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13q13.1–q13.2 deletion in tetralogy of Fallot: Clinical report and a literature review

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Abstract

Recent advances in microarray technology are helping to identify more genetic anomalies associated with tetralogy of Fallot and other congenital heart defects. We report on a 24-year-old woman with a syndromic form of tetralogy of Fallot who was found to have a novel *de novo* deletion of the proximal long arm of chromosome 13. History of developmental delay and learning difficulties, mild dysmorphic facial features, and anal atresia prompted genetic investigations. A review of the literature on deletions that overlap this region showed that several were associated with major congenital heart defects. The results suggest that the 13q13.1–q13.2 region may harbour a gene or genes important in cardiac development.

Keywords

Tetralogy of Fallot; Congenital heart defect; Chromosome deletion; Chromosome 13; Copy number variation

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1. Introduction

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart defect, accounting for approximately 10% of all congenital heart disease (CHD) [1]. Deletions of chromosome 22q11.2, trisomies, and other less common chromosomal abnormalities occur in an estimated 25% of patients with TOF [2–4]. Recent advances in microarray technology promise to help identify more anomalies associated with TOF and other CHD [5]. The recognition of such abnormalities has relevance for clinical practice and can help target regions that may contain genes important in cardiac development. We present a recently identified *de novo* deletion of the proximal long arm of chromosome 13 and a comprehensive review of the literature on this region showing a high prevalence of associated CHD.

2. Clinical report

A 24-year-old woman presented with a history of TOF and other congenital defects, learning difficulties, and mild dysmorphic facial features. The patient was ascertained through the Toronto Congenital Cardiac Centre for Adults. Assessment using clinical criteria previously established to identify 22q11.2 deletion syndrome and other genetic syndromes [6] lead to selection of this patient in a pilot study of copy number variation (CNV) in TOF (unpublished). Informed consent was obtained to participate in a study to identify and characterize genetic syndromes in adults with CHD, which was approved by the Research Ethics Boards of the University of Toronto and University Health Network.

2.1. Clinical manifestations

The patient is the second of two children born to a 26-year-old mother of French Canadian and Native Canadian origin, and a 28-year-old father of Serbian descent. She was born after an uncomplicated pregnancy. Her mother had a history of a first trimester spontaneous abortion. An older brother is alive and well. There was no family history of any congenital cardiac or other defects, or consanguinity.

The diagnosis of TOF was made shortly after birth. At 3 months of age, the patient had a modified Blalock–Thomas–Taussig shunt. This was followed by an intracardiac repair with a transannular patch at age 27 months. The surgical notes commented that there was a “somewhat hypoplastic pulmonary artery.” The surgery was uncomplicated with good results. She has had no adverse cardiac events in childhood or in adulthood. At last follow-up, she had only mild residual pulmonary regurgitation with preserved right ventricular size and function.

Additionally, anal atresia was repaired at birth. Surgery for a benign throat cyst was undertaken at age 6 months, followed by a tonsillectomy and adenoidectomy at age 4 years. Recurrent otitis media was managed with myringotomy tubes at age 4 years. Speech was delayed, and speech therapy was necessary because of articulation difficulties. Learning difficulties were present and special education was necessary throughout schooling which continued to age 19 years. Attention deficit disorder, diagnosed at age 9 years on the basis of inattention, impulsivity, and difficulty with peer relationships, was treated with

methylphenidate for four years with positive results. Tics that were a side effect stopped once methylphenidate was discontinued. She was diagnosed with major depression at age 23 years. Citalopram 20 mg resulted in complete resolution of symptoms. There was a history of daily marijuana use of undetermined duration.

On physical examination at age 24 years, the patient's height was 162 cm (~20th percentile), weight was 63 kg (BMI 24.0), OFC was 52 cm (~25th percentile), and she had a nasal voice. Subtle dysmorphic facies were present (Fig. 1), including: almond shaped eyes with partial epicanthal folds; slightly protuberant, low-set, and posteriorly rotated ears; low forehead; fish-shaped mouth; and other features: bilateral dislocating shoulders; long 4th and 5th fingers and mild bilaterally camptodactyly of all four fingers. Neuropsychological testing using the WAIS-III and WRAT revealed functioning below the 1st percentile on Full Scale, Verbal, and Performance IQ, and at a grade two level in reading, spelling, and arithmetic, consistent with a DSM-IV diagnosis of mild mental retardation. An abdominal ultrasound and magnetic resonance imaging (MRI) of the brain showed no abnormalities. On the basis of her syndromic clinical presentation, the patient was genotyped with a SNP-based microarray as part of a research study, yielding a putative deletion at 13q13.

2.2. Molecular genetic and cytogenetic investigations

The patient was suspected of having a genetic syndrome in childhood and was first referred to genetics services at age 11 years. Both 22q11.2 deletion syndrome and fragile X syndrome were considered on the basis of her congenital abnormalities, learning difficulties, and dysmorphic features (although these were acknowledged to be atypical for either syndrome). Standard cytogenetic and molecular testing at that time, including fluorescence in-situ hybridization (FISH) using 22q11.2 probe HIRA, revealed a normal female karyotype with no deletion in chromosome region 22q11.2 or evidence of fragile X.

We genotyped the patient's DNA for approximately 260,000 SNPs using the Affymetrix GeneChip® Human Mapping 250 K NspI Array and analyzed the data for CNV content according to established protocols described elsewhere [7]. This revealed an apparent hemizygous 4.7 Mb interstitial deletion in the proband at 13q13.1–q13.2 with estimated breakpoints at 31,073,908 and 35,802,300 (NCBI Build 35). No other CNVs of significance were detected in the proband.

To confirm the novel deletion revealed by the pilot array results, we performed FISH on cultured lymphocytes using a chromosome 13q subtelomeric probe (Abbott Molecular), and BAC clone RP11-87G1 (located at 13q13.1–q13.2). The latter probe was directly labeled with Spectrum Green. Hybridized metaphase spreads were analyzed using a Zeiss Axioplan 2 epifluorescence microscope. Images were captured by an Axiocam MRm Camera (Imaging Associates, Bicester, UK) and analyzed using an imaging system with MetaSystems Isis Software version 5.1.110 (Boston, MA) (Fig. 2). Further examination showed that this deletion was visible in a G-banded karyotype at 550 band resolution. High-resolution karyotypes and FISH testing of both parents did not reveal any abnormalities, thus indicating the proband's 13q13.1–q13.2 deletion as a *de novo* change. The patient and her family subsequently received genetic counselling and referral to a medical geneticist.

Table 1 and Fig. 3 summarize a comprehensive review of the literature, which revealed 35 cases with deletions that likely overlap the 13q13 region. Including the current report, 11 (32%) were associated with CHDs, four of which were TOF and the remainder a variety of other anomalies (Table 1). Deletions associated with ring chromosomes or mosaicisms were not included. There are also two reports of CHD in patients with ring chromosomes with breakpoints in proximal 13q regions: karyotype 46,XY,r(13)(p11q13) [8], and karyotype 46,XX,r(13)(p11q14)/46,XX,der(13)(t13;13)(q10;q14) with a muscular ventricular septal defect [9].

3. Discussion

To our knowledge, this is the first report of deletion 13q13.1–q13.2 and the first review of 13q deletions that include the gene-rich band 13q13.

Several features of the chromosomal anomaly in this patient with TOF enhance the likelihood of causative link with the phenotype. First, this hemizygous deletion is large (>1 Mb). Second, our findings and the available literature indicate a high prevalence of associated CHD. As for other microdeletions, incomplete penetrance and variable expressivity are likely in hemizygosity of 13q13. This would predict that some patients with a deletion in this region would have a subclinical cardiac defect, or no cardiac anomaly whatsoever. Micro-deletions apart from 22q11.2 deletions are likely to be rare in patients with TOF, and no CNVs involving chromosome 13 were reported in a recent study of 114 patients with TOF [5]. Nevertheless, the recognition of rare genetic abnormalities in patients with CHD is clinically relevant. In addition to multisystem manifestations, syndromic patients may be at increased risk for surgical complications or have worse outcome after surgical correction [10,11]. This information is also important for genetic counselling of family members.

The elevated prevalence of CHD associated with deletions overlapping this 13q13 region suggest that one or more of the 16 genes in the 13q13 region could be important in cardiac development (Fig. 3). For example, the protein coded by *SPG20* functions in the degradation and intracellular trafficking of epidermal growth factor (EGF) receptor [12]. Evidence from mouse models indicates that EGF signaling is crucial in cardiac morphogenesis [13]. Additionally, the gene *B3GALT1*, which is associated with Peters'-plus syndrome [14], is approximately 260 kb proximal to the proximal breakpoint of the 13q13 deletion in the current report (Fig. 3) and expression could be affected through a position effect. CHD is present in 31% of Peters'-plus syndrome cases [15]; however, our patient did not have the characteristic ophthalmic malformations (corneal opaqueness and iridocorneal adhesions; Peters' anomaly) of this syndrome.

There are few details pertaining to the cardiac diagnoses in previous publications, resulting in a limited understanding of the types of CHD associated with 13q13 deletions. It may be that, similar to individuals with 22q11.2 deletions [16], anatomic characteristics of TOF and other CHD in 13q13 deletions and perhaps other syndromal forms of CHD may be enriched for more severe cardiac phenotypes (e.g., major aorto-pulmonary collaterals). Generally,

however, additional cardiovascular anomalies associated with TOF are unlikely to be as predictive of a chromosomal abnormality as one or more extra-cardiac abnormalities [6].

With respect to congenital abnormalities other than CHD, and excluding conditions that have already been mapped to this region (e.g., retinoblastoma and locus 13q14), there are no obvious patterns of specific associated congenital anomalies with 13q13 deletions other than the possible exception of anal atresia (2 of which are in patients with TOF; Table 1). The concordance of CHD and anorectal malformations is most often connected with the VACTERL (formerly VATER) association [17,18]. Although most patients with the VACTERL association have normal karyotypes, a few reports have been published of large chromosomal abnormalities in patients with the VACTERL association [19]. Array-based technologies are likely to help in identifying submicroscopic chromosomal imbalances in many more cases [20]. Our patient does not meet diagnostic criteria for VACTERL, which requires the presence of at least three of: vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, esophageal atresia, renal anomalies, and limb defects. However, individuals such as our patient with VACTERL-like features in addition to facial dysmorphic features, learning disabilities, or abnormalities of growth, are likely to have a syndromic diagnosis. Evidence supporting an association between proximal 13q deletions and anorectal anomalies is more limited, but proximal 13q deletions should be added to the growing list of single gene and chromosomal disorders with features in common with the VACTERL association [20].

Cardiologists should maintain a high index of suspicion when dealing with a patient with syndromic CHD. Recent advances in microarray technology are revealing previously undetectable genetic anomalies of clinical significance. Identification and categorization of these anomalies will help in delineating the molecular pathways associated with CHD, in which one or more genes in chromosome region 13q13 are likely involved.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [48].

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Fig. 1.
Patient at age 24 years with 4.7 Mb 13q13.1–q13.2 deletion.

Fig. 2. Fluorescence in-situ hybridization of metaphase chromosomes demonstrating simultaneously the hybridization of the 13q subtelomeric probe (red) to both chromosomes, and the hybridization of the BAC clone RP11-87G1 probe (green; located at 13q13.1–q13.2) to one chromosome only.

Fig. 3. Chromosomal deletions reported in the literature that overlap 13q.13.1 and/or 13q13.2, highlighting in red those cases with associated CHD. Deletions are ordered by proximal breakpoint, and then by length. Where precise breakpoints were not provided, conservative estimates were used. Genes located within 500 kb of the deletion region in the current report are displayed using NCBI Build 35. Open reading frames ($n=2$; total splice variants=7) are not shown.

Table 1

Summary of the reported cases involving deletions overlapping the chromosome 13q13.1–q13.2 region.

Case	Karyotype	Age	CHD	MR/DD	Other ND	GD	RB	Dysmorphic features	Palate	OFC	Tone	Other	Reference
1	45,XX,-13,-18,+der(18)t(13;18)(q13;q23)	2.5 y	Subaortic stenosis	✓		✓		✓					[21]
2	Partial monosomy 13q	IU	AVSD									Anal atresia (autopsy)	[22]
3	46,XX,del(13)(q12q14)	6.5 y		✓		✓	R	✓			↓		[23]
4	46,XX,del(13)(q12q14)	3 y		✓		✓	L					Microphthalmia	[24]
5	46,XX,del(13)(q12q14)	3 y		✓			B						[25]
6	46,XY,del(13)(q12q14)	7.5 y		✓		✓	L	✓	High arched				[26]
7	46,XX,del(13)(q12q14)	16 d	Single ventricle; Absent MV; Patent DA	✓	Small cerebellum	✓		✓			↓	Microphthalmia; Major congenital defects	[27]
8	46,XX,del(13)(q12q21)	24 y		✓			L						[28]
9	46,XX,del(13)(q12q21)	18 y		✓		✓		✓			↓	Craniosynostosis; Internal hydrocephalus; Synostosis of C2–C3	[29]
10	46,XY,del(13)(q12q21)	8 m	TOF ^a										[30]
11	46,XX,del(13)(q12q22)	5 m		✓		✓	L				↓	Unbilical hernia	[31]
12	46,XX,del(13)(q12q22)	9 m		✓		✓	B						[31]
13	46,XX,del(13)(q12q22)	5 m		✓		✓	R		Cleft			Congenital omphalocele; Ileal atresia	[32]
14	46,XX,del(13)(q12q31)	21 m		✓			B			↓			[28]
15	46,XX,del(13)(q12.1q14)ish del(13)(q12.1q14.1)	2.5 m				✓		✓		↓	↓		[33]
16	46,XX,del(13)(q12.3q14.2)	19 m		✓			B	✓		↓	↓		[34]
17	46,XX,del(13)(q12.3q21.31)	9 m	TOF	✓			B	✓		↓	↓		[35]
18	46,XY,del(13)(q12.3q22.3)	14 d	Aneurysm of DA		Intermittent severe convulsions and burst suppression on EEG			✓		↓	↓		[36]
19	46,XY,del(13)(q12.3q14.1)	3 m				✓					↓	Severe GERD	[37]
20	46,XY,del(13)(q12.3q13.1)	18 y ^b	Present but unspecified	✓		✓			Bilateral cleft			Peters' anomaly	[14]
21	46,XY,del(13)(q12.3q13.1)	25 y ^b	Present but unspecified	✓		✓			Unilateral cleft			Anterior eye-chamber anomaly	[14]
22	46,XX,del(13)(q13q13).ish del(13)(q13.1q13.2)	24 y	TOF	✓	No	No	No	✓	Normal	Normal	Normal	Anal atresia	This report
23	46,XX,del(13)(q13q14.3)	3 m					B	✓					[38]
24	46,XX,del(13)(q1303q14.3)	20 m					B			↑			[39]

Case	Karyotype	Age	CHD	MR/DD	Other ND	GD	RB	Dysmorphic features	Palate	OFC	Tone	Other	Reference
25	46,XY,del(13)(q1307q14.3)	13 m					R			↑			[39]
26	46,XY,del(13)(q13q21.1)	3 y		✓	Corpus callosum agenesis	✓	B	✓					[40]
27	46,XX,del(13)(q13q21.1)t(11;22)(q23.1;q11.1)	11.5 m		✓	Frontal cortical atrophy; Biventricular dilatation	✓		✓			↓		[40]
28	46,XY,del(13)(q13.1q21.1)	3 y			Slight cortical atrophy			✓			↑	Calve-Perthe disorder	[41]
29	46,XY,t(2;10)(q21;q24),inv(9),del(13)(q13q21.3)	4 m		✓		✓	B	✓			↑	Cryptorchidism	[42]
30	46,XY,del(13)(q13q22.1)	11 d	Massive universal myocardial hypertrophy; Ventricular septal hypertrophy		Diffuse edema of the brain; Satellitosis; Lack of distinct demarcation of cerebral cortex		B	✓	Narrow		↓	Hyperbilirubinemia; Congestive heart failure; Recurrent infections	[43]
31	46,XX,del(13)(q13q22)	3 m		✓		✓	B						[34]
32	46,XY,del(13)(q13q22)	10 m		✓		✓	B	✓	High arched	↑	↓	Hirschsprung disease	[44]
33	46,XY,del(13)(q13qter)	SB	TOF		Semilobar holoprosencephaly			✓		↓		Anal atresia; Major congenital defects	[45]
34	46,XX,del(13)(q13qter)	IU										Anencephaly (no autopsy)	[46]
35	46,XY,del(13)(q13.2q14.1)	8.5 y		✓	Autism; Auditory processing defect	✓							[47]

AVSD, atrial ventricular septal defect; B, bilateral RB; CHD, congenital heart defect; d, day; DA, ductus arteriosus; DD, developmental delay; EEG, electroencephalography; GD, growth delay; GERD, gastroesophageal reflux disease; IU, in utero; L, left RB; m, month; MR, mental retardation; MV, mitral valve; ND, neurodevelopmental; OFC, occipital–frontal circumference; R, right RB; RB, retinoblastoma; SB, stillbirth; TOF, tetralogy of Fallot; y, year.

^aThe presence of a TOF in this patient was reported by Moteji and colleagues [35].

^bPersonal communication, October 2009.