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Short report

BMPR1A is a candidate gene for congenital heart defects associated with the recurrent 10q22q23 deletion syndrome

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ABSTRACT

Congenital heart defects (CHD) are associated with the recurrent 10q22q23 deletion syndrome and with partially overlapping distal 10q23.2.q23.31 microdeletions. We report on a *de novo* intragenic deletion of the *BMPR1A* gene in a normally developing adolescent boy with short stature, delayed puberty, facial dysmorphism and an atrioventricular septal defect. Based on this finding, complemented with computational prioritization data and molecular evidence in literature, the critical region for CHD on 10q23 can be downsized to a single gene, *BMPR1A*. Although loss-of-function mutations in *BMPR1A* typically result in juvenile polyposis syndrome, none of the patients with the typical 10q22q23 microdeletion syndrome, comprising this gene, were reported to have juvenile polyposis thus far. We reason that, even in the absence of juvenile polyposis syndrome, sequencing and copy number analysis of *BMPR1A* should be considered in patients with (atrioventricular) septal defects, especially when associated with facial dysmorphism and anomalous growth.

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1. Introduction

Interstitial copy number variants of 10q22q23 are flanked by low copy repeats (LCR3 and LCR4) which serve as substrates for non-allelic homologous recombination. Despite this predestined genomic architecture, clinical reports on chromosomal rearrangements between these homologous regions are scarce, totalizing eleven deletions and three duplications [1–3].

The frequent *de novo* occurrence of this novel 10q22q23 microdeletion syndrome (in 7 of 11 patients) indicates that this imbalance is associated in most cases with a reduced reproductive fitness. Cognitive development is mildly to moderately delayed, and behavioral problems, including autism, hyperactivity and aggressive behavior, are common. The majority of patients are macrocephalic, and are present with mild but variable dysmorphic features, like low-set dysplastic ears, hypertelorism and a flat nasal bridge. Congenital heart defects (CHD) of various types, including atrioventricular septal defects (AVSD), were reported in three patients carrying a typical 10q22q23 deletion [2, 3] (Fig. 1).

More distally extending 10q23 deletions, involving both tumor suppressor genes *PTEN* and *BMPR1A*, are associated with macrocephaly, developmental delay, juvenile or infantile gastrointestinal polyposis, and various congenital anomalies, including cardiac septal defects [3–10]. Germ-line *PTEN* mutations have been associated with a group of hamartoma tumor syndromes, frequently featuring macrocephaly and intestinal polyps [11], whereas loss-of-function mutations of *BMPR1A* typically result in juvenile polyposis syndrome (JPS) [12–15]. The *BMPR1A* gene is mapped proximally to LCR4 and is thus comprised by the 10q22q23 microdeletion syndrome as well, although none of these patients were reported to have juvenile polyposis, thus far.

We report on a *de novo* intragenic deletion of the *BMPR1A* gene, detected in a normally developing 17-year-old boy with an atrioventricular septum defect, short stature and a distinct facial gestalt, but without evidence for intestinal polyposis at present. Clinical and molecular data point towards a key role for *BMPR1A* in the genesis of congenital heart defects (CHD) in patients with interstitial 10q deletions.

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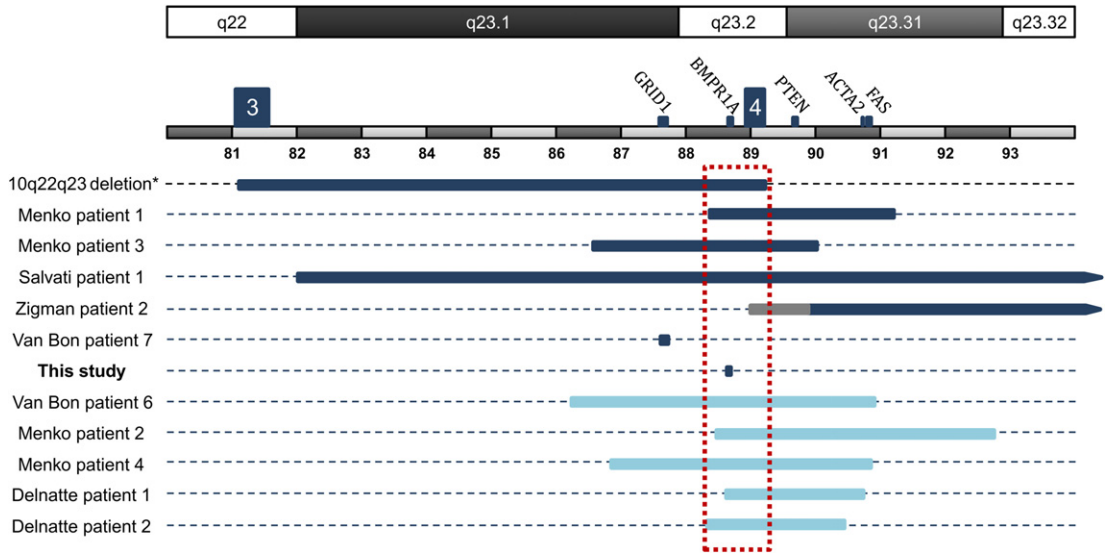

Fig. 1. Overview of submicroscopic imbalances on 10q22q23.32 with LCR3-4 and the positions of relevant genes on the axis. CHD-positive deletions are depicted in dark blue, CHD-negative deletions in light blue. The red box represents the minimal overlapping region of the 10q22q23 deletion syndrome and CHD-positive distal 10q23 microdeletions (chr10:88,310,020-89,010,020). The 22 kb deletion in our patient falls within this CHD-related region. *Congenital heart defects have been described in 3 out of 11 cases (27%) with the 10q22q23 deletion syndrome, mediated by LCR3 and LCR4 [2, 3].

2. Case report

This 17-year-old boy was the only child of healthy non-consanguineous parents. Familial history was unremarkable with respect to congenital anomalies or developmental delay. He was born at term after an uneventful pregnancy. His birth weight was 3.230 g (−1 SD) and his length was 47 cm (−2.2 SD). At birth he presented with microretrognathia, clinodactyly of the 5th fingers and a systolic heart murmur with weak femoral pulsations. Cardiac ultrasound revealed a complete atrioventricular septum defect (AVSD Rastelli type C) with a large ventricular shunt and a dominant right ventricle. In addition, a narrow preductal coarctation was detected by cardiac catheterization at day 2. Cardiovascular surgery including coarctation repair by subclavian flap angioplasty (Waldhausen procedure), banding of the pulmonary arteries, and clipping of the ductus arteriosus was performed at day 5. Failure to thrive and feeding problems required tube feeding until the age of 14 months. Aged 6 years, a Glenn procedure with a bidirectional cavo-pulmonary shunt and patch-plasty of the pulmonary artery bifurcation were performed because of progressive cyanosis and exercise intolerance.

He was followed by a pediatric endocrinologist for short stature and delayed puberty. At 11 years of age, his bone age corresponded to that of 8 years and 7 months (below 3rd centile). Growth hormone therapy was initiated at the age of 12 years and 6 months, measuring 130.8 cm (−2.7 SD) at the start of the treatment. Puberty was induced at 14 years of age by testosterone supplementation. His father and mother measured 171 cm and 155 cm, respectively (target height 169.5 cm+/−8.5 cm).

The patient was referred to the genetic clinic at 16 years of age because of short stature and delayed puberty. His weight was 38.6 kg (−3 SD), his height 154.8 cm (−3 SD) and his head circumference 51.5 cm (−3 SD). This boy presented facial dysmorphic features, including downslanting palpebral fissures, ptosis of the eyelids, microretrognathia, microstomia with dental crowding, a thin upper lip and hypoplastic earlobes. He showed mild webbing of the neck and bilateral clinodactyly of the fifth finger. He was myopic and had astigmatism. He presented with a pronounced thoracolumbar scoliosis with a right-sided thoracic gibbus, requiring bracing. Thoracic and lumbar Cobb angle measured 32° and 39°, respectively. His skin was normal, except from surgical scars and some pinpoint petechiae on the elbow and on the back of his knee. Extensive screening for bleeding diathesis (including thrombocyte aggregation function) was normal. No arteriovenous malformations were detected on hepatic ultrasound. Medical history was negative with respect to anemia, rectal prolapse, intussusceptions, diarrhea or bloody stools. Screening for juvenile polyposis by colonoscopy and gastroscopy are pending.

During the first year of life, his gross motor development was mildly delayed. However, normal results on the Bayley scale of motor and cognitive development were obtained at the age of 24 months. He was following normal school. Cranial ultrasound at birth was normal. No further brain imaging was performed.

3. Methods of detection

A standard metaphase karyotype by G-banding was normal for both the patient and his parents. Fluorescence *in situ* hybridization (FISH) with the probe LSI 22q11, performed as described [16], was normal. However, a *de novo* deletion on chromosome 10q23.2 was detected in the patient by means of comparative genomic hybridization (CGH) using a 105 k oligo array platform (syndrome plus v2 array, OGT CytoSure Syndrome Plus array, OGT Oxford, UK), performed according the manufacturer's instructions (supplementary figure 1). The deleted region spans maximally 22 kb, disrupting the promoter and first non-coding exon of the *BMPR1A* gene, and did not involve a known copy number polymorphism. The proximal and distal breakpoint containing regions were situated between 88,514,385 and 88,535,831, respectively (Fig. 1). This deletion was confirmed in the patient by quantitative PCR (supplementary figure 1), and its presence was excluded in both parents using the same 105 k oligo array platform and by means of quantitative PCR, performed as described [16]. Primers are available upon request. All genome coordinates were according to NCBI human genome build 37 (hg19, Feb 2009).

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4. Gene prioritization

Integrative data analysis strategies have been proposed for the prioritization of genes potentially involved in a given biological process, phenotype, or disease [17, 18], and are an established tool for selecting candidate genes for congenital heart defects [19, 20]. Automated gene prioritization was performed to identify candidate genes for congenital heart defects within chromosome 10q22q23.

For gene prioritization, Endeavour command line version 2.44 (August 2010) was used [17, 18]. Data sources are derived either from Ensembl 44 based on the NCBI build 36 or the corresponding databases. As a training set for CHD, we extracted all 27 non-syndromic cardiac genes from CHDWiki, a collaborative knowledge base on cardiogenetics (http://homes.esat.kuleuven.be/~bioiuser/chdwiki/index.php/CHD:Genes), on December 2010. The training set was complemented with the syndromic genes *JAG1*, *TBX5* and *TBX1*, since haplo-insufficiency of these genes is associated with a high penetrance of CHD (supplementary table 1). First, a leave-one-out cross-validation was performed on the set of these 30 cardiac training genes using all available human models. The area under the receiver operating characteristic curve (AUC) was calculated and used as an estimate of the performance for each model. Only the best performing models with an AUC above 65% were kept for a genome-wide gene prioritization (supplementary table 2). The overall AUC was 93%, suggesting that candidates for CHD would rank on average within the top 7% of prioritized genes. In addition, a heart specific mouse microarray dataset was added, regardless of its performance [20]. Subsequently, genome-wide prioritization was performed. The results of the genome-wide prioritization were used to rank the genes within an imbalanced region.

Delineation of the CHD-related region may be hampered by reduced penetrance for CHD and by platform-related breakpoint discrepancies (e.g. standard karyotyping or microsatellite analysis). Therefore, only CHD-positive imbalances detected by means of array CGH were taken into account to delineate the critical CHD-related region on 10q23. This CHD-related region was downsized to a 700 kb region on 10q23.2 (chr10:88,310,020-89,010,020). This region represented the minimal overlap between the 10q22q23 deletion syndrome and the CHD-positive submicroscopic distal 10q23 deletions, reported by Menko *et al.* [4].

The 22 kb deletion in our patient falls within this CHD-related region (Fig. 1). To tackle the possibility that genes outside this region may independently affect cardiac development, separate *in silico* analyses were performed on the recurrent 10q22q23 deleted region, delineated by LCR3 and LCR4 (chr10:81,610,020-89,010,020), and on the CHD-related region on distal 10q23.2q23.31, defined by the CHD-positive submicroscopic imbalances reported by Menko *et al.* [4] (chr10:86,530,020-91,190,020).

BMPR1A was the highest ranking candidate for congenital heart defects in the three delineated candidate regions. No significant prioritization was obtained for any other gene proximal to LCR4. Other high ranking genes distal to LCR4 were *PTEN*, *ACTA2* and *FAS* (Table 1).

5. Discussion

Congenital heart defects are associated with large 10q22q23 deletions (Table 2). Deletions between LCR3 and LCR4 are associated with CHD in 3 out of 11 cases (27%) [2, 3], one of which additionally carried a 47, XYY aneuploidy. Although the patient's phenotype might have been influenced by this aneuploidy, it is unlikely to have caused the cardiac defect, since CHD are not a common feature in patients with 47, XYY [21]. An AVSD was also reported in a boy with a small embedded 10q23 deletion, disrupting only the *GRID1* gene, 500 kb upstream of *BMPR1A* [3]. The inheritance of this deletion is unknown, thus limiting the interpretation on its pathogenicity. Distal 10q23.2q23.31 deletions, comprising both *PTEN* and *BMPR1A*, manifest cardiac (septal) defects in 5 out of 14 clinically well-characterized patients (36%) [4-6, 9]. A 700 kb critical region for CHD emerges from the data compiled in Table 2 and Fig. 1. The 22 kb deletion detected in our patient, featuring short stature, facial dysmorphism and an AVSD, falls within this region. This deletion only encompasses the promoter and first non-coding exon of *BMPR1A*.

Computed gene prioritization shows that *BMPR1A* is the highest ranking candidate for CHD. BMP signaling is involved in the regulation of cell proliferation, migration, differentiation, and apoptosis, through binding of bone morphogenetic proteins (BMPs) to a heterodimeric complex of two transmembrane receptors, termed BMPR type I and type II. Cardiac-specific deletion of *BMPR1A* (*alk3*) disrupts cardiac morphogenesis in mice, showing ventricular septum, trabeculation and endocardial cushion defects [22]. Conditional inactivation of Alk3 in the atrioventricular (AV) canal myocardium provides evidence that ALK3 signaling is obligatory for the morphogenesis of the AV valves and the annulus fibrosus [23]. This cardiac phenotype is highly consistent with that observed in our patient as well as in patients with larger 10q deletions (AVSD, ASD, VSD and tricuspid insufficiency).

Intragenic *BMPR1A* deletions have been detected occasionally by multiplex ligation-dependent probe amplification (MLPA) in screening surveys for JPS [13, 15, 24]. One of these equally involves the promoter and first non-coding exon, corroborating that the detected deletion interferes with normal human physiology [24].

Table 1
Combined ENDEAVOUR prioritization results. All genes within the minimal critical region (chr10:88,310,020-89,010,020), the recurrent 10q22q23 deleted region (chr10:81,610,020-89,010,020), and the CHD-related region on distal 10q23.2q23.31 (chr10:86,530,020-91,190,020) were ranked towards their potential involvement in CHD development, using 29 known CHD genes (retrieved from CHDWiki) as a training set. The candidate regions comprised respectively 11, 31 and 34 genes. The gene ranking of every dataset was combined in a general ranking. For each gene, the *p*-value represents the probability to observe such a ranking based on similarity with the training set, rather than by chance alone. The highest ranking gene is *BMPR1A*. No significant prioritization was obtained for any other gene within the minimal critical region for CHD.

R	Gene ($N = 11$)	Ensembl ID	*p*-value	*R*	Gene ($N = 31$)	Ensembl ID	*p*-value	*R*	Gene ($N = 34$)	Ensembl ID	*p*-value
1	***BMPR1A***	ENSG00000107779	**0.005**	1	***BMPR1A***	ENSG00000107779	**0.0003**	1	***BMPR1A***	ENSG00000107779	**0.0001**
2	MMRN2	ENSG00000173269	0.359	2	ANXA11	ENSG00000122359	0.068	2	**ACTA2**	ENSG00000107796	**0.002**
3	LDB3	ENSG00000122367	0.427	3	GLUD1	ENSG00000148672	0.088	3	**FAS**	ENSG00000026103	**0.002**
4	SNCG	ENSG00000173267	0.538	4	NRG3	ENSG00000185737	0.110	4	**PTEN**	ENSG00000171862	**0.017**
5	FAM35A	ENSG00000165874	0.648	5	SFTPD	ENSG00000133661	0.116	5	GLUD1	ENSG00000148672	0.127
6	GLUD1	ENSG00000148672	0.737	6	SNCG	ENSG00000173267	0.183	6	SNCG	ENSG00000173267	0.130
7	FAM22A|FAM22D	ENSG00000184923	0.895	7	GRID1	ENSG00000182771	0.183	7	MINPP1	ENSG00000107789	0.224
8	ENSG00000188100	ENSG00000188100	0.899	8	LDB3	ENSG00000122367	0.201	8	LDB3	ENSG00000122367	0.244
9	OPN4	ENSG00000122375	0.914	9	MMRN2	ENSG00000173269	0.260	9	GRID1	ENSG00000182771	0.255
10	ENSG00000151303	ENSG00000151303	0.925	10	TSPAN14	ENSG00000108219	0.315	10	WAPAL	ENSG00000062650	0.310
11	C10orf116	ENSG00000148671	0.963	11				11			

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Table 2
Clinical and molecular details of CHD-positive patients with deletions of 10q22q23 or 10q23.2q23.31. AVSD: atrioventricular septal defect, ID: intellectual disability, H: height, OFC: occipital-frontal circumference, PI: pulmonary valve insufficiency, TI: tricuspid insufficiency.

Reference	Start (kb)	End (kb)	Main features	ID	JPS	Growth	CHD type
10q22q23 deletion syndrome							
Van Bon 2011 patient 2	81,610 (LCR3)	89,010 (LCR4)	Telecanthus, low-set ears, hypertelorism, anteverted nares, flat nasal bridge, large mouth	+	−	OFC p3 H < p3	AVSD
Van Bon 2011 patient 4	81,610 (LCR3)	89,010 (LCR4)	Long face, hypertelorism, radioulnar synostosis, scoliosis, kyphosis, pectus excavatum, café-au-lait spots; **47,XYY**	+	−	OFC & H > p97	TI, PI
Alliman 2010 case 1	81,610 (LCR3)	89,010 (LCR4)	Micrognathia, thin upper lip, hypertelorism, upslanting palpebral fissures, earlobe creases, overfolding ears, arachnodactyly, joint laxity	+	−	NA	PDA
Distal 10q23.2q23.31 deletions							
Salviati 2006	82,004	94,612	Sparse hair, epicanthus, hypoplastic nasal bone, protruding lower lip, small ears, high palate, 1 café-au-lait spot	+	6y	OFC p5-10; H p50	ASD VSD
Delnatte 2006 patient 4[a]	NA	NA	Frontal bossing, depressed nasal bridge, high arched palate, broad thumbs and toes, portal vein atresia; **46,XX,t(2;10)(q31;p15)**	−	18m	OFC > p97	ASD VSD
Menko 2003 patient 1	88,310	91,190	Low-set ears, telecanthus, proptosis, long philtrum, generalized hypotonia	+	3y	OFC > p97	VSD left VCS
Menko 2003 Patient 3	86,530	90,080	Vesicoureteral reflux, cleft palate	+	4y	OFC > p97	VSD
Jacoby 1997[c]	NA	NA	Club foot, broad nasal apex, long philtrum, epicanthus, hypoplastic ears, umbilical hernia, short hands & feet	+	4y	OFC & H < p3	TI
Zigman 1997 patient 2[b]	88,800	98,301	Hypotonia, bilateral club feet	+	+	?	ASD VSD left VCS

[a] Deletion of *PTEN* and *BMPR1A* was found by MLPA and qPCR.
[b] Delineated by microsatellite analysis (maximal deleted region: chr10: 88,799,671-98,300,735, not comprising *BMPR1A*).
[c] Deletion was not molecularly delineated.

Unfortunately, besides the presence of JPS no further phenotypic details for this patient are available. As *BMPR1A* expression is not restricted to cardiac tissue, mutations in *BMPR1A* are more likely to emerge in syndromic rather than non-syndromic CHD. Zhou *et al.* and Friedl *et al.* report on ventricular septal defects or Ebstein anomaly in about 1 out of 5 clinically well-characterized JPS patients with *BMPR1A* mutations [12, 25]. The reduced penetrance for CHD with reported *BMPR1A* mutations and deletions may be induced by other genetic modifiers in the BMP/TGF-β signaling pathway. In distal 10q23, altered gene dosage of contiguous genes such as *PTEN*, *ACTA2* or *FAS*, may contribute to the cardiac pathogenesis. However, the cardiac phenotype induced by cardiomyocyte-specific inactivation of *Pten* in mice [26], seems not to be reproduced in patients with distal 10q23 deletions. Likewise, no thoracic aortic aneurysms or dissections, associated with human *ACTA2* mutations, have been reported in these patients so far [27].

Conditional inactivation of *BMPR1A* in mice disturbs homeostasis of intestinal epithelial regeneration with an expansion of the stem cell population, eventually leading to intestinal neoplasms resembling human juvenile polyposis syndrome [28]. The current deletion is detected in an adolescent boy presenting with short stature, delayed puberty, facial dysmorphism and AVSD, but without signs of JPS at the time present. In addition, none of the 11 patients with the typical 10q22q23 deletion, embracing *BMPR1A*, was reported to have JPS either, although this finding might be biased due to young age.

The current patient shares some of the recurrent dysmorphic features of the 10q22q23 deletion syndrome, such as low-set dysplastic ears and hypertelorism [3]. These features are frequently reported in more distally extending deletions as well, often in association with macrocephaly and macrosomia. Surprisingly, our patient presented with short stature and microcephaly, similar to patient 2 reported by Van Bon *et al.* [3] (Table 2).

In conclusion, this intragenic *BMPR1A* deletion provides further evidence for a pivotal role of *BMPR1A* in the genesis of AV cushion defects in the 10q22q23 deletion syndrome and distal 10q23 deletions. Even in the absence of juvenile polyposis syndrome, sequencing and copy number analysis of *BMPR1A* should be considered in patients with (atrioventricular) septal defects, especially when associated with facial dysmorphism and anomalous growth.

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Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ejmg.2011.10.003.

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