CASE REPORT

Monosomy 3pter-p25.3 and Trisomy 1q42.13-qter in a Boy With Profound Growth and Developmental Restriction, Multiple Congenital Anomalies, and Early Death

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Albeit rare, 3pter-p25 monosomy or 1q42-qter trisomy syndromes have been documented in the literature. Here, we report a unique case with a combination of 3pter-p25 monosomy and 1q42-qter trisomy, delineated by array comparative genomic hybridization analysis. The proband was a newborn male with multiple congenital anomalies that included brain malformation, ocular anomalies, trachea-laryngomalacia, cardiac defects, intestinal malrotation, and cutaneous findings in conjunction with biochemical anomalies, profound growth and developmental restriction, and early death. To our knowledge, this is the first case report of this unique chromosomal imbalance.

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1. Introduction

There have been few reports documenting the phenotypic characteristics and cytogenetic findings on chromosomal imbalances involving the subtelomeric regions of 1q and 3p. The facial features of the involved cases differ based on the derivative chromosome and the resulting balanced or unbalanced rearrangements in the respective probands. A significant proportion of pregnancies culminate in spontaneous abortions or early neonatal and childhood death. The majority of the survivors have significant aberrant growth patterns with neurodevelopmental delay. This report describes the first case of a chromosomal anomaly involving trisomy 1q42.1 with associated monosomy for 3p25.

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2. Case Report

The male infant was the firstborn child of a healthy 20-year-old gravid 2 para 1 woman from the Philippines who had recently immigrated to Canada. The pregnancy was unremarkable, but there was scant prenatal care prior to her arrival in Canada. The mother denied use of medication, recreational drugs, alcohol, tobacco, and previous illness. An elective cesarean section was performed at 38 weeks’ gestation for breech presentation. The birth weight was 2463 g, length was 42.5 cm, and both were significantly under the third percentile. Head circumference was 34.5 cm, near the 25th percentile.

This patient had a large anterior fontanelle measuring 4 × 4 cm and facial dysmorphism (Figure 1). The facial profile was flat, with a depressed nasal bridge and anteverted nares. The mouth was open, with a tented upper lip and poorly defined philtrum. The patient had a prominent gum and alveolar ridge, but the palate was intact. The ears were low-set and angulated. The chin was small. In addition, the chest appeared short and the abdomen was distended. The external genitalia were male, with a penile length measurement of 1.5 cm, a hypoplastic scrotum, and cryptorchidism bilaterally. Musculoskeletal examination revealed a short neck, short sternum, and a sacral dimple. The extremities were grossly normal but with clinodactyly of the fifth fingers. Skin examination revealed one melanocytic nevus measuring 3 × 1 cm in size on the right side of the chest in addition to generalized hirsutism, more severe on the patient’s back and sides of the face.

The patient had severe laryngeo-tracheomalacia with marked stridor requiring emergency tracheostomy. He subsequently developed refractory seizures shortly after birth as well as chronic lung disease. Feeding problems were significant, along with gastroesophageal reflex.

A review at 7 months of age revealed severe growth restriction and profound psychomotor retardation. The head circumference was 40.5 cm (<3rd percentile), weight was 4835 g (<3rd percentile), and length was 55 cm (<3rd percentile). Head control, gaze fixation, social smile, and localization to sounds were not clinically detectable. The patient died at 9 months of age following cardiopulmonary arrest.

Family history was significant for one maternal miscarriage at 8 weeks’ gestation, and one of the mother’s siblings had died as a neonate. Both events occurred in the Philippines, without any investigations. The couple was healthy and nonconsanguineous.

Informed consent was obtained from the mother for use of the infant’s photographs with a signed agreement for publication.

2.1. Investigations

Echocardiography showed dysplastic pulmonary valves with stenosis, an atrial secundum defect, a large patent ductus arterious, dysplastic mitral valves, an aberrant right subclavian artery, and left superior vena cava. Upper gastrointestinal studies revealed intestinal malrotation. On brain MRI, the frontal lobes were relatively smaller than the posterior lobes, with abnormal gyral pattern and associated enlargement of

![Figure 1](A) Facial dysmorphic features: facial hirsutism (note the “sideburn”) and flat facial profile with a depressed nasal bridge, anteverted nares, poorly formed philtrum, and tented upper lip. The ears were low-set and posteriorly rotated. There was micrognathia. Note the short neck and a melanocytic nevus on the right chest measuring ~3 × 1 cm; (B) hypoplastic scrotum. The penis measured 1.5 cm in length.
the lateral ventricles. Electroencephalography was positive for epileptic activity. A retinal examination revealed bilateral optic nerve hypoplasia with pallor of the discs. Visual evoked potentials showed markedly underdeveloped response from the left eye and delayed low voltage response in the right. Abdominal ultrasonography revealed grade 1 hydronephrosis of the right kidney.

Biochemistry revealed transient hyponatremia (122–127 mmol/L) and hyperkalemia (7.1–7.9 mmol/L) for the first 2 days of life. Endocrine investigations showed fluctuating levels of thyroid-stimulating hormone (TSH; range 0.05–0.82 mU/L), growth hormone (range 3.0–9.1 nmol/L), and free thyroxin (range 9.8–22.2 pmol/L) with normal levels of adrenocorticotropic hormone, cortisol, aldosterone, dehydroepiandrosterone sulphate, renin, and 17-hydroxyprogesterone. Newborn screen for organic aciduria, amino acidopathies, congenital hypothyroidism, and 17-hydroxyprogesterone were all negative.

2.2. Chromosomal analysis, confirmation, and causative phenotype

Metaphase chromosomes were prepared from peripheral blood and analyzed by standard G-banding techniques. Array comparative genomic hybridization (aCGH) was performed by using the constitutional chip 4.0 whole genome array with targeted design (Perkin Elmer, Inc., Waltham, MA, USA). The array is composed of about 5000 bacterial artificial chromosome (BAC) clones, which contain large segments (~100–300 kb) of human DNA. Dye-swap strategy was implemented, i.e., two independent experiments were performed for each sample to increase the sensitivity and specificity. The experimental procedures were performed in accordance with the manufacturer’s instructions.

Routine and molecular cytogenetic analyses revealed an unbalanced male karyotype (Figure 2A) of der(3)t(1;3)(q42;p25). Using BAC array CGH with a dye-swap strategy, the breakpoints were further delineated to be 1q42.13 to 1qter and 3p25.3 to 3pter (Figure 2B). This patient was trisomic for 1q42.13-qter and monosomic for 3pter-p25.3. The proximal start clone for the gain was RP11-27504 (chr1:225,693,580-225,841,146), while aCGH also demonstrated a loss from 3pter to 3p25.3 that extended from 3pter to RP11-115G3 (chr3:10,788,426-10,947,365). The anomalies were a combination of a duplication of 21.556 Mb on chromosome 1 and a deletion of 10.788 Mb on chromosome 3. All the base positions were based on UCSC Human Genome Browser March 2006 NCBI36/hg18. Since the deletion was detected by cytogenetic G-banding before array-CGH investigation, no further confirmation was performed.

The mother is phenotypically normal and her karyotype was 46,XX,t(1;3)(q42.13;p25.3); thus, she is a carrier of a reciprocal balanced translocation between chromosomes 1 and 3. The father was not available for karyotype analysis. The derivative karyotype in the proband was considered causative of the patient’s phenotype because: (1) the imbalance on each chromosome has been shown to be associated with clinical anomalies; (2) both imbalances were large enough to be cytogenetically visible and likely encompassed over 100 genes; and (3) a history of maternal pregnancy loss at 8 weeks’ gestation and one neonatal death of one maternal sibling. Although these two incidences were not cytogenetically investigated and other factors could be at play, it is conceivable that a chromosomal imbalance, either der(3) or der(1), as a result of the familial balanced translocation, could be causative for these losses.

3. Discussion

Chromosomal translocations involving distal chromosome 1q and distal chromosome 3p include t(1;3)(q32;p25), t(1;3)(q25;p23), and t(1;3)(q43;p25). Kozma et al reported segregation of a balanced t(1;3)(q42.3;p25) translocation in a three-generation family and identified two types of viable unbalanced complements with distinct phenotypes. For both rearrangements, consistent findings included profound psychomotor and growth retardation, severe neurologic abnormalities, heart defects, and poor survival. Facial dysmorphism with trisomy 1q/monosomy 3p was distinct from the phenotype associated with monosomy 1q/trisomy 3p and allowed categorization of affected family members.

Trisomy 1q has been described in more than 80 case reports. The majority of cases have arisen from the unbalanced segregation of 1q translocations, but approximately 20% are “pure” trisomy 1q, distinguished by their cytogenetic breakpoints. There are at least 19 case reports involving the duplication/deficiency of chromosomes 1 and 3 and more than 100 cases of constitutional partial dup1q have been documented and reviewed by Utine et al. The breakpoint hotspots appear to be 1q25 (interstitial duplication), 1q32, and 1q42. Where partial duplications involving segments proximal to 1q42 have been typically associated with multiple birth defects in conjunction with significant cognitive delays, distal duplication involving 1q42-qter has mostly been associated with facial dysmorphism with a mildly impaired cognitive profile. Low birth weight, postnatal growth restriction, and cardiac, urogenital, and brain malformations have also been reported in cases of distal partial dup1q22, but birth defects were not the norm, and there was no clearly defined karyotype—phenotype correlation. Likewise, constitutional partial deletion of 3p25-pter has been associated with low birth weight, growth restriction, characteristic facial features, congenital heart defects, and psychomotor delay. However, the phenotypic variability is quite wide both within and between families, and some cases manifest with near normal or very mild phenotype.

A search of PubMed, the European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (www.ecaruca.net), and Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (http://decipher.sanger.ac.uk) did not reveal an identical finding of the combination del 3p25.3 and dup1q42.13 as seen in our case. Our patient presented with asymmetric intrauterine growth restriction at birth with relatively preserved head size. He was dysmorphic with tracheal-laryngomalacia, congenital heart defects, hypogonadism,
intestinal malrotation, and brain malformation; all of these features have been documented in either dup1q42 or del3p25. The facial dysmorphisms in our case, including a depressed nasal bridge, microcephaly, bushy eyebrows, narrow palpebral fissures, ear abnormalities, retrognathia, and a short neck, had some similarity with the previous cases of t(1;3)(q32;p25), t(1;3)(q25;p23), and t(1;3)(q43;p25).3 The MRI findings of small frontal lobes and abnormal sulcation have not been previously described. In reported translocations, only three infants had demonstrated brain findings: one with arhinencephaly and cerebellar heterotopias, a second with absence of the corpus callosum and septum pellucidum, and a third with thin cortical tissue.7 What was most striking in our case was the severity of postnatal growth restriction and profound psychomotor retardation, not previously reported in either dup1q42 or del3p25. Also curious was the biochemical instability as reflected in inconsistent levels of electrolytes, TSH, and growth hormone, which, in conjunction with intractable seizures and brain malformation as well as profound developmental delay, seems to reflect a poor central endocrine regulatory control. No defined endocrine abnormalities have been previously reported, apart from one case of adrenal insufficiency. Kozma et al7 reported gastrointestinal motility disorder in his case series, and there is a single documented case of pyloric stenosis with a t(1;3)(q25;p23) chromosomal anomaly.4 Our infant had significant bowel malrotation requiring surgical intervention, which was not documented with previous duplications/deficiency of chromosomes 1 and 3.

Attempts to establish a genotype—phenotype or karyotype—phenotype correlation did not yield linear results. There are at least 71 genes in 3p25-pter and over 100 genes in 1q42-qter in the Online Mendelian Inheritance in Man (OMIM) database. However, with the exception of SCA29, VHL, and OXTR (oxytocin receptor) genes, most other genes in the region deleted in our patient are of uncertain function or clinical significance or encode a recessive trait. Among the genes within the region duplicated in our patient were NEM1 for nemaline myopathy, EDA3 for ectodermal dysplasia, and SHFL1 for split hand/foot malformation. None of the known genes in these regions explain the clinical phenotype of this patient. As mentioned above, none of reported patients with "pure" duplication 1q42-qter or deletion 3p25-p25 manifested such a severe phenotype as our patient. Therefore, it is tempting to speculate that haploinsufficiency of a number of genes in the deletion region in addition to overexpression of a number of duplicated genes, in conjunction with possible disruption of a critical gene or genes at the breakpoints and/or unmasking of a recessive allele, may all have contributed to the clinical phenotype. Reporting of more patients with the same or similar karyotype anomalies is needed for better understanding and correlation of a phenotype—karyotype—genotype relationship.

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References