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Genotype/phenotype analysis in a male patient with partial trisomy 4p and monosomy 20q due to maternal reciprocal translocation (4;20): A case report

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Abstract. Translocations are the most frequent structural aberration in the human genome. Carriers of balanced chromosome rearrangement exhibit an increased risk of abortion and/or a chromosomally-unbalanced child. The present study reported a clinical and cytogenetic analysis of a child who exhibited typical trisomy 4p and monosomy 20q features, including intellectual disability, delayed speech, tall stature, seizures and facial dysmorphism. The karyotype of the proband exhibited 46, XY, add(20) (q13.3). The karyotype of the mother indicated a balanced translocation karyotype: 46, XX, *t*(4;20) (p15.2;q13.1). The array-based comparative genomic hybridization (aCGH) analysis identified partial trisomy of the short arm of chromosome 4 and partial monosomy of distal 20q in the proband due to maternal balanced reciprocal translocation 4;20. The analysis of genotype/phenotype correlation demonstrated that fibroblast growth factor receptor 3 and msh homeobox 1 may be the important genes for 4p duplication, and that potassium voltage-gated channel subfamily Q member 2, myelin transcription factor 1 and cholinergic receptor nicotinic α4 subunit may be the important genes for 20q deletion. To the best of our knowledge, the present study was the first to report an unbalanced translocation involving chromosomes 4p and 20q. The present study additionally demonstrated that aCGH analysis is able to reliably detect unbalanced submicroscopic chromosomal aberrations.

Introduction

Translocations are the most frequent structural aberration in the human genome, with an incidence of 0.178% (1). Carriers of balanced chromosome rearrangement exhibit an increased risk of abortion and/or a chromosomally unbalanced child (2). The type of unbalanced translocation is dependent upon the mode of segregation. A 2:2 segregation event may result in gametes with partial trisomy/monosomy of the chromosomes involved in the translocation (3). Conventional cytogenetic analysis is unable to detect small rearrangements due to its low resolution. The wide use of whole-genome array-based comparative genomic hybridization (aCGH) techniques has allowed for the detection of submicroscopic chromosomal aberrations and the establishment of genotype-phenotype correlations, by delineating at high resolution the regions involved in genomic copy number variations. The present study assessed a pediatric patient with partial trisomy 4p and partial monosomy 20q, resulting from a 2:2 segregation of a maternal balanced *t*(4;20) translocation. The karyotype of the proband exhibited 46, XY, add(20) (q13.3) and the aCGH analysis identified partial trisomy of the short arm of chromosome 4 and partial monosomy of distal 20q. The patient exhibited typical trisomy 4p and monosomy 20q features, including intellectual disability, delayed speech, tall stature, seizures and facial dysmorphism. The present study supports the use of aCGH as the first-tier cytogenetic diagnostic tool for patients with unexplained delays in development, intellectual disability or multiple congenital anomalies.

Case report

Clinical features. The patient was a 6-year-old male born to a 33-year-old father and a 32-year-old mother via vaginal delivery at 39 gestational weeks. During pregnancy, no specific problems were identified. The birth weight was 3.8 kg (50th centile), birth length was 53 cm (>75th centile) and occipital frontal circumference was 36 cm (>95th centile). The Apgar scores were 9 and 10 at 1 and 5 min, respectively. Seizures began at ~2 months of life. The proband began to walk at 2 years 4 months of age. At 4 years of age the proband had minimal expressive language and minimal social interactions. The patient presented to Henan Provincial People's Hospital (Zhengzhou, China) at age 6 years, due to intellectual disability, delayed speech, tall stature, seizures, delayed fine

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and gross motor skills and facial dysmorphism (macrocephaly, prominent nasal bridge, low-set ears, epicanthus). The parents had previously experience two spontaneous abortions occurring at 7 and 11 weeks of gestation, respectively, although product of conception (POC) samples were not analyzed.

Cytogenetic and aCGH analysis. Peripheral blood samples were obtained from the proband and the parents for examination of chromosomes by metaphase G-banding and aCGH. The Henan Provincial People's Hospital Ethics Committee approved the sample collection procedures and the family gave written informed consent. Standard procedures were used isolate the genomic DNA of the proband and the parents from whole blood using the QIAamp DNA Mini kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's protocol. DNA was assayed for quantity and purity using the NanoDrop ND-2000 Spectrophotometer (Thermo Fisher Scientific, Inc., Wilmington, DE, USA). aCGH analysis was performed using Agilent 4x180 K commercial arrays (Agilent Technologies, Inc., Santa Clara, CA, USA), which consist of 110,712 oligonucleotide probes and 59,647 single nucleotide polymorphism probes, to evaluate the entire genome with an effective backbone resolution of ~25.3 kb [5 kb in International Standards for Cytogenomic Arrays (ISCA) regions]. A total of 1,500 ng of experimental and gender-matched reference DNA (Promega Corporation, Madison, WI, USA) was digested with *Alu*I and *Rsa*I restriction endonucleases (Promega Corporation) and fluorescently-labeled with cyanine 5-dUTP and cyanine 3-dUTP, respectively. Labeled experimental and reference DNA was purified, combined, denatured and hybridized to the microarrays in a rotating oven (20 rpm) at 67˚C for 24 h. Data were analyzed using Cytogenomics 2.9 software (Agilent Technologies, Inc.). The Cytogenomics 2.9 software, via the Aberration Detection Method-2 algorithm with a sensitivity threshold of 6.0 and a data filter, identified aberrations and rejected those did not include at least three probes with a log2 set of 0.25. All quality control metrics were passed. The copy number variations were compared with the Database of Genomic Variants, Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER v9.10; decipher.sanger.ac.uk), the ClinGen Dosage Sensitivity Map (www.ncbi.nlm.nih.gov/projects/dbvar/clingen), the RefSeqGene database (https://www.ncbi.nlm.nih.gov/refseq/rsg/), OMIM (http://omim.org/) and the relevant publications in PubMed (www.ncbi.nlm.nih.gov/pubmed). Genome coordinates among different assemblies were converted to Hg19 using the LiftOver tool (genome.ucsc.edu/cgi-bin/hgLiftOver).

Results. The karyotype of the proband (Fig. 1) exhibited 46, XY, add(20) (q13.3). The karyotype of the mother (Fig. 2) indicated a balanced translocation karyotype: 46, XX, *t*(4;20) (p15.2; q13.1). The father exhibited a normal male karyotype (data not shown). The aCGH analysis demonstrated a 12.8 Mb terminal duplication at 4p16.3-p15.33 (72,447-12,900,236) (hg19) (Fig. 3) and a 1.2 Mb terminal deletion at 20q13.33 (61,722,950-62,908,674) (hg19) (Fig. 4) in the proband, while no duplication or deletions were detected in the parents.

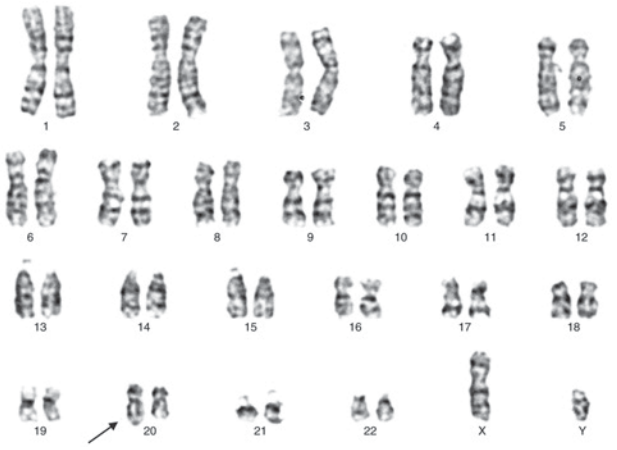

Figure 1. Karyotype of the proband. The karyotype of the proband indicated an abnormal karyotype: 46, XY, add(20) (q13.3).

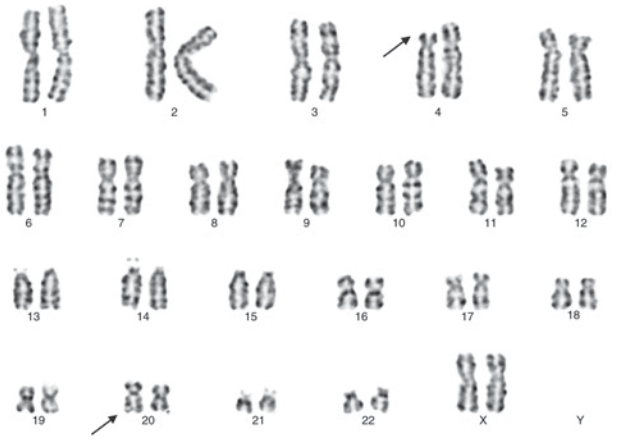

Figure 2. Karyotype of the mother of the proband. The karyotype of the mother of the proband indicated an abnormal karyotype: 46, XX, *t*(4;20) (p15.2; q13.1).

Discussion

The present case report demonstrated that the proband carried an unbalanced translocation inherited from a balanced translocation carrier mother, which resulted in partial trisomy for 4p (spanning ~12.8 Mb) and partial monosomy for 20q (spanning ~1.2 Mb). Karyotyping did not reliably detect the unbalanced rearrangement. The aCGH analysis identified genetic anomalies in the patient. Although the clinical features of the two variants have been separately described in the literature (4,5), there are no published cases illustrating the two variants occurring in the same patient. To the best of our knowledge, the present study is the first report of an unbalanced translocation involving chromosomes 4p and 20q.

Trisomy 4p syndrome was first reported as a distinct clinical entity ~40 years ago (6). This syndrome is characterized by intellectual disability, delayed speech, facial dysmorphism (prominent nasal bridge, and low-set and malformed ears) and, in certain cases, overgrowth and macrocephaly (7-9) (Table I). However, diagnosis is not definitive, since the phenotypic features are variable and not unique to trisomy 4p. A number of trisomy 4p cases occur as a result of unbalanced meiotic

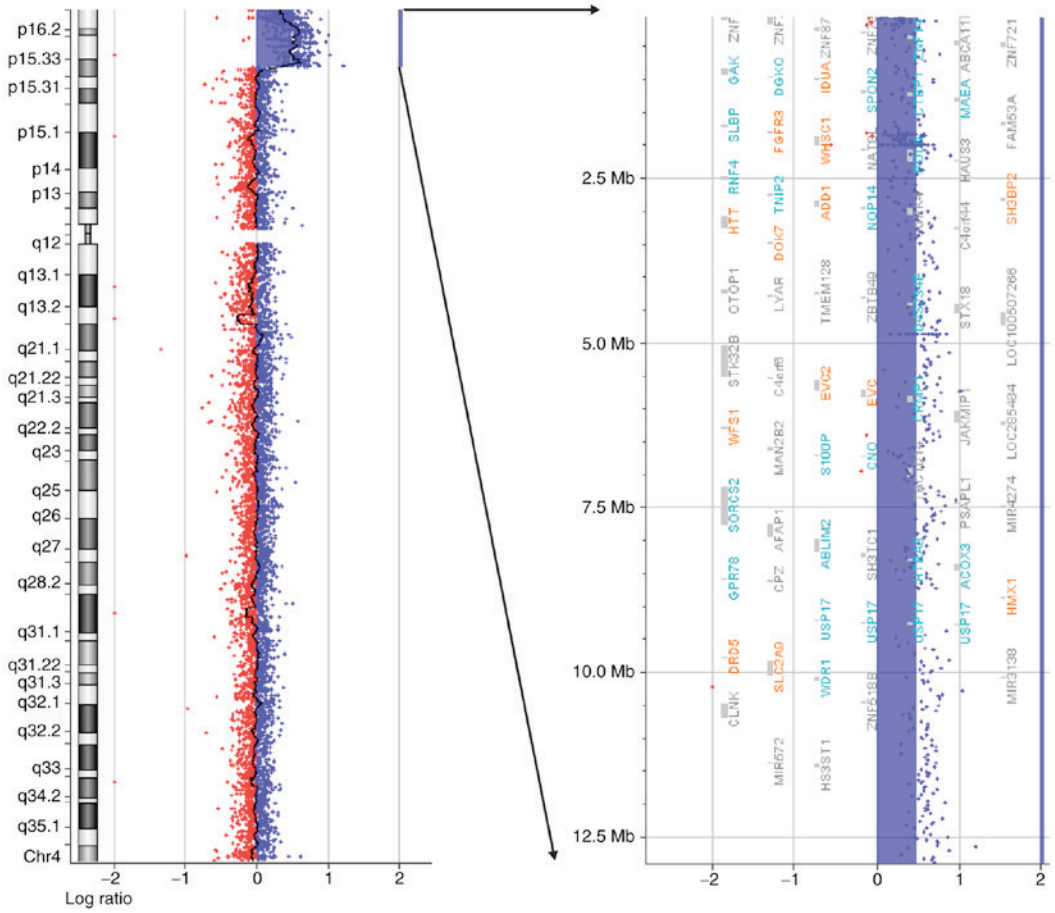

Figure 3. Array-based comparative genomic hybridization analysis results of the 4p duplication. Left, the 12.8 Mb duplication in 4p16.3-p15.33; right, the genes contained within the region.

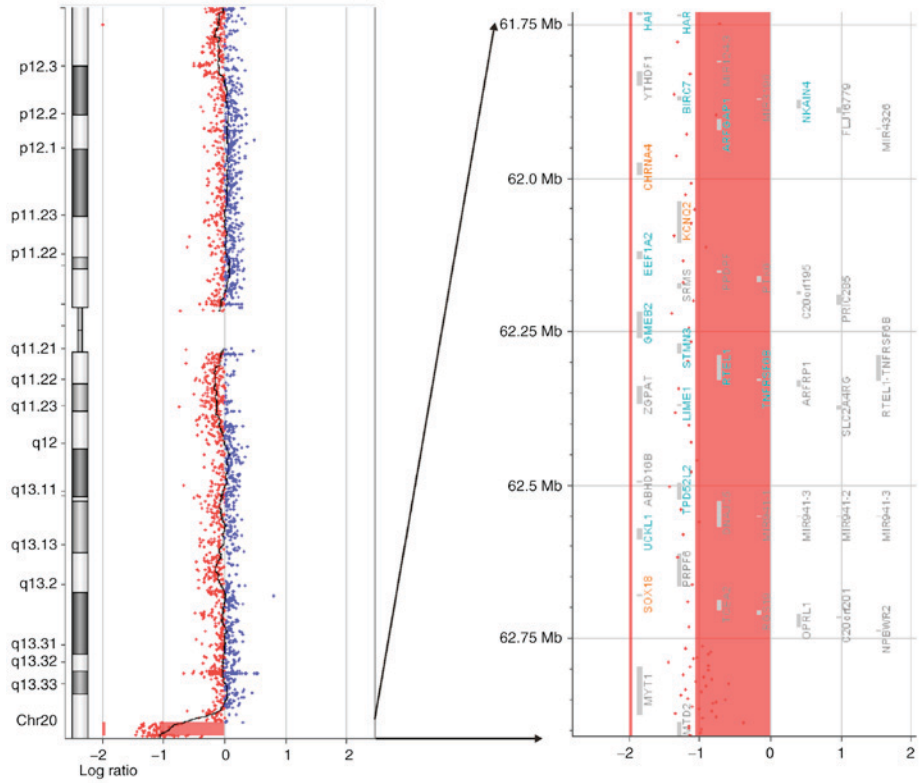

Figure 4. Array-based comparative genomic hybridization analysis results of the 20q deletion. Left, the 1.2Mb deletion in 20q13.33; right, the genes contained within the region.

Table I. Clinical features of the proband compared with previous cases of 4p duplication and 20q deletion.

Author	Aberration	Other chromosomal aberration	Age at diagnosis	Sex	Intellectual disability	Delayed speech	Growth delay	Overgrowth	Seizures	Hypotonia	Cardiac defects	Psychomotor developmental defects	Microcephaly	Microcephaly	Brachycephaly	Bitemicrognathia	Prominent narrowing	inentnasal bridge	Low-set ears	Malformed ears	Thin upper Epicanthus	Epicanthus lip vermilion	Other phenotypes	(Refs.)
Schönewolf-Greulich *et al*	arr[hg19] 4p16.3 (73,645-3,072,968)x3	-	6 years	Female	+	+	-	+	-	-	-	-	-	+	-	-	-	+	+	+	-	+	Proximal placement of thumbs; small eyes	(7)
Iype *et al*; case III:4	arr[hg19] 4p16.3-16.1 (0-10,290,552)x3	arr[hg19] 3p26.3 (0-2,118,422)x1	40 years	Female	+	+	-	-	-	+		+	-	-	+		-	+	+	+	-	+	Campodactyly; strabismus; cleft lip; gum hypertrophy	(8)
Hannes *et al*	arr[hg19] 4p16.3 (1,458,385-1907,425)x3	-	11 months	Male	+	+	+	-	+	+	-	+	-	-	-	-	+	-	+	+	+	-	Malformation of right hand (shortened fingers); glaucoma of the left eye short neck	(9)
Mefford *et al*	arr[hg19] 20q13 (chr20:60,700,000–62,435,964)x1	-	7 years	Male	+	+	+	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-	Blind	(12)
Marques *et al*	arr[hg19] 20q13.33 (61,643,144-63,003,805)x1	arr[hg19] arr17q25.3 (78,952,204-81,060,886)x3	6 years	Male	+	+	+	-	+	+	+	+	+	-	-	-	+	+	-	-	+	-	Short neck; syndactyly; asymmetric legs	(13)
Traylor *et al*; case 2	arr 20q13.33 (60,760,865–62,379,119)x1	-	4 years	Female	-	+	+	-	+	-	-	+	-	-	-	-	+	-	-	-	-	-	-	(14)
Wu *et al*	arr[hg19] 4p16.3-p15.33 (72,447-12,900,236)x3	arr[hg19] 20q13.33 (61,722,950-62,908,674)x1	6 years	Male	+	+	-	+	+	+	-	+	-	+	-	-	-	+	+	-	+	-	-	Present study

segregation from a parental balanced translocation and may consequently be accompanied by monosomy of the partner chromosome, which may contribute to the phenotype (10). The variable size of the duplicated 4p segment and the phenotypic features make the clinical diagnosis of trisomy 4p syndrome difficult.

In the present study, the duplication in 4p16.3p15.33 observed in the proband overlapped with 122 RefSeq genes, including 20 morbid genes in the database of OMIM. It is difficult to confirm that one specific gene is responsible for the specific phenotype. Notably, certain parameters of the features concerning growth in 4p duplication (macrocephaly, overgrowth and tall stature) are opposed to those of 4p deletion (microcephaly, small for gestational age and delayed growth) (11). The mirror phenotypes may result from reciprocal deletion/duplication in chromosomal regions containing dosage-sensitive genes. Therefore, the ClinGen Dosage Sensitivity Map was searched, and no genes with evidence of triplosensitive phenotypes were identified. In the DECIPHER database, the haploinsufficiency scores of the genes fibroblast growth factor receptor 3 (*FGFR3*; OMIM, 134934), huntingtin (OMIM, 613004), macrophage erythroblast attacher (OMIM, 606801), msh homeobox 1 (*MSX1*; OMIM, 142983) were 6.40, 7.59, 7.12 and 1.21%, respectively; this indicated that these genes were more likely to exhibit haploinsufficiency and dosage sensitivity.

Regarding the growth alterations and musculoskeletal malformations, the gene *FGFR3*, which regulates the growth of bone, may be a candidate gene for the anomalous growth in patients with 4p duplication. Mutations in the gene *FGFR3* are associated with 14 human disorders, and skeletal malformations represent the principal clinical presentations. Mutations in the gene *MSX1* are associated with ectodermal dysplasia 3 (Witkop type), orofacial cleft 5 and tooth agenesis (with or without orofacial cleft). Therefore, *MSX1* may be the candidate gene for facial dysmorphism in patients with 4p duplication.

The phenotype of the present patient was modified by the 1.2Mb terminal deletion 20q. Terminal deletions of the long arm of chromosome 20 have been reported previously in a number of patients, with phenotypes including neonatal or infantile seizures, intellectual disability, language deficits and behaviors characteristic of autism spectrum disorder (12-14) (Table I). Similar to the previously-described trisomy 4p syndrome, the variable size of the deleted 20q segment and the phenotypic features make it difficult to identify one gene to be responsible for the specific phenotype. In the present study, the deletion in 20q13.33 described in the proband overlapped 37 RefSeq genes, including 7 OMIM morbid genes. Potassium voltage-gated channel family Q member 2 (*KCNQ2*; OMIM, 602235) exhibited haploinsufficiency phenotypes of benign familial neonatal seizures in the ClinGen Dosage Sensitivity Map. *KCNQ2* encodes a subunit of the voltage-gated potassium channel, and mutations have been observed in patients with benign familial neonatal seizures and unexplained neonatal epileptic encephalopathy (15). Myelin transcription factor 1 (*MYT*1; OMIM, 600379) may affect myelination and the regulation of neural differentiation (16,17), while mutations in cholinergic receptor nicotinic α4 subunit (*CHRNA*4; OMIM, 118504) have been observed to be associated with autosomal dominant nocturnal frontal lobe epilepsy (18). Thus, *KCNQ*2, *MYT1* and *CHRNA4* may be the candidate genes for seizures and delayed cognitive development in patients with 20q terminal deletion.

The parents of the proband experience two spontaneous abortions at 7 and 11 weeks of gestation, respectively, although POC samples were not analyzed. A total of ~50% of first-trimester miscarriages result from fetal chromosomal abnormalities (19). Using aCGH to analyze POC samples may determine possible genetic causes of miscarriage and predict the recurrence risk for subsequent pregnancies. Since an increased rate of miscarriage exists in couples with balanced chromosomal rearrangements, cytogenetic analysis and/or aCGH analysis for all POC samples may be recommended.

In conclusion, the present case report described a partial 4p duplication and partial monosomy of 20q in a patient with the majority of the typical phenotypes of 4p duplication and 20q deletion (intellectual disability, delayed speech, tall stature, seizures and facial dysmorphism). The use of aCGH may facilitate a sensitive and powerful approach towards the diagnosis of submicroscopic unbalanced genomic rearrangements. *FGFR3* and *MSX1* may be the important genes for 4p duplication, and *KCNQ2*, *MYT1* and *CHRNA4* may be the important genes for 20q terminal deletion. Additional studies may help to refine the relevant genes associated with the variable clinical features.

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