Roles of insulin-like growth factor 1 receptor in growth regulation in 15q26 deletion and duplication syndrome

KEXIN YU[1], XIN XU[2], BO LIU[3], KE ZHANG[4], YULAN LU[5], XINRAN DONG[3], LAISHUAN WANG[4], GUOQIANG CHENG[4], JIN WANG[4], WEI LU[1], BINGBING WU[3], HUIJUN WANG[3], FEIHONG LUO[1], WENHAO ZHOU[5] and LIN YANG[1]

[1]Department of Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University, Shanghai 201102, P.R. China; [2]Division of Neonatology, Children's Hospital of Fudan University (Xiamen Branch), Xiamen Children's Hospital, Xiamen, Fujian 361006, P.R. China; [3]Center for Molecular Medicine of Children's Hospital of Fudan University, Shanghai 201102, P.R. China; [4]Division of Neonatology, Children's Hospital of Fudan University, Shanghai 201102, P.R. China; [5]Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong 510623, P.R. China

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Abstract. The 15q26 deletion and duplication syndromes are rare chromosome diseases with growth deviation and structural anomalies such as facial abnormality, cardiac malformation and hand/foot/skeleton malformations. Insulin-like growth factor 1 receptor (IGF1R), located on chromosome 15q26, is key for pre- and postnatal growth. The present study aimed to determine whether IGF1R serves as a key factor in growth regulation in 15q26 deletion and duplication syndromes. Patients with 15q26 deletions and duplications enrolled in the China Neonatal Genomes Project (CNGP) were recruited. A systematic review of 15q26 deletion and duplication cases was performed, followed by meta-analysis to evaluate the roles of IGF1R and three other genes [myocyte enhancer factor 2A (MEF2A), leucine-rich repeat kinase 1 (LRRK1) and nuclear receptor subfamily 2 group F member 2] involved in growth regulation. A total of 10 eligible patients from the CNGP, including seven with deletions and three with duplications, were identified. The literature search and screening yielded 78 patients with 15q26 deletions and 10 with 15q26 duplications. Clinical features observed in >70% of the patients in the deletion group were facial abnormalities, developmental delay, short stature and hand/foot/skeleton malformations, whereas the duplication group exhibited facial abnormality, hand/foot/skeleton malformation and speech development delay. In 15q26 deletion, three candidate genes were associated with an increased risk of short stature: IGF1R [odds ratio (OR): 8.43; 95% confidence interval (CI): 2.22-32.00], LRRK1 (OR: 100.00; 95% CI: 11.86-843.23) and MEF2A (OR: 32.21; 95% CI: 3.81-272.47). In 15q26 duplication, none of the candidate genes significantly affected tall stature. Using meta-analysis, the present study revealed that IGF1R is not the only key gene responsible for growth abnormalities in 15q26 deletion and duplication syndromes.

Introduction

Abnormalities in the distal long arm of chromosome 15 are associated with various clinical manifestations. Specifically, 15q26 deletion is associated with intrauterine growth restriction (IUGR), small for gestational age (SGA), microcephaly, developmental delay, skeletal abnormality and dysmorphic facial features (1). Distal duplication of 15q is involved in overgrowth syndrome and other congenital malformations, including craniosynostosis, cardiac and renal malformation, genital and limb abnormality (2). Chromosomal alterations on 15q26 may occur as a *de novo* event leading to deletion/duplication or as a consequence of ring chromosome formation and unbalanced translocation (2,3).

Insulin-like growth factor 1 receptor (IGF1R), located on chromosome 15q26.3, is dosage-sensitive (4). Biological functions of IGF-1, including its roles in intrauterine development, postnatal growth and metabolism, are primarily mediated by IGF1R (5). Associations between poor growth and overgrowth in 15q26 deletion and duplication syndromes, respectively, are associated with the dysregulation of IGF1R expression. To the best of our knowledge, however, research on this has been limited to case reports or reviews (1,3), yielding inconsistent results. Therefore, comprehensive evaluation using a large sample size is necessary to clarify this association.

The present study involved patients with 15q26 deletion/duplication from the Chinese Neonatal Genomes Project (CNGP) (6) enrolled at Children's Hospital of Fudan University, Shanghai, China. The clinical symptoms of patients with 15q26 deletions and duplications were systematically reviewed

Correspondence to: Dr Lin Yang, Department of Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, P.R. China
E-mail: yanglin_fudan@163.com

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through a comprehensive literature review. Furthermore, a meta-analysis was performed to assess the effects of IGF1R, nuclear receptor subfamily 2 group F member 2 (NR2F2), myocyte enhancer factor 2A (MEF2A) (3) and leucine-rich repeat kinase 1 (LRRK1) (7) on the poor growth and overgrowth of patients with 15q26 deletion/duplication. The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (8). Identification of key genes associated with growth in 15q26 deletion/duplication may provide insights into the pathological mechanisms underlying cytogenetic defects, facilitating the development of effective management strategies.

Patients and methods

Study population. Ethics approval was provided by the Ethics Committee of the Children's Hospital of Fudan University, Shanghai, China (approval nos. 2021-375 and 2025-40). The parents of participants provided informed written consent for genetic testing. The inclusion criteria were as follows: i) Patients admitted to the neonatal intensive care unit of the Children's Hospital of Fudan University between August 2016 and July 2022 as part of CNGP; ii) patients with deletion or duplication copy number variations (CNVs) on chromosome 15q26 and iii) cases with CNVs >1 Mb.

The exclusion criteria were as follows: i) Patients with CNVs other than 15q26 deletion or duplication; ii) patients with single nucleotide variants (SNVs); and iii) patients with incomplete clinical information.

A total of 10 newborns, including four females and six males were enrolled in the study. The median last follow-up age was 6.4 years (range, 3.0-9.7 years). Clinical data were collected, including discharge diagnosis, physical examination, hospitalization history during the neonatal period and health examination record during follow-up. The assessment of body size at birth and follow-up was according to growth standard curves and standardized growth charts for Chinese newborns and children (9,10). Most of the available data were confined to the neonatal period. Therefore, the present study used a composite outcome that encompassed either IUGR/SGA at birth or short stature in childhood as an indicator of a growth disorder. Similarly, overgrowth was defined by a composite outcome comprising either large for gestational age (LGA) or tall stature.

Whole exome sequencing and CNV analysis based on sequencing data. At enrollment, 1 ml blood was drawn from each patient and anticoagulated with EDTA. Genomic DNA was extracted using the QIAamp DNA kit (Qiagen GmbH; cat. no. 51185). The concentration was measured using a NanoDrop 2000 ultraviolet spectrophotometer (Thermo Fisher Scientific, Inc.). Agilent SureSelect XT Human All Exon V5 kit (Agilent Technologies, Inc.; cat. no. 5190-6209) was used for library capture. The loading concentration of the final library was 10-14 pM. Paired-end sequencing (125/150 bp) was performed using the Illumina, Inc. HiSeq 2000/2500 platform. The average coverage for the yielded data was 124.05X, and the average fraction of target covered with at least 10X and 20X were 99.11% and 97.17%, respectively. Low-quality reads (reads containing >10% unknown bases or >50% bases with a sequencing quality <5) were removed from the raw fastq data to generate clean reads. Clean reads were aligned to the reference human genome (University of California, Santa Cruz (UCSC hg19) using the Burrows-Wheeler Aligner (BWA; v.0.5.9-r16, sourceforge.net/projects/bio-bwa/files/), sorted by SAMtools (v.1.8,https://sourceforge.net/projects/samtools/files/samtools/), and deduplicated using Picard (v.2.20.1, https://github.com/broadinstitute/picard/releases/tag/2.20.1). CNGP clinical sequencing pipeline was as previously described (11).

CNVs were screened via second-generation sequencing as follows (11): i) CNV data of duplication fragments >500 kb and deletion fragments >200 kb were selected; ii) false positive results were excluded; iii) CNVs reported as a normal population in the International Genome CNV Polymorphism database (Database of Genomic Variants, dgv.tcag.ca/); ≥80% overlap of fragments and the same type of duplication or deletion were excluded; and iv) CNVs that did not contain genes in the region were excluded.

The molecular diagnostic laboratory at Children's Hospital of Fudan University implemented a well-established CNV analysis pipeline using exome sequencing (ES), called PICNIC, encompassing CNV detection, annotation and filtration (11,12). The accuracy of the ES call CNV performance >1 Mb has been demonstrated in identifying pathogenic/likely pathogenic (P/LP) CNVs (12-14). PICNIC identifies candidate CNVs (predicted P/LP or variants of uncertain significance CNVs) in each case for manual review. Breakpoints and sizes were determined according to the predefined exome. PICNIC default settings favor sensitivity to prevent the loss of positive results and false-positive results were excluded through manual review.

Systematic review. The present study aimed to assess the impact of IGF1R gene along with NR2F2, LRRK1 and MEF2A genes on poor growth and overgrowth in patients with 15q26 deletion/duplication. A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (8).

Literature search was performed in the PubMed database (pubmed.ncbi.nlm.nih.gov) using the search term ((15q26[Title/Abstract]) OR (15q terminal[Title/Abstract])) AND (English[Filter]) from February 1983 to August 2025. The individual-level data of the patients involving 15q26 deletion/duplication and the genotype and primary phenotypes of both deletion and duplication cases were collected. EndNote 20.4 (endnote.com/) was used for the reference management. The inclusion criteria were as follows: i) Case reports or reviews; ii) genetic testing results indicating a 15q26 deletion or duplication; iii) cases with detailed phenotypic and genotypic data; iv) Only cases of 15q26 syndrome published in the English language were included. The exclusion criteria were as follows: i) Studies without detailed information on phenotype and genotype; ii) unrelated studies, such as those focusing on SNVs or cancer research; iii) tetraploidy on 15q26 chromosome; and iv) patients with CNVs other than 15q26 deletion/duplication.

A total of two investigators reviewed the titles and abstracts of all publications identified in the literature search. The data were extracted and assigned to the following domains: i) Literature characteristics (author and year); ii) patient demographic information (age and sex); iii) clinical manifestations (IUGR, SGA, LGA, cardiac malformation, tall stature, growth retardation/failure to thrive/short stature, developmental delay,

microcephaly, macrocephaly, facial abnormality, speech development delay and hand/foot/skeleton malformations); and iv) genotypes (chromosome band, location, deletion/duplication, CNV size, ring chromosome 15). If the gene was not mentioned and the chromosomal location was not provided, the involvement of the gene could not be confirmed. Individuals with partial genetic information were retained for clinical profiling. However, genes that could not be confirmed were annotated as not available and were not included in the final statistical analysis. If main clinical information was present, cases passed the quality assessment.

Statistical analysis. Clinical manifestations were summarized as frequency counts and compared using the Pearson χ^2 or the Fisher exact test. Microcephaly was defined as an occipitofrontal head circumference (OFC) below the third centile or >2 SD below the mean for sex, age and ethnicity (15). Macrocephaly was defined as an OFC >2 SD or 0.5 cm above the 97th percentile (16). SGA and LGA were defined as a birth weight and/or length <10th percentile or >90th percentile, or with a Z-score less than -2 or greater than +2 for gestational age and sex, respectively (9,17,18). Short and tall stature were defined as a height with a Z-score <-2 or greater than +2, or below the 3rd or above the 97th percentile for age and sex (10,19). The mechanism by which the target genes contributed to short/tall stature in patients with 15q26 syndrome was assessed using Review Manager 5.4 (Nordic Cochrane Centre). IUGR, SGA, short stature, growth retardation and failure to thrive were regarded as short stature-positive events in 15q26 deletion, whereas LGA and tall stature were regarded as tall stature-positive events in 15q26 duplication. Mantel-Haenszel (M-H) test was used for stratified analysis. All outcomes are reported as odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data. I^2 statistic was used to measure the heterogeneity of studies. A random-effects model was used for meta-analyses. SPSS software version 26 (IBM Corp) was used for the data analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features and genetic results of patients enrolled in CNGP. A total of 10 eligible patients from CNGP were included (Table I). There were three patients in the duplication and seven patients in the deletion group. The duplication group consisted of one female and two male patients. One patient was diagnosed with SGA (Patient 1) and one with LGA (Patient 2). The deletion group consisted of four males and three females. Among them, six patients (patient 4, 5, 7, 8, 9, 10) were diagnosed with short stature. Patient 6 was born with SGA and was not of sufficient age to undergo follow-up measurement. A total of four patients (patients 4, 7, 8 and 10) were diagnosed with developmental delay and two patients (patients 4 and 5) had hip abnormalities. Patient 7 was diagnosed with congenital heart disease and cryptorchidism.

In the duplication group (Table I), there were two duplications at 15q26.1 and 15q26.3 in patient 1. Among the candidate genes, NR2F2 was normal, whereas the others were duplicated in Patient 1. Patient 2 had a 10.95 Mb duplication at 15q26.1-q26.3, involving all four genes. Patient 3 had a duplication at 15q26.1, but the candidate genes had a normal karyotype. In the deletion group, six patients (patients 5-9) exhibited a deletion at 15q26.3 and one patient (patient 10) exhibited a deletion at 15q26.1. IGF1R and MEF2A were involved in the CNVs of four patients (patients 4-7). The sizes of deleted regions varied from 1.2 to 4.2 Mb. LRRK1 was only normal in patient 10. Notably, NR2F2 was not deleted in any patient of the deletion group.

Literature review and study characteristics. A total of 326 studies was retrieved from PubMed (Fig. 1). Of these, 176 articles were excluded after title selection and 37 were excluded after abstract selection. In total, 113 studies were eligible for detailed review. Clinical manifestations and genetic findings of cases were collected; 44 cases were excluded as they involved other CNVs, and 21 were excluded because they lacked detailed clinical or genetic information. Finally, 88 cases from 64 studies were subjected to meta-analysis (Tables II and SI) (1-4,7,20-78). A total of 78 patients had deletions and 10 had duplications. The length of deletions ranged from 2 kb to 13.3 Mb, whereas that of duplications ranged from 290 kb to 4.71 Mb.

Phenotype characteristics. A total of 88 cases were collected (Table I and Table SI). Excluded studies/patients (mostly cases with chromosomal translocations) are presented in Table SII.

In the deletion group (Table I), the most frequently observed clinical features were facial abnormality (65/77, 84.4%), developmental delay (49/61, 80.3%), growth retardation/short stature (58/71, 81.7%), hand/foot/skeleton malformation (55/76,72.4%), SGA (43/64, 67.2%), speech developmental delay (31/50, 62.0%) and microcephaly (39/66, 59.1%). Cardiac malformations were observed in 38.7% of cases (29/75).

In the duplication group (Table I), the most frequently observed clinical features were facial abnormality (10/10, 100.0%), hand/foot/skeletal malformation (6/7, 85.7%), speech development delay (5/6, 83.3%) and tall stature (4/7, 57.1%). Macrocephaly was observed in 28.6% (2/7), LGA in 25.0% (2/8), developmental delay in 16.7% (1/6), SGA in 12.5% (1/8) and cardiac malformation in 12.5% (1/8) of cases.

Significant differences in age were observed between the deletion and duplication groups. The literature review also revealed significant differences in SGA/LGA, growth retardation, short/tall stature, developmental delay and microcephaly between the deletion and duplication groups. However, no significant differences in cardiac malformation, macrocephaly, facial abnormality, speech development delay and hand/foot/skeleton malformation were observed between the two groups.

Effects of candidate genes on patient growth. Chromosome locations of deletion and duplication cases with specific positions are presented in Fig. 2. The present study assessed the effects of candidate genes on the growth of patients with 15q26 duplication/deletion syndrome using M-H test (Figs. 3 and 4). In 15q26 deletion, three candidate genes were associated with an increased risk of short stature: IGF1R (OR: 8.43; 95% CI: 2.22-32.00), LRRK1 (OR: 100.00; 95% CI: 11.86-843.23) and MEF2A (OR: 32.21; 95% CI: 3.81-272.47). LRRK, not IGF1R, was more likely to result in short stature. NR2F2 (OR: 3.48; 95% CI: 0.69-17.64) was

Table I. Clinical and genetic information of patients enrolled in the China Neonatal Genomes Project.

A, Duplication

Patient no.	Sex	Band	Length, kb	*IGF1R* involvement	*LRRK1* involvement	*MEF2A* involvement	*NR2F2* involvement	SGA/ short stature	LGA/tall stature	Other clinical features
1	F	15q26.1/ 15q26.3	4209.50/ 2600.49	Yes	Yes	Yes	No	+	-	Café au lait spots, seizure, microcephaly, developmental delay and congenital heart disease
2	M	15q26.1-q26.3	10947.50	Yes	Yes	Yes	Yes	-	+	Congenital upper and lower limb deformity and obesity
3	M	15q26.1	4209.50	No	No	No	No	-	-	Congenital heart disease and developmental delay

B, Deletion

Patient no.	Sex	Band	Length, kb	*IGF1R* involvement	*LRRK1* involvement	*MEF2A* involvement	*NR2F2* involvement	SGA/ short stature	LGA/tall stature	Other clinical features
4	M	15q26.3	2600.49	Yes	Yes	Yes	No	+	-	Dislocation of hip joint, café au lait spots, developmental delay
5	F	15q26.3	3856.47	Yes	Yes	Yes	No	+	-	Congenital hip dysplasia
6	M	15q26.3	3856.47	Yes	Yes	Yes	No	+	-	Hypotonia and cryptorchidism
7	M	15q26.3	2600.49	Yes	Yes	Yes	No	+	-	Cryptorchidism, developmental delay, congenital heart disease and squint
8	F	15q26.3	1280.61	No	Yes	No	No	+	-	Developmental delay
9	F	15q26.3	1203.19	No	Yes	No	No	+	-	-
10	M	15q26.1	4216.30	No	No	No	No	+	-	Developmental delay and congenital coxa vara

IGF1R, insulin-like growth factor 1 receptor; LRRK1, leucine-rich repeat kinase 1; MEF2A, myocyte enhancer factor 2A; NR2F2, nuclear receptor subfamily 2 group F member 2; SGA, Small for gestational age; LGA, Large for gestational age; M, male; F, female; +, positive; -, negative.

Table II. Demographic information and clinical features of patients from the literature.

Characteristic	15q26 deletion (n=78)	15q26 duplication (n=10)	P-value
Age (%)			0.007[a]
0-1 months	7/78 (9.0)	3/10 (30.0)	
>1 month-3 years	22/78 (28.2)	0/10 (0.0)	
>3-18 years	39/78 (50.0)	3/10 (30.0)	
>18 years	10/78 (12.8)	4/10 (40.0)	
Female (%)	54/78 (69.2)	3/8 (37.5)	0.157[b]
SGA (%)	43/64 (67.2)	1/8 (12.5)	0.009[b]
LGA (%)	0/64 (0.0)	2/8 (25.0)	0.011[a]
Short stature (%)	58/71 (81.7)	0/7 (0.0)	<0.001[b]
Tall stature (%)	0/71 (0.0)	4/7 (57.1)	<0.001[a]
Cardiac malformation (%)	29/75 (38.7)	1/8 (12.5)	0.281[b]
Developmental delay (%)	49/61 (80.3)	1/6 (16.7)	0.003[b]
Microcephaly (%)	39/66 (59.1)	0/7 (0.0)	0.010[b]
Macrocephaly (%)	0/66 (0.0)	2/7 (28.6)	0.009[a]
Facial abnormality (%)	65/77 (84.4)	10/10 (100.0)	0.391[b]
Speech development delay (%)	31/50 (62.0)	5/6 (83.3)	0.562[b]
Hand/foot/skeleton malformation (%)	55/76 (72.4)	6/7 (85.7)	0.750[b]

[a]Fisher's exact test; [b]continuity correction. SGA, small for gestational age; LGA, Large for gestational age.

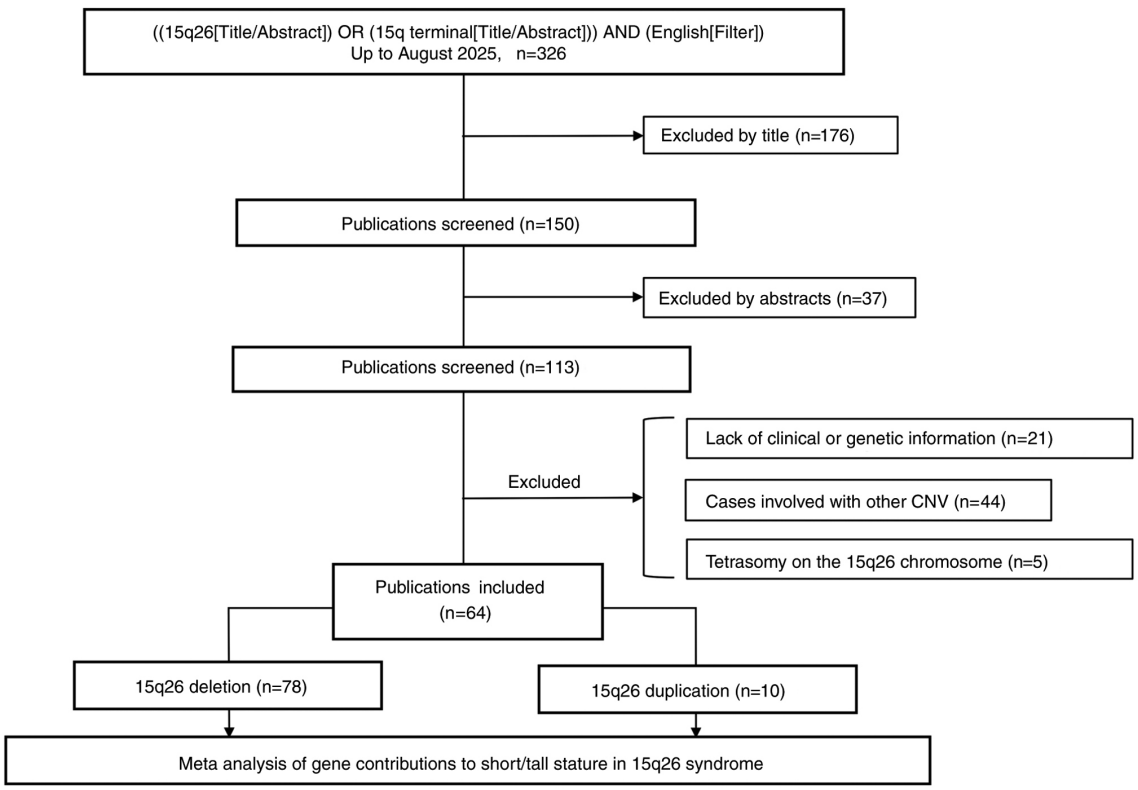

Figure 1. Flow chart of the literature screening and reviewing procedure using PubMed and case selection process for meta-analysis. CNV, copy number variation.

not significantly associated with short stature. In 15q26 duplication, all candidate genes, IGF1R (OR: 2.67; 95% CI: 0.28-25.64), LRRK1 (OR: 11.00; 95% CI: 0.46-263.53), MEF2A (OR: 10.50; 95% CI: 0.67-165.11) and NR2F2 (OR: 12.14; 95% CI: 0.46-323.23) were not significantly associated with tall stature. In addition, there were 18 ring chromosome 15 cases, including 17 in the deletion and one in the duplication group (Table SI).

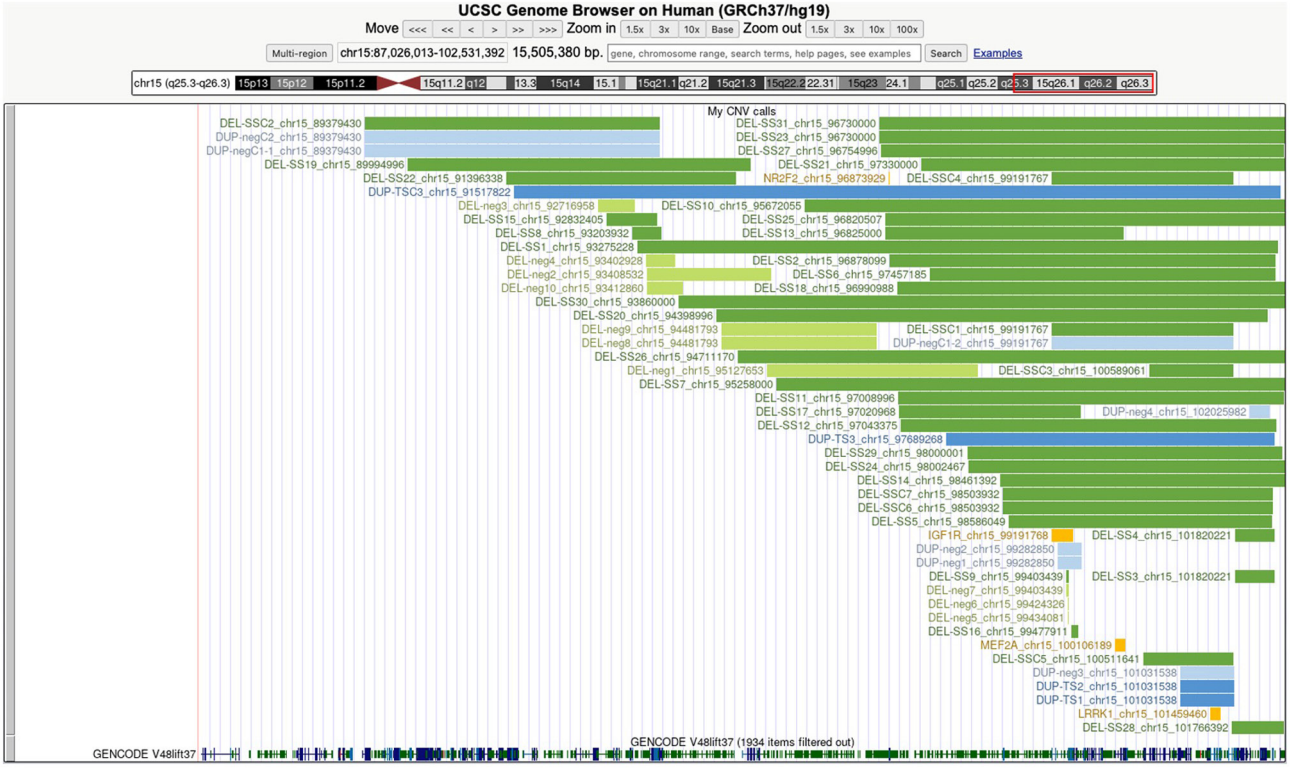

Figure 2. Chromosome locations of deletion and duplication cases with specific positions in UCSC genome browser assembly (GRCh37/hg19). Orange, candidate genes; dark blue, duplication cases with tall stature; light blue, duplication cases without tall stature; dark green, deletion cases with short stature; light green, deletion cases without short stature. UCSC, University of California, Santa Cruz.

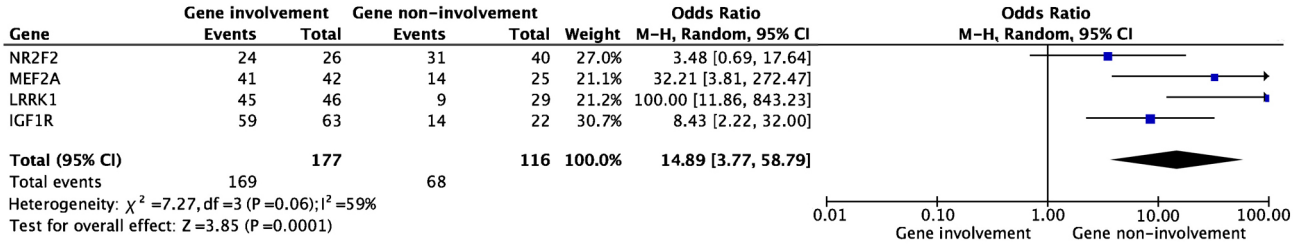

Figure 3. Meta-analysis of the roles of candidate genes in 15q26 deletion syndrome. IGF1R, insulin-like growth factor 1 receptor; LRRK1, leucine-rich repeat kinase 1; MEF2A, myocyte enhancer factor 2A; NR2F2, nuclear receptor subfamily 2 group F member 2; M-H, Mantel-Haenszel.

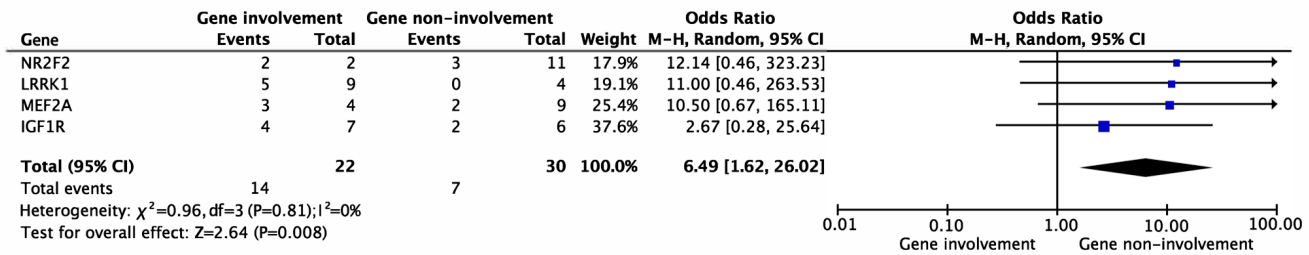

Figure 4. Meta-analysis of the roles of candidate genes in 15q26 duplication syndrome. IGF1R, insulin-like growth factor 1 receptor; LRRK1, leucine-rich repeat kinase 1; MEF2A, myocyte enhancer factor 2A; NR2F2, nuclear receptor subfamily 2 group F member 2; M-H, Mantel-Haenszel.

Discussion

The 15q26 deletion/duplication syndrome is a rare genetic disease that causes syndromic manifestations such as facial abnormality, growth problems, cardiac and hand/foot/skeleton malformation and developmental delays. A total of 58 cases of pure 15q26 deletions have been reported up to September 2021 (3) and >70 patients with chromosome 15q terminal duplications were reported in 2017 (28). The present study collected cases with 15q26 deletions or duplications to

delineate the role of implicated genes within this region and characterize the spectrum of associated clinical features. The analysis of 98 cases (88 cases in literature and 10 cases from CNGP) in the present study revealed that IGF1R may not be the only gene responsible for the phenotype of chromosome 15q26 deletion/duplication syndrome. The present study performed meta-analysis to explore the 15q26 region for key genes associated with growth regulation of 15q26 deletion/duplication syndrome.

Previous reports (1,21,67,73) mostly attribute growth abnormality to IGF1R gene in 15q26 deletion/duplication syndrome. IGF1R gene, which is mapped to chromosome 15q26.3, is a member of the insulin receptor family. It functions by activating the downstream mitogen-activated protein kinase and phosphatidylinositol 3-kinase/protein kinase B signaling pathways (79). Holzenberger *et al* (80) introduced a neomycin resistance cassette into intron 2 of IGF-1R. This insertion interfered with the processing of the primary transcript, resulting 12% fewer IGF-binding sites at the cell surface in heterozygous mice and 41% fewer in homozygous mice. Hetero- and homozygous offspring grew more slowly than wild-type littermates. Functional deficit of IGF1R gene affects the postnatal growth (80). A previous report showed that a patient with 15q-trisomy had postnatal overgrowth and three copies of IGF1R, whereas a fetus with 15q-monosomy showed IUGR with one copy of IGF1R gene; these were all derived from paternal balanced translocation (81). IGF1R gene defects cause intrauterine and postnatal growth failure, microcephaly and developmental delays in autosomal dominant (AD) and autosomal recessive (AR) inheritance models (82-84). Patients with AR inheritance are more severely affected than those with AD inheritance by IGF1R defect with developmental and speech delays (85). IGF1R is key for normal embryonic and postnatal growth (86), especially skeletal growth, brain development and carbohydrate metabolism (1). Patients with IGF1R mutations exhibit biochemical features of IGF-I resistance, with high circulating concentrations of IGF-I and growth hormone (86). Veenma *et al* (45,46) considered that in addition to short stature, most clinical features of 15q26 deletion syndrome are similar to those caused by single mutations in IGF1R. Walenkamp *et al* (87) developed a clinical scoring system for the diagnosis of IGF1R defect that was tested in single cohort (88). Since the present cases did not receive IGF level testing as a routine during their hospitalization in the neonatal period, independent sample tests could not be conducted. The clinical score should be conducted in future longitudinal studies.

The present and previous studies reported short and tall stature cases without IGF1R deletions or duplication (7,54). A total of three of the present patients (patients 8-10) had SGA/short stature without IGF1R deletion. The deletions in patients 8 and 9 overlapped those reported by Bellucco *et al* (89) and Szabo *et al* (90). Conversely, certain duplication cases may not demonstrate an LGA phenotype. Patients may exhibit IUGR (2). In addition to the IGF1R gene, haploinsufficiency of the 15q26 genomic region distal to IGF1R gene may be related to growth disturbance without loss of the IGF1R gene. MEF2A, NR2F2 and LRRK1 were considered candidate genes that contributed to 15q26 deletion/duplication syndrome (3,6).

LRRK1 gene is a strong candidate gene, as evidenced by prior literature implicating its contribution to growth phenotype in the 15q26 deletion/duplication syndrome (6,75). LRRK1 encodes a multi-domain protein that is a leucine-rich repeat kinase and a GDP/GTP binding protein. The encoded protein is hypothesized to play a role in the regulation of bone mass. In Online Mendelian Inheritance in Man database (91), mutations in the LRRK1 gene are associated with osteosclerotic metaphyseal dysplasia, an AR disorder presenting with skeletal abnormality and notably short stature. The protein encoded by MEF2A gene is a DNA-binding transcription factor that activates numerous muscle-specific and growth factor- and stress-induced genes, such as PIK3CG and MMP9 genes (92,93). MEF2A gene mediates cellular functions not only in skeletal and cardiac muscle development, but also in neuronal differentiation and survival. NR2F2 encodes a ligand-activated transcription factor. NR2F2 gene defects cause a variable syndrome of congenital anomalies, commonly associated with heart defect, developmental delays/intellectual disability, dysmorphic features, feeding difficulties, hypotonia and genital anomalies (94). In the Genecards database (genecards.org), LRRK1, MEF2A and NR2F2 genes are associated with body height. The deletions of these genes on 15q26 region may be involved in the occurrence of short stature, along with abnormalities in cardiovascular, skeletal and nervous systems. LRRK1 and MEF2A gene demonstrated higher OR than IGF1R gene. However, these results exhibited relatively wide CIs, indicating a higher degree of uncertainty. The present sample size was relatively limited, particularly for cases with duplications. To investigate the impact of genetic alterations within the 15q26 region on phenotypic outcomes, the present study excluded cases with additional chromosomal abnormalities other than this region, including those involving chromosomal translocations and cases with breakpoints proximal to 15q26 region, which lead to the censored data of numerous candidate samples. The majority of individuals affected by 15q26 alterations presented with physical developmental disorder. The present study aimed to delineate the underlying gene-phenotype associations through calculating OR. However, CNV-associated phenotypes are not only driven solely by single genes, but also typically involve multiple contiguous genes. When genes are located in close proximity and are concurrently deleted or duplicated, the combined effects may confound analyses (95-98). As a result, the CI in the present study may be relatively wide.

The present study focused on analyzing the association between deletion/duplication of genes and growth phenotypes, specifically the impact of sequence alterations, and therefore excluded cases with aberrations in other chromosomal segments. The present literature review included 18 cases with ring chromosomes. Previous studies (28,68,70) have suggested that patients with ring chromosome 15 present with similar clinical features to those with pure 15q26 deletion, and short statures observed in r(15) patients are likely related to reduced dosage of the IGF1R gene. In our study, we aimed to explore the effects of IGF1R gene on growth phenotype. Therefore, we considered r(15) as a type of 15q26 deletions/duplications and included cases with r(15) according with our inclusion criteria. However, due to the limited number of r(15) cases, the present study did not perform a separate analysis of the

impact of the ring structure on short stature. Another potential factor is that a promoter region change affects gene expression: Different breakpoints may lead to the juxtaposition of IGF1R near an active promoter or to alteration of normal regulatory sequences of the gene. Also, embryonic development and growth may not only be influenced by genetic factors, but also affected by environmental factors, including maternal factors and nutrition.

Here, duplication cases were relatively rare compared with deletion cases. Although none of the four genes showed a significant contribution to tall stature in the duplication group, a consistent trend of positive effects on overgrowth was observed. However, the insufficient sample size led to a decrease in the statistical power and findings should be interpreted with caution. During data extraction and screening, chromosome abnormalities other than 15q26 were excluded, including cases that had deletions or duplications in the proximal region of 15q26 because other chromosome anomalies may lead to more complex phenotypes in patients. Numerous cases of 15q duplication involved large-scale duplications, which exceeded 15q terminal (15q26) region and were excluded from the present study.

The present retrospective study reported 10 cases of 15q26 deletion and duplication syndrome in CNGP, including three patients with 15q26 duplication and seven with 15q26 deletion. Additional phenotypes associated with the IGF1R were reported, such as microcephaly and hypotonia. The clinical features were similar to those reported in the literature (31,35). Microcephaly was more prevalent in 15q26 deletion cases, while macrocephaly was more prevalent in 15q26 duplication cases. Congenital heart disease was present in both deletion and duplication cases. A high prevalence of congenital heart defects has been reported in cases of IGF1R gene defects (28). A previous study in mice have suggested conditional deletion of IGF-1R and the insulin receptor genes in the myocardium results in decreased cardiomyocyte proliferation and ventricular wall hypoplasia (99). However, alterations in the NR2F2 and MEF2A gene may explain heart defects found in the 15q26 syndrome as well. The pathogenic mechanisms underlying congenital heart defects of the 15q26 syndrome remain to be fully elucidated. A total of two male patients with CNGP were diagnosed with cryptorchidism, consistent with previous studies, which suggest IGF1R is involved in testicular function (1,100).

The association between genes and 15q26 deletion/duplication syndrome remains unclear, warranting further study. The present meta-analysis assessed the association between the growth phenotype and genotype in 15q26-associated syndromes. The present study investigated the association between IGF1R (along with NR2F2, LRRK1 and MEF2A) and short/tall stature phenotype in patients with 15q26 deletion/duplication syndrome. Although not all genes on 15q26 were subjected to meta-analysis, the present study demonstrated that, in addition to IGF1R, other key genes, such as LRRK1, also contributed to the growth abnormality in 15q26-related syndromes. Future studies should further explore the functions and expression patterns of 15q26 deletion/duplication syndrome.

The present study had certain limitations. The CIs may be relatively wide because of a limited sample scale and combined effects from adjacent genes, which led to a lack of statistical power. The lack of validation of the functions of the CNGP cases was another limitation of the present study. Most of the available data were confined to the neonatal period. Therefore, the present cases lack well-established follow-up data, which should be collected in future longitudinal studies. As certain cases present with spontaneous catch-up growth following birth and the application of growth hormone may lead to atypical manifestations of short stature, assessing the true impact on growth becomes challenging, as these factors may not preclude the later manifestation of stunted growth. It may lead to an inaccurate assessment of body size. These factors may introduce potential bias into the findings, which should be interpreted with caution.

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Availability of data and materials

The data generated in the present study may be found in the Genome Variation Map in National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences under accession number GVM001225 or at the following URL: ngdc.cncb.ac.cn/gvm/getProjectDetail?project=GVM001225.

Authors' contributions

LY, WZ and FL conceived and designed the study. BW and HW performed whole-exome Sequencing. KY and BL were responsible for CNV analysis. XX and KZ were responsible for clinical data collection. KY, XX and KZ performed the literature review. KY and XX confirm the authenticity of all the raw data. YL, XD, LW, GC, JW and WL analyzed data. KY wrote the manuscript. YL, LW, GC, JW and WL edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was provided by the Ethics Committee of the Children's Hospital of Fudan University, Shanghai, China (approval nos. 2021-375 and 2025-40). The parents of participants provided informed written consent for genetic testing. The present study conformed to the principles of the Helsinki Declaration.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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