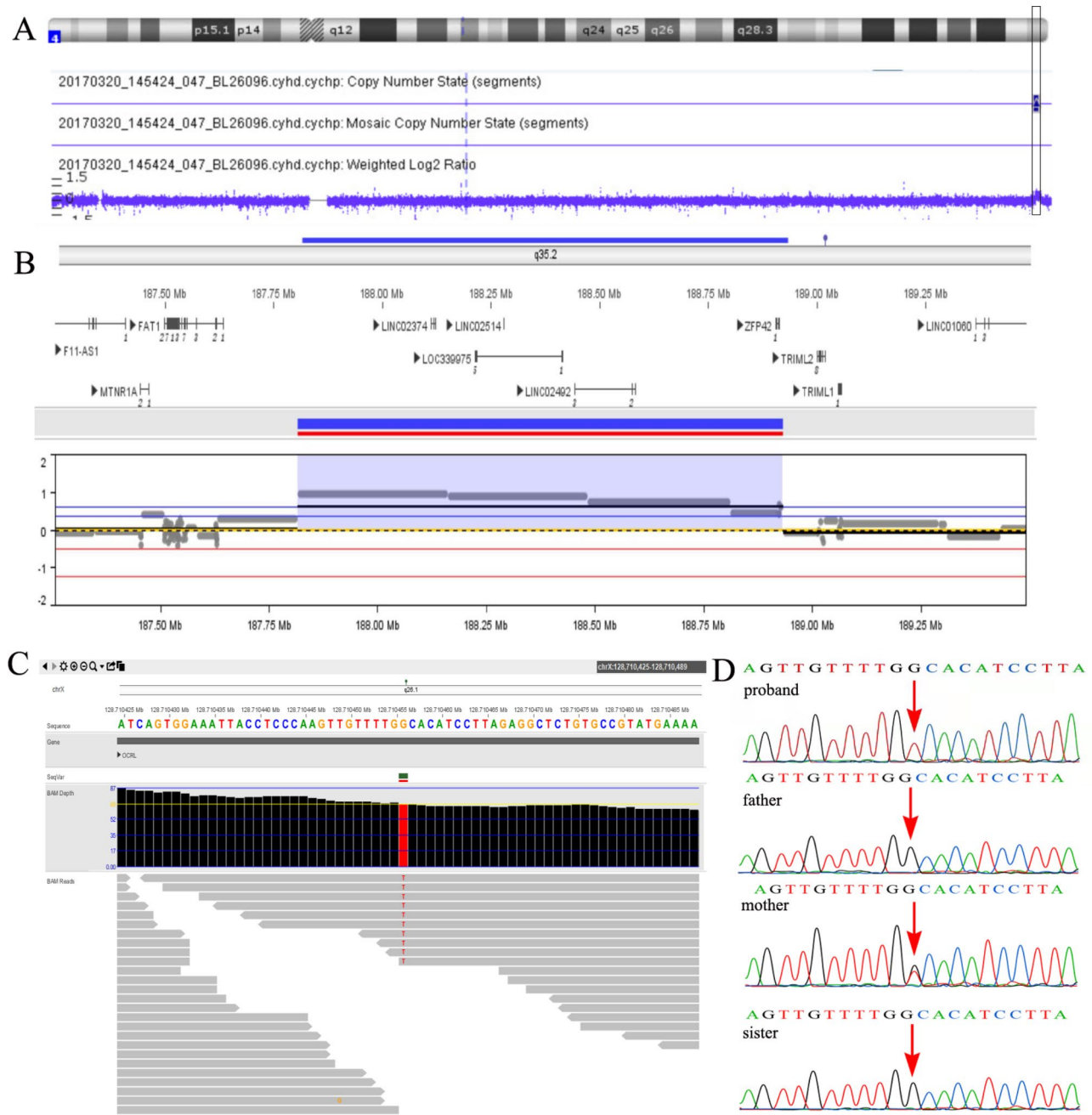


Fig. 1 Recurrent 4q35.2 microduplication and *OCRL* gene variant detected in family 1 using CMA, WES and Sanger sequencing. **(A):** A 1.0-Mb microduplication in 4q35.2 region was observed in the proband of family 1 using CMA. **(B):** The WES detection results also demonstrated the 4q35.2 microduplication in the patient. **(C):** A novel hemizygous variant of c.2042G>T (p.G681V) in *OCRL* gene on the X chromosome was identified in the proband by means of WES. **(D):** The *OCRL* gene variant detected by WES was verified by means of Sanger sequencing in the proband. The parental verification results elicited that the hemizygous variant in *OCRL* gene in the proband was inherited from his mother. In addition, Sanger sequencing demonstrated that the *OCRL* gene variant was not present in the proband's sister

in *OCRL* gene was identified in Case 1. The *OCRL* gene, located on chromosome X, consists of 23 exons and encodes a phosphatidylinositol 4,5-bisphosphate-5-phosphatase that acts on phosphoinositides [21]. Pathogenic mutations in *OCRL* gene would lead to Lowe syndrome, a rare X-linked recessive hereditary disease, which is

characterized by congenital cataracts, central hypotonia, intellectual disability and renal Fanconi syndrome [22]. Congenital cataracts have consistently been observed in male patients, most of whom also exhibit varying degrees of intellectual disability, with some individuals experiencing seizures, as reported in the literature [23–26]. Further,

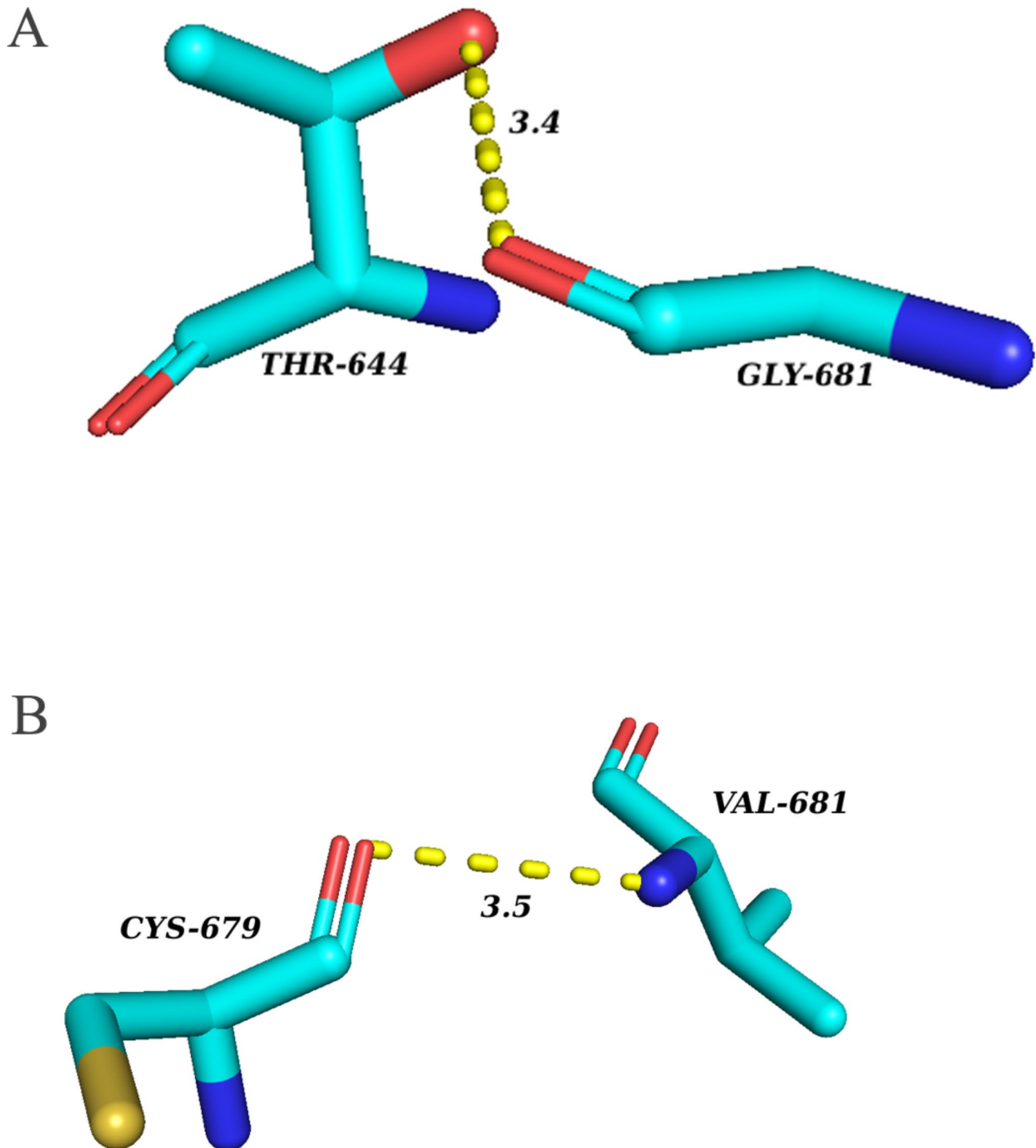


Fig. 2 Three-dimensional structures prediction of the c.2042G>T (p.G681V) variant in *OCRL* gene. **(A)**: In the wild-type *OCRL* protein, the glycine at position 681 forms hydrogen bonds with threonine at position 644. **(B)**: In the mutant *OCRL* protein, where glycine at position 681 is substituted with valine, hydrogen bonds are formed with cysteine at position 679

in a prior retrospective study involving 12 male patients with Lowe syndrome, short stature and developmental delay were observed in all patients, and seizures occurred in 50% of the patients [23]. In Case 1 of the present study, congenital cataracts, developmental delay, severe

intellectual disability, short stature and seizures were also observed, aligning with the clinical phenotypes of Lowe syndrome. The belief of the present authors is that the variant of c.2042G>T in the *OCRL* gene may account for

the severe clinical features observed in Case 1, who harbored an isolated recurrent 4q35.2 microduplication.

In the present study, 12 fetuses with isolated recurrent 4q35.2 microduplication were also enrolled, six of them had normal prenatal ultrasound examination results. Notably, renal duplication and hydronephrosis were observed in Case 4. Additionally, renal developmental anomaly of unilateral renal agenesis was also observed in pediatric patient of Case 2. Moreover, Case 11 and Case 14 also presented with an ultrasonic soft marker anomaly of renal pelvis dilation. Given the clinical findings in individuals with 4q35.2 microduplication, renal developmental abnormalities may be associated with the microduplication. Notably, a previous study by Bogs et al. [6] reported a 3.73–4.43 Mb 4q35.2 triplication in a patient with congenital heart defects, unilateral renal agenesis, and ear anomalies, suggesting that 4q35.2 duplications or triplications may be susceptibility factors for renal abnormalities. As such, the belief of the present authors is that the renal abnormality observed in the present study could be ascribed to 4q35.2 microduplication.

An overview of the present findings indicates that most individuals with recurrent 4q35.2 microduplication may present with a normal clinical phenotype. Further research is needed to gather additional functional evidence regarding the *OCRL* variants detected in our cases that are linked to Lowe syndrome. Moreover, additional scientific studies are required to establish clear phenotype-genotype correlations between renal developmental abnormalities and the 4q35.2 microduplication.

In conclusion, 14 cases of isolated recurrent 1.0-Mb 4q35.2 microduplication in the Chinese population were investigated, providing valuable information for understanding the genotype and phenotype correlations. The belief of the present authors is that the isolated recurrent 4q35.2 microduplication may result in normal or mild clinical features, but may increase susceptibility to renal abnormalities. In addition, the present findings revealed a novel variant in the *OCRL* gene causing Lowe syndrome, which may broaden the mutation spectrum of Lowe syndrome. The present study further underscores the value of WES technology in diagnosing the etiology of unexplained CNVs with phenotypical variability.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12884-024-06818-z>.

Supplementary Material 1

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Author contributions

JZ wrote the article; SZ, QW and YJ recruited the participants and performed clinical consultation; SZ was responsible for the karyotype analysis and data analysis; HL performed bioinformatics analysis; NZ, CC and JZ revised and polished the paper. All authors have approved the final version of the article.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Ethics Committee approval was obtained from the Institutional Ethics Committee of Quanzhou Women's and Children's Hospital for the commencement of this study (2022No.46). Informed consent was obtained from all study participants, who agreed to the publication of the study report. All procedures involving human participants adhered to the ethical standards of the institutional and/or national research committees and were in accordance with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from the parents of the patients for the publication of their genetic data and relevant information, including that of their children. The written informed consent is available upon request.

Competing interests

The authors declare no conflict of interest.

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