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ABSTRACT

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant predisposition to hamartomatous polyps within the gastrointestinal tract, at high risk for malignant transformation. *BMPR1A* and *SMAD4* loss-of-function variants account for 50% of the cases. More specifically, point mutations and structural abnormalities in BMPR1A lead to a highly

penetrant yet variable phenotype of JPS. Intriguingly, in the developmental disorder caused by a recurrent 10q22.3q23.1 7Mb deletion which includes BMPR1A, juvenile polyps have never been reported. We present the case of a young adult harboring this recurrent deletion, in a context of intellectual disability, ventricular septal defect and severe juvenile polyposis syndrome diagnosed at the age of 25 years, requiring a surgical preventive colectomy. She developed a gastric adenocarcinoma from which she died at the age of 32. We hypothesize that with the current available pangenomic CNV arrays, the diagnosis of 10q22.3q23.1 deletion is often made several years before the onset of the digestive phenotype, which could explain the absence of reports for juvenile polyps. This observation highlights the importance of an active digestive surveillance of patients with 10q22.3q23.1 deletion.

INTRODUCTION

Juvenile polyps are a rare histologic type of digestive hamartoma. They can occur anywhere in the gastro-intestinal tract mucosa from the stomach to the rectum and are isolated in most of the affected individuals (Jelsig et al., 2016). The association of multiple juvenile polyps (typically more than five) defines juvenile polyposis syndrome (JPS). Juvenile polyps can cause bleeding and anemia, and are at risk for malignant transformation, particularly in JPS, positioning JPS as a digestive cancer predisposition syndrome. Unlike isolated juvenile polyps, JPS often results from germline heterozygous genetic variants leading to autosomal dominant transmissions of the disease in families. Two genes have been associated with JPS: *SMAD4* and *BMPR1A*. Both genes combined account for about half of the JPS cases (Aretz et al., 2007). Similar to several other predispositions to digestive polyps and cancer, pathogenic variants act via a loss-of-function (LOF) mechanism, and a second hit in the wild-type allele can occasionally be found within the polyps (Blatter et al., 2015). Both sequence variants and copy number variations leading to loss-of-function alleles have been reported. It is well established that the expression of the disease is highly heterogeneous in affected individuals, in terms of age at diagnosis, symptoms and number of polyps. Despite *BMPR1A* haploinsufficiency being known as a cause of JPS, the penetrance of juvenile polyps in patients with large deletions including *BMPR1A* has been questioned. Notably, in the 7.3Mb 10q22.3q23.1 recurrent deletion syndrome, reported in 15 families within the literature and associated with a syndromic developmental disorder of variable severity, JPS hasn't been described in any patient. Here, we present a patient harboring this recurrent deletion, who developed a severe juvenile polyposis syndrome at the age of 25. We then discuss the seemingly low penetrance of JPS in pediatric patients with 10q22.3q23.1 deletion in the literature.

CLINICAL REPORT

Clinical description

We report a 32 year-old female patient presenting with the association of polyposis coli and a developmental disorder. No known history of either developmental abnormalities or digestive tumors was identified in her family. She was born from healthy non-consanguineous parents, after a full-term uneventful pregnancy. Clinical examination at birth revealed a systolic heart murmur due to a ventricular septal defect. Pediatric follow-up showed delayed psychomotor acquisitions, as well as facial dysmorphic features and convergent strabismus. At the age of 25, diffuse digestive polyposis was diagnosed in a context of iron deficiency anemia associated with digestive pain and diarrhea. Gastroscopy revealed more than 30 polyps ranging from 5 to 20 mm. Colonoscopy revealed 25 sessile or pedunculated polyps ranging from 3 to 15 mm in the rectum and the sigmoid colon, and one 30 mm pedunculated polyp in the left colonic angle. A few polyps were collected and their anatomopathological examination at this point was in favor of adenomas. Therefore, coloproctectomy was performed in order to control the polyposis. Anatomopathological analysis of the excised colic tissues showed no adenomas but refined the diagnosis to juvenile polyps. Follow-up of gastric lesions also identified hamartomas compatible with juvenile polyps. Patient was lost to follow-up for 13 months. She developed a gastric cancer, with peritoneal carcinomatosis at the time of diagnosis, from which she died at the age of 32.

Molecular analysis

After obtaining informed written consent from the patient's legal guardian, we included this patient in our in-house workflow for the molecular analysis of mendelian predisposition to digestive polyposis and colorectal cancer, as recently described (Baert-Desurmont et al., 2018). Briefly, sequencing of *BMPR1A* as well as 9 other genes was performed by targeted NGS on DNA extracted from whole blood sample. Simultaneously to single nucleotide variants (SNVs) detection, we performed copy number variants (CNVs) detection with the CANOES software, which is based on read depth profile comparison to a set of control samples (Backenroth et al., 2014). This approach showed a complete heterozygous deletion

of the *BMPR1A* gene. *PTEN*, which is also located in chr10q23.2, was not involved in this deletion according to CANOES. The deletion was validated by Multiplex Ligation Probe Analysis (MLPA) in the proband. Segregation analysis showed that it was not inherited from the asymptomatic mother, but no sample was available from the father. We hypothesized that a contiguous gene syndrome could explain both the juvenile polyposis and the developmental disorder presented by this patient. We therefore refined the CNV boundaries by array-CGH. Agilent SurePrint 4x180k microarray kit was used with standard protocol. Deletion of the whole BMPR1A gene was confirmed by the identification of a deletion encompassing chr10(hg19):81651077-88906961 (Fig.1). The deleterious nature of the deletion regarding the digestive phenotype was clear since heterozygous loss-of-function mutations in *BMPR1A*, either by point mutations or whole gene deletions, are known to cause juvenile polyposis syndrome (Aretz et al., 2007; Howe et al., 2001). This deletion was not present in general population databases such as the Database of Genomic Variants (DGV) or the Exome Aggregation Consortium (ExAC). On the other hand, twenty similar deletions were reported in the Decipher database (https://decipher.sanger.ac.uk/, lastly assessed 2019-04-23), which gathers CNV data from patients with presumed genetic affections and mostly developmental disorders. Most of the Decipher cases in which parental information was available occurred *de novo* or from an affected parent (Supplementary Table 1). The clinical phenotype of these patients, as well as other patients from the literature, is presented in the discussion. The large size of the deletion (7.3Mb), its absence in control population databases and its apparent enrichment in patients with developmental disorders allowed us to consider this deletion as pathogenic with full contribution to the phenotype, both regarding the digestive and the extra digestive presentation of the proband.

DISCUSSION

We identified a deletion of *BMPR1A* in our proband, in a context of severe gastric and colonic juvenile polyposis, which led to the diagnosis of 10q22q23 recurrent deletion. Of note, it has been observed that gastric polyps were rare in juvenile polyposis caused by alterations in *BMPR1A* (Aretz et al., 2007).

Clinical phenotype associated to 10q22q23 deletion

We systematically reviewed the phenotype of patients harboring a similar 10q22.3q23.1 deletion in both Decipher database (20 patients, Supplementary table 1) and in the literature (15 families, Table 1). Various degree of phenotypic information was available for 12/20 patients within the Decipher database. The most recurrent consistent features included global developmental delay or intellectual disability, delayed language, behavioral abnormalities and facial dysmorphic features. Some of the less commonly reported features seen in more than one proband include talipes equinovarus, generalized hypotonia and teeth abnormalities. Among the twelve patients with available clinical information, digestive polyposis was mentioned in one single patient. The literature has been recently reviewed (Coelho Molck et al., 2017) and comprises 25 patients from 15 families described in 7 studies (Alliman et al., 2010; Balciuniene et al., 2007; Coelho Molck et al., 2017; Petrova et al., 2014; Reddy et al., 2011; Singh et al., 2011; van Bon et al., 2011), including one family with 11 individuals (Balciuniene et al., 2007). Strikingly, none of these patients had had a diagnosis of JPS or even juvenile polyps (Table 1).

Mechanism and candidate genes for the non-digestive abnormalities

Recurrence of deletions with the same boundaries is explained by the mechanism of non-allelic homologous recombination (NAHR), mediated by low copy repeats (LCRs), as seen on the "Segmental Dups." track in Figure 1B. Intriguingly, the amount of reported deletions with boundaries within these LCRs is quite low compared to other NAHR mediated recurrent syndromes. Indeed, Van Bon et al. evaluated its prevalence to 0.016% within their cohort of intellectual disability/multiple congenital abnormality (van Bon et al., 2011), which seems to be much less frequent than other recurrent deletions. It has been proposed that the large genomic distance between the two LCRs was responsible for this quite infrequent rearrangement event. The deletion encompasses 47 genes, including 7 genes flagged by OMIM as involved in Mendelian diseases: *ANXA11, MAT1A, CDHR1, RGR, LDB3, BMPR1A* and *GLUD1*. However, besides *BMPR1A*, none of these genes is known to cause a disease by a heterozygous loss-of-function mechanism. The gene or the minimal region involved in the neurodevelopmental abnormalities in this contiguous gene syndrome is still unknown. Two genes appear to be good candidates since they reach the statistical significance of loss-of-function intolerance as defined by ExAC pLI (probability of loss-of-function intolerance)(Lek

et al., 2016). The first one, *GRID1*, is mainly expressed in the brain and encodes an ionotropic glutamate receptor subunit that has been associated to schizophrenia by GWAS analysis (Treutlein et al., 2009). A small number of truncating variants and deletions are present in population databases (ExAC and DGV, respectively). The second one, *WAPAL*, is ubiquitously expressed, with a central role in chromatin regulation via cohesin positioning on the genome (Busslinger et al., 2017). *WAPAL* is drastically depleted in truncating variants in ExAC despites its high predicted mutability and no deletion of this gene are reported in DGV, suggesting that individuals with loss of function alleles are not included in these control populations, potentially due to a severe pediatric disorder. In addition to our patient, several patients from the literature had heart malformations, notably ventricular and atrioventricular septal defect, patent ductus arteriosus and valvular defects. The association of cardiac abnormalities and 10q22q23 deletions had already been observed, and 2 candidate genes have been proposed. Breckpot *et al.* proposed the implication of *BMPR1A* since they identified a de novo intragenic deletion of *BMPR1A* in a patient with atrioventricular septal defect, short stature, delayed puberty and facial dysmorphic features (Breckpot et al., 2012). However, this clinical presentation does not match JPS caused by loss-of-function variants of *BMPR1A*, questioning the implication of *BMPR1A* heterozygous loss-of-function variants in the cardiac phenotype. *GRID1* has been pointed out as another candidate, as Van Bon *et al.* identified an intragenic GRID1 deletion in a patient with atrioventricular septal defect (van Bon et al., 2011). Yet the inheritance of this CNV was unknown, and the deletion was predicted to potentially result in an in-frame exon skipping. Also, the expression of *GRID1* is very low in the heart according to the GTEx database. Thus, there is no certainty about the mechanism underlying heart defects in 10q22q23 deletions.

The risk of JPS in 10q22.3q23.1 deletion

The risk of juvenile polyposis in 10q22.3q23.1 deletion has been debated. The implication of *BMPR1A* has made several authors anticipate the risk of JPS in their patients (Alliman et al., 2010; Petrova et al., 2014; Reddy et al., 2011; Singh et al., 2011), but the observation of juvenile polyps in carriers had still never been described in the literature (Petrova et al., 2014). We can hypothesize that most patients are currently diagnosed at pediatric age in the context of genetics investigations of a developmental disorder, and that they might be too

young to be symptomatic regarding the digestive presentation. Indeed, most patients in the literature have been evaluated at less than 6 years (Table 1) while the median age at diagnostic in *BMPR1A* related juvenile polyposis has been shown to be 18 year-old (Aytac et al., 2015), but some polyps are sometimes diagnosed within the first decade (Lieberman et al., 2019). However, Balciuniene *et al.* described a three-generation family with numerous individuals carrying the deletion, none of whom being described as with digestive symptoms (Balciuniene et al., 2007), suggesting an incomplete penetrance for polyposis. Alliman *et al.* described a patient carrying a similar deletion, in whom colonoscopy was performed at the age of 17 years 10 month, revealing no polyps. Another patient from the same study underwent esophagogastroduodenoscopy at age 4 months, which was also normal (Table 1). Apart from these two cases, the other reports do not mention any invasive screening for digestive polyps. It is possible that some patients may not have been actively investigated, while some others might have been followed after the initial publication. The identification of another closely related contiguous gene deletion syndrome including *BMPR1A* but also *PTEN* in individuals with severe forms of juvenile polyposis occurring in young infancy (Delnatte et al., 2006), together with the apparent absence of digestive symptoms in children with the recurrent deletion of *BMPR1A* but not *PTEN*, have led some to suggest the requirement of a contiguous deletion of both genes for polyposis to take place (Dahdaleh et al., 2012). However, both the present case report (and the additional patient within the Decipher database) and the clear implication of *BMPR1A* null variants as a major cause of JPS argues that patients with 10q22.3q23.1 recurrent deletion that do not include *PTEN* are at substantial risk for JPS. We propose that the risk of digestive symptoms of these two entities should be stratified. On the one hand, deletions encompassing both genes might lead to a severe pediatric JPS; on the other hand, individuals harboring 10q22.3q23.1 recurrent deletion encompassing BMPR1A but not PTEN are at risk of developing JPS in young adulthood, similar to patients with pathogenic point mutations and structural variants restricted to *BMPR1A*. A recent study provides evidence for a high penetrance of JPS in deletions of the BMPR1A gene (Lieberman et al., 2019). In this study, the authors investigated the clinical consequences of a founder 429 kb deletion encompassing the whole coding sequence of *BMPR1A* in more than 50 individuals from 7 families from of a Bukharin Jewish origin. This analysis showed a full penetrance of polyps in adults, with a high degree of intra- and inter-familial nonallelic variability.

The risk of developing a colorectal cancer in patients with JPS has been estimated between 38% and 68% (Brosens et al., 2007; Campos et al., 2015), and the risk of gastric and duodenal tumors between 10% and 20% (Dunlop et al., 2002). We therefore strongly recommend the implementation of an active digestive surveillance in patients harboring 10q22.3q23.1 deletion. The surveillance protocol may be based on the existing recommendation established in JPS (Achatz et al., 2017; Syngal et al., 2015) including, starting from 15 year-old: (i) a colonoscopy performed annually and deferred up to 3 years if no colonic polyps are found, (ii) upper gastrointestinal endoscopy and (iii) capsule endoscopy for the surveillance of the small bowel.

CONCLUSIONS

We present the first diagnosis of juvenile polyposis syndrome in a patient harboring recurrent 10q22.3q23.1 deletion. Although the penetrance of JPS in 10q22.3q23.1 deletion in still unclear, the greatest caution is required in patients harboring this recurrent CNV, which should trigger an active digestive surveillance.

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FIGURES

Figure 1: Refinement of deletion breakpoints by array-CGH.

A. Array-CGH profile of chromosome 10.

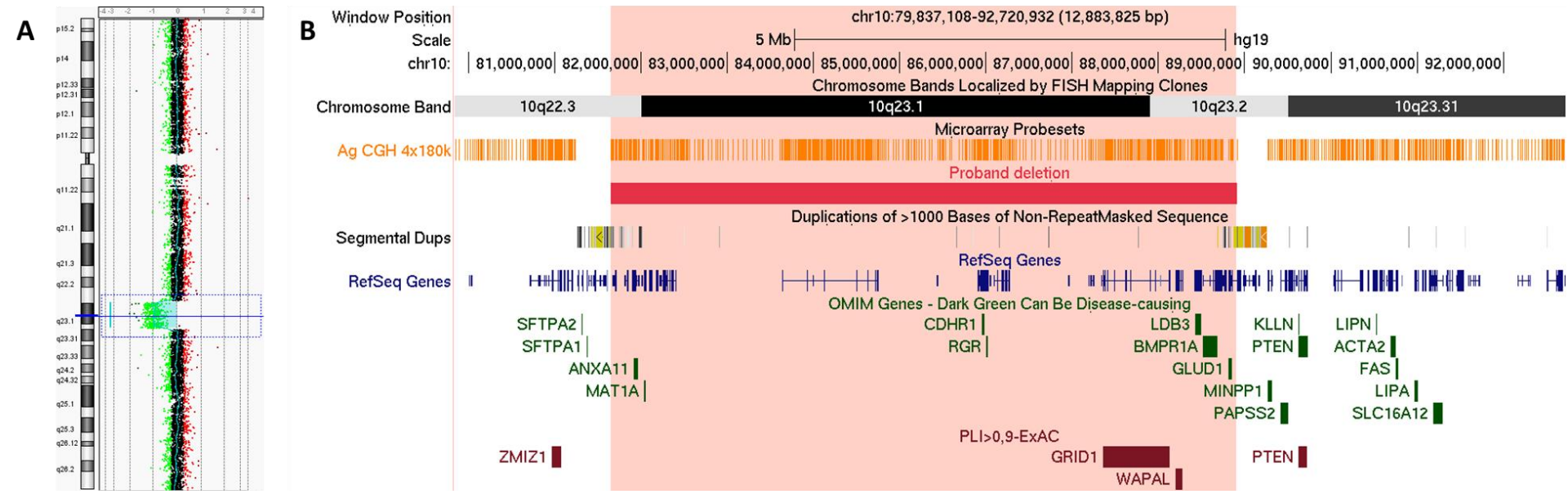
B. Visualization of the deletion in the UCSC genome browser. The reference assembly used is GRCh37/hg19. Deletion boundaries are located in segmental duplications, which regions are depleted of array-CGH probes. The deletion of the patient is highlighted in red. All RefSeq transcripts are merged into a single row, for a clearer visualization. OMIM genes implicated in mendelian diseases are displayed in green (including *BMPR1A* and *PTEN* genes on both sides of the telomeric breakpoint), and genes that are loss-of-function intolerant are displayed in brown (PLI>0,9 ExAC track).

TABLE

Study	Patient ID	Age at evaluation	Number of infividuals	Extra-digestive phenotype	Digestive phenotype	Inheritance
Balciuniene et al. 2007	UM10qDel-01 family	Various ages	11	Proband: developemental delay, minor dysmorphic features, autism. Many affected individuals within family, presenting with a wide spectrum ranging from school difficulties to intellectual disability	None mentioned	Autosomal dominant in family
Balciuniene et al. 2007	JHU10qDel-01	1.5 y	1	Third trimester hydrocephaly due to retrocerebellar cyst. Mild developemental delay	None mentioned	Unknown
Alliman 2010	Case 1	2.6 y	1	Developmental delay, facial dysmorphic features, behavioral abnormalities, PDA	None mentioned	De novo
Alliman 2010	Case 2	17 y	1	Developmental delay, facial dysmorphic features, rectal bleeding	Colonoscopy at 17 years and 10 month: no polyps	De novo
Alliman 2010	Case 3	0.3 y	1	Talipes equinovarus, facial dysmorphic features, bilateral hearing loss	Esophagogastroduodenoscopy at 4 month: no polyps	De novo
Alliman 2010	Case 4	1.6 y	1	Developmental delay, facial dysmorphic features, macrocephaly	None mentioned	De novo
Singh et al. 2011	Patient	5 y	1	Developmental delay, VSD, recurrent middle ear infections	No symptoms at 4 years	De novo
Reddy et al. 2011	Case 2	4 y	1	Developmental delay, facial dysmorphic features	None mentioned	De novo
Van Bon et al. 2011	Patient 1	22 y	1	Developmental delay, facial dysmorphic features, unilateral breast aplasia	None mentioned	De novo
Van Bon et al. 2011	Patient 2	2.5 y	1	Developemental delay, facial dysmorphic features, AVSD, growth delay	None mentioned	Unknown
Van Bon et al. 2011	Patient 3	3.5 y	1	Developemental delay, facial dysmorphic features, behavioral abnormalities, Chiari malformation	None mentioned	De novo
Van Bon et al. 2011	Patient 4	12 y	1	Developmental delay, facial dysmorphic features, overgrowth, macrocephaly, cardiac valvular regurgitations, skeletal abnormalities, cafe-au-lait spots	None mentioned	De novo
Van Bon et al. 2011	Patient 5	5 y	1	Talipes equinovarus, developmental delay, facial dysmorphic features	None mentioned	Inherited from mother
Petrova et al. 2014	-	2 y	1	Unilateral talipes equinovarus, VSD with PFO, cleft palate, facial dysmorphic features	No symptoms at 2 years	De novo
Coelho Molck et al. 2017	-	3 y	1	Tetralogy of fallot, talipes equinovarus, facial dysmorphic features, recurrent upper respiratory infections	None mentioned	Unknown
This study	-	30 y	1	VSD, intellectual disability, facial dysmorphic features	JPS, gastric cancer	Unknown

Table 1: Clinical summary of the 25 patients from the literature with 10q22.3q23.1 deletion with similar breakpoints.

VSD: ventricular septal defect; AVSD: atrioventricular septal defect; PDA: patent ductus arteriosus


A
B
Window Position
chr10:79,837,108-92,720,932 (12,883,825 bp)
Scale
5 Mb
hg19
chr10:
81,000,000
82,000,000
83,000,000
84,000,000
85,000,000
86,000,000
87,000,000
88,000,000
89,000,000
90,000,000
91,000,000
92,000,000
Chromosome Bands Localized by FISH Mapping Clones
Chromosome Band
10q22.3
10q23.1
10q23.2
10q23.31
Microarray Probesets
Ag CGH 4x180k
Proband deletion
Duplications of >1000 Bases of Non-RepeatMasked Sequence
Segmental Dups
RefSeq Genes
RefSeq Genes
OMIM Genes - Dark Green Can Be Disease-causing
SFTPA2
SFTPA1
ANXA11
MAT1A
CDHR1
RGR
LDB3
BMPR1A
GLUD1
MINPP1
PAPSS2
KLLN
PTEN
LIPN
ACTA2
FAS
LIPA
SLC16A12
PLI>0,9-ExAC
ZMIZ1
GRID1
WAPAL
PTEN