Novel Insights from Clinical Practice

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Interstitial 1q21.1 Microdeletion Is Associated with Severe Skeletal Anomalies, Dysmorphic Face and Moderate Intellectual Disability

Bruno F. Gamba[a] Roseli M. Zechi-Ceide[a] Nancy M. Kokitsu-Nakata[a] Siulan Vendramini-Pittoli[a] Carla Rosenberg[b] Ana C.V. Krepischi Santos[b] Lucilene Ribeiro-Bicudo[c] Antonio Richieri-Costa[a]

[a]Department of Clinical Genetics, Hospital for Rehabilitation of Craniofacial Anomalies (HRCA), University of São Paulo, Bauru, [b]Centro de Estudos do Genoma Humano, University of São Paulo, São Paulo, and [c]Departamento de Genética, Instituto de Ciências Biológicas, Universidade Federal De Goias, Goiania, Brazil

Established Facts

- Deletions reported in the 1q21.1 region are clinically heterogeneous, ranging from subtle phenotypic manifestations to severe congenital heart defects and/or neurodevelopmental findings.

Novel Insights

- Deletions of some genes related to the process of bone modeling in our patient – *ITGA10* and *PIAS3* – could be contributing to the phenotypic skeletal findings observed.

Key Words
Dysmorphic features · Intellectual disability · Microdeletion 1q21.1 · Skeletal anomalies

Abstract
We report on a Brazilian patient with a 1.7-Mb interstitial microdeletion in chromosome 1q21.1. The phenotypic characteristics include microcephaly, a peculiar facial gestalt, cleft lip/palate, and multiple skeletal anomalies represented by malformed phalanges, scoliosis, abnormal modeling of vertebral bodies, hip dislocation, abnormal acetabula, feet anomalies, and delayed neuropsychological development. Deletions reported in this region are clinically heterogeneous, ranging from subtle phenotypic manifestations to severe congenital heart defects and/or neurodevelopmental findings. A few genes within the deleted region are associated with congenital anomalies, mainly the *RBM8A*, *DUF1220*, and *HYDIN2* paralogs. Our patient presents with a spectrum of unusual malformations of 1q21.1 deletion syndrome not reported up to date.

Deletions involving the 1q21.1 region are mainly associated with neurodevelopmental disorders [Basel-Vanagaite et al., 2011], congenital heart disease [Digilio et al., 2013], variable dysmorphic features, as well as

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Antonio Richieri-Costa, MD
HRAC, University of São Paulo
PO Box 620
Bauru, SP 17012-900 (Brazil)
E-Mail richieri@usp.br

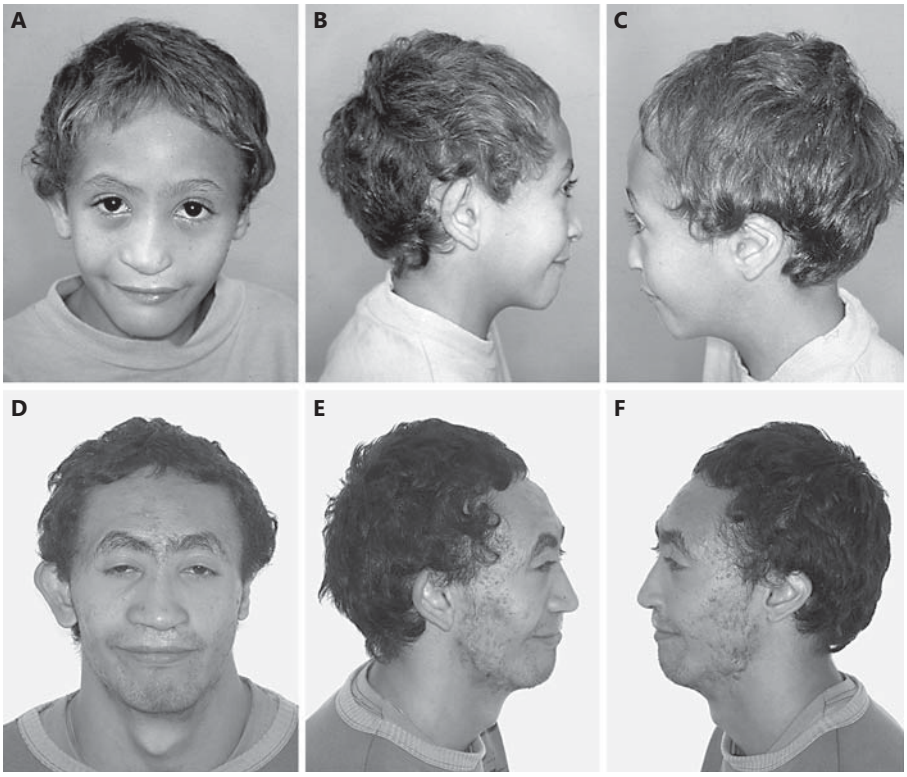

Fig. 1. A–F The patient at age 9 (**A–C**) and 19 years (**D–F**). A small skull, sloping forehead, synophrys, arched eyebrows, a flat nose, prominent ears, large conchae, hypoplastic tragus and lobules, left cleft lip/palate, and a large mouth are shown.

congenital anomalies [Brunetti-Pierri et al., 2008; Velinov and Dolzhanskaya, 2010], and with thrombocytopenia-absent radius syndrome (OMIM 274000) due to a deletion in the *RBM8A* gene [Papoulidis et al., 2014]. Phenotypically normal carriers have also been reported [Mefford et al., 2008]. In this study, the patient presents with several clinical findings rarely observed in patients with a 1q21.1 deletion, which include cleft lip/palate, dental anomalies (involving size, shape, and form), hearing loss, and skeletal involvement not related to thrombocytopenia-absent radius syndrome. These findings could be attributed to the effect of other genes encompassed in this deletion and manifesting as a contiguous gene syndrome.

Patient and Methods

Case Report

The male patient (fig. 1A–F) is the sixth child of a 28-year-old woman G7P6A1 and her 29-year-old nonconsanguineous husband. Minor anomalies were not detectable in the parents. The pregnancy was uncomplicated with no history of exposure to teratogens. The mother had a history of threatened miscarriage at 4 months of pregnancy. Delivery was normal at term and birthweight was 2,450 g (<3rd percentile); length was not recorded. A cleft lip/palate was detected. Clinical examination at age 19 months showed: weight 7,600 g (<3rd percentile), length 71 cm (<3rd percentile), and OFC 43 cm (>2nd percentile). A reevaluation at the age of 22 years and 8 months revealed: weight 25 kg (<3rd percentile), length 130.5 cm (<3rd percentile), and OFC 48 cm (<3rd percentile). He presented with microcephaly, a sloping forehead, synophrys, arched eyebrows, a flat nose, prominent ears, large conchae, hypoplastic tragus and lobules, left cleft lip/palate, a large mouth, hypodontia, large left central maxillary incisor, aberrant crown morphology, short hands, mild camptodactyly (mainly of 5th finger), bilateral hypoplasia of the distal phalanges of fingers 2 and 3, with agenesis/hypoplasia of the nails (fig. 2A, B), halluces valgi, a wide gap between toes 1 and 2, proximal syndactyly between toes 2 and 3, a short 5th toe (fig. 3A, B), and bilateral hip dislocation. Neuropsychological development and language acquisition were delayed. X-rays of the hands (fig. 2C, D) showed gross and misshapen proximal phalanges of fingers 2–3, radial clinodactyly of finger 2, hypoplastic distal phalanges of fingers 2–3, abnormal 'bird-like beak' modeling of the right distal phalanx of finger 2, and a small bony fragment distal to the phalanx of finger 3 as well as a dislocation of the metacarpal phalangeal joint of both thumbs. In both feet, the median and distal phalanges of toes 3–5 are hypoplastic with halluces valgi (fig. 3C). X-rays of the vertebral column revealed a narrow intervertebral disc space at T10-L5, thoracolumbar scoliosis, and sacral hemivertebra. MRI showed a left choanal atresia; the central nervous system was normal. Audiological evaluation performed at the age of 21 years revealed a bilateral mixed hearing loss. The results of routine laboratory blood tests were normal.

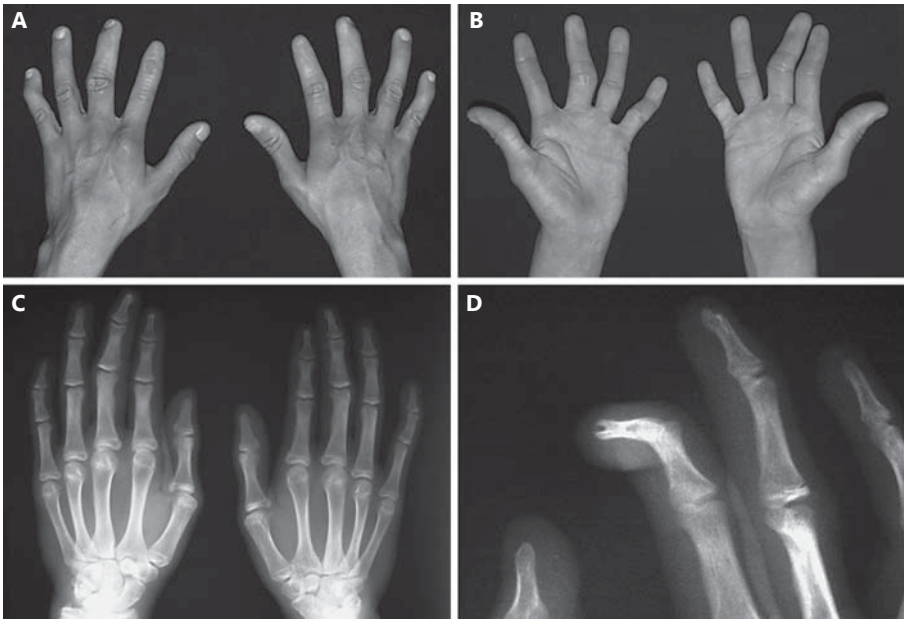

Fig. 2. A–D The hands of the patient showing mild camptodactyly (mainly of 5th finger), short hands, bilateral hypoplasia of the distal phalanges of fingers 2 and 3, with agenesis/hypoplasia of the nails (**A**, **B**). X-rays of the hands show gross and misshapen proximal phalanges of fingers 2 and 3, radial clinodactyly of finger 2, hypoplastic distal phalanges of fingers 2 and 3, abnormal 'bird-like beak' modeling of the right distal phalanx of finger 2 as well as a small bony fragment distal to the phalanx of finger 3, and a dislocation of the metacarpal phalangeal joints of both thumbs (**C**, **D**).

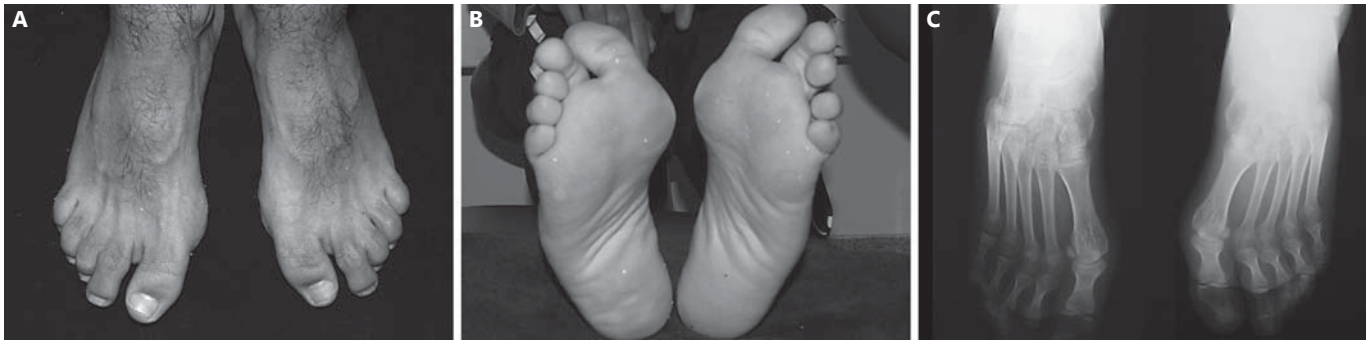

Fig. 3. A–C The feet of the patient showing a wide gap between toes 1 and 2, proximal syndactyly between toes 2 and 3, a short 5th toe (**A**, **B**), and marked hypoplasia of median and distal phalanges of toes 3 and 5 with bilateral halluces valgi (**C**).

Cytogenetic and Molecular Analysis

Cytogenetic analysis of peripheral blood lymphocytes from the patient, performed using standard techniques and processed by G-banding (550 bands), was normal. Screening for mutations in *SHH*, *TGIF*, *SIX3*, *PTCH1*, *GLI2*, *GAS1*, and *ZIC2* genes was unremarkable. Array-CGH using the Human Genome CGH Microarray 60K detected an interstitial deletion in band 1q21.1 of 1.7 Mb, spanning from position 144.610.516 to 146.354.478 bp (UCSC Genomic Bioinformatics, GRCh37/hg19, http://genome.ucsc.edu) and encompassing 44 RefSeq annotated genes (22 protein coding genes, 6 tRNA coding genes, 1 snRNA coding gene, 6 hypothetical genes, and 9 pseudogenes; http://www.ncbi.nlm.nih.gov/mapview). Parental DNA was not available for molecular testing.

Results and Discussion

The 1q21.1 deletions have been associated with a heterogeneous clinical phenotype mainly presenting with intellectual disabilities, seizures, psychosis, language disorder, autism, and microcephaly [Brunetti-Pierri et al., 2008; Stefansson et al., 2008; Basel-Vanagaite et al., 2011; Natera-De Benito et al., 2015; Bernier et al., 2016]. Congenital heart defects and a wide range of minor congenital anomalies such as frontal bossing, deep-set eyes, camptodactyly, postaxial polydactyly, mild interdigital membranes, clavicular pseudoarthrosis, rib anomalies, and syndactyly of toes 2 and 3 have been observed in these

patients, however, without characterizing a distinct facial gestalt [Christiansen et al., 2004; Brunetti-Pierri et al., 2008; Mefford et al., 2008; Velinov and Dolzhanskaya, 2010; Houeijeh et al., 2011; Rosenfeld et al., 2012; Digilio et al., 2013]. Asymptomatic carriers are found in family studies with this microdeletion [Brunetti-Pierri et al., 2008; Mefford et al., 2008; Bottillo et al., 2013; Bernier et al., 2016]. According to DECIPHER (http://decipher.sanger.ac.uk), microdeletions encompassing the region 1q21.1 (144,610,516–146,354,478 bp) are associated with different phenotypic combinations of the listed disorders, reinforcing the causal relationship of this microdeletion with the phenotype of our patient. However, the additional findings represent a unique cluster of congenital malformations mainly characterized by a unilateral cleft lip/palate, abnormal teeth, atypical digital anomalies, abnormal hands, and a peculiar facial gestalt.

Clinical and molecular studies have associated microcephaly with the hemizygous state of 2 main genes: *HYDIN* and *RBM8A* [Brunetti-Pierri et al., 2008; Haldeman-Englert and Jewett, 2015]. Evidence from mouse studies showed that homozygous inactivating mutations of the *Hydin* gene result in hydrocephalus mice due to impairment of the ciliated ependymal cell lining of the lateral third and fourth ventricles [Davy and Robinson, 2003]. Therefore, the observation of the *HYDIN* paralog expressed in humans may be a candidate gene for microcephaly, since it is only expressed in the brain and is important in head size determination [Brunetti-Pierri et al., 2008; Olbrich et al., 2012]. Recently, it was shown that the *RBM8A* gene within the 1q21.1 region, besides its role in the thrombocytopenia-absent radius syndrome genesis, also disrupts the embryonic cortical development resulting in neurodevelopmental phenotypes associated to microcephaly [Mao et al., 2015; Zou et al., 2015].

Some of the signs seen in our patient are related to the involvement of skeletal structures both in differentiation as well as in modeling, which is clearly observed in the abnormal modeling and misshaping of the phalangeal complement. The axial skeleton represented by the vertebral column and ribs was also involved, and the main malformations observed were abnormally modeled vertebral bones, hemivertebra, and spina bifida. Recently, it was shown that mutations in the *ITGA10* gene in the Norwegian Elkhound and Karelian Bear Dog breeds result in a recessive autosomal chondrodysplasia; however, up to date, no evidence of involvement of this gene in human disease was demonstrated [Kyöstilä et al., 2013]. It is possible that *ITGA10* and *PIAS3,* both related to the process of bone remodeling [Liu et al., 2014; Napimoga et al., 2015] and deleted in our patient, could be contributing to the phenotypic variability observed, next to other unidentified genetic or environmental factors that remain essential for the expression of the clinical signs in each individual [Rosenfeld et al., 2012].

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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