A Genotype First Approach in Currarino Syndrome

Donatella Milani[1,#], Francesca Andrea Bonarrigo[1,#], Silvana Guerneri[2], Marco Baccarin[2], Francesca Menni[1] and Susanna Esposito[1,*]

[1]*Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

[2]*Medical Genetics Laboratory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

Abstract: We describe a 3-year-old girl presenting with psychomotor delay and facial dysmorphisms. Array CGH showed a region of duplication and a contiguous deletion on the long arm of chromosome 7. The genetic results allowed us to discover previously unsuspected sacral agenesis and presacral teratoma typical of Currarino syndrome, whose gene maps to the deleted region. So we used a genotype first approach to better discover the phenotypic traits of our patient, highlighting the advantages of an appropriate clinical use of genetic methods.

Keywords: Array CGH, 7q36.2q36.3 deletion, 7q36.1q36.2 duplication, sacral agenesis, teratoma.

CASE REPORT

The patient is a 3-year-old girl born to non-consanguineous parents by means of a caesarean section at a gestational age of 37 weeks following a normal pregnancy. Her birth weight was 2,380 g, birth length 42 cm, occipitofrontal diameter (OFD) 31 cm, and Apgar score 9/10. She presented sucking difficulties and failed to thrive up to 12 months. Her neuropsychiatrist referred the child to us when she was two years old because of psychomotor delay, poor growth, upper respiratory infections and mesocardia, with a patent foramen ovale, non-compaction of the left ventricle and persistent left superior vena cava. Magnetic resonance imaging (MRI) previously performed at another centre revealed dysmorphic and slightly hypoplastic cerebellar vermis, delayed myelination of the subcortical frontal white matter, and moderate accentuation of the perivascular, paraventricular and subcortical spaces. When she first visited our clinic, her weight was 9,900 kg (3rd percentile), height 78 cm (<3rd percentile), and OFD 44 cm (<3rd percentile). Her facial dysmorphisms consisted of brachycephaly, almond-shaped palpebral fissures, mild hypotelorism, malar hypoplasia, thick lips, an open mouth appearance, and mild prognathism (Figure **1**). She had not reached independence in walking or sphincter control and, as her verbal language was very poor (only babbling), she started speech therapy, which led to an improvement in her psychomotor development. Given her frequent upper respiratory infections, she underwent an otolaryngology evaluation that revealed a bifid uvula, grade III extra-velar tonsils and adenoid vegetations occupying 80% of the choanae. Because of her features and clinical history, a standard karyotype analysis was performed but the results were normal. The patient's blood was subsequently analysed by means of array comparative genomic hybridisation (a-CGH) using an Agilent SurePrint G3 human 8x60K at a resolution of about 130 Kb, which revealed a duplication of about 2.9 Mb between nucleotides 150659772 and 153569168 on 7q36.1-q36.2, and a deletion of about 5.3 Mb between nucleotides 153617970 and 158909738 on 7q36.2-q36.3 (Figure **2**). Gene content analysis by the University of California Santa Cruz (UCSC), the

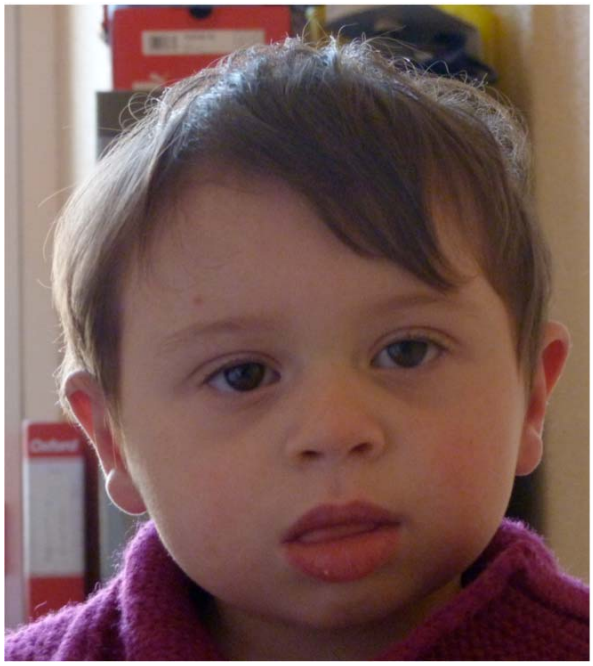

Figure 1: Facial dysmorphisms of the proband.

*Address correspondence to this author at the Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via della Commenda 9, 20122 Milano, Italy; Tel: +39-02-55032498; Fax: +39-02-50320206; E-mail: susanna.esposito@unimi.it
#These two authors contributed equally to this study.

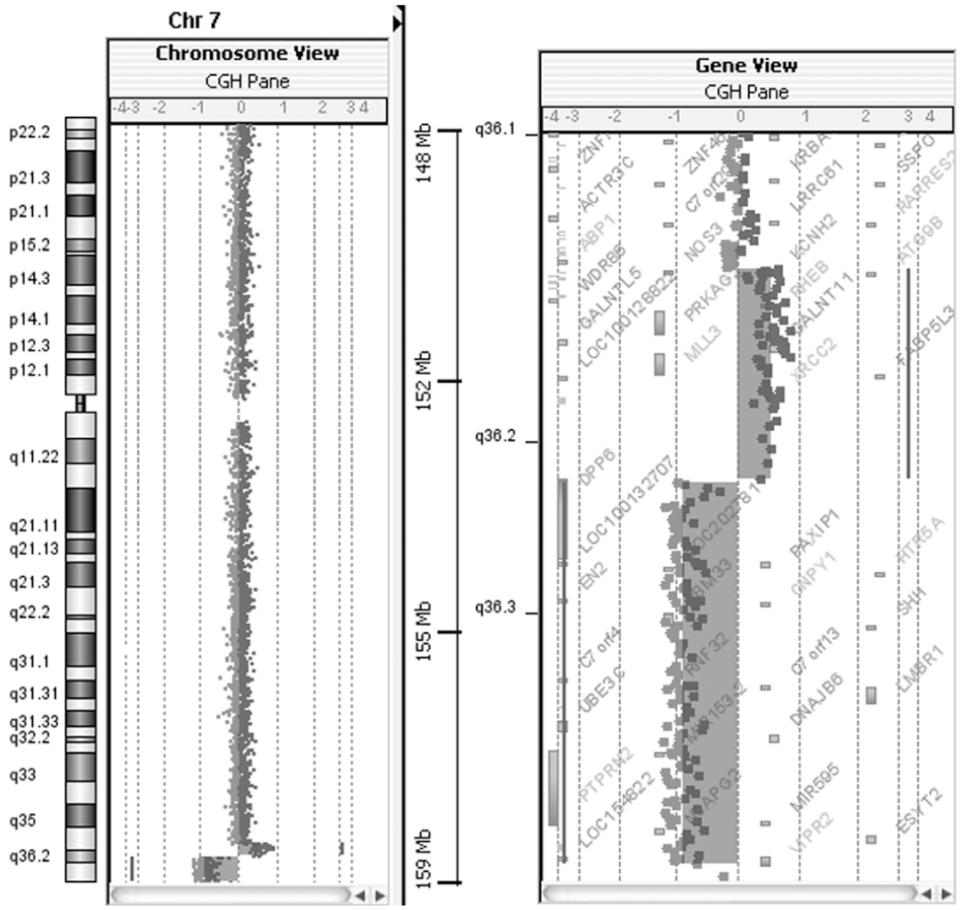

Figure 2: Chromosome view: idiogram of chromosome 7 and a-CGH results. The gene view shows the duplication (right side of the $\log_2$ ratio = 0) and the contiguous deletion (left side of the $\log_2$ ratio = 0) of the q36.1q36.3 bands of chromosome 7 together with the involved genes.

Database of Genomic Variants (DGV) and the International Standards for Cytogenomic Array (ISCA) Genome Browsers allowed correlation with the known phenotype and the identification of otherwise unsuspected clinical manifestations. The duplicated region contains a number of genes whose specific roles in the proband are unknown. The literature contains descriptions of a number of patients with more or less extensive duplications of the terminal region of the long arm of chromosome 7. Novales *et al*. and Morava *et al*. have reported cases of larger duplications (respectively of 7q32-qter and 7q35-qter) in patients with some features in common with those of our patient (facial dysmorphisms and language delay), but also others not identified in our case, including skeletal and severe central nervous system alterations [3,4]. Another case with a smaller duplication of the 7q36.1-3 chromosomal region is more similar to ours [5]. These phenotypical differences can be explained by the different gene content of the variously sized duplications. Interestingly, the deleted region in our patient contains a number of genes with a variety of known functions, including *SHH* (OMIM #600725), *PAXIP1* (OMIM #608254) and *EN2* (OMIM #131310), which are strictly related to central nervous system (CNS) anomalies and neurological development, and *DPP6* (OMIM #126141) and *LMBR1* (OMIM #605522) whose anomalies are respectively related to idiopathic ventricular fibrillation (IVF) and finger malformations. In our patient, *SHH* and *EN2* involvement could explain the CNS anomalies, but *DPP6* deletion cannot cause IVF, whose most likely pathogenetic mechanism is increased gene expression. As our patient has no limb anomalies, the contribution of *LMBR1* is uncertain but it is worth noting that such malformations have been found when the mutations lie in the zone of polarising activity (ZPA) regulatory sequence (ZRS) with an intact *SHH* gene [2]. Another gene included in the deleted region is *MNX1* (OMIM #142994). This is involved in Currarino syndrome (OMIM #176450), which is characterized by the clinical triad of a pre-sacral mass, and urogenital and anorectal malformations [1]. For this reason, our patient underwent a radiological examination that revealed the sub-total agenesis of the sacrum and coccyx. Encephalic and spinal MRI was performed in view of the deletion of *SHH* and *MNX1*.

There were no significant differences in encephalic appearance from those revealed by the previous scan, but spinal MRI confirmed partial sacral and complete coccygeal agenesis, and identified a tethered cord and an expansive pre-sacral mass with irregular margins and an inhomogeneous signal (suspected teratoma) (Figure **3**). Subsequent abdomino-pelvic ultrasonography and MRI confirmed the presence of this area of adipose tissue containing hypoechoic cysts (thus confirming it as a teratoma) and identified the presence of a horseshoe kidney. It is interesting to note that it was the gene content (particularly the relationship between *MNX1* and Currarino syndrome) that led us to perform the radiological examinations in a search for the typical sacral alterations and pre-sacral tumour. Although our patient was in good general condition and completely asymptomatic, the radiological examinations revealed the presence of the pelvic mass: this allowed us to perform surgery quickly, with less risk of long-term complications and obvious implications for the maintenance and monitoring of the related neurological functions. It is therefore clear that genotype analyses using new genetic techniques are essential for both diagnostic and therapeutic purposes. We started from the genotype in order to find out more about our patient, but returned to the phenotype in order to be able to treat and follow her over time. Our case therefore highlights the broader advantages of genetic methods as a bridge between basic molecular studies and general practice.

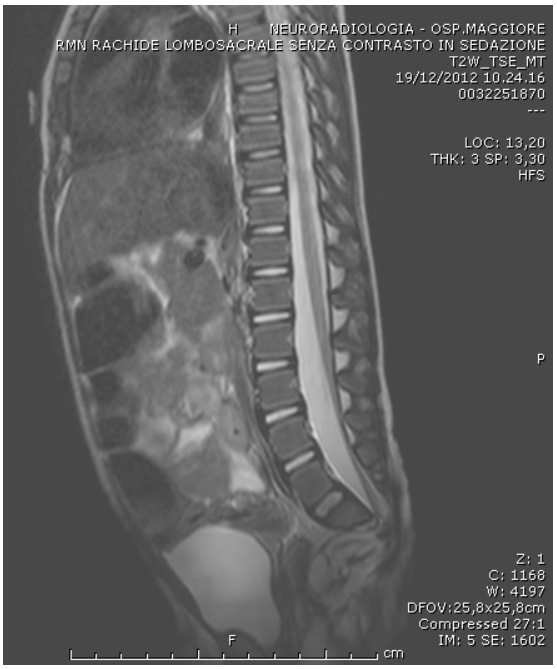

Figure 3: Spinal MRI confirmed partial sacral and complete coccygeal agenesis, and identified a tethered cord and an expansive pre-sacral mass with irregular margins and an inhomogeneous signal (suspected teratoma).

ACKNOWLEDGEMENTS

We would like thank the patient and his family for their willingness to participate in this study.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that they have no potential conflicts of interest relating to the research, authorship, and/or publication of this article.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

The informed consent of the patient's parents was obtained before the preparation of this case report.

ABBREVIATIONS

a-CGH = Array comparative genomic hybridisation

CNS = Central nervous system

DGV = Database of Genomic Variants

IVF = Idiopathic ventricular fibrillation

ISCA = International Standards for Cytogenomic Array

MRI = Magnetic resonance imaging

OFD = Occipitofrontal diameter

UCSC = University of California Santa Cruz

ZPA = Zone of polarising activity

ZRS = Zone of regulatory sequence

REFERENCES

[1] Currarino G, Coln D, Votteler T. Triad of anorectal, sacral, and presacral anomalies. Am J Roentgen 1981; 137: 395-8. http://dx.doi.org/10.2214/ajr.137.2.395

[2] Lettice LA, Heaney SJH, Purdie LA, Li L, de Beer P, Oostra BA, *et al*. A long-range Shh enhancer regulates expression in the developing limb and fin and is associated with preaxial polydactyly. Hum Molec Genet 2003; 12: 1725-35. http://dx.doi.org/10.1093/hmg/ddg180

[3] Morava E, Bartsch O, Czakó M, Frensel A, Kalscheuer V, Kárteszi J, Kosztolányi G. Small inherited terminal duplication of 7q with hydrocephalus, cleft palate, joint contractures, and severe hypotonia. Clin Dysmorphol 2003; 12: 123-7. http://dx.doi.org/10.1097/00019605-200304000-00010

[4] Novales MA, Fernandez-Novoa C, Hevia A, San Martin V, Galera H. Partial trisomy for the long arm of chromosome 7. Case report and review. Hum Genet 1982; 62: 378-81. http://dx.doi.org/10.1007/BF00304563

[5] Unique International [homepage on the Internet]. Available from http://www.uniqueinternational.org/html/home.asp Accessed on 21 August 2013.

Received on 11-12-2013 Accepted on 17-12-2013 Published on 26-12-2013

DOI: http://dx.doi.org/10.12974/2311-8687.2013.01.01.3