Chromosome 1p31.1p31.3 Deletion in a Patient with Craniosynostosis, Central Nervous System and Renal Malformation: Case Report and Review of the Literature

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Key Words

Chromosome 1 · Craniosynostosis · Deletion

Abstract

Interstitial deletions in the short arm of chromosome 1 are infrequent. We report a female with a 1p31.1p31.3 deletion and cloverleaf skull, who presented with renal and central nervous system malformations, cleft palate, severe ocular anomalies, and cutis laxa, in addition to the previously described clinical data present in other cases with deletions encompassing this region, such as developmental delay, seizures, round face with a prominent nose, micro/retrognathia, half-opened mouth, short neck, hand/foot malformations, hernia, congenital heart malformations, and abnormal external genitalia. The deletion spanned ~18.6 Mb and included a total of 68 OMIM protein coding genes. We have reviewed 17 cases previously described in the literature and in DECIPHER involving the chromosomal region 1p31.1p31.3. Only 3 of these affect the whole region, 9 are partial deletions of this region, and 5 are much smaller deletions. Taking

into account the MORBID ID and the haploinsufficiency score of the genes, we go on to propose which genes may explain particular clinical features observed in the patient. *IL23R* may be responsible for the craniosynostosis, *FOXD2* for the renal anomalies, *LHX8* for closure defects of the palate, and *ST6GALNAC3* for skin anomalies. In summary, we have identified a chromosome 1p31.1p31.3 deletion in a patient with an atypical presentation of craniosynostosis amongst other more typical features observed in individuals with similar deletions.

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Genomic rearrangements refer to alterations in the genome such as duplications, deletions, insertions, inversions, and translocations. They can cause a phenotype by various molecular mechanisms, including the alteration in the copy number of genes sensitive to dosage, by dis-

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Fig. 1. Genetic analysis of the proband. **A** The location of the identified deletion (§) and the chromosome 1p31 deletions reported in the literature as well as in the DECIPHER database: Bene et al., 1978 (a), Lai et al., 1991, patient 2 (b), Sivasankara et al., 1997 (c), Campbell et al., 2002, and Lu et al., 2007, patient 1 (d), Campbell et al., 2002, and Lu et al., 2007, patient 2 (e), Shaw-Smith et al., 2004 (f), Chen et al., 2011 (g), Ji et al., 2014 (h), Zinner and Batanian, 2003, and Labonne et al., 2016 (i), Petersen and Warburg, 1987 (j), Lai et al., 1991, patient 1 (k), Mircher et al., 2003 (l), Gillberg and FitzPatrick, 2010 (m), Tassano et al., 2015 (n), DECIPHER 1927 (o), DECIPHER 250300 (p), and DECIPHER 277832 (q). The colors of the deletion blocks correspond to the colors of the column heads for each patient in online supplementary table 3. Tel = Telo-

mere; Cent = centromere. **B** The Infinium Cyto-SNP-850K Bead-Chip (Illumina) showing the log₂ ratio data. The deletion is shown between the dashed lines and corresponds to hg19 coordinates 63,871,758–82,484,133 in 1p31.1p31.3. **C** Coffalyser plot of the custom-designed chromosome 1p31.1p31.3 MLPA, confirming the presence of the deletion. Normal peaks were classified as having a ratio of 0.7–1.3 and deletions were classified as <0.7. The deletion includes *EFCAB7*, *JAK1*, *SGIP*, *PTGER3*, *LHX8*, *ELTD1*, and *LPN2* probes, whilst probes for *NFIA* and *USP1* (telomeric to the deletion) as well as *SMD113* and *DDAH1* (centromeric to the deletion) are present in 2 copies. Asterisks represent autosomal control probes.

rupting a gene causing its loss of function, by unmasking a recessive allele, or by affecting a region subject to imprinting.

With the exception of the 1p36 syndrome (MIM 607872), interstitial deletions affecting the short arm of chromosome 1 are rare, with only ~20 cases reported in the literature [Labonne et al., 2016]. Three of these are deletions encompassing the whole 1p31.1p31.3 region

(fig. 1A, a–c), whilst 9 are partial deletions of this region (fig. 1A, d–l) and constitute the 1p32p31 syndrome (MIM 613735). The most frequently associated clinical findings are global developmental delay, central nervous system (CNS) malformations, dysmorphic features, and urinary tract malformations. Individuals with partial deletions present with a phenotype similar to those with a deletion of this entire region [Bene et al., 1979; Lai et al., 1991;

Sivasankaran et al., 1997; Zinner and Batanian 2003; Shaw-Smith et al., 2004; Gillberg and FitzPatrick, 2010; Chen et al., 2011; Ji et al., 2014; Tassano et al., 2015; Labonne et al., 2016]. There are also 5 cases with significantly smaller deletions, all presenting with a milder phenotype (fig. 1A, m–q).

Some of the phenotypic features have been previously associated to the haploinsufficiency of the nuclear factor I/A gene (*NFIA*, MIM 600727), mainly corpus callosum hypoplasia/absence, hydrocephalus/ventriculomegaly, and urinary tract malformations, since the *Nfia* knockout mice showed agenesis of corpus callosum, communicating hydrocephalus, female subfertility, and male sterility [das Neves et al., 1999; Lu et al., 2007]. But, more recently, a single patient with craniosynostosis and a family with phenotypic 1p32.p31 syndrome and craniosynostosis were found to have microdeletions which affected only *NFIA*, thus suggesting that this gene was also important in craniofacial development [Rao et al., 2014; Nyboe et al., 2015].

Here, we report the identification of an ~18.6-Mb deletion of chromosome 1p31.1p31.3 involving the loss of 68 genes in a patient referred with craniosynostosis and multiple congenital malformations. We subsequently review the available literature regarding chromosome 1p31.1p31.3 deletions.

Clinical Report

A 27-day-old infant born to nonconsanguineous parents, who have an older healthy son, was referred for genetic testing. The mother was 19 years old at the time of birth. Prenatal ultrasound revealed polyhydramnios, intrauterine growth restriction, hydrocephalus with enlargement of lateral ventricles, a prominent mid-frontal line, exophthalmos, hypotelorism, and micrognathia. Amniocentesis was performed, and a normal female karyotype was obtained. The family refused further testing.

An uneventful caesarean section was performed at 38 weeks of gestation. Birth weight 2,590 g (P3–P10), length 45 cm (P10–P25), and head circumference 35.5 cm (P75–P90). Physical examination revealed a cloverleaf skull, hypotelorism and severe exophthalmos with absence of eyelids, ectopia lentis, sclerocornea, cleft palate, low-set ears, and cutis laxa. The hemogram, chemical analysis, and arterial blood gases were normal. Radiographic analysis showed craniosynostosis. Brain echography revealed biventricular enlargement with collapse of the third and fourth ventricles, small posterior fossa, and focal intracerebral hemorrhage in the left temporal lobe. Computed axial brain tomography showed pansynostosis with a cloverleaf skull, including sutures at the base of the cranium; hypotelorism, and obstructive hydrocephalus with enlargement of the temporal regions (fig. 2). MRI of the brain revealed severe enlargement of temporal ventricles with 2 hemorrhagic cortical foci in the right temporal and frontal regions, and

Fig. 2. Computed axial tomography image of the proband at 28 days, anterior (A) and posterior projection (B) and axial section (C, D) showing cranial asymmetry with a cloverleaf-shaped skull.

subcortical subacute hemorrhage. Echocardiogram was normal. Renal ultrasound assessment showed bilateral hypoplasia with abnormal cortical echogenicity and altered corticomedullary differentiation.

The patient was referred for array analysis and screening of craniosynostosis-related genes. The girl died at 7 months of age after a respiratory tract infection.

Materials and Methods

DNA from the patient was screened for mutations in the craniosynostosis genes as previously described [Paumard-Hernández et al., 2015] and for chromosomal rearrangements using the Infinium Cyto-SNP-850K BeadChip (Illumina), according to the manufacturer's instructions and analyzed on an Infinium iScan™ System platform (Illumina). The data was analyzed using the GenomeStudio™ software (Illumina). The deletion was confirmed by a chromosome 1p31 custom-designed MLPA, including 11 probes spanning the region and 3 control probes (online suppl. table 1; for all suppl. material, see www.karger.com/doi/10.1159/000452609). The data was analyzed using the Coffalyser MLPA analysis program (MRC-Holland).

Results

The patient was referred for genetic testing of craniosynostosis-related genes. No mutations or deletions were detected in *FGFR1*, *FGFR2*, *FGFR3*, *TWIST*, *EFNB1*, and

TCF12 [Paumard-Hernández et al., 2015]. Subsequently, a SNP-array was performed.

A deletion of chromosome 1p31.1p31.3 was detected using the CytoSNP-850K array, hg19:1(63,871,758–82,484,133)×1 (fig. 1B). This ~18.6-Mb deletion included 68 OMIM protein coding genes (<http://www.ncbi.nlm.nih.gov/omim>; online suppl. table 2). *NFIA* was not included in the deletion interval. No other copy number variation (CNV) was detected with the array. A custom-designed MLPA confirmed the presence of the deletion (fig. 1C) and verified that 2 copies of *NFIA* were present. Both healthy parents refused genetic testing.

Discussion

We have identified an ~18.6-Mb deletion of 1p31.1p31.3 in a newborn patient with multiple and severe congenital malformations, including craniosynostosis, cutis laxa, dysmorphic facial features, and abnormalities of the CNS, eye, and kidneys. A total of 68 OMIM-listed genes were located within the deleted region.

To date, 17 cases with deletions of varying size of 1p31.1p31.3 have been reported in the literature or in the DECIPHER database (<https://decipher.sanger.ac.uk/>). Clinical features included developmental delay, seizures, CNS malformations, macrocephaly (40% of the cases), elongated or rounded facies with a prominent nose, micro/retrognathia, half-opened mouth, short neck, congenital heart malformations, hernia, hand/foot malformations, renal anomalies, abnormal external genitalia, joint hyperlaxity, and cutis laxa (online suppl. table 3). Two were intragenic deletions of *NFIA*, identified in individuals with craniosynostosis, and it was hypothesized that this clinical feature was due to *NFIA* haploinsufficiency [Rao et al., 2014; Nyboe et al., 2015]. A 1p34.1p31 inversion-duplication was also described in a patient with craniosynostosis, but the breakpoints were not characterized [Garcia-Heras et al., 1999]. However, the patient reported in this study has a normal copy number for this gene; thus, it is unlikely that this gene is the cause for the craniosynostosis observed in our patient.

It has been reported that 7.5% of the cases with craniosynostosis involving one suture display a previously unreported CNV [Mefford et al., 2010]. In our laboratory, 3.5% of the cases with one or more affected sutures have a pathogenic CNV (unpublished data). We then tried to determine which gene may be responsible for the craniosynostosis. We searched the DECIPHER database for craniosynostosis cases and deletions in chromosome 1 and

found an individual with a smaller 1p31.3 deletion including 10 OMIM genes (*IL23R*, *IL12RB2*, *SERBP1*, *DDIT1*, *GNG12*, *GNG12AS1*, *DIRAS3*, *WLS*, *RPE65*, and *DEPDC1*) in a father and his son (DECIPHER 277832) both with sagittal craniosynostosis, hypercalcemia, and postnatal growth delay. Some of these genes have been reported as partially or completely deleted (in heterozygous state) in the ‘healthy control’ population, with variable frequencies (MAF 0–0.03%; online suppl. table 4). Only one of these genes, *IL23R*, encoding a subunit of the receptor for IL23A/IL23, could have a potential relationship with craniosynostosis. This protein pairs with *IL12RB1* to conform the specific region of the heterodimeric interleukin (IL)-23 receptor required for signaling via the JAK/STAT pathway. *IL23R* associates constitutively with Janus kinase 2 (JAK2) and can also bind to transcription activators STAT3, STAT1, STAT4, and STAT5 in a ligand-dependent manner [Parham et al., 2002]. Heterozygous *STAT3* mutations are associated with autosomal dominant hyper IgE syndrome (ADHIES), a primary immune deficiency. Craniosynostosis has been described in 4 ADHIES cases [Smithwick et al., 1978; Hoyer et al., 1985]. Homozygous mutations in the interleukin 11 receptor alpha gene (*IL11RA*) were also identified in a family with Crouzon-like craniosynostosis [Keupp et al., 2013]. Thus, we propose that the craniosynostosis in our patient may be due to the heterozygous deletion of *IL23R*.

NFIA haploinsufficiency has also been proposed to be responsible for CNS malformations such as ventriculomegaly, hydrocephalus, corpus callosum anomalies, tethered spinal cord, or Chiari malformation which were observed in 5 cases with deletions overlapping the region deleted in our patient [Lu et al., 2007]. Indeed, the *Nfia* knockout mouse (*Nfia*^{−/−}) shows a lethality rate of >95%, with hydrocephalus and corpus callosum agenesis, whilst the heterozygous mice (*Nfia*^{+/-}) display urinary tract and CNS malformations [das Neves et al., 1999; Lu et al., 2007]. However, despite our patient shows ventriculomegaly and hydrocephalus, the deletion does not include *NFIA*. The breakpoint is >1 Mb from this gene; thus, the disruption of regulatory elements is also unlikely. But since we are unable to analyze *NFIA* expression in this patient, our opinion is that another gene within the deleted interval may be the cause of the CNS malformations.

Of the 68 affected genes, 12 of them have a MIM MORBID ID: *FOXD2*, *ALG6*, *PGM1*, *DNAJC6*, *LEPR*, *SLC35D1*, *IL23R*, *RPE65*, *CTH*, *TNNI3K*, *ACADM*, and *NEXN*. We performed an evaluation of the genes deleted in our patient using the haploinsufficiency score [Huang et al., 2010]. Of the 68 OMIM protein coding genes, 10 were

found to have a high haploinsufficiency score: *PDE4B*, *GADD45*, *LRRRC7*, *ZRANB2*, *NEGR1*, *LHX8*, *ST6GALNAC3*, *ZZZ3*, *FUBP1*, and *ELTD1*. The frequencies of reported CNVs for these genes are variable and are present in 0–0.03% of the control population, according to Exome Aggregation Consortium (<http://exac.broadinstitute.org/>; online suppl. table 5).

FOXD2 is the kidney-expressed human forkhead gene; thus, it could be a candidate for the kidney malformations presented by our patient because this gene is transcribed exclusively in the kidney [Ernstsson et al., 1997].

The presence of a cleft palate combined with microcephaly and severe learning difficulties has also been reported in a patient with a smaller chromosome 1 deletion [Shaw-Smith et al., 2004]. *LHX8* haploinsufficiency was present in both cases. This gene encodes a transcriptional regulator of the family LIM-homeobox, which are expressed in the first branchial arch and the basal forebrain [Grigoriou et al., 1998]. Mice mutant for *Lhx8* revealed a crucial role for *LHX8* in palatogenesis: the bilateral primordial palatal shelves are formed and elevated correctly, but they often failed to make contact and fuse properly, resulting in a cleft secondary palate [Zhao et al., 1999]. Although this gene is highly expressed in skin and connective tissue, there is no clear relation between its haploinsufficiency and the cutis laxa phenotype described in our patient. The gene that may be responsible for this clinical feature is *ST6GALNAC3*, which has been intra-

genically partially deleted in 1 patient who presented excessively wrinkled skin amongst other anomalies (DECIPHER 249129). The remaining dose-responsive genes have been linked to the clinical features observed in patients with chromosome 1p32p21 deletion syndrome.

In summary, we report a chromosome 1p31.1p31.3 deletion encompassing ~18.6 Mb and including 68 OMIM genes in a patient with multiple malformations. Using clinical data from other chromosome 1 deletion patients and mice models, we propose that *IL23R* may be responsible for the craniosynostosis, whilst various deleted genes may explain the other clinical features.

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Statement of Ethics

The parents have given written informed consent, and ethical approval was obtained from the local ethics committee.

Disclosure Statement

The authors declare no conflicts of interest.

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