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RAPID COMMUNICATION

A novel mutation in *CDH11*, encoding cadherin-11, cause Branchioskeletogenital (Elsahy-Waters) syndrome

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Abstract

Cadherins are cell-adhesion molecules that control morphogenesis, cell migration, and cell shape changes during multiple developmental processes. Until now four distinct cadherins have been implicated in human Mendelian disorders, mainly featuring skin, retinal and hearing manifestations. Branchio-skeleto-genital (or Elsahy-Waters) syndrome (BSGS) is an ultra-rare condition featuring a characteristic face, premature loss of teeth, vertebral and genital anomalies, and intellectual disability. We have studied two sibs with BSGS originally described by Castori et al. in 2010. Exome sequencing led to the identification of a novel homozygous nonsense variant in the first exon of the cadherin-11 gene (*CDH11*), which results in a prematurely truncated form of the protein. Recessive variants in *CDH11* have been recently demonstrated in two other sporadic patients and a pair of sisters affected by BSGS. Although the function of this cadherin (also termed Osteoblast-Cadherin) is not completely understood, its prevalent expression in osteoblastic cell lines and up-regulation during differentiation suggest a specific function in bone formation and development.

This study identifies a novel loss-of-function variant in *CDH11* as a cause of BSGS and supports the role of cadherin-11 as a key player in axial and craniofacial malformations.

KEYWORDS

Branchioskeletogenital, Elsahy-Waters, CDH11, Cadherin-11

1 | INTRODUCTION

Cadherins are Ca2+-dependent, homophilic, cell-adhesion molecules expressed in many different embryonic and adult tissues (Yagi & Takeichi, 2000). Their function is important for the dynamic regulation of adhesive contacts that are associated with diverse morphogenetic processes (Gumbiner, 2005). To date, different classical cadherins are associated to genetic disorders in humans. Germline mutations in

CDH1, encoding E-cadherin, cause at least three distinct conditions, namely hereditary diffuse gastric cancer, nonsyndromic cleft lip/palate and blepharocheilodontic syndrome, whose phenotypic heterogeneity recapitulates the pleiotropic nature of these molecules (Guilford et al., 1998; Vogelaar et al. 2013; Ghoumid et al., 2017; Kievit et al. 2018). Biallelic variants in *CDH3*, the gene encoding P-cadherin, cause hypotrichosis with juvenile macular dystrophy (HJMD, MIM 601553) and ectodermal dysplasia, ectrodactyly, and macular dystrophy (EEM, MIM 225280). Germline variants in *CDH23* have been identified in people with Usher syndrome 1D (MIM 601067) and nonsyndromic autosomal-recessive deafness (MIM 601386), and more recently in both familial and sporadic pituitary adenoma (Schultz et al., 2011; Zhang et al., 2017).

Branchioskeletogenital syndrome (BSGS), also termed Elsahy-Waters syndrome (OMIM 211380), was first described in three sons of first-cousin parents by el-Sahy and Waters (1971). The condition was subsequently reported in two sib pairs from consanguineous parents (Balci et al., 1998; Castori et al., 2010). A further sporadic patient is considered affected by the same condition (Shafai et al., 1982). The phenotype of BSGS is striking and features typical craniofacial anomalies (i.e. brachycephaly, extreme hypertelorism, blepharochalasis, underdeveloped midface and facial asymmetry), premature tooth loss with radicular dentin dysplasia and dentigerous cysts, vertebral fusions, hypospadias and intellectual disability (Castori et al., 2010). In 2017, while the present manuscript was in preparation, two groups reported homozygous variants in the cadherin-11 gene (*CDH11*) in two sporadic patients and a couple of sibs affected by BSGS (Taskiran et al., 2017; Harms et al., 2018).

Here, we report the identification by exome sequencing of the genetic cause of BSGS in the family originally described by Castori et al. (2010).

2 | METHODS AND MATERIALS

2.1 | Patient samples

This study was carried out using stored samples from a previously described family (Castori et al., 2010). After institutional review board approval of this study and informed consent from the family, we collected blood samples from the patients and their parents, and extracted DNA using standard procedures.

2.2 | "Whole" exome sequencing

Exome capture was accomplished using the SureSelect XT Clinical Research Exome kit (Agilent Technologies, Santa Clara, CA) according to SureSelect QXT Target Enrichment for Illumina Multiplexed Sequencing protocol, and sequencing was performed using the Illumina NextSeq500 platform (Illumina, San Diego, CA) at an average coverage depth of 70x.

2.3 | Data generation and analysis

The quality of the generated sequences (a.k.a. reads) was checked using FastQC. Reads were eventually trimmed with Trimmomatic, before being aligned to the hg19 version of the human reference genome with Bowtie2. Mapped reads were recalibrated based on quality constraints and then processed by GATK ver. 3.7 for the variant calling analytical step. Variants (SNVs and short insertion/deletions) were annotated by ANNOVAR considering the RefSeq transcriptome as the reference annotation system. DbSNP, ClinVar and ExAC were queried to retrieve allele frequency information and clinical associated phenotypes for known variants. Variants underwent a series of consecutive filtering steps. Interesting variants were those falling in exons or affecting canonical splicing sites. Common (MAF > 0.01) and synonymous variants were discarded. Finally, only segregating variants among relatives were selected for further *in silico* validation. The R TEQC package was used for quality assessment of target regions.

2.4 | Mutation validation

Primers were designed to confirm the homozygous variant identified in exon 1 of *CDH11* (CDH11_ex1F: 5'- AGCAAGACCACCGTACAGTT -3' and CDH11_ex1R: 5'- TTCTGGCCACAGACGACTATT -3'). Sequencing was performed using BigDye Terminator V.1.1 on an ABI 3130 (Applied Biosystems, Carlsbad, CA). PCR conditions are available on request. Nucleotide numbering of CDH11 variant was based on reference sequence NM_001797.3 according to recommendations for the description of sequence variants of the Human Genome Variation Society (http://www.HGVS.org/varnomen).

3 | RESULTS

3.1 | Clinical data

The complete clinical features of the affected sibs are described in Castori et al. (2010). Follow-up after 7 years indicated that their phenotypes had remained unchanged. In particular, the brother, now aged 52 years, appeared with the typical facial gestalt consisting in brachycephaly, facial asymmetry, right head tilting, high forehead, broad nose with bulbous tip, prominent mandible secondary to an underdeveloped midface and extensive premature tooth loss (Figure 1B). Skeletal abnormalities in the male included vertebral body fusion of C2-C3 and posterior arch fusion of L2-L3, which were lacking in his 51-year-old sister who displayed microcephaly. She had a mild intellectual disability. Both lived with their parents, without occupational activity. Important additional findings were mixed hearing loss and radicular dentin dysplasia (Figure 1C) associated with recurrent dentigerous cysts, and hypospadias in the male. The dental problems inhibited both to chew solid foods. Several surgeons indicated after careful clinical and X-ray evaluation that implants were not possible. Their skin was thick and remarkably furrowed (pachydermia), especially over the forehead and the glabella (Figure 1B). Progressive alopecia was evident over the scalp in both.

3.2 | Molecular investigations

In search for the causative gene, we performed exome sequencing in the affected sibs and their parents (Figure 1A). Sequencing reads

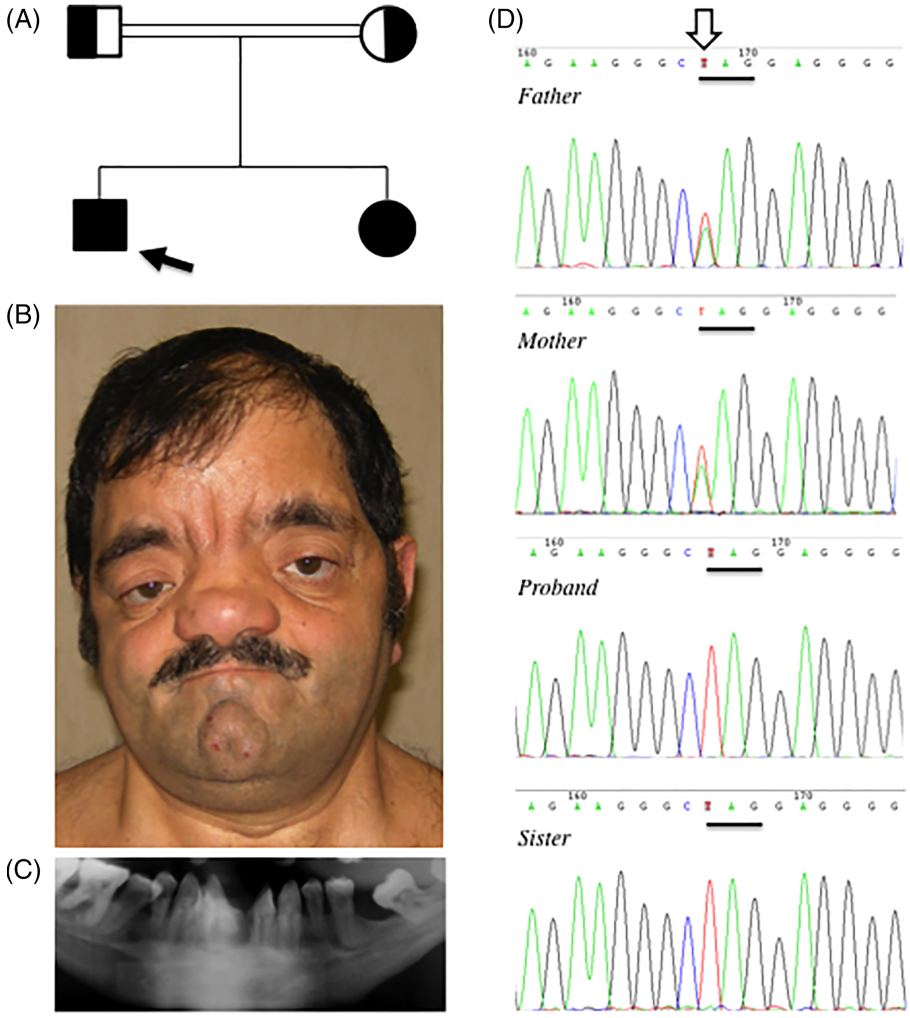

FIGURE 1 (A) Simplified pedigree and structure of the studied family with BSGS. Square and circles indicate males and females, respectively. Solid symbols indicate affected brother (proband, arrow) and sister, born to consanguineous (double horizontal bars) healthy parents. (B) Typical craniofacial dysmorphism observed in the proband at the age of 46 years include asymmetric face with midface hypoplasia, broad forehead, bitemporal narrowing, hypertelorism, proptosis, asymmetric blepharochalasis of the upper eyelids, broad nose with depressed nasal ridge and pointed chin. The skin is thick and furrowed, while alopecia is evident over the scalp. (C) Detail of orthopanoramic radiography in the proband shows mandible bone hypoplasia, bone dental loss, malformed teeth and alveolar bone resorption. (D) Electropherograms obtained by Sanger sequencing to confirm the *CDH11* variant (c.127A>T) in all family members. The open arrow at the top of the figure indicates the mutated residue (Adenine to Thymine), while the line below the letters defines the coding-frame codon AAG (Lys) changing into the stop codon TAG (p.Lys43*) in the affected sibs [Color figure can be viewed at wileyonlinelibrary.com]

statistics and coverage information are reported in Supplementary Table S1. 28,037 exonic or splicing variants were found in at least one family member, of which 14,099 were not synonymous. 3,435 variants were rare or novel (MAF ≤ 0,01 or "NO MAF") in dbSNP ver. 150 and ExAC database, but only 2 variants segregated within the family, being homozygous in the probands and heterozygous in their parents, fitting with the parents being consanguineous. Among these, only one variant had not been reported before: c.127A>T. This is a homozygous nonsense variant, which affects the first exon of the *CDH11* gene and is deemed to cause a very early prematurely truncated Cadherin-11 protein, p.Lys43*. The variant was covered with a high sequencing quality (*phred* value), exceeding 1500 in both siblings. A table containing all putative disease causing variants is provided in Supplementary Table S2. We interrogated the Genome Aggregation Database (gnomAD) database (http://gnomad.broadinstitute.org/) (v2 accessed 26.4.2017) of 126,136 exomes and 15,496 genomes and we did not find any heterozygous or homozygous carrier of the c.127A>T in *CDH11*. Segregation analysis by Sanger sequencing confirmed the affected sibs to be homozygous and their parents were heterozygous for the variant (Figure 1D).

4 | DISCUSSION

Cadherins are integral membrane proteins that mediate calcium-dependent cell-cell adhesion, composed of a large N-terminal domain with extracellular repeats (EC1-5), a single membrane-spanning domain, and a small, highly conserved C-terminal cytoplasmic domain (Yagi & Takeichi, 2000). Their function is important for intercellular remodelling that occurs during several processes such as

TABLE 1 Comparison between Blepharocheilodontic and Branchioskeletogenital (or Elsahy-Waters) syndromes

Characteristics	Blepharocheilodontic syndrome		Branchioskeletogenital syndrome
Causative gene(s)	*CDH1*	*CTNND1*	*CDH11*
Protein(s)	Cadherin 1	Catenin Delta 1	Cadherin 11
Inheritance	AD	AD	AR
Molecular mechanism	LoF *Dominant negative*	LoF *Haploinsufficiency*	LoF *Haploinsufficiency*
Number of distinct mutations	11	6	4*
Number of families (patients)	18 (26)	6 (10)	4 (6)
Asymmetric face	-		+++
Thick highly arched eyebrows	-		+++
Euryblepharon	+++		+++
Lagophthalmos	+++		++
Proptosis	-		+++
Eyelid coloboma	-		+
Distichiasis	+++		-
Hypertelorism	+++		+++
Midface hypoplasia	-		+++
Broad nose (bifid tip)	-		+++
Cleft lip/Palate	+++		-
Bifid uvula	-		++
Hypodontia	+++		++
Delayed dentition	+++		++
Abnormal crown form	+++		++
Dental cysts	-		+++
Early tooth loss	-		+++
Prognathism/malocclusion	-		+++
Malformed ears	++		-
Sparse hair	++		++
Skin furrowing (face)	-		+++
Hypospadias	-		+++
Vertebral fusions	-		+++
Intellectual disability	-		+++
Neural tube defect	+		-

Legend: absent (-); present in less than 1/3 (+), half (++), or more than 2/3 (+++); AD: autosomal dominant; AR: autosomal recessive; LoF: loss-of-function; *all in the homozygous state.

morphogenesis, tissue homeostasis, and recovery from injury (Gumbiner, 2005). Atypical (or type II) cadherins, such as cadherin-11, differ from classical cadherins based on their lack of the histidine-alanine-valine (HAV) sequence from the EC1 repeat and exert their function based on preferential tissue expression (Perez & Nelson, 2004).

Several studies outlined the role for cadherin-11 in development and morphogenesis, especially relevant though its preferential early expression in several mesodermal structures, especially the head mesoderm, of mouse embryos (Kimura et al. 1995). All mesenchymal cells throughout the embryo, as well as mesenchymal stem cells originating from the pre-chordal and paraxial mesoderm show elevated expression of cadherin-11 (Alimperti & Andreadis, 2015). Cadherin-11 is particularly expressed in osteoblastic cell lines, and the up-regulation during differentiation suggests a specific function in bone development and maintenance (Mbalaviele et al. 2006; Marie et al. 2014). Moreover, mice genetically deficient of *Cdh11* exhibit widened cranial sutures and develop osteopenia, indicating a functional defect in bone-forming cells (Kawaguchi et al. 2001). In our patients with homozygous truncating variants in *CDH11* the skeleton is severely involved. Indeed the cranial deformities with underdeveloped midface, axial defects (mainly vertebral), and alveolar bone resorption can be considered core features of BSGS. The milder phenotype in mice may to some extend be explained by partial redundancy between *Cdh11* and the other cadherin mainly expressed in bone tissue, N-cadherin (or *Cdh2*). In fact, compound *Cdh2* heterozygous/*Cdh11* null mice show a more pronounced bone phenotype than single *Cdh11* null mice (Di Benedetto et al. 2010). Further studies into the pathogenesis and the interplay of the different co-expressed cadherins in bone turnover and formation will be useful. It is noteworthy that cadherin-11 was found highly expressed in developing mouse brains and its differential expression in central synaptic junctions (mainly in the hippocampus) might

explain altered behavioural responses observed in these mutant animals (Kimura et al. 1996; Suzuki et al. 1997; Manabe et al. 2000). This might mirror the neurodevelopmental phenotype in BSGS.

Some of the features observed in BSGS such as alopecia and skin furrowing, indicate a role for cadherin-11 in ectodermal derivatives and hair cycling. The combination of skeletal and ectodermal anomalies is not unique to *CDH11* among the phenotypes associated with cadherin abnormalities. In addition to *CDH3*, whose variants cause ectodermal dysplasia associated with ectrodactyly, heterozygous changes in the cadherin-catenin complex components *CDH1* and *CTNND1* have been identified in blepharocheilodontic (BCD) syndrome, an ultrarare autosomal dominant condition characterized by eyelid (euryblepharon, lagophthalmia and distichiasis), cleft lip/palate, and dental anomalies (Ghoumid et al., 2017; Kievit et al., 2018). Although BCD syndrome and BSGS are non-overlapping disorders, some parallels exist in the craniofacial morphology and in the palpebral abnormalities (Table 1). In the present probands laxity of the periorbital soft tissue is appreciable (see Figure 1A and Castori et al., 2010) and cleft uvula was a feature in one. Furthermore, a role for cadherin-11 as a novel regulator of extracellular matrix synthesis was proposed based on reduced collagen and elastin content in Cdh11(-/-) mouse tissues, such as the aorta, bladder and skin (Row et al. 2016). In BSGS, only the redundant facial skin may be an indication for a connective tissue abnormality.

While the present manuscript was in preparation, two studies reported three families with four subjects affected by BSGS and loss-of-function variants in *CDH11* (Taskiran et al., 2017; Harms et al., 2018). The clinical overlap between all reported patients is striking outlining the homogenous phenotype of BSGS linked to *CDH11* variants. All variants detected until now were homozygous, truncating, and inherited from healthy carrier parents. These data support loss-of-function of cadherin-11 as the pathogenic mechanism at the basis of the disease. Further studies are warranted to explore whether indeed the phenotypic spectrum of *CDH11* variants is this limited, and whether compound heterozygous or other variants may cause a different phenotype.

In summary, we describe a novel *CDH11* loss-of-function variant causative for BSGS. Currently available data indicate that mutations in *CDH11* are invariably associated with mild intellectual disability, behavioural disturbances, distinctive craniofacial signs, axial skeleton defects and hypospadias in males, together described as BSGS or Elsahy-Waters syndrome. The data outline Cadherin-11 as a key player in morphogenesis, especially in craniofacial development.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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