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A Pure 2-Mb 3q26.2 Duplication Proximal to the Critical Region of 3q Duplication Syndrome

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Abstract
Partial duplication of chromosome 3q – dup(3q) – is a recognizable syndrome with dysmorphic facial features, microcephaly, digital anomalies, and genitourinary and cardiac defects, as well as growth retardation and developmental delay. Most cases of dup(3q) result from unbalanced translocations or inversions and are accompanied by additional chromosomal imbalances. Pure dup(3q) is rare, and only 31 cases have been reported so far. We report a new case of a girl with a pure 2-Mb duplication at 3q26.2 not encompassing the known critical region 3q26.3q27. After an extensive review, to the best of our knowledge, the case herein presented harbors the shortest 3q duplication of this region. The clinical phenotype of this patient resembles previously reported cases of pure dup(3q) syndrome, including intellectual disability, synophrys, a wide nasal bridge, dysmorphic ears, clinodactyly, and cardiac defects. We suggest that the 3q26.2 duplication is a candidate copy number alteration explaining our patient's clinical phenotype.

The genetic analysis of infants with multiple congenital anomalies frequently helps to understand the child's prognosis and development. Microarray technologies have become the tool of choice to accurately determine the genetic causes of phenotypes [Miller et al., 2010]. dup(3q) syndrome is a genomic imbalance resulting in intellectual disability, seizures, a broad nose, cardiac, renal and genital malformations [Schinzel, 2001]. This syndrome has overlapping clinical features with Cornelia de Lange syndrome, although there are distinguishing features with different etiology [Iacoboni et al., 2013].

The phenotypes and breakpoints in 3q are variable, and in general, smaller duplications are related to milder phenotypes. The most frequent features are typical facial dysmorphisms, hirsutism, microcephaly, intellectual disability, growth retardation, genitourinary anomalies, limb abnormalities, renal and congenital heart defects [Dworschak et al., 2017]. It has been discussed that duplications involving a critical region at 3q26.3q27 [Aqua et al., 1995] or 3q26.3q29 [Faas et al., 2002; Grossmann et al., 2009] are implicated in the main clinical signs of dup(3q) syndrome. Recently, Dworschak et al. [2017] described 3q26.3q27 as the critical region for dup(3q) syndrome.

Most cases of dup(3q) appear to be the result of an unbalanced translocation or inversion; as a consequence,

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there is often an accompanying cytogenetic anomaly such as a deletion of another chromosomal segment [Salazar et al., 1979]. Therefore, pure dup(3q) is rare, and only 31 cases (25 unrelated cases) have been described until now [reviewed by Dworschak et al., 2017]. In this study, we report a pure duplication of 2 Mb at 3q26.2 not encompassing the previously proposed critical region of dup(3q) syndrome.

Methods

The patient was first evaluated during a study focused on congenital heart disease and 22q11.2 deletion syndrome. Besides a complete clinical evaluation by experienced clinical geneticists, a specific checklist was filled out, comprising clinical and family history information as well as dysmorphic features.

G-banding at the level of 550 bands was performed. Chromosomal microarray analysis using the CytoScan HD chip (Affymetrix®, Santa Clara, CA, USA) analyzed with the Chromosome Analysis Suite (ChAS) software (Affymetrix) was also done. Confirmation of copy number variations (CNVs) was achieved by array CGH using the SurePrint G3 Human GE 8x60K Microarray (Agilent Technologies, Santa Clara, CA, USA) and analyzed with the Agilent Cytogenomics software (Agilent Technologies). The Scripps Genome ADVISER CNV (SG-ADVISER CNV; https://genomics.scripps.edu/ADVISER/Home.jsp) was used for interpretation of CNV pathogenicity.

Clinical Report and Results

The female patient was first evaluated due to congenital heart disease. She is the second child of a nonconsanguineous couple (father 29 years old, mother 37 years old) with a previous spontaneous abortion; her mother had a normal son from her first marriage. Family history includes a paternal aunt and a maternal first cousin with unspecified congenial heart disease and a maternal first cousin with hydrocephaly. Pregnancy and delivery were uneventful. At birth, the newborn did not cry and had cyanosis; anthropometric data were not mentioned. She was diagnosed with tetralogy of Fallot, infundibular-valvular pulmonary stenosis, ostium secundum atrial septal defect, persistent left superior vena cava, and had corrective heart surgery at 18 months of age. She walked without support at 19 months and spoke her first words at 2 years of age.

Initial evaluation at 1 year and 8 months showed a length of 74 cm (<3rd centile), weight of 8,350 g (<3rd centile), and an OFC of 44 cm (<3rd centile). Dysmorphology examination at this age demonstrated a flat occiput, bilateral low-set ears with long and fleshy earlobes, hooded eyelids, bilateral epicanthic folds, a broad and depressed nasal root, a bulbous nose tip (Fig. 1A, B), high-arched palate, bilateral bridged palmar creases, and 5th finger clinodactyly (Fig. 1C, D).

A follow-up evaluation at 6 and 8/12 years revealed: weight 17 kg (3rd centile), length 108 cm (3rd centile), and OFC 49 cm (3rd centile). Her facial appearance is not similar to her mother; her father is unavailable. The following dysmorphisms were observed: flat occiput; triangular face; abnormally formed low-set ears; mild synophrys, making a whorl in the glabella; malar hypoplasia; epicanthus; nose with wide base, low bridge, and bulbous tip (Fig. 1E, F); high-arched palate; bifid uvula (Fig. 1G); bilateral, incomplete palmar crease; 5th finger clinodactyly, and a sacral dimple. Despite hyperactivity and attention deficit disorder, she can read and write with only mild difficulties. Dysphagia was also mentioned.

The G-banded karyotype was normal (46,XX). Chromosomal microarray analysis of the patient revealed a duplication of 2 Mb at 3q26.2, arr[GRCh37] 3q26.2(168509531_170483061)×3, which was confirmed by another platform. The same duplication was neither found in 112 in-house control individuals from the Brazilian population, nor in the Database of Genomic Variants (DGV; http://projects.tcag.ca/variation). No other causal CNVs were observed in the patient. The parents were not interested in parental investigation or genetic counseling.

Discussion

The duplicated segment in the patient described here does not encompass the previously proposed critical region of 3q26.3q27 for dup(3q) syndrome [reviewed by Dworschak et al., 2017]; nevertheless, when comparing the phenotype of our patient with the clinical manifestations of the few cases of pure dup(3q) syndrome previously reported encompassing the q26.2 region (Table 1), they share the main characteristics of the syndrome, including intellectual disabilitity, synophrys, wide nasal bridge, dysmorphic ears, clinodactyly, and cardiac defects.

Some of the facial features related to the critical region of dup(3q) syndrome are present in our patient (Table 1); she also has a wide nasal bridge (16/20), synophrys (15/20), and dysmorphic ears (9/19), but she does not show micro/retrognathia (10/20). Also, the only limb abnormality present in our patient was clinodactyly (16/19), and there are some characteristics, although not present in all reported cases, that are very frequent, such as growth retardation and microcephaly. Growth retardation has

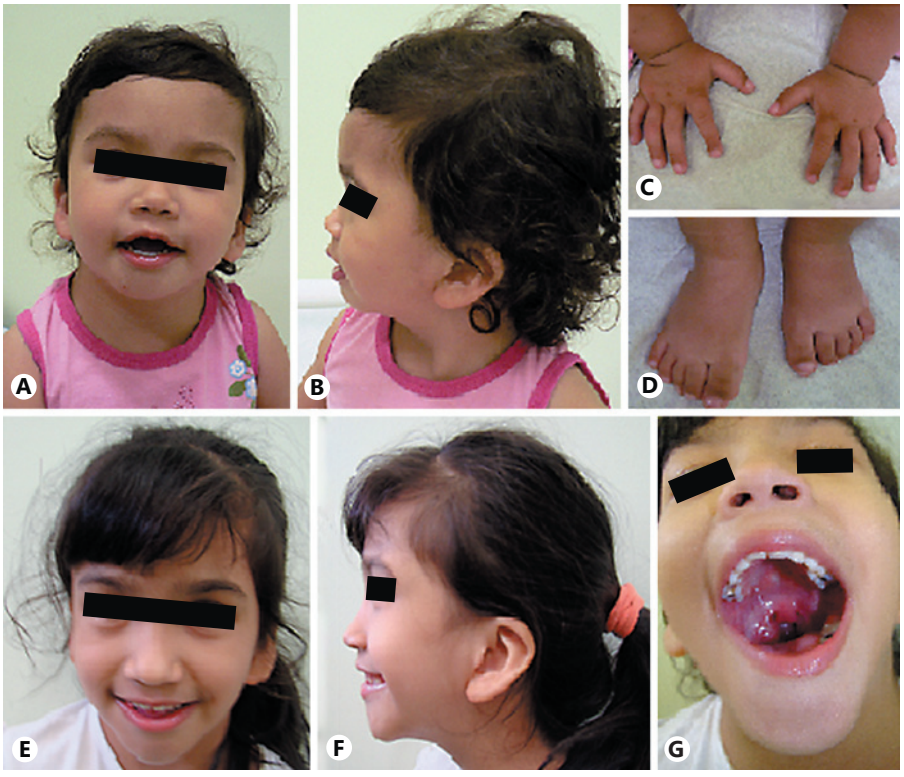

Fig. 1. Facial features, hand dysmorphisms, and palate anomalies of the patient. Frontal (**A**) and lateral (**B**) view of the patient at 1 year and 8 months of age. Note the bilateral epicanthic folds, large nose with a low nasal bridge and bulbous tip. Dorsal view of the hands (**C**) and feet (**D**) of the patient at 1 year and 8 months. Note the bilateral incomplete palmar arch and 5th finger clinodactyly. Frontal (**E**) and lateral (**F**) view of the patient at 6 and 8/12 years of age. Note the flat occiput, triangular face, dysmorphic and low-set ears, mild synophrys making a whorl in the glabella, malar hypoplasia, bilateral epicanthic folds, wide nose with a low nasal bridge and bulbous tip. Palatal (**G**) view of the patient at 6 and 8/12 years of age. Note the ogival palate and bifid uvula.

been described in 63% (12/19) of the cases. There is no information about prenatal data; however, she currently presents with anthropometrical measurements on the 3rd centile. Microcephaly has been described in 53% (10/19) of the cases – however, not in our patient. Other common anomalies described in dup(3q) syndrome are intellectual disabilitity (20/20), cardiac defects (11/20), and seizures (6/15). Our patient had intellectual disability and cardiac defects, but no history of seizures.

Due to the urge of genetic delineation of dup(3q) syndrome, we analyzed the cases with pure duplication with the duplicated region partially flanking the region involved (3q26.2) in our case. The patients compared in Table 1 are very different from the molecular cytogenetic point of view as they have duplications of various sizes and clinical data are thus difficult to compare.

Cases with proximal duplications of 3q25.1q26.1 or 3q25q26.2 have been described without typical features of dup(3q) syndrome and a milder or nearly normal phenotype [Lopez-Rangel et al., 1993], or only developmental delay with minor facial dysmorphism [Ireland et al., 1995; Rizzu et al., 1997], as well as one case with additional mild limb anomalies and a sinus pilonidalis [Meins et al., 2005]. On the other hand, our patient presents with some features related to pure dup(3q) syndrome, and her duplication comprises only the region q26.2, which is proximal to the previously proposed critical region.

The present case has the smallest pure dup(3q) region of overlap among cases reported in the literature encompassing the q26.2 band (Fig. 2). This duplication was not detected among individuals in the DGV (http://projects.tcag.ca/variation). Furthermore, in the same database, there are no CNVs (gains or losses) overlapping more than 10% within this region. On the other hand, there are several cases of duplications reported in cases from the DECIPHER (http://decipher.sanger.ac.uk) and ClinGen (https://www.clinicalgenome.org/) databases, showing that this region is possibly triplosensitive. Only much larger duplications have been described as a sole finding in 11 individuals from DECIPHER (1561, 250564, 251819, 258098, 268004, 282426, 283584, 289520, 294103, 299885, 305708) (Fig. 2). Cases 1561 and 250564, respectively, have abnormal palmar creases and finger abnormalities in common with our patient.

Additionally, an interpretation using the SG-ADVISER CNV was done, which revealed this duplication as predicted pathogenic, based on a high degree of overlap with reported pathogenic CNVs and deleterious effect on

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Table 1. Genetic and clinical findings presented in the current case and those with pure (3q) duplication encompassing the q26.2 region

	Falek et al., 1966[a] (4 cases)	Wilson et al., 1978[b] (2 cases)	Stengel-Rutkowski et al., 1979	Van Essen et al., 1991	Sciorra et al., 1979	Holder et al., 1994 (2 cases)	Lim et al., 2004	de Azevedo Moreira et al., 2005	Meins et al., 2005	Shanske et al., 2010	Jung et al., 2013	Zhu et al., 2013	Abreu-González et al., 2013 (4 cases)	Our study
3q duplication region	q26.2qter	q25q29	q21q27	q25q28	q23q27	q25.1q26.2	q26.2q27[c]	q21q27[d]	q24q26.31	q22.2q29	q26.1q29[e]	q24q28[f]	q26.2qter	q26.2
Inheritance	mat/pat familial	de novo	de novo	de novo	de novo	pat	mat	ND	de novo	de novo	de novo	pat	mat familial	ND
Cytogenetic analysis	GTG/FISH/CGH[g]	GTG	GTG/RBA	GTG/SB	GTG	GTG/FISH	GTG/FISH/MFISH	GTG	GTG/QFQ/RBA/FISH	GTG/FISH/SNPa	CTG/aCGH/FISH	GTG/FISH/SKY/SNPa	GTG/NOR/FISH	CMA/aCGH
Size of duplication	ND	ND	ND	ND	ND	ND	ND	ND	ND	61 Mb	33 Mb	44 Mb	ND	2 Mb
Gender	3 F/1 M	F/M	F	F	F	F/M	ND	F	M	M	M	M	2 F/2 M	F
Intellectual disability	4/4	2/2	ND	+	+	2/2	+	+	+	+	ND	+	4/4	+
Growth retardation	4/4	2/2	+	ND	+	0/2	ND	+	+	+	ND	+	0/4	–
Microcephaly	4/4	2/2	ND	–	+	0/2	ND	–	+	+	ND	+	0/4	–
Low hairline	1/4	2/2	+	ND	+	0/2	ND	–	–	–	ND	–	4/4	–
Hirsutism	4/4	2/2	+	+	+	0/2	ND	+	–	+	ND	–	4/4	–
Synophrys	4/4	2/2	–	+	+	1/2	ND	–	–	+	ND	–	4/4	+
Bushy eyebrows	4/4	2/2	–	+	+	0/2	ND	+	–	+	ND	–	4/4	–
Long eyelashes	4/4	2/2	–	+	+	0/2	ND	+	–	+	ND	–	3/4	–
Wide nasal bridge	4/4	0/2	+	+	+	0/2	ND	+	+	+	ND	+	4/4	+
Anteverted nostrils	4/4	2/2	+	ND	+	2/2	ND	+	+	+	ND	+	4/4	–
Downturned corners of mouth	4/4	1/2	+	ND	+	0/2	ND	+	+	+	ND	+	4/4	–
High/cleft palate	0/4	0/2	ND	+	–	0/2	ND	+	–	–	ND	+	0/4	–
Micro/retrognathia	3/4	2/2	+	+	–	0/2	ND	+	+	+	ND	–	0/4	–
Dysmorphic ears	3/4	0/2	+	ND	–	0/2	ND	+	+	–	ND	+	1/4	+
Brachydactyly	4/4	2/2	–	+	–	0/2	ND	–	+	+	ND	–	1/4	–
Clinodactyly	3/4	2/2	+	+	+	1/2	ND	+	–	+	ND	–	4/4	+
Other limb abnormalities	0/4	0/2	+	–	–	0/2	ND	+	+	+	ND	+	0/4	–
Short neck	3/4	2/2	+	ND	–	0/2	ND	+	+	+	ND	–	0/4	–
Cardiac defects	2/4	ND	+	+	+	0/2	+	–	+	–	+	+	1/4	+
Seizure disorders	0/4	2/2	ND	ND	ND	ND	ND	+	ND	+	+	–	1/4	–

aCGH: array comparative genomic hybridization; CGH, comparative genomic hybridization on metaphase; CMA, chromosomal microarray; GTG, G-bands by trypsin using Giemsa; mat, maternal; MFISH, multiplex fluorescence in situ hybridization; ND, not determined; NOR, nucleolar organizer region-bands by silver-staining (Ag-I); pat, paternal; QFQ, Q-bands by fluorescence using quinacrine; RBA, R-bands by BrdU using acridine orange; SB, Southern blot; SKY, spectral karyotyping; SNPa, single nucleotide polymorphism array; +, present; –, absent.

[a] In one clinically affected case, initial karyotype without banding was performed.

[b] One case also had a monosomy of 3p27.

[c] The fetal karyotype was 46,XY,der(5)ins(5;3)(q33.1;q26.2q27)mat.

[d] Karyotype: 46,XX,ins(3)(pter→p25::q27→q21::p25→qter).

[e] The fetal karyotype was 46,XY,add(14)(p11).ish der(14)t(3;14)(q26.1;p11)(tel3q+).arr 3q26.1q29(166249469–199288361)×3.

[f] Karyotype: 46,XY,ins(6;3)(q21;q24q28).

[g] The karyotype was done by Rizzu and Baldini [1994]; the final karyotype was 46,XY,der(22)t(3;22)(q26;p11). Adapted from Abreu-González et al. [2013].

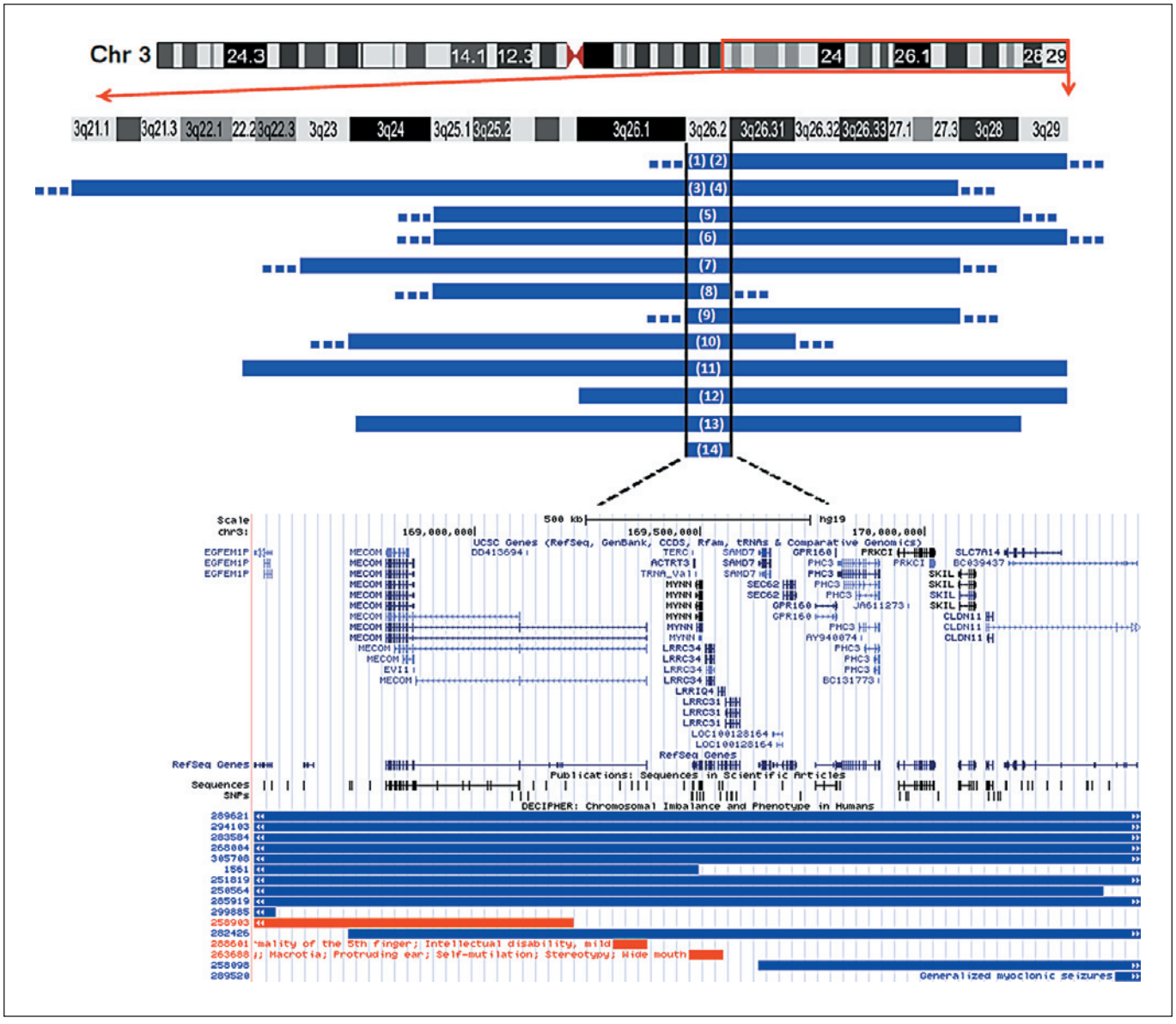

Fig. 2. Ideogram of chromosome 3 and magnification of the 3q21qter region. Schematic presentation of previously reported pure duplication cases flanking the q26.2 region involved in the present case. (1) Falek et al., 1966; (2) Abreu-González et al., 2013; (3) Stengel-Rutkowski et al., 1979; (4) de Azevedo Moreira et al., 2005; (5) van Essen et al., 1991; (6) Wilson et al., 1978; (7) Sciorra et al., 1979; (8) Holder et al., 1994; (9) Lim et al., 2004; (10) Meins et al., 2005; (11) Shanske et al., 2010; (12) Jung et al., 2013; (13) Zhu et al., 2103; (14) the current case. The breakpoint regions for those cases without array-CGH analysis or breakpoint characterization are shown with dashed lines. The localization of the candidate genes and DECIPHER cases overlapping the q26.2 region are shown.

genes known to be associated with disease. This tool is a Web-based automated CNV interpretation system by performing in-depth annotations and functional predictions for CNVs and is based on the American College of Medical Genetics and Genomics scoring guidelines [Erikson et al., 2015].

According to the extent of the duplication and the variability of the clinical phenotype in patients with dup(3q) syndrome, it has been suggested that the syndrome should be considered a contiguous gene syndrome [Meins et al., 2005; Shanske et al., 2010] with several genes in the critical region. There are 8 OMIM (https://omim.org//) candi-

Table 2. Candidate genes in the 3q26.2 region

Gene	OMIM	Functions	Process
MECOM	165215	DNA, metal ion, protein and sequence-specific DNA binding; histone-lysine N-methyltransferase and transcription factor activity	apoptotic process; cell differentiation; hematopoietic stem cell proliferation; histone lysine methylation; negative regulation of JNK cascade and programmed cell death; transcription DNA templated; regulation of transcription, DNA templated and cell cycle
TERC	602322	reverse transcriptase enzyme activity, template for telomere repeat	cellular senescence, chromosomal repair
ACTRT3	608534	actin ATP binding and signals nuclear export	cytoskeletal organization
MYNN	606042	DNA, sequence-specific DNA and zinc ion binding, transcription factor activity	transcription and regulation of transcription, DNA templated
SEC62	602173	protein transporter activity, receptor activity	IRE1-mediated unfolded protein response, cotranslational and posttranslational protein targeting to membrane
PRKCI	600539	ATP, metal ion, phospholipid, protein kinase and protein domain-specific binding; protein kinase C and protein serine/threonine kinase activity	Golgi vesicle budding; actin filament organization; cell migration; cell-cell junction organization; cellular response to insulin stimulus; cytoskeleton organization; eye photoreceptor cell development; intracellular signal transduction; regulation of apoptotic, glial cell apoptotic, and neuron apoptotic process; peptidyl-serine phosphorylation; regulation of neuron projection development
SKIL	165340	RNA polymerase II core promoter proximal region sequence-specific DNA, SMAD, chromatin, protein and repressing transcription factor binding; transcriptional repressor activity	blastocyst formation; cell cycle arrest; lens fiber cell differentiation; lymphocyte homeostasis; negative regulation of BMP signaling pathway, cell differentiation, transcription from RNA polymerase II promoter and transforming growth factor beta receptor signaling pathway; positive regulation of axonogenesis, extrinsic apoptotic signaling pathway via death domain receptor and intrinsic apoptotic signaling pathway in response to DNA damage; response to cytokine; spermatogenesis
CLDN11	601326	identical protein binding, structural molecule activity	axon ensheathment, calcium-independent cell-cell adhesion via plasma membrane cell-adhesion molecules, spermatogenesis

date genes in the duplicated region for which related functions and processes are described in Table 2. Among those, *MECOM* (MDS1 and EVI1 complex locus) is expressed in hematopoietic stem cells in humans and plays an important role in hematopoiesis and stem cell self-renewal [Kataoka and Kurokawa, 2012]. In mice, it has a pattern of expression suggesting an important function in organogenesis of the limbs, kidney, lung, and heart [Perkins et al., 1991]. *MECOM* missense mutations have been reported in individuals with radioulnar synostosis with amegakaryocytic thrombocytopenia (RUSTAT), an inherited bone marrow failure syndrome with skeletal anomalies [Niihori et al., 2015]. *MECOM* haploinsufficiency may be sufficient to cause bone marrow failure; however, no limb anomalies were described in individuals with the 3q26 deletion [Nielsen et al., 2012], suggesting that the missense mutations may act as gain-of-function, partial loss-of-function, or possibly dominant-negative rather than the complete loss-of-function mutations affecting the bone development of forearms and fingers [Niihori et al., 2015]. Until now, our patient did not present with any hematological abnormalities and only showed clinodactyly.

TERC (telomerase RNA component) is a non-translated essential RNA-component serving as a template for telomere elongation for telomerase activity in the maintenance of telomere integrity. Mutations in *TERC* have been identified in autosomal dominant dyskeratotis congenital [Vulliamy et al., 2001] and isolated aplastic ane-

mia or myelodysplastic syndrome [Yamaguchi et al., 2003]. Our patient did not exhibit any clinical features of dyskeratosis congenita nor aplastic anemia or myelodysplastic syndrome.

Also, *CLDN11* (claudin-11) has been identified in the central nervous system (CNS) myelin and was shown to be necessary for normal murine CNS function [Gow et al., 1999]. Its expression is highly regulated during development and, therefore, may play an important role in growth and differentiation of oligodendrocytes and other cells outside the CNS [Bronstein et al., 2000]. This gene could be implicated in the learning disabilities and behavioral disturbances observed in our patient. Until now, it seems that the role of the other candidate genes is not associated with the features present in our patient.

Our data contribute to the genotype-phenotype correlation in dup(3q) syndrome, suggesting narrowing the critical region for some specific clinical signs such as intellectual disability, synophrys, dysmorphic ears, wide nasal bridge, clinodactyly, and cardiac defects. We would like to highlight the importance of chromosomal microarray analysis for determining the breakpoints and detecting smaller duplications. To determine the significance of this duplication on the phenotype, further investigation on other individuals carrying similar duplications and more information about the function of the genes in the affected region will be necessary in the future.

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Statement of Ethics

This study was approved by the Ethics Committee Board of the University of Campinas (487/2009 and 433/2010). Written informed consent and permission to publish the images were obtained from the patient's parents.

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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