



Contents lists available at ScienceDirect

Meta Gene

journal homepage: www.elsevier.com/locate/mgene

A 10.43 Mb duplication of chromosome region 5q31.2-q32 associated with a general delay in psychomotor development

Eduardo Santoro^{a,*}, Henrique Pandolfo^{b,**}, Jill Rosenfeld^{c,1}, Salmo Raskin^{b,d,e}

^a Pontifical Catholic University of Paraná, PUC-PR, Brazil

^b Positivo University (UP), Brazil

^c Signature Genomic Laboratories, PerkinElmer, Inc., Spokane, WA 99207, USA

^d Group for Advanced Molecular Investigation, Graduate Program in Health Sciences, School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

^e Genetika-Centro de Aconselhamento e Laboratório de Genética, Curitiba, Paraná, Brazil

ARTICLE INFO

Article history:

Received 14 July 2016

Accepted 2 September 2016

Available online xxxx

Keywords:

CGH

Delay

Development

Psychomotor

Retardation

Mental

Duplication

Chromosome 5

5q31.2-q32

ABSTRACT

We report a 4-year, 4-month-old male with a 10.43 Mb duplication of chromosome region 5q31.2-q32 presenting with a general delay in psychomotor development including moderate to severe intellectual disability, language delays and gross and fine motor delays. Based on comparison with the only case of a similar duplication reported in the literature, we suspect that an extra copy of *PURA* in our patient may be involved in the early onset intellectual disability and seizures. Further studies and reports of cases with similar duplications could provide additional information about the influence of this gene on the phenotype of patients with a 5q31.2-q32 duplication.

© 2016 Elsevier B.V. All rights reserved.

Delayed psychomotor development (DPMD) is defined as a delay in various developmental domains such as fine and/or gross motor skills, language, cognition, social and personal competencies and activities of daily living. As any of these domains can be more or less compromised, DPMD is a heterogeneous entity not only in terms of its etiology but also in terms of its phenotypic profile (Ferreira, 2004). The prevalence of the condition is estimated to be 1 to 3% in children below the age of three years (Hochstenbach et al., 2009). A significant delay is defined as one that is two standard deviations below the mean for children of the same age.

The subject of this case report is a 4-year, 4-month-old boy with a general delay in psychomotor development (Table 1). He was delivered by preterm cesarean section (35 weeks and 4 days) following a dizygotic twin pregnancy complicated by intrauterine growth restriction and

single umbilical artery. The patient was twin A and had a birth weight of 1.5 kg, while his twin brother had a birth weight of 3.665 kg. He was kept in an incubator for one week and discharged without any intercurrent events. The patient's parents are non-consanguineous, are both healthy and were 36 years old at the time the children were born. The patient was identified as having moderate development delay at the age of 1 year and started having epileptic seizures at five months, as well as hypothyroidism and repeated cases of bronchiolitis until the age of eight months. The patient currently has approximately one epileptic seizure per week. Branchiootorenal syndrome was suspected as the patient presented with bilateral preauricular tags (Fig. 1), but normal abdominal ultrasound and otoscopy showed that the patient did not meet diagnostic criteria (Palheta-Neto et al., 2007).

At 4 years and 4 months of age the patient is 94 cm tall (P5), weighs 13.2 kg (P10) and has a head circumference of 46.5 cm, indicating mild growth retardation. Clinical examination revealed the preauricular tags mentioned above and a triangular face (Fig. 2) without any other facial dysmorphism. Gait was broad-based with external rotation of the feet, and the parachute reflex was absent. Muscle tone was normal. The patient goes to school with his brother, and according to his parents his social interaction with family members and classmates is good although he does not feed himself or eat solid food. His parents say that he is afraid of loud noises.

* Correspondence to: Eduardo Santoro, Rua 7 de Abril, 1241, Curitiba, Paraná CEP: 80040-120, Brazil.

** Correspondence to: Henrique Pandolfo, Av. Silva Jardim, 994, Ed. Cordilheiras, Rebouças, Curitiba, Paraná CEP: 85230-000, Brazil.

E-mail addresses: eduu_sl@hotmail.com (E. Santoro), hen.celta@hotmail.com (H. Pandolfo), jill.mokry@bcm.edu (J. Rosenfeld), genetika@genetika.com.br (S. Raskin).

¹ Present address: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, 77030, USA.

Table 1
Patient's general developmental delay.

Milestones	Age
Developmental milestones	
Recognized mother's face and voice	Normal
Social laugh	3 months
Responded to games, held foot and put it in his mouth	2.5 years
Helped when being dressed, ate with his fingers	1.5 years
Ate on his own with a spoon	4 years
Ate well on his own	4 years
Controlled sphincters and referred to himself by his name	4 years and 4 months
Played in a group	2 years
Brushed his teeth	3 years and 4 months
Undid his buttons	Not yet
Put on his shoes	Not yet
Washed his face	Not yet
Language milestones	
Responded to his name	Normal
Spoke two or more meaningful words	2.5 years
Spoke 10 or more words	3 years
Said short phrases	Not yet
Made complete sentences	Not yet
Conjugated verbs	Not yet
Motor milestones	
Supported his head	1 year
Lifted his head and shoulders when prone	1.5 years
Sat without support	1.5 years
Walked with help or with support	2.5 years
Ran	3 years and 4 months
Walked in a coordinated manner	Not yet
Rode a tricycle	Not yet



Fig. 2. Triangular face.

Laboratory tests (amino acids and plasma quantitative chromatography) were all normal. Kidney, liver, gastrointestinal and ophthalmological exams were normal. The only endocrinological disease identified was hypothyroidism; diabetes was ruled out. His echocardiogram was normal. MRI at the age of 1.5 years revealed frontal polymicrogyria. EEG at 3 years diagnosed epilepsy. His karyotype was normal. The patient is currently receiving therapy for vitamin D deficiency.

Array-CGH was first performed with DNA extracted from peripheral blood of the patient and his parents using a bacterial artificial chromosome (BAC)-based microarray (SignatureChip Whole Genome; Signature Genomic Laboratories, Spokane, WA) as described elsewhere (Ballif et al., 2008). The size of the duplication was established more accurately with a 135 K-feature oligonucleotide-based array (SignatureChip Oligo Solution™, version 2.0, custom-designed by Signature Genomics and made by Roche NimbleGen, Madison, WI) using methods described elsewhere (Duker et al., 2010). Metaphase fluorescent *in situ* hybridization (FISH) was performed with chromosomes



Fig. 1. Appendages on the right and left tragi in a patient with DPMD and a 10.43 Mb duplication on chromosome 5q31.2–q32.

from the patient and his parents using BAC clone CTD-2589F14 from 5q31 as described in Traylor et al., 2009.

Oligonucleotide-based array-CGH revealed a 10.43 Mb duplication of the coordinates (hg19) chr5:137887286–148318387 (Fig. 3), which was confirmed by interphase FISH. Based on its size and the number of affected genes, this duplication was expected to be clinically significant. The 10.43 Mb duplication included at least 120 OMIM genes. Parents were not tested for the duplication.

The most similar case reported in the literature was that of a 44-year-old female with an approximately 10 Mb duplication of the 5q31.3–5q32 region associated with late-onset partial lipodystrophy like that found in Barraquer-Simons syndrome, ichthyosis, epilepsy and glomerulonephritis (Faguer et al., 2011). The patient had a moderate-to-severe intellectual disability during childhood and developed epilepsy at the age of 19 years (Faguer et al., 2011). Lipodystrophy started at the age of 10 years, and at 44 years the patient developed focal and segmental glomerulonephritis with glomerulosclerosis and non-monoclonal mesangial IgA deposits, culminating in acute kidney failure, swelling of the legs and hypertension (Faguer et al., 2011). Chromosome analysis revealed a partial trisomy in the 5q31.3–5q32 region, and array-CGH analysis allowed this approximately 10 Mb duplication to be mapped precisely (minimum size chr5:139869758.149581689 (9.71 Mb); maximum size chr5:139535886.149759172 (10.22 Mb), UCSC hg19 coordinates (Fig. 3) (Faguer et al., 2011).

There is ~1.3 Mb duplicated in this previously reported patient (Faguer et al., 2011) and not in ours (involving at least 24 genes, including *PPARGC1B* and *MIR143HG*). The authors attributed the patient's late-onset lipodystrophy to the *PPARGC1B* gene (Faguer et al., 2011), which is not included in our patient's duplication. The only similarities between this previously reported patient and our proband are intellectual disability and epilepsy, which in the adult female patient manifested only after the age of 10 years (Faguer et al., 2011). Her additional symptoms, including lipodystrophy, ichthyosis and glomerulonephritis, were also later-onset, so it is possible that our patient could be at risk for these conditions in the future. Alternatively, as these symptoms could be due to genes not duplicated in our patient, he may not develop these features. Proximally, ~2 Mb duplicated in our patient was not included in that were not in the previously reported patient's duplication (involving at least 30 genes, like *PURA*). However, at least at age 5, there are not significant phenotypes present in our patient and absent in the other.

A gene of clinical importance, located within the proband's duplication, would be *PURA* (purine-rich element binding protein A). Heterozygous mutations and deletions of this gene, as in 5q31.3 microdeletion syndrome, cause neonatal hypotonia, encephalopathy with or without

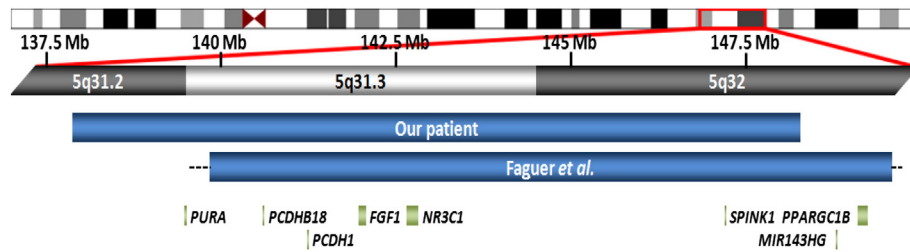


Fig. 3. Genomic positions of the duplications in our patient and a previously reported patient. An ideogram of chromosome 5 is shown at the top of the figure, with an enlarged view of 5q31.2q32 beneath (using hg19 coordinates). Blue bars represent the minimum size of duplications; dashed horizontal lines extend through gaps in coverage to show the maximum size of duplications. Green boxes represent genes of note within the region; all gene content is not shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

epilepsy, seizures, moderate to severe developmental delay and learning disability (Seema et al., 2014; Bonaglia et al., 2015). Given that many dosage-sensitive genes will result in abnormal phenotypes when deleted and duplicated, it is possible that inclusion of *PURA* in our patient's duplication (and its absence from the previously reported duplication) may be clinically significant and contribute to his early onset neurodevelopmental abnormalities.

Further studies and reports of cases with similar duplications could provide additional information about the influence of these genes on the phenotype of patients with a 5q31.2–q32 duplication.

Conflicts of interest

None.

References

- Ballif, B.C., Theisen, A., Coppinger, J., et al., 2008. Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. *Mol. cytogenet.*
- Bonaglia, M.C., Zanotta, N., Giorda, R., D'Angelo, G., Zucca, C., 2015. Long-term follow up of a patient with 5q31.3 microdeletion syndrome and the smallest de novo 5q31.2q31.3 deletion involving *PURA*. *BioMed Central.*
- Duker, A.L., Ballif, B.C., Bawle, E.V., Person, R.E., Mahadevan, S., Alliman, S., Thompson, R., Traylor, R., Bejjani, B.A., Shaffer, L.G., Rosenfeld, J.A., Lamb, A.N., Sahoo, T., 2010. Paternally inherited microdeletion at 15q11.2 confirms a significant role for the SNORD116C/D box snoRNA cluster in Prader Willi syndrome. *Eur. J. Hum. Genet.* 18, 1196–1201.
- Faguer, S., A., D.S.–G., M., H., N., L., et al., 2011. A 10 Mb duplication in chromosome band 5q31.3 – 5q33.1 associated with late-onset lipodystrophy, ichthyosis, epilepsy and glomerulonephritis. *Eur. J. Med. Genet.* 54, 310–313.
- Ferreira, J.C., 2004. Atraso global do desenvolvimento psicomotor. *Rev Port Clin Geral* 20, 703–712.
- Hochstenbach, R., Binsbergen, E., Engelen, J., Nieuwint, A., Polstra, A., Poddighe, P., Claudia Ruivenkamp, C., Sikkema-Raddatz, B., Smeets, D., Poot, M., 2009. Array analysis and karyotyping: workflow consequences based on a retrospective study of 36,325 patients with idiopathic developmental delay in the Netherlands. *Eur. J. Med. Genet.* 52, 161–169.
- Palheta-Neto, F.X., Silva, D.L., Santos, E.M.B., et al., 2007. Síndrome brânquio-otorrenal. Um importante alerta, Moreira Jr Editora.
- Seema, R., Lalani, J.Z., Schaaf, C.P., et al., 2014. Mutations in *PURA* cause profound neonatal hypotonia, seizures, and encephalopathy in 5q31.3 microdeletion syndrome. *Am. J. Hum. Genet.* 95, 579–583.
- Traylor, R.N., Fan, Z., Hudson, B., Rosenfeld, J.A., Shaffer, L.G., Torchia, B.S., Ballif, B.C., 2009. Microdeletion of 6q16.1 encompassing *EPHA7* in child with mild neurological abnormalities and dysmorphic features: Case report. *Mol. Cytogenet.* 2, 17.