Clinical Case Reports

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CASE REPORT

22q11.2 microduplication syndrome with associated esophageal atresia/tracheo-esophageal fistula and vascular ring

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Funding Information
No sources of funding were declared for this study.

Received: 6 July 2016; Revised: 14 November 2016; Accepted: 19 November 2016

Clinical Case Reports **2017; 5(3): 351–356**

doi: 10.1002/ccr3.815

Key Clinical Message

This case report describes a patient with a 22q11.2 duplication. His features, which include VACTERL association with an esophageal atresia/tracheo-esophageal fistula and a vascular ring, expand the previously described phenotype for this duplication.

Keywords

22q duplication, esophageal atresia, VACTERL.

Introduction

The 22q11.2 duplication syndrome (MIM #608363) is a disorder with varied features. Its phenotype overlaps 22q11.2 deletion syndrome, commonly known as DiGeorge/velocardiofacial syndrome (DG/VCFS; MIM #188400, #192430), but it is a separate and distinct syndrome. Manifestations of 22q11.2 duplication syndrome range from normal to mild-moderate phenotypes. The spectrum includes milder manifestations such as learning disabilities, autism, motor impairment, hypotonia, and dysmorphic features, as well as more severe phenotypes with hearing loss and multiple congenital malformations including congenital heart defects, velopharyngeal insufficiency, cleft lip, and/or cleft palate [1, 2, 3, 4]. The size of the duplication does not appear to correlate with a patient's clinical phenotype [5].

In this report, we present a patient with confirmed 22q11.2 duplication, occurring at the distal end, spanning 1.4 Mb. This unique patient has features of VACTERL (acronym for vertebral defects, anorectal malformation, cardiac defects, tracheo-esophageal fistula (TEF), renal anomalies, and limb abnormalities) association (MIM #192350). His specific phenotype includes vertebral anomalies, esophageal atresia (EA) with TEF, ventricular septal defect (VSD), double aortic arch, and limb anomaly. This is the second case, to our knowledge, of VACTERL reported in association with 22q microduplication [6] and the only case to our knowledge that is specifically associated with EA/TEF and a vascular ring. This report extends the phenotypic spectrum of 22q11.2 duplication syndrome and further supports a predisposition to VACTERL association.

Case Report

This case is discussed with approval of the institutional review board of Drexel University. SR was a 40 0/7-week-

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old male infant born to a 31-year-old father and unrelated 31-year-old G2P0010 mother with a history of bipolar disorder, anxiety, ADHD, and depression. Family history includes father with dyslexia, but no history of learning disabilities or congenital anomalies. The mother was on Lamictal, Ability, Zoloft, Zofran, and Pepcid during her pregnancy. Her pregnancy was generally uncomplicated, and she received adequate prenatal care. A vascular ring was noted on fetal ultrasound, for which cardiology was consulted and recommended genetic testing after birth to evaluate for 22q11.2 deletion syndrome. The mother's prenatal laboratories were unremarkable. She presented in labor and delivered via a normal vaginal delivery after 13 h of rupture of membranes. The baby received routine initial resuscitation with Apgars of 8 and 8 at 1 and 5 min, respectively. At 10 min of life, he developed cyanosis and stridor. His growth parameters were as follows: birth weight 2770 g (8th percentile), length 49.5 cm (69th percentile), and head circumference 33.25 cm (10th percentile).

On physical examination, notable features included a two-vessel cord, downslanting palpebral fissures, diminished tone, widely spaced nipples, and a dysplastic right thumb (Fig. 1). No murmur was auscultated, lungs were clear, and anus was patent. No other visible limb abnormalities or spinal defects were seen. He was transferred to another acute facility while on 2 L nasal cannula, FiO2 0.3, for further management of his vascular ring.

At the receiving hospital, he was diagnosed with EA with TEF (type C) after review of suggestive chest and abdominal X-rays, followed by confirmatory esophagram to assure the vascular ring was not the singular cause of the esophageal obstruction (Fig. 1D). Due to concern for VACTERL association, renal, cranial, and spinal ultrasounds were performed, all of which were unremarkable. Skeletal X-rays revealed right thumb anomalies (dysplastic, shortened first metacarpal) and hemivertebrae at L5-S1. Ophthalmologic examination was normal. Echocardiogram confirmed a vascular ring and a double outlet right ventricle with subaortic VSD, with left to right flow explaining his cyanosis. Given the vertebral anomalies, the EA with TEF, the cardiac defect, and preaxial upper extremity radial findings, he was given a diagnosis of VACTERL association. Chromosomal microarray was ordered to assess for aneuploidy.

He went to the operating room within 3 days of admission for repair of his vascular ring, division of his

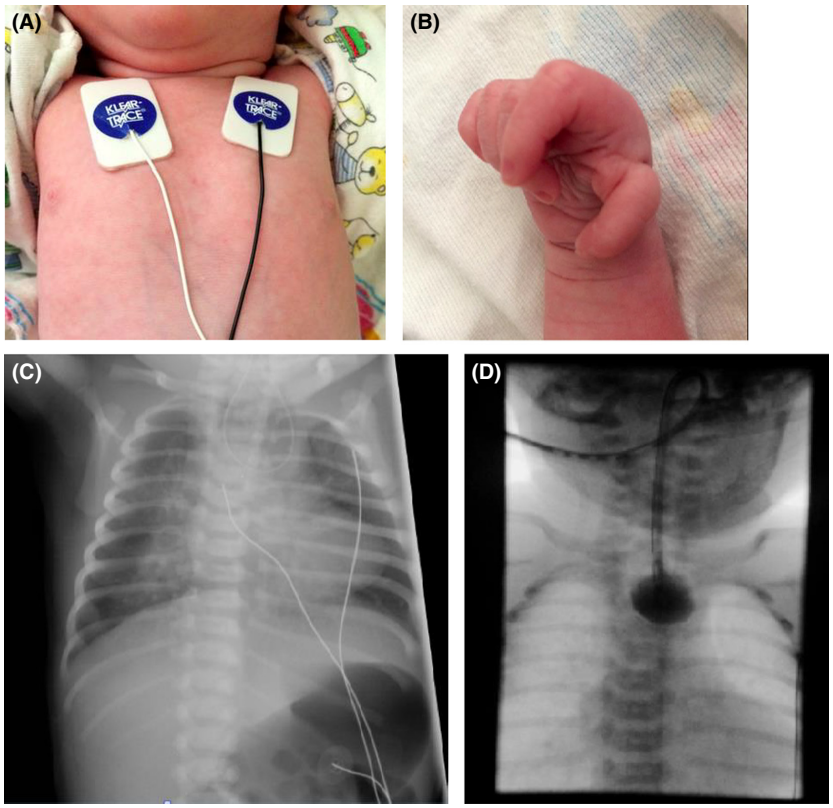

Figure 1. (A) Widely spaced nipples. (B) Right dysplastic thumb. (C) Chest X-ray showing looping of orogastric tube coiling within esophagus, air in the stomach, and prominent pulmonary vasculature. (D) Esophagram showing contrast pooling within an esophageal atresia.

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TEF and primary esophagoesophagostomy via left thoracotomy. As his vascular ring involved a double aortic arch, with the right being dominant, his left aortic arch was ligated prior to repair of the EA/TEF. His postoperative course was complicated with left chylothorax, treated with chemical pleurodesis and chest tube maintenance for 12 days. Follow-up echocardiogram showed increase in main pulmonary artery and branch pulmonary artery velocities, with stable mild right heart dilation and moderate to large ventricular shunt.

He was eventually discharged home from the neonatal intensive care unit orally feeding ad lib on high calorie formula for his failure to thrive in the context of cyanotic congenital heart disease, as he was <2% on his growth curve for weight. He was on digoxin and Lasix for signs and symptoms of congestive heart failure to facilitate growth while awaiting definitive cardiac repair. His VSD was repaired when he was 5 months old.

During the admission, the chromosomal microarray revealed a distal 22q11.23 microduplication, spanning 1.41 Mb (arr22q11.23(23,652,517–25,066,472)X3). There are 21 genes from the OMIM database in this region. Parental testing was offered and performed. A FISH analysis with the LSI BCR/ABL1 Dual Color Dual Fusion Probe (Abbott Molecular/Vysis, Inc.) was performed, in which the BCR locus was at 22q11.2. The mother's result was 46,XX.nucish(BCRX2), indicating that she did not carry the duplication, and the father's result was 46,XY.nucish (BCRX3) in 16/200 cells (~8%), indicating low-level mosaicism. With this level of mosaicism, the father would not necessarily have a clinical phenotype but likely has other tissue cell lines that are variably affected (including gonadal tissue, which would lead to an increased recurrence rate in his offspring). Low-level parental somatic mosaicism may be seen in cases of transmitted copy number variants that are associated with genetic disorders. The father himself did not report any signs or symptoms consistent with the microduplication on family history.

Table 1. Reported clinical features of 22q11.2 microduplication.

Facial dysmorphisms
Eyes: downslanting or upslanting palpebral fissures, short palpebral fissures, ptosis, epicanthal folds, hypertelorism, superior placement of eyebrows
Ears: dysplastic ears, preauricular tags and pits, low-set posteriorly rotated ears
Nose: short upturned nose, broad flat nose
Mouth/Oral cavity: thin lips, long/smooth philtrum, micrognathia, velopharyngeal insufficiency, cleft or high arched palate, hyperdontia, bifid uvula, ankyloglossia
Face: pointed chin, frontal bossing, long and narrow face
Ophthalmologic
Marcus Gunn jaw winking, glaucoma, hyperopia, myopia, strabismus, astigmatism, retinal vascular tortuosity, oculomotor abnormalities, nystagmus, coloboma
Cardiovascular
TOF, interrupted aortic arch, right-sided aortic arch, HLHS, aortic insufficiency, mitral valve prolapse, TAPVR
Cognitive/development
Learning disabilities, behavioral problems, growth/motor/speech delays, hypernasal speech, autism
Neurologic
Hypotonia, seizures, microcephaly, brachycephaly, pachygyria, polymicrogyria, callosal agenesis
Musculoskeletal
Hypoplastic toenails, increased fetal fingerpads, brachydactyly, long or tapered fingers, clinodactyly, brachymesophalangia, abnormal palmar creases, developmental dysplasia of hip, amyoplasia, contractures, scoliosis
Urogenital
Hypospadias, hydronephrosis, vesicoureteral reflux, cryptorchidism, urethral stenosis, bladder exstrophy
Gastrointestinal
Intestinal malrotation/volvulus, GER, failure to thrive
Immunologic
Asplenia, absent thymus, pre-B acute lymphoblastic leukemia
Endocrine
Thyroid agenesis/hemiagenesis

GER, Gastroesophageal reflux; HLHS, Hypoplastic left heart syndrome; TAPVR, Total anomalous pulmonary venous return; TOF, Tetralogy of Fallot.

Discussion

The chromosome 22q11.2 region is highly susceptible to both microdeletions and duplications due to its misalignment of eight low copy repeats (LCR) regions, LCR22-A through LCR22-H, which mediate nonallelic homologous recombination. Both microdeletions and microduplications might be expected to occur at the same frequency; however, 22q11.2 deletions occur at a frequency of 1 in 4000–6000 live births while the reciprocal 22q11.2 duplications are diagnosed far less often [4].

Rearrangements within the LCR regions are known to cause various congenital anomalies, such as the well-described 22q11.2 deletion syndrome DG/VCFS. More recently, microduplications have been described in the literature with features that overlap DG/VCFS but represent a distinct syndrome with high phenotypic variability (Table 1).

The most commonly duplicated region extends 3 Mb from LCR22-A to LCR 22-D, which encompasses 40 genes [7], and is the reciprocal of the common DG/VCFS deletion. Larger duplications up to 6 Mb have been reported, as well as smaller duplications within distal regions LCR 22-E to LCR 22-H in a minority of cases [8]. In fact, two separate case reports cited isolated 437 and 614 kb microduplications, which may be the two smallest to date [9, 10]. The size of the duplication and the severity of the phenotype are not well correlated.

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As of 2008, the literature contained 63 specific reported cases of this duplication [11], with more recent published reports finding the duplication in many as 94 individuals [12–14]. Despite more published reports identifying individuals with the 22q11.2 duplication, the prevalence in the general population is difficult to determine as there may be more unrecognized cases due to the highly variable phenotype [11]. In most published reports, the duplication was detected in patients who were initially suspected to have DG/VCFS-like features and were referred by a medical specialist for 22q11.2 deletion testing [1, 15–17]. As a result, both ascertainment bias and the phenotypic variability may explain the underestimation of the true prevalence of the duplication.

It has been previously suggested that the duplication syndrome was associated with specific facial features, such as a narrow face, downslanting palpebral fissures with or without ptosis, hypertelorism, superior placement of eyebrows, mild micro- or/retrognathia, and minor ear anomalies [2, 4, 18]. Duplications are usually inherited from a phenotypically unaffected or mildly affected parent, with manifestations such as mild cognitive deficits, facial anomalies, or hand abnormalities [1, 4, 19, 20].

Affected individuals showed high phenotypic variability ranging from nondysmorphic features and normal intelligence to an isolated learning disability or autism [21, 22]. Therefore, subtle phenotypes with or without cognitive delay or autism may prompt clinicians to expand on their genetic evaluation to include the analysis of the 22q11.2 chromosomal region for duplications. There can also be multiple severe congenital malformations, including congenital heart defects, velopharyngeal insufficiency and cleft lip or palate as well as hearing loss, and seizures. Intrafamilial inheritance also shows considerable variability with a high rate of familial transmission [1, 2, 4, 8, 11, 19].

As more case reports describe unique and newfound features associated with the duplication, such as hyperdontia [23], pachygyria [24], thyroid hemiagenesis [25], amyoplasia [9], polymicrogyria, and callosal agenesis [26], it becomes apparent that characterizing a phenotypic gestalt to the microduplication is not only challenging, but also exemplary of the difficulty in predicting phenotypic consequences in situations of a prenatal diagnosis and discussion about prognosis. The etiology of the phenotypic variability is not known, but proposed explanations include nonpenetrance, epigenetic factors, modifier genes, and environmental factors [17, 20, 24].

Once a 22q11.2 microduplication is confirmed, it is important to search for other mutations, as it is likely that other genes may play a role in the phenotypic expression. For example, more recent reports are describing concomitant chromosomal imbalances along with the 22q11.2 microduplication, such as coexisting deletions, additional duplications, missense mutations, and reciprocal translocations [27–31].

Our present case describes a male infant with an isolated 1.41 Mb 22q11.2 duplication, which is likely paternally inherited as the father was found to have ~8% somatic mosaicism for the microduplication. The father himself is asymptomatic, and the infant has four of the six cardinal features of VACTERL: (V): hemivertebrae L5-S1; (C): perimembranous VSD and double aortic arch; (TE): EA with TEF type C; and (L): right dysplastic thumb with shortened first metacarpal. Most cases of VACTERL are sporadic; however, genetic abnormalities have been described in rare cases, but without a common mutation [6].

Individuals with the 22q11.2 duplication may have isolated features of VACTERL association; however, few cases describe a patient who presents with three or more cardinal features of the association to meet the criteria for VACTERL. Schramm et al. found that in a group of 12 individuals with VACTERL association, one was found to have the 22q11.2 duplication, with features including fusion of the 4th and 5th lumbar vertebrae, anal atresia with recto-prostatic fistula, right-sided duplicate kidney with vesicoureteral reflux (VUR), and penile hypospadias. Additional characteristics included caudal regression syndrome and right-sided equinovarus deformity, without concern for facial dysmorphism [6]. Schramm's report was the first to publish an association between VACTERL and 22q11.2 microduplication.

Meins et al. had previously described an individual with three features of VACTERL with an interstitial duplication of 22q11.2, but due to the presence of colobomata of the iris, retina, and uvea, the patient was regarded to have cat eye syndrome (CES; MIM # 115470), for which the cytogenetics is characterized by a supernumerary bisatellite and dicentric marker chromosome containing duplicated material of chromosome 22 resulting in partial tetrasomy 22 [32]. This patient also had several physical features that are both common to CES and to 22q11.2 microduplication, such as downslanting palpebral fissures, hypertelorism, ptosis, posteriorly rotated ears, preauricular pits, flat nasal bridge, thin lips, highly arched palate, and micro/retrognathia. The four cytogenetic phenomena, 22q11.2 microduplication and DG/VCSF as well as CES and der (22q) syndrome, can include features of VACTERL. This may indicate that a gene dosage effect involving the 22q11.2 region predisposes to the manifestation of the clinical phenotypes.

Several features in our patient are also observed in other 22q11.2 microduplication carriers, such as downslanting palpebral fissures, mild hypotonia, and cardiovascular anomalies. However, our patient is the first that we know of in the literature to have syndromic EA with TEF (type C) in the setting of VACTERL associated with the

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microduplication. The prevalence of EA/TEF (MIM # 189960) is roughly 1–4 per 10,000 births, with approximately half of cases associated with other congenital defects, and about 11–12% of patients having a genetic cause [33]. In cases where EA/TEF is associated with other malformations, a considerable number are found with the features of VACTERL, but other non-VACTERL type features have been reported as well [33–35]. Though twin studies indicate that genetic factors do not necessarily play a role in the pathogenesis of EA/TEF, the anomaly is associated with certain genetic syndromes, implying that genetic factors can contribute. Currently, there are only a few genes associated with EA/TEF, but none of which involve chromosome 22 [35]. The cytogenetics of EA/TEF, as well as VACTERL, have yet to be elucidated due to the plethora of mutations that have been found with them. But the phenotypic overlap between the microduplication, DG/VCFS, CES, and der (22) syndromes may enable geneticists to categorize all four under one overarching syndrome involving chromosome 22 in the future.

There is great phenotypic variability among cases of 22q11.2 duplication, but phenotypic trends are certainly notable. Our case supports prior reports with features of VACTERL association and further expands the phenotype of 22q11.2 duplication syndrome. Microarray technologies are increasingly being used in individuals with multiple congenital anomalies without a clear genetic diagnosis, which may reveal a higher incidence of the duplication and phenotypic variability. New data, such as this case, present additional opportunities to further delineate the genetic etiologies of VACTERL and the phenotypic gestalt of this duplication. The variable expressivity of 22q11.2 microduplication makes correlations between genotype and phenotypes difficult, and thus, additional case reports are helpful in describing the full spectrum of possibilities to aid future families in counseling and support.

Conflict of Interest

None declared.

Authorship

LN: cared for the infant during his initial hospitalization and wrote the first draft of the manuscript. RF: cared for the infant during his initial hospitalization and facilitated all drafts of the manuscript and prepared it for submission. EF: cared for the patient during his initial hospitalization, performed the initial literature review, and revised the manuscript. RP: performed the surgical repair and revised the manuscript. AM: repaired the cardiac defect and vascular ring and reviewed the manuscript. CIM: managed the patient's congestive heart failure and reviewed the manuscript. SM: counseled the family about the genetic diagnosis, oversaw the paternal testing, and revised the manuscript. RJ: facilitated the genetics consultation and diagnosis and oversaw preparation of the manuscript.

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