Blepharophimosis, Ptosis, Epicanthus Inversus Syndrome: New Report with a 197-kb Deletion Upstream of *FOXL2* and Review of the Literature

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Abstract

Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) is due to heterozygous *FOXL2* intragenic mutations in about 70% of the patients, whereas total or partial gene deletions account for a minority of cases. Alteration of *FOXL2* regulatory elements has been rarely described in patients with BPES. In this study, a prepubertal girl with BPES due to a 197-kb de novo deletion of the regulatory elements upstream of *FOXL2* is reported. This girl presented with additional clinical features such as a soft cleft palate and microcephaly; thus, this copy number variant might have other somatic effects. The present deletion encompasses 2 coding genes (*MRPS22* and *COPB2*), whose homozygous mutations have been associated with microcephaly. In our case, the sequences of the non-deleted allele were normal, ruling out a compound genetic defect. Normal levels of new biomarkers

of ovarian reserve (anti-müllerian hormone, inhibin B) likely indicate an early diagnosis of type 2 BPES, but an evolutive gonadal damage will be excluded only by long-term follow-up. Additional reports of microdeletions upstream of *FOXL2* are needed to better define the underlying genetic mechanism and the related phenotypic spectrum; the ability of the new hormonal markers to predict ovarian function in adolescence and adulthood should be confirmed.

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Approximately 5% of the human genome is structurally variable in the normal population; it may be part of deletions and duplications, collectively referred to as copy number variants (CNVs). CNVs have received considerable attention as a cause for genetic diseases; their pathogenicity has been mainly explained as the result of altered gene dosage [Swaminathan et al., 2012], but CNVs can also harbor regulatory elements or alter the 3D structure

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of the genome, influencing the expression of distantly located genes [Lupiáñez et al., 2015].

The role of regulatory elements in disease etiology is known for a restricted number of genes, associated with about 30 pathologies, including blepharophimosis, ptosis, epicanthus inversus syndrome (BPES; OMIM 110100) [Bhatia and Kleinjan, 2014]. BPES is a rare disease (prevalence <1.0/50,000) characterized by complex eyelid malformations. In females, 2 forms of BPES have been described: in type 1, eyelid abnormalities are associated with ovarian failure; however, this is not the case in BPES type 2 [Zlotogora et al., 1983]. The discrimination between the 2 forms is usually performed at adolescence due to the quiescence of the hypophyseal-pituitary-gonadal axis before puberty [Styne and Grumbach, 2016]. On the contrary, all BPES-affected males have normal testicular function. The gene encoding forkhead transcription factor 2 (*FOXL2*; OMIM 605597) is known to be causative of BPES with an autosomal dominant pattern of inheritance [Crisponi et al., 2001]. In the majority of patients with BPES, *FOXL2* intragenic point mutations are causative, but deletions covering the entire gene have also been reported [Beysen et al., 2009]. Patients with BPES due to deletions upstream and downstream of the transcription unit of *FOXL2*, encompassing regulatory elements, are extremely rare [Beysen et al., 2005; D'haene et al., 2009; Verdin et al., 2013].

Here, a girl with BPES and a de novo 197-kb microdeletion upstream of the transcription unit of *FOXL2* is reported. She also presented with some additional somatic features and mild growth impairment. Non-steroid gonadal hormone assessment suggests preserved ovarian function at least in prepuberty.

Patient and Methods

Clinical Report

The girl was born at 39 weeks of gestation after a second uncomplicated pregnancy and an uneventful delivery from nonconsanguineous Italian healthy parents; family history was unremarkable.

At birth, the following auxological parameters were recorded: weight, 2,580 g (−1.83 SD); length, 47 cm (−1.50 SD), and head circumference, 32 cm (−1.79 SD). Apgar scores were 9 and 10 at 1 and 5 min, respectively. After birth, a soft cleft palate was detected, requiring surgery at 6 months of age. During infancy, hearing screening, cranial ultrasound, echocardiogram, and abdomen ultrasound examinations yielded normal results. When referred to our department for the first time at 3 years, 10/12 months, her gross motor development, receptive and expressive speech, and social skills were normal for age assessed by using adaptive behavioral and descriptive clinical criteria. She had a high forehead,

Fig. 1. Patient with BPES at the age of 3 years and 10 months.

Table 1. Auxological data of the present case

	Chronological age		
	2.2 years	3.8 years	5.9 years
Height	−0.78	−1.60	−1.41
Weight for age	−1.10	−1.20	−1.31
Weight for height	−1.01	−0.75	−0.65
Body mass index	−0.95		−0.66
Head circumference	−2.16	−2.31	−2.03
Midparental height ^a	−0.20	−0.20	−0.20

Values represent SD. ^a 14 familial cases.

arched eyebrows, blepharophimosis, left ptosis, bilateral epicanthus inversus, telecanthus, columella below alae nasi, a long and smooth philtrum, thin upper lip, and a pointed chin (Fig. 1). No functional visual deficit was found.

Methods

SD scores of birth weight, length, and head circumference were calculated according to Italian reference standards [Bertino et al., 2010]; postnatal height and weight were expressed as SD according to WHO standards (<http://www.who.int/childgrowth/software/en/>). Midparental height was calculated using measured parental heights adjusted for female sex: father's height + mother's height/2 minus 6.5 cm. Baseline blood samples were obtained in the fasting state between 8:00 and 9:00 a.m. to assess reserve of ovarian function by anti-müllerian hormone (AMH), inhibin B, LH, and FSH measurements. Normative levels were derived from values reported in a recent extensive review [Fanelli et al., 2018]. Ovarian volume was calculated by the formula $A \times B \times C \times 0.52$ and expressed as SD according to Badouraki et al. [2008].

Array CGH was performed according to standard methods. Sex-matched normal control DNAs were obtained from Agilent, Santa Clara, CA, USA. 500 ng of genomic DNA from both the patient and her parents (test sample) and from the controls (reference sample) were differentially labeled with Cy5-dCTP or

Fig. 2. A Detailed structure of the microdeletion. The genes harbored are indicated by blue boxes; the intervals between the deleted and non-deleted probes of the distal and proximal breakpoints are indicated by striped boxes. Probe and gene positions are referred to GRCh37/hg19. **B** Schematic representation of microdeletions upstream of *FOXL2* in patients with BPES. The numbers 1–9 correspond with those reported in Table 2. The shortest region of deletion overlap (SRO) and *FOXL2* are indicated.

with Cy3-dCTP using random primer labeling according to the manufacturer's protocol (Agilent). The labeling reactions were applied to the array and incubated in an oven for 24 h at 67°C. The array-CGH platform was a 180K SurePrint G3 Human CGH Microarray (Agilent), which has a 13-kb overall median probe spacing (11 kb in Refseq genes). In order to better define the deletion breakpoints, we also used a 180K Sure Print G3 Cancer Microarray (Agilent) that has a similar resolution, but a different probe distribution. The slides were washed and scanned using the Agilent scanner. Identification of individual spots on scanned arrays was performed with the Agilent Cytogenomics dedicated software, as well as filtration, normalization and exclusion of spots with aberrant morphology or high background. Any polymorphisms were analyzed using the Database of Genomic Variants (DGV; <http://dgv.tcag.ca/dgv/app/home>). Sequencing of *FOXL2* (NM_023067.3), mitochondrial ribosomal protein S22 (*MRPS22*; NM_605810) and coatomer protein complex subunit beta 2 (*COPB2*; NM_606990) were performed according to standard methods.

Results

The girl showed slightly reduced height and weight growth patterns; in particular, her height SD resulted –1.2 to –1.4 SD below midparental height. Microcephaly persisted during follow-up (Table 1). Mean ovarian volume was in the low-normal range for age (0.9 mL; n.v. 0.6–2.8 mL). Both AMH (19.3 pmol/L; n.v. 1.9–39.2 pmol/L) and inhibin B levels (9 pg/mL; n.v. <7–33.2 pg/mL) were within normal range; no other biochemical or endocrine abnormalities were found (data not shown).

FOXL2 sequencing demonstrated no intragenic mutations in 5' UTR or the coding sequence. Array-CGH data detected an interstitial deletion in 3q23. The centromeric breakpoint is comprised between probe in position 138,925,589 (not deleted) and probe in position 138,944,012 (deleted), whereas the telomeric breakpoint

Table 2. Genetic and clinical data in patients with BPES due to deletion of upstream regulatory elements

Patient No.	Reference	Deletion position (GRCh37/hg19)	Size, kb	Sex	Age, yrs	Microcephaly	Other clinical signs
Present case	–	138,944,012–139,141,037	197	F	3	Yes	Soft cleft palate, mild facial dysmorphisms, mild growth impairment
1	D'haene et al., 2009 (Pt. D) Verdin et al., 2013 (Pt. A)	138,949,150–138,956,510	7.4	M	7	No	–
2	Verdin et al., 2013 (Pt. B) Beysen et al., 2005 (Pt. BPES 15)	138,912,808–139,012,600	99.8	7 M 7 F	?	No	BPES type 2 II:6, III:2, III:5 e IV:3 had children
3	Verdin et al., 2013 (Pt. C) Beysen et al., 2005 (Pt. BPES 14) ^a	138,867,472–139,048,942	181.5	2 F	?	No	BPES type 2 I:2 three pregnancies, oligomenorrhea at age 40 yrs, and amenorrhea at age 47 yrs, astigmatism; II:1 normal menarche at age 12 yrs and oligomenorrhea at age 38 yrs, strabismus
4	Verdin et al., 2013 (Pt. E) D'haene et al., 2009 (Pt. C)	138,805,920–139,012,140	206	?	?	No	–
5	Verdin et al., 2013 (Pt. F) D'haene et al., 2009 (Pt. A)	138,938,973–139,294,473	356	?	?	?	–
6	Beysen et al., 2005 (Pt. BPES 13)	138,767,142–139,334,105	Max 567 Min 356	F	2	Yes	Stenosis of lacrimal duct, renal reflux
7	Verdin et al., 2013 (Pt. G)	138,745,991–140,393,036	1,647	?	?	?	–
8	Beysen et al., 2005 (Pt. BPES 12)	138,767,142–140,726,314	Max 1,959 Min 860	M	15	Yes	Intrauterine and postnatal growth retardation, ventricular septum defect, contracture of interphalangeal joints, right iris heterochromia
9	Verdin et al., 2013 (Pt. H)	138,741,281–141,762,242	3,021	?	?	?	–

BPES, blepharophimosis, ptosis, and epicanthus inversus syndrome; Pt, patient; yrs, years. ^a 2 familial cases.

is comprised between probe in position 139,141,037 (deleted) and the probe in position 139,157,532 (not deleted) (Fig. 2). The minimum deletion size is 197 kb (GRCh37/hg19 reference map) located 278 kb upstream of *FOXL2*. The deletion was not present in the parents.

No genetic variants were found in the coding genes of the deleted region (*MRPS22* and *COPB2*).

Discussion

A prepubertal girl with a de novo 197-kb microdeletion in 3q23 is reported. She presented with features of BPES associated with microcephaly, soft cleft palate, and some mild facial dysmorphisms (Fig. 1); mild growth impairment was also found. This deletion was unreported in the DGV database collecting data on healthy people. The deleted region harbors 2 protein-coding genes (*MRPS22*, *COPB2*) and the non-protein-coding gene, polled intersex syndrome regulated transcript 1 (*PIRST1*) (Fig. 2).

MRPS22 (OMIM 605810) encodes the 28S subunit protein of mitochondrial ribosomes; *COPB2* codes for a subunit of the Golgi coatomer complex, essential for Golgi budding and vesicular trafficking [De Baere et al., 1998].

The 3q23 deletion maps 278 kb upstream of *FOXL2*, the only gene whose heterozygous loss of function is known to cause BPES [Beysen et al., 2009]. Expression of *FOXL2* is tightly regulated by distant *cis*-regulatory elements located both upstream and downstream of the transcription unit [Beysen et al., 2005]. The existence of 5' regulatory elements was postulated even before the cloning of this gene since the breakpoints of 3 translocations in patients with BPES were found 130, 160, and 171 kb upstream of *FOXL2*, respectively [De Baere et al., 2000; Praphanphoj et al., 2000; Crisponi et al., 2004]. To date, a total of 9 microdeletions upstream of *FOXL2* was described in both familial and in de novo cases of BPES (Table 2) [Beysen et al., 2005; D'haene et al., 2009; Verdin et al., 2013]. These deletions range from 7.4 kb to ~3 Mb; the shortest region of deletion overlap (SRO) involves a

Fig. 3. Schematic representation of microdeletions characterized by molecular techniques in patients with BPES and microcephaly. The relative references are reported. Deletion sizes were all converted to GRCh37/hg19.

7.4-kb segment located 283 kb 5' to *FOXL2* (Fig. 2). This 7.4-kb deletion is sufficient per se to cause BPES because it was deleted in a 7-year-old sporadic male with the classic phenotype [D'haene et al., 2009]. In our case, the deletion encompasses SRO (Fig. 2), while no genetic variants were detected in the *FOXL2* transcription unit. Thus, the girl is a very rare patient with BPES due to a deletion of upstream regulatory elements (Table 2).

Some of her clinical features – such as soft cleft palate and microcephaly – may suggest that the 197-kb microdeletion may have other somatic effects besides BPES. Cleft palate was never reported in the other few patients sharing 5' *FOXL2* deletions (Table 2). Indeed, cleft palate and BPES have been described in 2 cases, both carriers of *FOXL2* intragenic mutations (family *FOXL2_00227* and patient *FOXL2_00222*) [Beysen et al., 2009], but additional reports are needed to establish whether this finding is an independent feature or a rare consequence of the altered *FOXL2* expression. Microcephaly was found in our case and 2 other patients with deletion of upstream regulatory elements (patient 6 and 8 in Table 2). It has also been described in about 20 patients with BPES; however, it has never been associated with *FOXL2* intragenic mutations, only with 3q23 deletions encompassing the gene [de Ru et al., 2005; D'haene et al., 2010; Dean et al., 2014]. Patients without microcephaly but with overlap-

ping deletions have also been described [de Ru et al., 2005; D'haene et al., 2010].

The 2 genes in the deleted region, *MRPS22* and *COPB2*, may have a role in causing microcephaly. *MRPS22* homozygous gene alterations have been associated with a single case of Cornelia de Lange-like phenotype, where microcephaly was reported along with other clinical signs [Smits et al., 2011]. In addition, antenatal mitochondrial disease caused by homozygous *MRPS22* mutation has been reported in 3 children born to the same set of consanguineous parents, who presented with antenatal skin oedema, hypotonia, cardiomyopathy, and tubulopathy [Saada et al., 2007]. A homozygous recessive variant in *COPB2* was identified in a pedigree with 2 affected siblings showing primary microcephaly, severe developmental delay, failure to thrive, cortical blindness, and spasticity [DiStasio et al., 2017]. Even if the phenotypic pictures of these patients are completely different from those of our case, sequencing of *MRPS22* and *COPB2* was performed to exclude point mutations in the non-deleted allele. No genetic variants were found; thus, these genes are unlikely involved in our patient's microcephaly. Nothing is known about the function of the non-protein-coding RNA, PIRST1.

It is worth noting that focusing on those patients whose imbalances were analyzed by molecular techniques, the present deletion is the smallest one, and it par-

tially overlaps all the others (Fig. 3). Thus, it represents a bridge between the more proximal and the more distal deletions. It could be hypothesized that this small region may be involved in the development of microcephaly through a control of 3D genome structure.

In females, one of the challenges of BPES is the establishment of genotype-phenotype correlations, mainly with respect to the ovarian phenotype. A clear differentiation between type 1 and type 2 BPES is usually performed at adolescence because in prepubertal girls, gonadotropin and steroid hormone levels are extremely low or undetectable [Styne and Grumbach, 2016], so invasive endocrine evaluation was used to reach early diagnosis of type 1 BPES [Ogata et al., 1998]. Recently, Lunding et al. [2015] demonstrated that low levels of AMH (<-2 SD) are able to predict failure to enter puberty or imminent premature ovarian failure in girls with Turner syndrome, while ongoing ovarian function was shown in early adulthood by patients with AMH within the reference range [Lunding et al., 2015]. To the best of our knowledge, we evaluated this new ovarian marker in a prepubertal girl with BPES for the first time. The results suggested an early diagnosis of type 2 BPES. Normal ovarian volume and normal inhibin B levels reinforced this hypothesis. In fact, low levels of inhibin B demonstrated 100% sensitivity and specificity for the detection of impaired pubertal development due to hypogonadotropic hypogonadism [Binder et al., 2015]. Albeit present hormonal data in a single girl and their predictive value must be confirmed in additional patients, they agree with previous reports, showing that women with BPES due to deletion of upstream regulatory elements showed normal ovarian function (patients 2 and 3, Table 2). Finally, an evolutive gonadal damage cannot

be excluded; thus, a long-term follow-up with serial measurements of the new ovarian markers is needed before reaching definitive conclusions.

Additional reports of microdeletions upstream of *FOXL2* will permit to better define the underlying genetic mechanism and related phenotypic spectrum as well as the true predictive values of the new hormonal markers of ovarian function during childhood.

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Statement of Ethics

Informed consent and the permission for the publication of the accompanying images were obtained from the parents before any diagnostic or therapeutic intervention. The study was conducted according to the Declaration of Helsinki.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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