ARTICLE

Overgrowth and trisomy 15q26.1-qter including the IGF1 receptor gene: report of two families and review of the literature

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Overgrowth is rarely associated with chromosomal imbalances. Here we report on four children from two unrelated families presenting with overgrowth and a terminal duplication of the long arm of chromosome 15 diagnosed using cytogenetic and FISH studies. In both cases, chromosome analysis of the parents showed a balanced translocation involving 15q26.1-qter. Molecular and cytogenetic studies showed three copies of the insulin-like growth factor 1 receptor (IGF1R) gene. This finding suggests that overgrowth observed in our patients might be causally related to a dosage effect of the IGF1R gene, in contrast to severe growth retardation observed in patients with terminal deletion of 15q. The present observation emphasises the importance of chromosome analysis in patients with overgrowth and mental retardation. Moreover, it further delineates a specific phenotype related to trisomy 15q26.1-qter with macrosomia at birth, overgrowth, macrocephaly and mild developmental delay being the major clinical features.

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Introduction

Although overgrowth is observed in several genetic syndromes, its molecular basis is unravelled only in a small number of them including Beckwith-Wiedemann syndrome,¹ Simpson-Golabi-Behmel syndrome² and more recently Sotos syndrome.³ Overgrowth is rarely associated with chromosome imbalances. Presumably, a detailed study of these unusual cases can give us a clue for candidate chromosome regions or genes involved in the pathogenesis of overgrowth. Four partial trisomies including growth-related genes have been seen in overgrowth syndromes, including

trisomy 4p16.3 and the FGFR3 gene,⁴ trisomy 11p15.5 and the IGF2 gene,⁵ trisomy 20p11.2 and the SSTR4 gene⁶ and trisomy 15q25-qter.⁷ Overgrowth has been reported as well in association with tetrasomy 15q25-qter.⁸ Observations of distal deletions of chromosome 15q including the IGF1R gene suggest that growth failure might be related to IGF1R hemizygosity.⁹ Here we report on four patients with overgrowth and trisomy 15q26.1-qter including the IGF1R gene.

Clinical reports

Family 1

At least four patients were affected in family 1 (Figure 1a). Individual IV-5 was referred to us for genetic counselling because her daughter (V-4) and her niece (V-1) presented with mild developmental delay and macrocephaly. She

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had a sister and three brothers, two of which (IV-3 and IV-6) had mild mental retardation with IQ between 50 and 70, slight dysmorphism including an elongated face and macrocephaly. Their height was reported to be between 1.75 and 1.80 m. Their karyotypes were initially considered as normal and fragile X syndrome was excluded. New clinical evaluation was denied.

Her daughter (V-4) was born at term after an uneventful pregnancy. At birth, length was 51 cm (+1 SD), weight was 4000 g (+2 SD) and occipito-frontal circumference (OFC) was 37 cm (+2 SD). Developmental delay was noted at 10 months, she began to walk at 20 months and was able to speak at 4 years. At 7½ years, her height was 1.25 m (+1 SD), weight was 29 kg (+2 SD) and OFC was 57.2 cm (+4 SD). She interacted well with her environment but had learning difficulties. She was mildly dysmorphic with a large head and frontal bossing, an elongated face, slight midface retraction, a pointed chin, and small low-set ears. Wrists and ankles were large and thumbs were short. Cardiac examination, renal ultrasound and neuroimaging were normal. Ophthalmologic examination showed a visual acuity of 5/10 bilaterally.

Her niece (V-1) was born at term after an uneventful pregnancy. At birth, length was 53 cm (+3 SD), weight was 3300 g (mean) and OFC 36 cm (+1 SD). Hypotonia was noticed in the first month of life. She was admitted at 4 months of life for progressive overgrowth with macrocephaly. She sat at age 8½ months, walked at age 2 years, and presented speech delay. At 6 years of age, her height was 127 cm (+3.5 SD), weight was 23 kg (+2 SD) and OFC was 57 cm (+4 SD). Dysmorphic features included a long triangular face, high, large and flat forehead, downslanting palpebral fissures, slight enophthalmia, small round and low set ears, and a large chin (Figure 2a). Hyperlaxity of fingers were noted, with long and slender hands and proximal implantation of the thumbs. There was a moderate psycho-

motor delay. Ophthalmologic and cardiac examination, neuroimaging and endocrine studies including growth hormone and 17 OH progesterone were normal. Diagnosis of Sotos syndrome was initially proposed. Her father's occipito-frontal circumference was 60 cm.

Family 2

Both siblings of family 2 were affected (Figure 1b). The parents originated from Antilles. The height and occipito-frontal circumference were respectively 163 and 57.5 cm in the mother and 190 and 58 cm in the father. The family history on the mother's side was unremarkable. The father had one half-sister, one half-brother and one brother. All of them presented with tall stature. The half-brother had developmental delay.

The pregnancy of the older sibling was uneventful and the baby was born at 38 weeks of gestation (WG). At birth, length was 49 cm (mean), weight 3590 g (+1.5 SD) and OFC 36 cm (+2 SD). She walked at 1½ years of age and was able to speak at 2½ years of age. She was referred to us at 6 years of age for overgrowth and psychomotor retardation. At this time, her height was 137 cm (+4 SD), weight was 32.4 kg (+4 SD) and OFC was 61 cm (+5 SD). Dysmorphic features including a long triangular face with high forehead, downslanting palpebral fissures, small round and low set ears, a flat nasal bridge, and a normal palate were noted (Figure 2b). Clinical examination of the extremities showed clinodactyly of the fifth left finger and pes planus and valgus. Hyperlaxity and a lumbar lordosis were also noticed. She was mildly retarded and needed special education at school. X-rays examination showed large epiphyses. Cardiac and renal ultrasound as well as neuroimaging showed no visceral malformations. Ophthalmologic examination showed a bilateral papillary coloboma. Endocrine studies including growth hormone and 17 OH progesterone were normal. IGF1 concentration was 166 ng/ml (N: 126–260). Metabolic

Figure 1 Pedigrees. (a) Family 1. (b) Family 2. Probands are shown by an arrow. Affected individuals are represented by black (unbalanced translocation) or hatched (not studied) symbols; N=normal karyotype; black dot: carriers of the translocation.

Figure 2 Photographs of the patients. (a) Patient (V-1) in family 1. (b) Older sib (III-1) of family 2 at age 6 years. (c) Her sister (III-2) at age 1 year. Note the long triangular face with high forehead and large chin.

studies including aminoacid and organic acid chromatography, isoelectric focusing of serum transferrin, very long chain fatty acids assay, mucopolysaccharides and oligosaccharides revealed normal results.

The second sibling was born at 37 WG after an uneventful pregnancy. At birth, length was 52 cm (+2.5 SD), weight 4120 g (+4 SD) and OFC 39 cm (+5 SD). She was hypotonic and suffered neonatal distress due to a pneumothorax. She was referred to us at 11 months of age for overgrowth and psychomotor retardation. At this time, her length was 80 cm (+3.5 SD), weight was 13.6 kg (+4 SD) and OFC was 51 cm (+4 SD). Dysmorphic features included a long face with high forehead and a prominent metopic suture, epicanthal folds, small, round and low set ears, a very flat nose and nasal bridge, and a normal palate (Figure 2c). Hyperlaxity and clinodactyly of the fifth finger were noticed. She sat at 11 months of age. Ophthalmologic examination showed hypermetropia. Ultrasound cardiac scan showed ductus arteriosus. Cerebral imaging and renal ultrasound were normal. Similar endocrine and metabolic studies performed in her sister were normal.

Cytogenetic and molecular studies

Family 1 High resolution chromosome analysis using R and G banding techniques reveals a balanced translocation between chromosomes 15 and 20 in individual IV-5 (Figure 3a). Chromosome painting with whole chromosome painting WCP15 and WCP20 showed additional material originating from chromosome 15 on chromosome 20p, but no material originating from chromosome 20 on chromosome 15q (Figure 3b). FISH analysis with subtelomeric probes of chromosome 20p (PAC 82O2) and 15q (PAC 124O5) confirmed that the translocation was reciprocal

(not shown). This suggest that the size of the translocated 20p segment is too small to be detected using chromosome painting. Comparative genomic hybridization (CGH)^{10,11} was performed in V-1 and confirmed the excess of material from 15q26.1-qter but did not show evidence of loss of 20p material (Figure 3d). Further FISH analyses with various probes of chromosome 15q^{9,12–13,15} defined that the size of the 15q duplication ranged between 6 and 12 Mb (Table 1). In particular, YAC 802B4 was not duplicated. The karyotype of IV-5 was therefore 46,XX,t(15;20)(q26.1;p13). The same translocation was present in her healthy brother and in her mother. All affected patients are carriers of the same unbalanced karyotype with a der(20) resulting in trisomy 15q26.1-qter and a very subtle monosomy 20pter (Figure 3c).

Family 2 High-resolution chromosome analysis of the older sibling was performed on cultured peripheral blood lymphocytes using R and G banding techniques. These studies showed additional chromosome material of unknown origin on the long arm of chromosome 13 in all cells examined (Figure 4c). Fluorescence in situ hybridization (FISH) analysis with a chromosome 15 painting probe was performed and confirmed that the additional material originated from chromosome 15 (Figure 4b). FISH analysis with subtelomeric probes of chromosome 13q (PAC 163C9) and 15q (PAC 124O5) showed one signal of chromosome 13q and three signals of chromosome 15q (not shown). CGH confirmed the excess of material from bands 15q26.1-qter, but did not show evidence of loss of 13q material (Figure 4d). Chromosome analysis of the parents showed that this unbalanced rearrangement resulted from the segregation of a paternal balanced trans-

Figure 3 Family 1: chromosome analysis and FISH studies. (a) Balanced translocation $t(15;20)(q26.1;p13)$. Abnormal chromosomes are on the right. (b) Whole painting of chromosome 15 (grey) and 20 (white) of the balanced translocation. The small size of the translocated 20p segment prevents its visualization. (c) Unbalanced translocation $der(20)t(15;20)$. (d) CGH showing trisomy 15q26.1-qter. The monosomy 20p is not detected.

Table 1 FISH characterisation of breakpoints of the two translocations

Chromosomal location	Family 1 proband	Family 2 proband	Clone	Locus	Distance telomere ^a
15q25.2	Disomy	Disomy	BAC RP11-81L17	SHGC-30592	18 Mb
15q26.1	Disomy	Disomy	YAC CEPH-802B4	D15S202	12 Mb
15q26.2	Trisomy	Trisomy	YAC CEPH-895H10	D15S207	6 Mb
15q26.3	Trisomy	Trisomy	BAC RP11-654A16	IGF1R	3 Mb
15qter	Trisomy	Trisomy	PAC RP1-124O5	WI-5214	300 Kb
13q34	Disomy		YAC CEPH-908C3	D13S261	3 Mb
13q34	Disomy		BAC RP11-65D24	stSG47845	2.5 Mb
13qter	Monosomy		PAC RP1-163C9	13QTEL56	80 Kb
20pter		Monosomy	PAC RP1-82O2	20PTL18	180 Kb

^aNCBI built 28.

location. The same unbalanced karyotype was found in the younger sister. Further FISH analyses with various probes of chromosome 15q^{12,13} defined that the size of the 15q duplication ranged between 6 and 12 Mb since YAC 802B4 was not duplicated (Table 1). Similarly, we showed that the size of the 13q deletion was small, ranging from 80 Kb to 2.5 Mb. The karyotype of the father was therefore 46,XY,t(13;15)(q34;q26.1) (Figure 4a) and the children karyotypes were 46,XX,der(13)t(13;15)(q34;q26.1)pat.

IGF1R gene

FISH studies using an IGF1R probe (BAC 654A16) showed one signal on each 15q and one on 20p for proband (V-1) of family 1 (Figure 5a), and one signal on each 15q and one on 13q for proband of family 2 (Figure 5b). Molecular studies using an intragenic polymorphic marker of the IGF1R gene performed in the proband of family 2 were fully informative. They showed three alleles of the IGF1R gene, two of which being of paternal origin (Figure 5c) as

Figure 4 Family 2: chromosome analysis and FISH studies. (a) Balanced translocation $t(13;15)(q34;q26.1)$. Abnormal chromosomes are on the right. (b) Whole painting of chromosome 13 (grey) and 15 (white) of the balanced translocation. The size of the translocated 13q segment prevents its visualization. (c) Unbalanced translocation $der(13)t(13;15)$. (d) CGH showing trisomy 15q26.1qter. The monosomy 13q is not detected.

expected. The polymorphic marker was identified from the published genomic sequence of IGF1R (<http://genome.ucsc.edu/>).

Discussion

Here, we report on two families with overgrowth and partial trisomy of chromosome 15q26.1-qter including the IGF1 receptor gene. In both cases, the associated monosomy is small in size.

The phenotype of distal trisomy 15q, with a breakpoint being usually between 15q15 and 15q22, is well delineated. It includes mental retardation, growth deficiency, microdolichocephaly, peculiar facial features, skeletal abnormalities, and cardiovascular defects.¹⁴ Most of these cases result from the malsegregation of a parental translocation. In a few cases, the trisomy is confined to chromosome 15q25-qter and a different phenotype is observed, including macrosomia at birth, overgrowth, macrocephaly and craniosynostosis.⁷ Also, mosaicism for an unstable interstitial duplication of chromosome band 15q25 was recently described as a susceptibility factor for panic and phobic disorders.¹⁵ The segment duplicated on 15q in our patients

is distal to this region as shown using YAC 802B4 which is located near its distal border.

Reports of six relevant patients with 15q25 or 26-qter trisomy and of the four present cases are summarised in Table 2.^{16–18,7} Patients IV-3 et IV-6 of family 1 were not included because there was not enough of clinical data available. One report with cloverleaf skull anomaly was also excluded because of insufficient data.¹⁹ From this analysis, it appears that 8 out of 10 cases (six families) are familial. All cases result from an unbalanced segregation of a parental translocation with a breakpoint in 15q25 or q26 and the breakpoint on the other chromosome located in the terminal band (except in one case). Interestingly, breakpoints found in our family 2 are similar to those found in the family reported by Zollino.⁷ Seven out of 10 cases presented with overgrowth between +2 SD and +6 DS. None of the patients presented with a size below the normal limit. Interfamilial variability in overgrowth is observed. There is also intrafamilial variability, as shown in our family 1 and the family reported by Zollino.⁷ The severity of overgrowth does not seem linked to the parental origin of the translocation. Indeed, overgrowth was noted in 3 out of 5 cases

Figure 5 IGF1R: molecular and FISH studies. (a) FISH experiments with BAC 654A16 containing the IGF1R gene showed an additional signal at the end of the der(20) in proband of family 1. (b) FISH experiments with BAC 654A16 showed an additional signal at the end of the der(13) in proband of family 2. (c) Proband of family 2: an intragenic polymorphic microsatellite of the IGF1R gene (primers 5'-GA-GTATGAACAGGTGGCATTAG-3' and 5'-ACATAGCCTTCATCCAATTCC-3') showed three alleles of the gene of which two are of paternal origin. F: Father, M: Mother, P: Proband.

of paternal origin, and 4 out of 5 cases of maternal origin. Macrosomia was present at birth in 7 out of 8 informative patients, birth length ranging from 49 to 59 cm and weight from 3.3 to 5 kg. If growth velocity seems to decelerate with age in some observations,⁷ tall stature is still present in adulthood in others.³ The adult size varies from 1.78 to 2.10 m. Macrocephaly was even more frequent than overgrowth and was ≥ 4 SD in 8 out of 10 cases. In one patient, macrocephaly is present without overgrowth.¹⁸ Craniosynostosis was associated in 3 out of 10 cases. Various cardiac defects or kidney malformations were found respectively in 3 out of 10 and 2 out of 9 cases, and scoliosis in 4 out of 10 cases. Psychomotor delay was a consistent feature and ranged from mild to severe. Distinctive facies found in most patients include a long and triangular face, downslanting palpebral fissures, and abnormal low-set ears. Finger abnormalities were often noted, such as arachnodactyly, flexed or tapering fingers.

It is well known that the insulin-like growth factors and their receptors are implicated in pre- and postnatal develop-

ment.²⁰ The IGF1R is a transmembrane heterotetramer, which mediates the mitogenic effect of IGF1 and IGF2. Distal deletions of chromosome 15q are associated with severe growth retardation.^{9,21-24} It has been suggested that growth failure might be related to IGF1R hemizygosity. On the contrary, in the present observations, overgrowth might well be related to a dosage excess of IGF1R gene.

Also, a gene for macrocephaly is likely to be located in this region. Interestingly a large family with autosomal recessive syndrome of macrocephaly, multiple epiphyseal dysplasia and distinctive facies was recently reported and a gene locus was identified in 15q26.²⁴ The aggrecan gene (AGC1), a chondroitin sulphate proteoglycan that was a possible candidate gene, was excluded.²⁵

In conclusion, we report on four further cases of overgrowth associated with trisomy 15q26.1-qter including the IGF1R locus. The present report gives further evidence for a specific phenotype related to trisomy 15q25 or 26-qter with macrosomia at birth, overgrowth, macrocephaly and mild developmental delay being the major clinical features.

Table 2 Clinical findings in 10 patients with 15q25 or 26-qter trisomy

	<i>Kristoffersson 1984 (1)</i>	<i>Kristoffersson 1984 (2)</i>	<i>Van Allen 1992</i>	<i>Wieczorek 1998</i>	<i>Zollino 1999 (1)</i>	<i>Zollino 1999 (2)</i>	<i>Patient V-4 Family 1</i>	<i>Patient V-1 Family 1</i>	<i>Patient III-1 Family 2</i>	<i>Patient III-2 Family 2</i>	<i>Total</i>
Trisomy	15q25-qter	15q25-qter	15q26-qter	15q26-qter	15q25-qter	15q25-qter	15q26.1-qter	15q26.1-qter	15q26.1-qter	15q26.1-qter	
Monosomy	6p25-pter	6p25-pter	2q37-qter	6q26-qter	13q34-qter	13q34-qter	20p13-pter	20p13pter	13q34-qter	13q34-qter	
Origin	Maternal	Maternal	Paternal	Maternal	Maternal	Paternal	Maternal	Paternal	Paternal	Paternal	
Sex	M	M	M	F	F	M	F	F	F	F	4M/6F
MR	Moderate	Moderate	Moderate	Severe	Severe	Severe	Mild	Mild	Mild	Mild	10/10
<i>Growth</i>											
Macrosomia	NR	NR	—	+	+	+	+	+	+	+	7/8
Overgrowth	+6 SD	+4 SD	Mean	+4 SD	+3 SD	+0.5SD	+1 SD	+3 SD	+4 SD	+3.5 SD	7/10
Macrocephaly	+	+	−1 SD	−1.5 SD	+4 SD	+4 SD	+4 SD	+4 SD	+5 SD	+5 SD	8/10
<i>Malformations</i>											
Craniosynostosis	—	—	+	—	+	+	—	—	—	—	3/10
Heart ^a	—	+	—	—	—	+	—	—	—	+	3/10
Kidney ^b	—	—	+	—	+	NR	—	—	—	—	2/9
Fingers	Flexed	Flexed	Flexed	Arachnodactyly	Tapering	Tapering	Short thumbs	Arachnodactyly	—	—	8/10
Scoliosis	—	—	—	+	+	+	—	—	+	—	4/10
Other	—	—	Hearing loss	Dystonia	—	—	—	Hyperlaxity	Hyperlaxity Papillary coloboma	Hyperlaxity	
<i>Facial dysmorphism</i>											
Long face	+	+	+	+	+	+	+	+	+	+	10/10
Triangular face	+	+	—	+	+	+	+	+	+	—	8/10
Facial asymmetry	—	+	+	—	+	+	—	—	—	—	4/10
Downslanting eyes	—	—	—	—	+	+	+	+	+	+	6/10
Prominent nose	+	+	+	—	+	+	—	—	—	—	5/10
Dysmorphic ears	+	+	+	—	+	+	+	+	+	+	9/10
Low-set ears	+	+	—	—	+	+	+	+	+	+	8/10
Short neck	+	+	—	—	+	+	—	—	—	—	4/10

SD, standard deviations; MR, mental retardation. ^aHeart malformations include persistent ductus arteriosus, bicuspidic aortic valve, aortic valve stenosis, and aneurysm of thoracic aorta. ^bKidney malformations include horseshoe kidney, pelvic duplication and abnormal rotation.

We suggest that overgrowth might be causally related to a dosage excess of IGF1R gene. Interestingly, overgrowth has also been reported in patients with tetrasomy of chromosome 15q25-qter,⁸ as well as in some patients with larger trisomy 15q22qter.^{26,27} Mainly, this report emphasizes the importance of chromosome analysis in the investigation of patients with overgrowth and mental retardation. Further studies of similar cases will provide a valuable opportunity for elucidating the molecular basis of overgrowth.

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