CLINICAL REPORT

The phenotype and rhGH treatment response of ring Chromosome 15 Syndrome: Case report and literature review

Meiping Chen1 | Xiaoan Ke1 | Hanting Liang1 | Fengying Gong1 | Hongbo Yang1 | Linjie Wang1 | Lian Duan1 | Hui Pan1 | Dongyan Cao2 | Huijuan Zhu1

1Key Laboratory of Endocrinology of National Health Commission, Department of Endocrinology, State Key Laboratory of Complex Severe and Rare Diseases Peking, Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

2Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Huijuan Zhu, Department of Endocrinology, Key Laboratory of Endocrinology of National Health Commission, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China.

Email: shengxin2004@163.com

Abstract

Background: Ring chromosome 15 [r (15)] is an uncommon finding with various clinical manifestations. A common phenotype for these patients has not been established and data on the efficacy of recombinant human growth hormone (rhGH) treatment in patients with r (15) syndrome are limited.

Methods: One short stature patient in our hospital with r (15) syndrome by whole exome sequencing (WES) and karyotype examination was included. All published r (15) syndrome cases as of March 15, 2021, were searched, and their clinical information was recorded and summarized.

Results: One 11.5-year-old female with prenatal and postnatal growth retardation, ventricular septal defect, intellectual disability, downward corners, short fifth metacarpal bone, scattered milk coffee spots, and a right ovarian cyst was included. Her height was 126.9 cm (−3.45 SDS). Karyotype analysis showed 46, XX, r (15). WES revealed a 4.5 Mb heterozygous deletion in the chromosome 15q26.2-q26.3 region, encompassing genes from ARRDC4 to OR4F15. Gonadotrophin-releasing hormone analogue (tiptorelin) and rhGH were administered for 6 months. The height has increased 3.8 cm (+0.2SDS) and the calculated growth rate has improved from 4.7 to 7.6 cm/y. The literature review indicated the main clinical manifestations of r (15) syndrome with prenatal and postnatal growth retardation, characteristic craniofacial features, and multisystem abnormalities, and rhGH treatment is beneficial for r (15) syndrome patients with short stature.

Conclusion: We delineate the clinical spectrum of r (15) syndrome with the identification of an additional individual and rhGH treatment is beneficial for r (15) syndrome patients with short stature.

KEYWORDS
clinical characteristic, rhGH treatment, ring chromosome 15, short stature
1 | INTRODUCTION

Ring chromosomes are randomly generated by the re-fusion of two chromosomal arms after breaking during cell replication (Yip, 2015). Ring chromosome 15 [r (15)] was first reported by Jacobsen in 1966 and more than 100 cases have been reported to date (Jacobsen, 1966). Due to the extent of the deletion and the stability of the ring chromosome in post-zygotic mitosis, the clinical manifestations of patients with r (15) syndrome vary greatly, ranging from slight development retardation and minor dysmorphisms to serious pathologies and intellectual disability (Paz et al., 2018). In addition, r (15) syndrome was mostly diagnosed at the cytogenetic analysis level because of the availability of technology in the past. It is even more difficult to establish an accurate correlation between genotype and phenotype among these patients. The instability of the ring chromosome itself and the heterozygous deletion of the terminal 15q deletions encompassing the insulin-like growth factor-1 receptor (IGF1R) (OMIM 147370) are usually associated with intrauterine growth retardation and short stature, but the efficacy of recombinant human growth hormone (rhGH) treatment for this condition is also not clear. Here, we report a female with r (15) syndrome and review the clinical manifestation, cytotgenetic analysis, molecular diagnosis, and the efficacy of rhGH in the treatment of previously reported r (15) syndrome cases, aiming to summarize the characteristics of reported patients with r (15) syndrome and further exploring more precise genotype-phenotype correlation and evaluate the efficacy of rhGH therapy.

2 | SUBJECT AND METHODS

2.1 | Editorial policies and ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Peking Union Medical College Hospital Ethics Committee. The parents signed informed consent forms regarding the research conducted on this proband.

2.2 | Subject

Clinical materials of the female proband’s history-taking, physical examination, and auxiliary examination were collected. Peripheral blood of the patient was collected for genetic study.

2.3 | Whole-exome sequencing (WES) analysis and deletion verification

Genomic DNA was extracted from peripheral blood from the participant by standard procedures and the WES was performed according to the manufacturer’s standard procedure. First, the genomic DNA concentrations were sheared with Covaris LE220 Sonicator (Covaris) to target of 150–200 bp average size. DNA libraries were prepared using SureselectXT Low Input reagent kit (Agilent). Then, the pre-capture libraries containing exome sequences were captured using SureSelect Human All Exon V5 kit (Agilent). Next, DNA concentration of the enriched sequencing libraries was measured with the Qubit 2.0 fluorometer dsDNA HS Assay (Thermo Fisher Scientific). Size distribution of the resulting sequencing libraries was analyzed using Agilent BioAnalyzer 2100 (Agilent). The libraries were used in cluster formation on an Illumina cBOT cluster generation system with HiSeq PE Cluster Kits (Illumina). Finally, Paired-end sequencing is performed using an Illumina HiSeqvaSeq6000 system following Illumina-provided protocols for 2x150 paired-end sequencing. Variants were identified using GATK software after mapping clear reads filtered by existing standards (Wei et al., 2011) to the Human Genome Reference (HG19) using the BWA (Burrows-Wheeler Aligner) Multi-Vision package (Li & Durbin, 2009). These sequence data have been submitted to the GenBank databases under accession number SUB9434277. The copy number of heterozygous deletion genes were validated by real-time quantitative polymerase chain reaction (RT-qPCR) in seven genes, including NR2F2 (NG_016753.1), ARRDC4 (NC_000015.10), FAM169B (NC_000015.10), IGF1R (NG_009492.1), MEF2A (NG_016443.2), TM2D3 (NC_000015.10) and OR4F15 (NC_000015.10), with three age- and sex-matched normal controls.

2.4 | Literature review

Up to March 15, 2021, clinical manifestations, genetic results, and treatment of all case reports and original articles of constitutional r (15) syndrome were collected from English journals archived in the PubMed and Web of Science databases. Data were summarized and analyzed with statistical methods by SPSS.

3 | RESULTS

3.1 | Case report

An 11.5-year-old female was admitted to Department of Endocrinology with the main complaint of “short stature”.

The parents signed informed consent forms regarding the research conducted on this proband.
The female proband was born as the only child of healthy, non-consanguineous parents and was delivered by cesarean section at full term, with a weight of 2000 g (Z-score: <−3) and a height of 42 cm (Z-score: <−3). The father was 174 cm (Z-score: +0.22) and the mother was 151 cm (Z-score: −1.78) in height, and both without any manifestations of the nervous system or intellectual abnormalities.

Seven months after birth, she was found to have ventricular septal defect and was surgically treated at the age of six. She was shorter than the peers at an early age, and her annual growth rate was less than 5 cm. Angelman/Prader-willii syndrome were ruled out by Methylation-Specific Multiplex Ligation Probe Amplification (MS-MLPA) for the 15q11.2–13 area. At the age of 11.5, she was admitted to our hospital for the first time because of short stature. Physical examination revealed that her height was 126.9 cm (Z-score: −3.45) with proportionate stature, her weight was 40 kg (Z-score: +0.2), and the body mass index (BMI) was 24.8 kg/m² (Z-score: +2.4). Other physical examination showed that the mouth angles were down, the fifth metacarpal bones was short, and there were scattered cafe-au-lait macules on the abdomen and neck (Figure 1). She had a good appetite and physical strength. Breast development was at Tanner stage I. The height growth rate in the past year was 4.7 cm and her intellectual development was backward. Bone age was consistent with chronological age.

Laboratory examination revealed the following: growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis: GH 0.3 ng/ml, IGF-1 448 ng/ml. GH stimulating test by Levodopa showed a peak of GH at 4.69 ng/ml. Thyroid function test: FT₄ 4.25 pg/ml, [Reference range (RR)]: 1.80–4.10 ng/ml, FT₃ 1.287 ng/dL (RR: 0.81–1.89 ng/dL), and TSH 2.826 µIU/ml (RR: 0.38–3.34 µIU/ml). Sex hormone: LH 2.37 IU/L, FSH 8.65 IU/L, E₂ 36 pg/ml, P 0.55 ng/ml, T 0.25 ng/ml, PRL 13.3 ng/ml. Gonadotrophin releasing hormone (GnRH) stimulating test showed FSH [60 min] 20.66 IU/L, LH [60 min] 38.28 IU/L. Liver and renal function tests, electrolytes, blood glucose, and blood ammonia were all within normal ranges. The results of cranial magnetic resonance imaging (MRI) were normal. A right ovarian cyst was found accidentally in routine ultrasound examination, and laparoscopic ovarian cyst resection was performed. Postoperative pathology indicated mesosalpinx cyst.

Karyotype examination and the WES were recommended. Karyotype analysis in metaphases from 20 cell clones showed 46, XX, r (15) karyotype, as shown in Figure 2. Meanwhile, WES analysis revealed a 4.5 Mb heterozygous deletion in the region of chromosome 15q26.2–q26.3, encompassing genes ARRD4, FAM169B, IGF1R, PGPEP1L, SYNM, TTC23, MEF2A, LYSMD4, DNM1P46, ADAMTS17, CERS3, LINS1, ALDH1A3, LRRK1, CHSY1, SELENOS, SNRPA1, PCSK6, TM2D3, TAR53 and OR4F15. RT-qPCR investigations showed approximately half-reduced DNA copy of the genes located between ARRD4 and OR4F15 in the index segment (15q26.2–26.3 with almost 4.5 Mb size), while the NR2F2 gene remained intact (Figure S1).

Then, at the age of 12.3, due to the very low predicted target height (approximately 142 cm) given the current short stature and bone age consistent with chronological age, very cautious use of rhGH with close clinical monitoring, especially for glucometabolic index and ovarian ultrasound, was adopted. Meanwhile, considering that she was at start of puberty, 3.75 mg Gonadotrophin-releasing hormone analogue (GnRHa) (Triptorelin) was also administered in combination with rhGH in order to inhibit bone age maturation to give a longer growth-promoting period. Triptorelin injected intramuscularly every 28 days for 4 times and rhGH with a dose of 3 U/day was administered for 3 months with the height increment of 2 cm. Her serum IGF-1 level increased to 1077 ng/ml. Since rhGH was used for 6 months, the height has increased 3.8 cm (Z-score: +0.2) and the calculated growth velocity was 7.6 cm/year. Her weight has dropped by 1.2 kg. There were no other discomforts and abnormalities.

**Figure 1** Physical examination showed short fifth metacarpal bones, and scattered milk coffee spots on the abdomen.
3.2  |  Literature review results

Through literature search, 116 cases of r (15) syndrome have been found in a variety of populations. Here we reviewed 78 patients and present one additional case with detailed clinical and genetic descriptions of r (15) syndrome. The literature review indicated the main clinical manifestations of r (15) syndrome with prenatal and postnatal growth retardation, characteristic craniofacial features, and multisystem abnormalities, and rhGH treatment is beneficial for r (15) syndrome patients with short stature.

4  |  DISCUSSION

In this study, one case of r (15) syndrome in a female with short stature and a novel phenotype, ovarian cyst, were identified by combining whole exome sequencing and cytogenetics technology. Literature review was conducted to delineate the clinical spectrum of r (15) syndrome and the efficacy of rhGH treatment.

4.1  |  Summary of clinical characteristics

Due to the heterogeneity with variable size and genetic content and imbalances from ring instability, the clinical phenotypes of circular chromosomes are highly variable. Several studies have shown some high frequency phenotypic features of r (15) syndrome with growth retardation, microcephaly, clinodactyly, triangular faces, brachymesophalangy and low weight, which were relatively nonspecific (Butler et al., 1988; Paz et al., 2018).

These manifestations in our study were mainly small for gestational age (SGA) (65.1%), short stature (93.0%), developmental delay (62.1%), granio-facial malformations (88.0%), skeletal deformities (54.9%) (Table 1). Granio-Facial anomalies mainly included microcephaly (74.2%), triangular face (40.9%), broad nasal bridge (29.0%), micrognathia (27.3%), hypertelorism (25.8%), high-arched palate (23.2%), low-set ears (21.7%), strabismus (16.7%) and down-turned mouth (14.3%). The main manifestations of skeletal deformities included clinodactyly (27.1%), brachydactyly (22.9%), small hands or feet (20.3%), talipes equinovarus (11.4%), kyphosis (8.6%). Limited bone age data indicated that the bone age of 77.8% patients was delayed. Other abnormalities for cardiac abnormalities (20.8%), skin such as café au lait macules (34%) and hypochromic or hyperchromic patches (16%), uro-genital abnormalities (33.3%) and central nervous system (CNS) malformations (65.2%) were also present. In addition, cases also reported some rare clinical manifestations such as congenital diaphragmatic hernia (CDH), hypotonia, joint hyperextension, hirsutism, ovary absent etc., as well as ovarian cysts in our patients, which have never been reported in previous medical records. Thus, r (15) carrier individuals could have variable manifestations as intrauterine and postpartum growth retardation, characteristic facial deformities, and minor dysmorphisms to serious pathologies with multisystem involvement.

Except for five cases were diagnosed prenatally, the average age at diagnosis of patients with r (15) syndrome was 9.7 years for the 40 females and 24 males. Among the five cases diagnosed prenatally, r (15) syndrome was founded in four fetuses with the intrauterine growth restriction (IUGR) from ultrasound exam (Glass et al., 2006;
Hatem et al., 2007; Liu, Chang, & Chen, 2001; Manolakos et al., 2009). Three-dimensional ultrasound in the rendering mode was also important in the assessment of facial deformations in fetus (low-set ears and depressed nasal bridge) (Britto et al., 2014). Due to the limited number of reported r (15) syndrome cases, and most of them were occurred before puberty, it was very difficult to assess the reproductive ability of subjects affected by ring chromosomes. Six females with r (15) syndrome, who could be fertile but with both an increased risk of miscarriage(s) and having abnormal offspring (Frys et al., 1986; Fujimaki et al., 1987; Horigome, Kondo, Kuwajima, & Suzuki, 1992; Kalantari et al., 2018; Matsuishi, Yamada, Endo, Sakai, & Fukushima, 1996; Smith et al., 1991). Four infertile males and one male with one offspring were reported, but they were usually accompanied by cryptorchidism, genital dysplasia and oligospermia or asthenospermia (Emberger, Rossi, Jean, Bonnet, & Dumas, 1971; Jacobsen, 1966; Kalantari et al., 2018; Meinecke & Koske-Westphal, 1980; Moreau & Teyssier, 1982). Thus, the predominance of female patients with r (15) syndrome is unknown. Incomplete penetrance and/or variable expression of genes in different genders may be involved, but further evidence is needed to support this idea.

### 4.2 Summary of molecular characterization and genotype-phenotype association

Our patient had some of the most common features of r (15) syndrome, but she was diagnosed not very early since she was already in early puberty when she screened chromosome for short stature. One possible reason is that although there are some phenotypes that occurs frequently, they are not specifical, making it difficult to diagnose the syndrome based on clinical findings alone. The diagnosis of r (15) syndrome requires identification of the ring chromosome by cytogenetic techniques and array-based studies detecting molecular deletions or duplications. Karyotype analysis and fluorecence in situ hybridization (FISH) are still the gold standards for detecting circular chromosomes, but these techniques cannot achieve accurate molecular detection. The WES algorithm in our case revealed about 4.5Mb heterozygous deletion in the region of chromosome 15q26.2-q26.3, encompassing genes from **ARRDC4** to **TARS3** and was confirmed with RT-qPCR, showing that WES is an efficient alternative approach to detect loss of heterozygosity. Further molecular testing such as multiplex ligation probe amplification (MLPA)
and array technique including array comparative genomic hybridization (aCGH) are specifically useful tools for copy number variants (CNVs) detection, where conventional cytogenetics is unable to detect submicroscopic differences between patients. In the literature, a total of 44 cases with limited genetic data of cytology showed that except for eight cases of mosaic r (15) karyotype (Glass et al., 2006; Kalantari et al., 2018; Manolakos et al., 2009; Paz et al., 2018; Shao, Wang, Wu, Liu, & Miao, 2020; Smith et al., 1991; Szabó et al., 2018), in most cases the ring chromosomes were found in all cells and almost always accompanied by deletions of 15pter and/or 15qter. Unusual mosaicism with r (15) and 15qs+ and a r (15) plus an additional small supernumerary marker chromosome 15 [sSMC(15)] were also reported (Smith et al., 1991; Szabó et al., 2018). The ring chromosomes have been reported in multiple tissues and have been seen prenatally in both amniocytes and chorionic villous samples (Manolakos et al., 2009), as well as in post-natal blood, lymphocytes, bone marrow, and skin (Britto et al., 2014; Smith et al., 1991).

In order to find and establish a more accurate association between genotype and phenotype, we reviewed eleven cases with r (15) syndrome which have been detected with genome-wide aCGH and single-nucleotide polymorphism (SNP) array. Array results from patients with 15q26 deletions of r (15) were showed in Figure 3 (Phenotypes were also compared in Table S1). Their breakpoints were between cytogenetic bands 15q26.1 and 15qter including eight terminal and three interstitial deletion, respectively, yielding a minimal deletion of 500kb and a maximal deletion of 8Mb. Some genes were reviewed in many studies, such as the NR2F2 (OMIM 107773) gene in the pathogenesis of cardiac abnormalities (Glass et al., 2006; Peoples, Milatovich, & Francke, 1995), MEF2A (OMIM 600660) a candidate gene for cardiac, CDH and neurological abnormalities (Cannarella et al., 2017; Glass et al., 2006), CHSY1 (OMIM 608183) might responsible for skeletal abnormalities, LINS1(OMIM 610350) reported to be responsible for delayed psychomotor development. None of the genes mapped in the chromosome 15q26.3 band seems to play a role in the etiology of gonadal abnormalities, apart from the IGF1R (Cannarella et al., 2017). However, it is still difficult to find an exact link between genotype and phenotype through the accumulation of many literatures. The NR2F2 and IGF1R are highlighted, and it is notable that not all r (15) syndrome patients with heart deficiency had deletions of NR2F2, and not all patients had deletion of IGF1R although their height Z-score were below −3.

Patients 6 and 8 of our patient of the present study, who shared the similar breakpoint around 98–99 Mb of chromosome 15 (Pan et al., 2017), relatively shared similar mild clinical manifestations, including short stature, mild intellectual disability, café au lait macules, no significant severe skeletal deformities, and incidentally, ovarian absence in patient 6. Although our patients had a ventricular septal

**FIGURE 3** Array results from patients with 15q26 deletions of r (15) syndrome
defect and patient 6 did not, it might be explained by a more proximal breakpoint in our patients, where there might be candidate genes associated with heart defects. Patients 2, 3, and 11 had very small fragment deletions, but still had obvious facial abnormalities and skeletal deformities, while patient 7 with similar size fragment deletions had a mild phenotype. This might be related to the mosaic karyotypes of chromosomes in patients 2, 3, and 11 but non-mosaic karyotype in patient 7. Therefore, the underlying etiology of the phenotype is still not understood as apart from the deletions, ring instability can also result in other genomic imbalances, with decrease or increase of genetic material, and the level of mosaicism of the ring chromosome and parent of origin of the r (15) chromosome are all proposed as possible contributing to the consequences on the phenotype (Butler et al., 1988; Guilherme et al., 2011; Horigome et al., 1992; Nuutinen, Kouvalainen, & Knip, 1995; Smith et al., 1991).

### 4.3 rhGH treatment in patients with r (15) syndrome

The height Z-score of our patient was below −3 with a 4.5 Mb heterozygous deletion of 15q26.2-15q26.3 region encompassing IGF1R and normal serum IGF-1. In addition, children with a pure terminal deletion of 15q (Ester et al., 2009; Okubo et al., 2003; Pelosi et al., 2017; Poot et al., 2013; Siebler et al., 1995; Walenkamp et al., 2008) without the presence of a ring chromosome, have a similar growth phenotype while the deletions of the IGF1R have not been observed in healthy individuals, which indicates a role of IGF1R haploinsufficiency in the observed growth retardation. Several studies have shown that r (15) syndrome patients could gain remarkable acceleration in growth velocity from rhGH therapy (Nuutinen et al., 1995; Xu et al., 2011) as well as the growth retardation caused by IGF1R haploinsufficiency can successfully be treated with rhGH, although full catch-up was not reached (Walenkamp et al., 2008). Although almost all r (15) syndrome patients showed short stature, limited data are available on the response to rhGH. Ten patients received rhGH treatment in the literatures and this study (Cannarella et al., 2017; de Lacerda et al., 1999; Glass et al., 2006; Nuutinen et al., 1995; Peoples et al., 1995; Puchalska-Niedbał, Zając, Petriczko, & Kulik, 2014; Tewari et al., 2017; Xu et al., 2011) were summarized, among whom two patients had combined treatment with GnRHa or oxandroline (de Lacerda et al., 1999). As shown in Table 2, the average age at diagnosis of these patients was 5.7 ± 3.6 years. The average age of treatment initiation was 6.5 ± 3.9 years, and the mean duration of treatment was 1.8 ± 1.4 years. The average height Z-score (available in six patients) were −4.9 ± 1.1 and −3.8 ± 0.6 before and after treatment within 1.9 ± 1.6 years, respectively. The height Z-score after rhGH treatment significantly increased 1.1 ± 0.9 compared with that of before treatment (p < .05) (Figure 4). The treatment of rhGH significantly improved the height Z-score of patients with r (15) syndrome with an average increase of 1.1 ± 0.9. Moreover, although only short-term benefits were observed due to limited height data from long-term follow-up, in the only patient with 20 years’ follow-up from eight years old, short stature was untreated resulting a terminal height in 146.5 cm (height Z-score: −2.6) (Guilherme et al., 2012) and the height Z-score of other four adult patients without treatment were also only between −6.8 and −2.5 (Horigome et al., 1992; Matsuishi et al., 1996; Smith et al., 1991; Tümer et al., 2004), while Tümer reported a boy treated with growth hormone injections and his height at the age of 18 years was 164 cm (height Z-score: −1.4) (Tümer et al., 2004). However, there had also been report of responding well for initial first year but plateauing at the second year (Glass et al., 2006). Thus, the significant growth rate improvement, and the future follow-up experience of our patients with long-term use of rhGH suggest that although a full catch-up may not be reached, rhGH is effective for patients with r (15) syndrome. Only our patient received the combination therapy of rhGH and GnRHa since she was at start of puberty. Our results suggest that GnRHa combined with rhGH can improve growth velocity and predicted final height considerable in r (15) syndrome in early puberty, and we have therefore decided to continue treatment. This positive growing response may can be explained by the direct effect of rhGH in growth plate chondrocytes which is independent of the biological actions of serum IGF-1, and elevated serum IGF-1 levels may partially overcome the decreased sensitivity (Ester et al., 2009).

The main limitation is the lack of uniformity among the r (15) syndrome cases, considering the variable size and genetic content and imbalances from ring instability. A general profile of this rare disease was developed from all available previously reported cases to help clinicians identify the disease. Another limitation is that our patient is currently under treatment for less than a year, and we are following up closely with relatively good treatment response and good feedback from both patient and parent perspectives.

In conclusion, previous reported cases were reviewed and a new case of r (15) syndrome was added which further enriched the spectrum of this disorder. R (15) syndrome and chromosome screening should be considered when the child has prenatal and postnatal growth retardation, characteristic craniofacial features, and multisystem abnormalities. This study highlights the potential of combining traditional cytogenetics and next-generation
|                | Our patient | Nuutinen et al. (1995) | Peoples R² 1995 | Peoples R² 1995 | de Lacerda et al. (1999) | Glass et al. (2006) | Xu et al. (2011) | Puchalska-Niedbal et al. (2014) | Cannarella et al. (2017) |
|----------------|-------------|------------------------|-----------------|-----------------|--------------------------|---------------------|----------------|--------------------------------|------------------------|
| Age of diagnosis (y) | 11.5        | 4.0                    | 9.5             | 9.5             | 5.0                      | 0                   | 4.5            | 1.3                           | 6.0                    |
| Age of treatment (y) | 11.5        | 2.2                    | 7.4             | 4.3             | 8.7                      | 3                   | 4.5            | 3.0                           | 14.0                   |
| Dose (mg/m²/day)    | 1.33 mg/day | 1 U/day                | 0.28 mg/kg/week | 0.28 mg/kg/week | 10 IU/kg/week            | NA                  | 0.1 U/kg/day | 0.035 mg/kg/day                  | NA                     |
| Duration (y)        | 0.5         | 2.0                    | 2.1             | 5.2             | 1.3                      | 2.0                 | 0.3            | 1.0                           | 2.0                    |
| GH peak by stimulation test | 4.69 ng/ml (L-DOPA) | 35.6 ng/ml (Clonidine) | 6.2 ng/ml (L-DOPA, Clonidine) | 10.1 ng/ml | 38.4 mU/l (Clonidine) | NA | Normal | 11.8 ng/ml (L-DOPA, 15.3 ng/ml (Clonidine) | NA |
| IGF1R dosage        | Hemi        | NA                     | Normal          | Hemi            | Hemi                     | Hemi               | NA             | NA                            | NA                     |
| IGF−1 before        | 448 ng/ml (143–693) | 4.2 nmol/L (4.4–15) | 43.2 mU/ml (440–3600) | 670 mU/ml (440–3600) | 37,426 mg/l (204) | NA | NA | NA | 186 ng/ml (87.4–399.3) |
| IGF−1 after         | 1077 ng/ml (13.8 nmol/L) | NA | NA | NA | NA | NA | NA | NA |
| Height-before (Z score) | −3.3        | −6.2                   | −5.4⁺          | −6.0⁺          | −4.3                     | <−3.0              | −4.0           | −5.6                          | NA                     |
| Height-after (Z score) | −3.1        | −4.4                   | −4.6⁺          | −3.4⁺          | −3.3                     | <−3.0              | −3.7           | NA                           | NA                     |
| Change Ht (Z score) | 0.2         | 1.8                    | −0.8           | −2.6           | 1.0                      | 0.3                | NA             | NA                           | NA                     |
| GV-before (cm/yr)   | 4.7         | 5.9                    | 2              | 4              | 4.2                      | 0.3                | NA             | NA                           | NA                     |
| GV-after (cm/yr)    | 7.6⁺        | 8.5                    | 8              | 8              | 9.2⁺                     | 9                  | NA             | NA                           | NA                     |
| Improvement of GV   | 2.9         | 2.6                    | 6              | 4              | 5 shooter               | NA                 | 5              | 6                            | 6                      |

*Estimated from the growth chart.
⁺Plus triptorelin.
#Plus oxandrolone.
$Responded well for initial first year but plateaued at the second year.

Abbreviations: GV, growth velocity; N, within normal range; NA, not available.
sequencing techniques to accurately locate breakpoints, thereby helping to establish more detailed genotype-phenotype relationships, and thus better assist in clinical diagnosis, treatment, and genetic counseling for patients with chromosomal abnormalities. In addition, rhGH treatment can improve the growth velocity and predicted adult height in r (15) syndrome patients with short stature and further studies in long-term follow-up and in large population are still needed.

ACKNOWLEDGEMENT
Meiping Chen and Huijuan Zhu designed the study. Meiping Chen, Xiaoan Ke and Hanting Liang collected the data. Dongyan Cao performed surgical resection for patients. Fengying Gong guided the experimental study. Meiping Chen drafted manuscript. Hongbo Yang, Linjie Wang, Lian Duan and Hui Pan interpreted the data and revised the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTERESTS
The authors have declared that no conflict of interest exists.

AUTHOR CONTRIBUTIONS
Meiping Chen and Huijuan Zhu designed the study. Meiping Chen, Xiaolan Ke and Hanting Liang collected the data. Dongyan Cao performed surgical resection for patients. Fengying Gong guided the experimental study. Meiping Chen drafted manuscript. Hongbo Yang, Linjie Wang, Lian Duan and Hui Pan interpreted the data and revised the manuscript. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding authors.

ORCID
Meiping Chen https://orcid.org/0000-0003-1998-9915
Dongyan Cao https://orcid.org/0000-0002-5699-8813

REFERENCES
Britto, I. S. W., Regina Silva Herbest, S., Tedesco, G. D., Drummond, C. L., Bussamra, L. C. S., Araujo Júnior, E., Ruano, R., Ruano, S. H., & Aldrighi, J. M. (2014). Prenatal diagnosis of a fetus with ring chromosomal 15 by two- and three-dimensional ultrasonography. *Case Reports in Obstetrics and Gynecology*, 2014, 495702. https://doi.org/10.1155/2014/495702.

Butler, M. G., Fogo, A. B., Fuchs, D. A., Collins, F. S., Dev, V. G., Phillips, J. A., Optiz, J. M., & Reynolds, J. F. (1988). Two patients with ring chromosome 15 syndrome. *American Journal of Medical Genetics*, 29(1), 149–154. https://doi.org/10.1002/ajmg.1320290119.

Cannarella, R., Mattina, T., Condorelli, R. A., Mongioi, L. M., Pandini, G., La Vignera, S., & Calogero, A. E. (2017). Chromosome 15 structural abnormalities: Effect on IGF1R gene expression and function. *Endocrine Connections*, 6(7), 528–539. https://doi.org/10.1530/ect-17-0158.

de Lacerda, L., Carvalho, J. A., Stannard, B., Werner, H., Boguszewski, M. C., Sandrini, R., & Underwood, L. E. (1999). In vitro and in vivo responses to short-term recombinant human insulin-like growth factor-1 (IGF-I) in a severely growth-retarded girl with ring chromosome 15 and deletion of a single allele for the type 1 IGF receptor gene. *Clinical Endocrinology - Oxford*, 51(5), 541–550. https://doi.org/10.1046/j.1365-2265.1999.00799.x.

Emberger, J. M., Rossi, D., Jean, R., Bonnet, H., & Dumas, R. (1971). Observation of the 13–15 chromosome group in a ring (46, XY,15r). *Humangenetik*, 11(4), 295–299. https://doi.org/10.1007/bf00278656.

Ester, W. A., van Duyvenvoorde, H. A., de Wit, C. C., Broekman, A. J., Ruivenkamp, C. A. L., Govaerts, L. C. P., Wit, J. M., Hokken-Koelega, A. C. S., & Losekoot, M. (2009). Two short children born small for gestational age with insulin-like growth factor 1 receptor haploinsufficiency illustrate the heterogeneity of its phenotype. *Journal of Clinical Endocrinology and Metabolism*, 94(12), 4717–4727. https://doi.org/10.1210/jc.2008-1502.

Fryns, J. P., Kleczkowska, A., Buttiens, M., Jonckheere, P., Brouckmans-Buttiens, K., & van den Bergh, H. (1986). Ring chromosome 15 syndrome. Further delineation of the adult phenotype. *Annales de Genetique*, 29(1), 45–48.

Fujimaki, W., Baba, K., Tatara, K., Umezui, R., Kusakawa, S., & Mashima, Y. (1987). Ring chromosome 15 in a mother and her children. *Human Genetics*, 76(3), 302. https://doi.org/10.1007/bf00283630.
Glass, I. A., Rauen, K. A., Chen, E., Parkes, J., Alberston, D. G., Pinkel, D., & Cotter, P. D. (2006). Ring chromosome 15: characterization by array CGH. Human Genetics, 118(5), 611–617. https://doi.org/10.1007/s00439-005-0030-z.

Guilherme, R. S., Ayres Meloni, V. F., Kim, C. A., Pellegrino, R., Takeno, S. S., Spinner, N. B., Conlin, L. K., Christofolini, D. M., Kulikowski, L. D., & Melaragno, M. I. (2011). Mechanisms of ring chromosome formation, ring instability and clinical consequences. BMC Medical Genetics, 12, 171. https://doi.org/10.1186/1471-2350-12-171.

Guilherme, R. S., Meloni Vde, F., Takeno, S. S., Pellegrino, R., Brunoni, D., Kulikowski, L. D., & Melaragno, M. I. (2012). Twenty-year cytogenetic and molecular follow-up of a patient with ring chromosome 15: A case report. J Med Case Rep, 6, 283. https://doi.org/10.1186/1752-1947-6-283.

Hatem, E., Meriam, B. R., Walid, D., Adenem, M., Moez, G., & Ali, S. (2007). Molecular characterization of a ring chromosome 15 in a fetus with intrauterine growth retardation and diaphragmatic hernia. Prenatal Diagnosis, 27(5), 471–474. https://doi.org/10.1002/pd.1707.

Horigome, Y., Kondo, I., Kuwajima, K., & Suzuki, T. (1992). Familial occurrence of ring chromosome 15. Clinical Genetics, 41(4), 178–180. https://doi.org/10.1111/j.1399-0004.1992.tb03659.x.

Jacobsen, P. (1966). A ring chromosome in the 13–15 group associated with microcephalic dwarfism, mental retardation and emotional immaturity. Hereditas, 55, 188–191. https://doi.org/10.1111/j.1601-5223.1966.tb02047.x.

Kalantari, H., Karimi, H., Almadani, S. N., Fakhri, M., Mokhtari, P., Gourabi, H., & Mohseni Meybodi, A. (2018). Fecundity in an infertile man with r(15)—A challenge to the current paradigm. Reproductive BioMedicine Online, 36(2), 210–218. https://doi.org/10.1016/j.rbmo.2017.10.115.

Li, H., & Durbin, R. (2009). Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics, 25(14), 1754–1760. https://doi.org/10.1093/bioinformatics/btp324.

Liu, Y. H., Chang, S. D., & Chen, F. P. (2001). Increased fetal nuchal fold leading to prenatal diagnosis of ring chromosome 15. Prenatal Diagnosis, 21(12), 1031–1033. https://doi.org/10.1002/pd.168.

Manolakos, E., Vetro, A., Kitzirides, S., Papoulidis, I., Kosyakova, N., Mrasek, K., Weise, A., Agapitos, E., Orru, S., Peitsidis, P., Liehr, T., & Petersen, M. B. (2009). Prenatal diagnosis of a fetus with ring chromosome 15 characterized by array-CGH. Prenatal Diagnosis, 29(9), 884–888. https://doi.org/10.1002/pd.2295.

Matsuishi, T., Yamada, Y., Endo, K., Sakai, H., & Fukushima, Y. (1996). Ring chromosome 15 syndrome in an adult female. Journal of Intellectual Disability Research, 40(Pt 5), 478–480. https://doi.org/10.1111/j.1365-2788.1996.tb00654.x.

Meinecke, P., & Koske-Westphal, T. (1980). Ring chromosome 15 in a male adult with radial defects. Evaluation of the phenotype. Clinical Genetics, 18(6), 428–433. https://doi.org/10.1111/j.1399-0004.1980.tb01788.x.

Moreau, N., & Teysier, M. (1982). Ring chromosome 15: Report of a case in an infertile man. Clinical Genetics, 21(4), 272–279. https://doi.org/10.1111/j.1399-0004.1982.tb00763.x.

Nuutinen, M., Kouvulainen, K., & Knip, M. (1995). Good growth response to growth hormone treatment in the ring chromosome 15 syndrome. Journal of Medical Genetics, 32(6), 486–487. https://doi.org/10.1136/jmg.32.6.486.
of Medical Genetics. Part A, 176(2), 443–449. https://doi.org/10.1002/ajmg.a.38566.

Tewari, S., Lubna, N., Shah, R., Al-Rikabi, A. B. H., Shah, K., Sheth, J., & Sheth, F. (2017). Molecular characterization and evaluation of complex rearrangements in a case of ring chromosome 15. Molecular Cytogenetics, 10, 38. https://doi.org/10.1186/s13039-017-0339-z.

Tümer, Z., Harboe, T. L., Blennow, E., Kalscheuer, V. M., Tommerup, N., & Brøndum-Nielsen, K. (2004). Molecular cytogenetic characterization of ring chromosome 15 in three unrelated patients. American Journal of Medical Genetics Part A, 130a(4), 340–344. https://doi.org/10.1002/ajmg.a.30035.

Walenkamp, M. J., de Muinck Keizer-Schrama, S. M., de Mos, M., Kalf, M. E., van Duyvenvoorde, H. A., Boot, A. M., & Wit, J. M. (2008). Successful long-term growth hormone therapy in a girl with haploinsufficiency of the insulin-like growth factor-I receptor due to a terminal 15q26.2->qter deletion detected by multiplex ligation probe amplification. Journal of Clinical Endocrinology and Metabolism, 93(6), 2421–2425. https://doi.org/10.1210/jc.2007-1789.

Wei, X., Ju, X., Yi, X., Zhu, Q., Qu, N., Liu, T., Chen, Y., Jiang, H., Yang, G., Zhen, R., Lan, Z., Qi, M., Wang, J., Yang, Y. I., Chu, Y., Li, X., Guang, Y., & Huang, J. (2011). Identification of sequence variants in genetic disease-causing genes using targeted next-generation sequencing. PLoS One, 6(12), e29500. https://doi.org/10.1371/journal.pone.0029500.

Xu, F. Z., Zhoa, C. C., Liang, L., Huang, X. M., & Shao, Y. N. (2011). Ring chromosome 15 syndrome: Case report and literature review. Hong Kong Journal of Paediatrics, 16(3), 175–179.

Yip, M. Y. (2015). Autosomal ring chromosomes in human genetic disorders. Translational Pediatrics, 4(2), 164–174. https://doi.org/10.3978/j.issn.2224-4336.2015.03.04.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Chen, M., Ke, X., Liang, H., Gong, F., Yang, H., Wang, L., Duan, L., Pan, H., Cao, D., & Zhu, H. (2021). The phenotype and rhGH treatment response of ring Chromosome 15 Syndrome: Case report and literature review. Molecular Genetics & Genomic Medicine, 9, e1842. https://doi.org/10.1002/mgg3.1842