Karyotype-Phenotype Correlation in Partial Trisomies of the Short Arm of Chromosome 6: A Family Case Report and Review of the Literature

A. Castiglione^a V. Guaran^b L. Astolfi^b E. Orioli^c G. Zeri^c D. Gemmati^c
R. Bovo^a A. Montaldi^d A. Alghisi^d A. Martini^a

^aDepartment of Neurosciences, Complex Operative Unit of Otorhinolaryngology and Otosurgery, Padua University Hospital, and ^bBioacoustics Research Laboratory, University of Padua, Padua, ^cDepartment of Medical Sciences, Centre Haemostasis & Thrombosis, Ferrara University, Ferrara, and ^dDepartment of Immunohaematology, Transfusion Medicine and Human Genetics, San Bortolo Hospital, Vicenza, Italy

Key Words

Arnold-Chiari malformation type I · Choanal atresia · Chromosome 6p · Coagulation factor XIII · Congenital heart defects · Congenital ptosis · D-dimer · Hearing loss · Partial trisomy · Renal hypoplasia

Abstract

The first child (proband) of nonconsanguineous Caucasian parents underwent genetic investigation because she was affected with congenital choanal atresia, heart defects and kidney hypoplasia with mild transient renal insufficiency. The direct DNA sequencing after PCR of the *CHD7* gene, which is thought to be responsible for approximately 60–70% of the cases of CHARGE syndrome/association, found no mutations. The cytogenetic analysis (standard GTG banding karyotype) revealed the presence of extrachromosomal material on 10q. The chromosome analysis was completed with array CGH (30 kb resolution), MLPA and FISH, which allowed the identification of three 6p regions (6p.25.3p23 × 3): 2 of these regions are normally located on chromosome 6, and the third region is translocated to the long arm of chromosome 10. The same chromosomal rearrangement was subsequently found in the father, who was affected with

congenital ptosis and progressive hearing loss, and in the proband's sister, the second child, who presented at birth with choanal atresia and congenital heart defects. The mutated karyotypes, which were directly inherited, are thought to be responsible for a variable phenotype, including craniofacial dysmorphisms, choanal atresia, congenital ptosis, sensorineural hearing loss, heart defects, developmental delay, and renal dysfunction. Nevertheless, to achieve a complete audiological assessment of the father, he underwent further investigation that revealed an increased level of the coagulation factor XIII (300% increased activity), fluctuating levels of fibrin D-dimer degradation products (from 296 to 1,587 ng/ml) and a homoplasmic mitochondrial DNA mutation: T961G in the *MTRNR1* (12S rRNA) gene. He was made a candidate for cochlear implantation. Preoperative high-resolution computed tomography and magnetic resonance imaging of the temporal bone revealed the presence of an Arnold-Chiari malformation type I. To the best of our knowledge, this study is the second report on partial 6p trisomy that involves the 10q terminal region. Furthermore, we report the first case of documented Arnold-Chiari malformation type I and increased factor XIII activity associated with 6p trisomy. We present a comprehensive report of the familial cases and an exhaustive literature review.

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Partial trisomy of the short arm of chromosome 6 is a rare chromosomal abnormality with a variable phenotype (table 1); it was first described by Therkelsen et al. [1971], who reported a familial case of 4 unbalanced translocations between the 6p and 20p chromosomes. Villa et al. [2000] published an extensive review of 40 previously reported cases and the description of a new partial trisomy 6p case. Similar cytogenetic diagnoses are increasing in number, and to date, there are more than 80 cases of 6p trisomies reported in the literature, to which at least 10 unpublished cases could be added (<http://www.rarechromo.org/html/home.asp>, last access April 2013) along with 3 chromosomal rearrangements thought to be polymorphisms [Bonaglia 2003, 2008; Hengstschläger et al., 2005]. Reviewing a published series on prenatal diagnosis and cytogenetic analysis revealed a 6p duplication recurrence rate of approximately 1–2 cases on 10,000 investigations [Ravnan et al., 2006; Lee et al., 2012; Shaffer et al., 2012]. Carriers of 6p trisomy can also be identified among patients who underwent cytogenetic investigations because of mental retardation [Anderlid et al., 2002], developmental delay and intellectual disabilities [Roberts et al., 2004; Belligni et al., 2009; Wu et al., 2010]. Nonetheless, it is difficult to calculate realistic rates of prevalence or incidence. In fact, selecting reports with strictly similar genetic conditions (in terms of the origin and extension of the involved 6p region, the concomitant deletions, pure trisomy, inversions, comorbidity, and available data) reduces the comparable studies to a few cases in which similar conditions have been identified (table 2).

A partial trisomy can originate in different ways: (1) from a previously more or less balanced translocation, (2) from an interstitial duplication, (3) from a chromosomal inversion, (4) from the presence of additional, extra chromosomes, or (5) from complex chromosomal rearrangements (table 2) [Krassikoff and Sekhon, 1989; Pettenati et al., 1995; Song and Li, 1996; Ng et al., 2001; Gruchy et al., 2010]. The proximal breakpoint in the short arm of chromosome 6 can vary from 6p11 to p25 (table 2). Despite different lengths and clinical features of previously reported trisomies, a characteristic phenotype has been established for duplications of the short arm of chromosome 6, and it includes low birth weight with developmental delay or growth retardation, mild to severe craniofacial abnormalities, feeding difficulties, recurrent respiratory infections, congenital heart defects, and renal abnormalities (table 1). Characteristic craniofacial findings include craniosynostosis, prominent forehead, blepharophimosis and blepharoptosis, hypotelorism, low-set or malformed ears, small pointed chin, short and

Table 1. Clinical signs of trisomy 6p

Clinical features	
Low birth weight	Proteinuria
Developmental delay	Vision problems
Psychomotor delay	Small corneas
Mental retardation	Cataracts
Feeding problems	Strabismus
Recurrent infections	Drooping upper eyelid
Immunodeficiency	Blepharoptosis
Craniosynostosis	Blepharophimosis
High, prominent forehead	Long or smooth philtrum
Flat occiput	Small mouth or thin lips
Closed anterior fontanelle	High arched palate
Wide fontanelle	Gingival hypertrophy
Choanal atresia	Micrognathia
Tiny nares	Clinodactyly or syndactyly
Anteverted nares	Pointed chin
Short nose	Low-set ears
Flat nose	Poor ear lobes
Bulbous nose	Malformed pinnae
Skin pigmentary anomalies	Cardiac defects
Angiomas	Heart murmur
Renal anomalies (hypoplasia)	Hearing loss

bulbous nose with tiny nares, choanal atresia, prominent nasal bridge, and small mouth with thin lips. Intellectual disability, epilepsy, mental retardation, autism, brain abnormalities, hearing loss, ocular defects, or immunodeficiency with susceptibility to pulmonary infections have also been reported [Smith and Pettersen, 1985; Fryns et al., 1986; Burd et al., 1988; Krassikoff and Sekhon, 1989; Katafuchi et al., 1992; Wauters et al., 1993; Giardino et al., 2002; Bart et al., 2011]. Furthermore, this chromosome anomaly is associated with a reduced life span [Villa et al., 2000; Stohler et al., 2007].

A total of 2,074 genes are located on chromosome 6 (<http://www.ncbi.nlm.nih.gov/projects/mapview/>, last access April 2013), and they have many and variable functions; 1,204 are located in the short arm, a fact that makes it quite impossible to estimate the contribution of the gene expression to the phenotype. Nonetheless, some authors reasonably speculate on the potential involvement of specific genes in determining the 6p trisomy phenotype (tables 2, 3). Eligible candidates are the genes *IRF4*, *BMP5*, *BMP6*, *RUNX2*, *FOXQ1*, *FOXF2*, *FOXC1*, *NRN1*, *EDN1*, *ATXN1*, *TFAP2B*, *VEGFA*, *DEK* oncogene, *E2F3*, *NRNS1*, *SERPINB1*, *SERPINB6*, *SERPINB9*, and the *HLA* (major histocompatibility complex) family (*A*, *B*, *C*, *E*, *F*, *G*) [Pearson et al., 1979; Fogu et al., 2007; Mandal et al., 2007;

Table 2. Previously reported cases of partial 6p trisomy with a critical analysis of genes that are potentially involved

No. of cases and sex trisomy/monosomy references	Karyotype; main phenotype	Notes (genes potentially involved)
1 M 6p10p21.1 Villa et al., 2007	47,XY,+mar[14]/46,XY[6] mosaicism for small supernumerary marker chromosome; A, B, I, L, and craniosynostosis (?); the authors reported a decrease (over early ages) in the level of mosaicism for the sSMC(6) from 70 (neonatal) to 30% (18 months) of the cells.	<i>BMP5</i> was suggested as a candidate gene. The same duplicated region contains the <i>RUNX2</i> transcription factor [Varvagiannis et al., 2013]. Nevertheless, Maurer et al. [2001] reported 1 case with a developmental delay and craniofacial dysmorphisms, but no evidence of craniosynostosis. Finally, Crolla et al. [1998] reported a case of uniparental paternal isodisomy for chromosome 6 (6p11p21.1) and very mild developmental delay.
1 M 6p11pter/9p24pter Lytle et al., 1989	<i>de novo</i> 46,XY,-9,+der(9)t(6;9)(p11;p24); B, C, growth retardation, micrognathia, short neck, camptodactyly, ambiguous genitalia, hydrocele, and inguinal hernia.	Deletions of the <i>DMRT1</i> , <i>DMRT2</i> and <i>DMRT3</i> genes in the 9p24pter region are responsible for sexual differentiation and maturation.
1 F 6p11.1pter/Xq22qter Petković et al., 2003	46,X,der(X)t(X;6)(q22;p11.1)pat; A, B, F, and G.	Ovarian dysgenesis is known to be related to the loss of Xq22 [Therman et al., 1990], but 1 patient is too young to evaluate premature ovarian failure or sexual development; the <i>FMRI</i> (or <i>POF</i> or <i>POFI</i>) gene is responsible for premature ovarian failure syndrome type 1, fragile X syndrome and fragile X tremor/ataxia syndrome.
1 F 6p11.2pter/Xq22qter Center et al., 1994	46,X,der(X)t(X;6)(q22;p11.2)mat; A, L and ovarian dysgenesis with primary amenorrhoea.	
1 F ?-6p12/18pter Mandal et al., 2007	? (deducted karyotype); 46,XX,der(18)t(6;18)(p12;pter); <i>VEGF</i> polymorphism; 634 G/G/G characterised by unusual retinopathy in a preterm infant (30 weeks of gestational age).	<i>VEGF</i> 634 G/G genotype is associated with increased <i>VEGF</i> production, leading to abnormal neovascularisation in the immature preterm eye [Cooke et al., 2004]. The <i>VEGFA</i> gene is located at 6p12p21.1.
1 M, 1 F 6p12.1p22.1 Fogu et al., 2007	46,XX,der(12)(12pter→12q21.33::6p12.1→6p22.1::12q21.33→12qter)dir ins(12;6)pat; patient 1: A, B, E, F, G, I, L, opisthotonus, anal atresia, and retinal pigmentary dystrophy. 46,XY,der(12)(12pter→12q21.33::6p12.1→6p22.1::12q21.33→12qter)dir ins(12;6)pat; patient 2: B, F, I, bilateral hydrocele, phimosis, hypertonia, opisthotonus, and respiratory distress.	There is not a sufficient amount of data available to estimate the effect of the insertion in the 12q21.33 region. As suggested by the authors, the <i>TFAP2B</i> gene (6p12p13) is a good candidate.
1 M 6p12.2p21.31 Bart et al., 2011	<i>de novo</i> 46,XY,dup(6)(p12.2p21.31); B, E, F, G, micrognathia, macroglossia, tracheomalacia, hypertrophic pyloric stenosis, and Crohn-like inflammatory bowel disease.	Interstitial tandem duplication of 6p; the involvement of <i>RUNX2</i> and <i>IL17F</i> genes could explain the phenotype [Bart et al., 2011; Varvagiannis et al., 2013].
1 M 6p12.3 and 6p21.1p22.2/18q21.32 Gruchy et al., 2010	46,XY,der(18)(18pter→18q21.32::6p22.2→6p21.1::6p12.3→6p12.3::18q21.32→18qter)pat; complex chromosomal rearrangement; A, B, L, hypotonia, and deafness.	The 6p12.3 region contains 2 <i>TFAP</i> family genes (<i>TFAP2B</i> and <i>TFAP2D</i>) that, as previously suggested, could be involved in dysmorphic features [Fogu et al., 2007]. The deleted region contains genes that are involved in hypotonia, psychomotor and developmental delay: <i>CCBE1</i> , <i>CPLX4</i> , <i>RAX</i> , <i>GRP</i> , and <i>LMAN1</i> [Bennett et al., 2008; Gijssbers et al., 2010].
1 M, 1 F 6p12.3p21.1 Mefford et al., 2010	directly inherited heterozygous inverted duplication of 6p12.3p21.1; C, craniosynostosis and hypodontia.	Lacking data; the authors discussed the potential role of the <i>RUNX2</i> gene.
3 M, 1 F 6p21pter/20p12p13 Therkelsen et al., 1971	directly inherited der(20)t(6;20)(p21;p12-p13); A, B, C (in 2 cases), D, G, H, and L.	The 20p12p13 contains <i>BMP2</i> and many members of the defensin family (DEFB cluster); these are located at approximately 60 kb from pter, and their involvement is highly probable. The deletion of β-defensin family members (<i>DEFB125</i> , <i>DEFB126</i> , <i>DEFB127</i> , <i>DEFB128</i> , <i>DEFB129</i> , and <i>DEFB132</i>) can explain susceptibility to the infections; <i>BMP2</i> (20p12), <i>RUNX2</i> (6p21) and <i>BMP6</i> (6p24p23) can contribute to defining the phenotype [McGill et al., 2010].
1 F 6p21pter/20p13 Breuning et al., 1977	46,XX,der(20)t(6;20)(p21;p13)pat; psychomotor retardation, A, B, C, D, F, H, G, L, and meningitis.	
1 M 6p21.3p25/20p13 Berner et al., 2012	46,XY,der(20)t(6;20)(p21.3;p13)mat; A, B, C, D, F, H, G, and L.	
1 M, 1 F 6p23pter/20p13 Delatycki et al., 1999	46,XY,der(20)t(6;20)(p23;p13) and 46,XX,der(20)t(6;20)(p23;p13)pat; A, B, D, H, I, and mild clinodactyly.	
1 F 6p21pter/15p12 or 13 Chiyo et al., 1975	46,XX,der(15)t(6;15)(p21;p12 or 13)pat; B, D, E, strabismus, and sacral dimple.	Essentially pure trisomies: no genes are known to be located on the short arm of chromosome 15.
1 M 6p22.1pter Engelen et al., 2001	<i>de novo</i> 46,XY,der(15)(6pter→6p22.1::15p12→15qter); B, C, D, F, H, and I.	Lacking data.

Table 2 (continued)

No. of cases and sex trisomy/monosomy references	Karyotype; main phenotype	Notes (genes potentially involved)
1 F 6p21pter/2p25 Bernheim et al., 1979	46,XX,der(2)t(2;6)(p25;p21)mat; A, B, F, L, right microcornea, and anterior polar opacities with normal ocular fundi.	Approximately 100 genes are located in region 2p25. E2F family members play a crucial role in the control of the cell cycle and in the action of tumour suppressor proteins. <i>E2F6</i> (2p25.1) can play a role in determining the phenotype.
1 M 6p21.2p21.3 Andrieux et al., 2008	de novo 46,XY,dup(6)(p21.2p21.3); B, L and epilepsy.	Interstitial tandem duplication of 6p; <i>GABBR1</i> , <i>BRD2</i> and <i>GRM4</i> genes could be responsible for epilepsy and other neurological findings.
1 F 6p22pter/10q26 Ferrando et al., 1981	46,XX,der(10)t(6;10)(p22;q26)pat; B, L and clinodactyly.	The <i>FGFR2</i> gene is located on the 10q26 region. Mutations in this gene are associated with craniosynostosis, Crouzon syndrome, Pfeiffer syndrome, Apert syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrata syndrome, and Saethre-Chotzen syndrome.
1 F 6p22pter/1p36.3 Su et al., 2012	de novo 46,XX,der(1)t(1;6)(p36.3;p22); B, C, general hypotonia, recurrent vomiting, and eye defects.	Essentially pure 6p22pter trisomy; <i>FOXQ1</i> , <i>FOXF2</i> , <i>FOXCI</i> , <i>NRN1</i> , <i>EDN1</i> , <i>ATXN1</i> , <i>DEK</i> , <i>E2F3</i> , and <i>NRSN1</i> can be good candidates [Su et al., 2012].
1 M 6p22.3pter/1q44 Belligni et al., 2009	46,XY,ish der(6)t(6;1)(p22.3;q44)mat; B (craniosynostosis), D, H, membranous glomerulonephritis, and chronic renal failure leading to kidney transplantation and hypoplastic corpus callosum.	The <i>NLRP3</i> gene (1q44) approximately maps at 1–2 Mb from 1qter; mutations in this gene are known to be responsible for Muckle-Wells syndrome. The olfactory receptor family members (OR cluster) that are located on 1q44 could also be considered to have a role in determining the phenotype.
1 F 6p21pter/6q27qter Pearson et al., 1979	46,XX,pat rec(6)inv dup(6pter→6p21, def 6q27→6qter (pter→p21::q27→p21::p21→pter); B (craniosynostosis), C, I, talipes equinovarus, absence of uterus and upper vagina, polymicrogyria, and arhinencephaly.	At least 4 genes, which are located on the distal 6q chromosome, are thought to be involved in sex determination and differentiation: <i>T</i> , <i>TCPI</i> , <i>TCPI0</i> , and <i>TCPI0L2</i> [Ion et al., 2000]. Of these, 3 are located in the q27 region. <i>TCPI</i> (6q25q27) is highly expressed in the uterus and ovaries.
1 F 6p21pter/18p11pter Rudnik-Schöneborn et al., 1997	de novo unbalanced translocation (6;18)(p21;p11) with variable mosaicism in different tissues; B, L and hypotonia.	Lacking data; possible effect of the mosaicism on the phenotype.
1 F 6p21pter/6q25qter Gazala et al., 2010	unbalanced pericentric inversion 46,XX,rec(6)dup(6p)inv(6)(p21.2q25.3)mat; A, B, clinodactyly overlapping digits, preterm growth retardation, microcephaly, clitoral hypertrophy, and kyphoscoliosis of the spine.	The 6q25.3qter region contains approximately 125 genes, and the partial loss of such DNA information could be responsible for the specific clinical picture; furthermore, the authors cannot exclude the disruption of some genes at the breakpoints or the formation of new pathological DNA sequences with parts of the disrupted genes.
1 F 6p21.1p22.2 Ng et al., 2001	46,XX,dir dup(6)(p21.1p22.2); B, F, G, L, and clinodactyly.	De novo interstitial tandem duplication of 6p; the entire major histocompatibility complex is duplicated.
1 M 6p21.2p23 Dominguez et al., 2003	directly inherited interchromosomal insertion 46,XY,ins(16;6)(p12;p21.2p23)mat; B, G, L, and heterotopia of cerebral tissue.	It is not possible to estimate the effect of the insertion on the chromosome 16p12. The 6p21.2p23 region contains gene clusters, HLA system and <i>E2F2</i> . It does not include the following genes: <i>RUNX2</i> , <i>BMP5</i> , <i>BMP6</i> , <i>FOXQ1</i> , <i>FOXF2</i> , <i>FOXCI</i> , <i>NRN1</i> , and <i>EDN1</i> .
1 M, 1 F 6p21.3pter/4p16.3pter Pierpont et al., 2000	46,XY,der(4),t(4;6)(p16.3;p21.3)mat and 46,XX,der(4),t(4;6)(p16.3;p21.3)mat; A, B, D, F, H, moderate mixed hearing loss, hypertension, and renal transplantation.	The 4pter region contains: <i>WHSC1</i> (Wolf-Hirschhorn syndrome), <i>FGFR3</i> (Muenke syndrome, achondroplasia, hypochondroplasia), <i>IDUA</i> (mucopolysaccharidosis type I), <i>PDE6B</i> (retinitis pigmentosa), and <i>HTT</i> (Huntington's disease).
1 M 6p22pter/22q13 Côté et al., 1978	46,XY,der(22),t(6;22)(p22;q13)mat; A, B, F, H, L, and encephalitis due to pertussis.	The 22q13.3 deletion is responsible for the Phelan-McDermid syndrome; the <i>SHANK3</i> gene is a good candidate even if the clinical picture is most likely related to the loss of multiple genes [Phelan and McDermid, 2012]
1 M 6p22pter/Yq12 Giardino et al., 2002	de novo mos 46X,add(Y)(q12)[92]/45,X[8]der(Y)t(Y;6)(q12;p22); A, B, D, E, H, I, L, myopia, scoliosis, and hyperglycemia.	Even if it is reported as an essentially pure trisomy, Yq12 (Yter) contains the <i>VAMP7</i> and <i>SPRY3</i> genes. The mosaicism and <i>VAMP7</i> deletion can explain hyperglycemia [Randhawa et al., 2004]; <i>SPRY3</i> can contribute to defining the phenotype.
1 M 6p22pter/21p13pter Nakajima et al., 1995	directly inherited from consanguineous parents 46,XY,-21,+der(21),t(6;21)(p22;p13)mat; B, C, F, growth retardation, microcephaly, hypoplastic corpus callosum (?), and abnormal auditory brainstem response.	This pattern could be considered to be a 'pure' 6p22pter trisomy because of the lack of genes in the 21p13pter region.

Table 2 (continued)

No. of cases and sex trisomy/monosomy references	Karyotype; main phenotype	Notes (genes potentially involved)
1 M 6p22-pter/13q33qter Rosi et al., 1979	46,XY,der(13),t(6;13)(p22;q34 or 33)pat; B, C, D, I, syndactyly, microphthalmia, partial bilateral cataract, 2–3/6 systolic heart murmur, left to right shunt, and biventricular hypertrophy.	The last gene (<i>CHAMP1</i>) maps at a distance of approximately 70 kb from the chromosome end; it is reasonable to think that several genes are involved in the deletion.
1 F 6p22.2p25.2 Scott et al., 2007	46,XX,inv dup(6)(p25.2p22.2); A, D and congenital diaphragmatic hernia.	This trisomy does not involve <i>FOXC1</i> , <i>IRF4</i> , <i>FOXF2</i> , <i>FOXQ1</i> , and <i>RUNX2</i> .
1 M 6p23pter and 9pterq21.2 Cetin et al., 2012	4:2 segregation 47,XY,der(7)t(6;7)(pter→p23::p15→qter),+der(9)t(7;9)(pter→p15::q21.2→pter)t(6;7;9)(p23;p15;q21.2)mat[20]; B, C, H, polydactyly, syndactyly, hydrocephaly, colpocephaly, dilated lateral ventricles, and hypogenesis of the corpus callosum.	Double partial trisomy due to a complex chromosomal rearrangement.
1 F 6p23pter/Xq22qter Sills et al., 2012	46,X,der(X)t(X;6)(q22;p23); primary amenorrhea and infertility.	Lacking data.
2 M 6p23pter/17p13.3pter Röthlisberger et al., 1999	46,XY,der(17)t(6;17)(p23;p13.3)mat; A, B, D, E, I, and L.	Even if reported as a ‘pure’ trisomy, the deletion/monosomy of genes that are located on the 17pter is highly probable. The 2 brothers’ phenotypes are coherent with similar reported pure trisomies.
1 M, 1 F 6p23pter/6q27qter Anderlid et al., 2002	46,XY,rec(6)dup(6p)inv(6)(p23q27)pat and 46,XX,rec(6)dup(6p)inv(6)(p23q27)pat; B, autistic features and heterotopia.	Lacking data.
1 F 6p24.1p25.3/? Vermeesch et al., 2004	46,XX,der(12)inv(12)(p13q12)t(12;6)(p13p25;3p24.1)mat; A, B, L, tonic-classic epileptic attack, hirsutism of the back, truncal obesity, and short stubby hands and feet with dorsal restoedema.	Lacking data.
1 M 6p25pter and 22q11.2pter Scarborough et al., 1986	47,Y,+der(22)(22pter→22q11.2::6p25→6pter)mat; 3:1 meiotic disjunction leading to 6p25pter and 22q11.2pter trisomies; A, D, I, holosystolic murmur, partial soft tissue syndactyly of the second to fourth toes, penile chordee, and cryptorchidism.	Lacking data.
1 F 6p25.1p25.3/6p24.26p24.3 Kerrigan et al., 2007	de novo interstitial tandem duplication 46,XX,dup(6)(p25.1p25.3); B, D, I, L, hypothalamic hamartoma, epilepsy, hypotonia, and recurrent laughing spells.	<i>FOXC1</i> gene; furthermore, the deleted region can partially involve the <i>OFCC1</i> DNA sequence that starts at 9,596,343 bp from pter and ends at 10,211,841 bp from pter; the <i>OFCC1</i> deletion can explain neurological findings and dysmorphic features.
1 F 6p25.1p25.3 Stohler et al., 2007	46,XX,der(8)t(6;8)(p25.1;p23.3)dup(6)(p25.1p25.3); B, C, D, H, eyelid colobomas, respiratory distress, cyanosis, and moderate to severe sensorineural hearing loss.	De novo, essentially pure tetrasomy; considering the case reported by Scott et al. [2007] suggested that candidate genes can be located between 6p25.1 and p25.2: <i>ECI2</i> , <i>NRN1</i> , <i>FARS2</i> , <i>TUBB2A</i> , <i>TUBB2B</i> , <i>SERPINB1</i> , <i>SERPINB6</i> , <i>SERPINB9</i> , <i>NQO2</i> , <i>RIPK1</i> , and <i>BPHL</i> .
1 F 6p12.3p21.1 Varvagiannis et al., 2013	B, G, L, and craniosynostosis.	Pure de novo partial trisomy; the authors discuss the potential role of the <i>RUNX2</i> gene.
1 M 6p12p21.3 Villa et al., 2000	de novo interstitial tandem duplication; pure trisomy of 6p12p21.3; B, G, L, corneal clouding, respiratory distress secondary to choanal atresia, bilateral inguinal hernia, cerebellar hypoplasia, right cryptorchidism, hypertonia, and seizures.	Lacking data.
1 M 6ptel, 20qtel Bonaglia et al., 2003	polymorphism 6ptel (250 kb) and 20qtel (300 kb) trisomies 46,XY,ish der(22)t(22;20;6)(q13.33;q13.33;p25.3)pat; bilateral retinal coloboma of the macular region, nystagmus, and vesicoureteral reflux.	Polymorphism [Hengstschläger et al., 2005]; nevertheless the 20q13.3 region contains the <i>MYT1</i> gene that plays an important role in myelination and regulating neural differentiation; it is around 90 kb long. It could be involved in retinal oligodendrocyte maturation. The microdeletion 15q11.2 is responsible for the Angelman syndrome.
1 M 6ptel, 20qtel (in 22qtel) Bonaglia et al., 2008	polymorphism 6ptel (250 kb) and 20qtel (300 kb) trisomies on 22qtel and concomitant deletion 15q11.1q11.2; Angelman syndrome.	

Specific findings are usually reported in full. A = Developmental delay; B = craniofacial abnormalities, including one or more of the following signs: mild to severe dysmorphic features, low set ears, prominent forehead, blepharophimosis, choanal atresia, arcuate palate, bulbous nose, craniosynostosis, thin lips, tiny nares; C = congenital heart defects; D = palpebral ptosis; E = mental retardation; F = feeding problems including swallowing difficulties;

G = immunodeficiency or other immune-system disorders with recurrent infections, mostly of the respiratory and gastrointestinal tracts; H = kidney abnormalities, including hydronephrosis, hypoplasia, renal insufficiency and proteinuria; I = skin pigmentary anomalies or angiomas; L = psychomotor delay or difficulties and other neurological disorders. Particular findings are generally reported.

Table 3. The main genes or the better-known genes are located in the distal tract of the 6p chromosome

Gene	Locus	Main function	Expression	Evidence of pathogenicity if overexpressed	Reference
<i>DUSP22</i>	6p25.3	phosphatase	ubiquitous, mostly in heart, placenta, lung, liver, kidney, and pancreas	–	Feldman et al., 2011; Sekine et al., 2007
<i>IRF4</i>	6p25p23	transcription factor	immune system cells, kidney	++	Shaffer et al., 2009
<i>EXOC2</i>	6p25.3	exocyst complex component	widely expressed with highest levels in brain and placenta	?	
<i>FOXC1</i>	6p25	transcription factor	ubiquitous	+ ?	Xia et al., 2013
<i>SERPINB1</i>	6p25	proteinase inhibitor	widely expressed	++	Tseng et al., 2009
<i>SERPINB9</i>	6p25	proteinase inhibitor	widely expressed	++	
<i>SERPINB6</i>	6p25	proteinase inhibitor	blood, liver, widely expressed	+/-	Soriano et al., 2012; El Haddad et al., 2011; Buzza et al., 2006
<i>NQO2</i>	6p25.2	flavoprotein, quinone reductase	ubiquitously expressed	–	Long and Jaiswal, 2000
<i>RIPK1</i>	6p25.2	involved in apoptosis regulation and inflammatory response	T and B cells, blood, kidney, widely expressed	?	
<i>TUBB2A</i>	6p25	microtubule transport	widely expressed, brain	–	Leandro-García et al., 2012
<i>FARS2</i>	6p25.1	synthesis of PHE tRNA	widely expressed	–	Banerjee et al., 2011
<i>RPP40</i>	6p25.1	maturation of tRNA molecules	blood, kidney	?	
<i>NRN1</i>	6p25.1	neurite outgrowth and arborisation	widely expressed, brain	+/-	Zhang et al., 2011b
<i>F13A1</i>	6p25.3p24.3	blood coagulation	blood, lung, widely expressed	+++	Bereczky and Muszbek, 2011
<i>RREB1</i>	6p25	transcription factor	blood, kidney, widely expressed	?	
<i>DSP</i>	6p24	component of desmosomes	blood, kidney and liver, widely expressed	?	
<i>BMP6</i>	6p24p23	bone growth	bone, cartilage, widely expressed	+++	Luo et al., 2011; Diekman et al., 2010; Westerweel et al., 2010
<i>TXNDC5</i>	6p24.3	protect hypoxic cells from apoptosis	blood, liver, kidney	– ?	
<i>ECI2</i>	6p24.3	β-oxidation of unsaturated fatty acids	blood, heart, skeletal muscle, kidney, liver, T-cells, and bone marrow cells	– ?	
<i>TFAP2A</i>	6p24	transcription factor	widely expressed	++	Schulte et al., 2008
<i>GCNT2</i>	6p24.2	formation of the blood group I antigen	in the adult, prostate, small intestine and colon; in fetus, expressed in brain, lung and kidney	+	Zhang et al., 2011a
<i>GCM2</i>	6p23	transcription factor, parathyroid gland development	widely expressed	++	Nonaka et al., 2011
<i>NEDD9</i>	6p25p24	to mediate protein-protein interactions	widely expressed, higher levels detected in kidney, lung and placenta	++	Tikhmyanova and Golemis, 2011; Kim et al., 2006
<i>HIVEP1</i>	6p24p22.3	transcription factor	widely expressed	?	
<i>EDN1</i>	6p24.1	regulation of vasoconstriction	lung, placenta, widely expressed	+++	Cheung et al., 2011; Ishikawa et al., 2005; Lo et al., 2005
<i>PHACTR1</i>	6p24.1	regulator of endothelial cell function	widely expressed	++/- ?	Kim et al., 2012
<i>SIRT5</i>	6p23	intracellular regulatory proteins (?)	widely expressed	?	
<i>RANBP9</i>	6p23	translocation of RNA and proteins through the nuclear pore complex	testes, placenta, heart, neurons, muscle, and lung	+/- ?	Nakamura et al., 1998

DUSP22 = Dual specificity phosphatase 22; *IRF4* = interferon regulatory factor 4; *EXOC2* = exocyst complex component 2; *FOXC1* = forkhead box C1; *SERPINB1* = serpin peptidase inhibitor, clade B (ovalbumin), member 1; *SERPINB9* = serpin peptidase inhibitor, clade B (ovalbumin), member 9; *SERPINB6* = serpin peptidase inhibitor, clade B (ovalbumin), member 6; *NQO2* = NAD(P)H dehydrogenase, quinone 2; *RIPK1* = receptor (TNFRSF)-interacting serine-threonine kinase 1; *TUBB2A* = tubulin, beta 2A class IIa; *FARS2* = phenylalanyl-tRNA synthetase 2, mitochondrial; *RPP40* = ribonuclease P/MRP 40 kDa subunit; *NRN1* = neuritin 1; *F13A1* = coagulation factor XIII, A1 polypeptide; *RREB1* = ras responsive element binding protein 1; *DSP* = desmoplakin; *BMP6* = bone morphogenetic protein 6;

TXNDC5 = thioredoxin domain containing 5 (endoplasmic reticulum); *ECI2* = enoyl-CoA delta isomerase 2; *TFAP2A* = transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha); *GCNT2* = glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group); *GCM2* = glial cells missing homolog 2 (*Drosophila*); *NEDD9* = neural precursor cell expressed, developmentally down-regulated 9; *HIVEP1* = human immunodeficiency virus type 1 enhancer binding protein 1; *EDN1* = endothelin 1; *PHACTR1* = phosphatase and actin regulator 1; *SIRT5* = NAD-dependent protein deacetylase sirtuin-5, mitochondrial; *RANBP9* = RAN binding protein 9.

Villa et al., 2007; Su et al., 2012; Varvagiannis et al., 2013]. Additionally, the translocation can involve different chromosomes, and disruption or deletion of different located genes could have a significant pathogenic effect that contributes to define specific phenotypes (table 2). In summary, it is difficult to reveal a strong genotype-phenotype correlation that usually results in unclear, poor evidence and variable penetrance and expression, when the disease occurs. The hypothesis of an excess of gene products, even if reliable, is not easy to prove or sufficient to fully explain the clinical picture. The purpose of this paper is to present a familial case of partial 6p trisomy, to perform an extensive review of the literature and to discuss controversial aspects of this rare condition.

Clinical Reports

Materials and Methods

We describe the case of an Italian family (fig. 1a–e) that carries partial trisomy of the distal tract of the short arm of chromosome 6. The chromosomal rearrangement was initially identified in the first child (the proband) of nonconsanguineous parents. Genetic investigations were initiated after the discovery of congenital choanal atresia, mild renal insufficiency with hypoplastic kidneys and congenital heart defects. The clinical picture suggested looking for mutations in the gene *CHD7*, due to the suspicion of the CHARGE association. Nonetheless, genetic investigation did not lead to the identification of pathological mutations. In the meantime, the analysis proceeded to karyotype analysis by standard GTG banding, which was apparently normal, and afterwards, the analysis was completed with array CGH for the suspicion of extrachromosomal material on the long arm of chromosome 10 (fig. 2a). Array CGH (Human Genome CGH 244A kit and DNA Analytics 4.0 software) allowed the identification of duplicated genetic material of the distal tract of the short arm of chromosome 6 (fig. 2b). The extension of the duplication was found to be approximately 13.7 Mb with breakpoints estimated at 97.63 kb (essentially in the pter region) and 13.77 Mb (between 13.77 and 13.79 Mb), which correspond to the region 6p23. The duplication was also confirmed by MLPA using MRC-Holland panels P036, P070 and P208 (fig. 2c). To localise the duplicated segment and to define the proband's karyotype, the investigation was completed with FISH using specific cosmid probes for subtelomeric regions of chromosome 6. FISH revealed that the duplicated chromosomal material was located on the terminal tract of the long arm of chromosome 10 (10qter) (fig. 3a–c).

Afterwards, the same investigations were conducted on her parents. The same chromosomal abnormality has been identified in the father, who most likely inherited it from his mother, even if she was not available for cytogenetic investigation because of her death. The karyotype of his father (the proband's grandfather) and his wife (proband's mother) were normal. The chromosomal rearrangement was then found in the second child, the proband's sister (fig. 4). Written informed consent was obtained from all the family members according to current national rules and laws for genetic investigations and publication of these cases and any accompanying images.

Fig. 1. Family members with $\text{der}(10)\text{t}(6;10)(\text{p}23;\text{qter})$ determined to show a $6\text{p}23\text{pter}$ trisomy; **a** the first child (the proband); **b** the proband's sister (second born); **c** the proband (on the right) and her sister (on the left); **d** the father; and **e** a lateral view of the proband.

Finally, a comprehensive review of the literature was conducted using computer search engines and internet databases; the search terms 'partial', 'trisomy', '6p', 'translocation', 'inversion', and 'duplication' were variously combined; the English language articles were retrieved and included in the review. The URLs for other data presented herein are as follows: <http://www.ncbi.nlm.nih.gov/pubmed/>, <http://www.ncbi.nlm.nih.gov/Omim/>, <http://www.ncbi.nlm.nih.gov/projects/mapview/>, <http://www.gene-cards.org/>, and <https://www.genevestigator.com/gv/>.

The Proband

The first daughter was born at 38 weeks of gestation by caesarean section carried out for anomalies in the cardiotocogram after an uneventful pregnancy. Serologic investigations conducted on the mother (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus, rubella, toxoplasma, and treponema pallidum haemagglutination test) were all negative. The vaginal swab culture was positive for β -haemolytic streptococcus group b. The foetus was in a correct cephalic position, and the amniotic fluid was normal in colour and volume. Her Apgar score was 7 at the first minute and 9 at the fifth minute. At birth, her weight was 2,430 g (10.3 percentile), her length 48 cm (25–50 percentile) and her head circumference 32.6 cm (10–25 percentile).

Fig. 2. Cytogenetic analysis that shows the 6p duplication: **a** standard GTG banding karyotype; **b** array CGH, which shows the duplication of the terminal region of chromosome 6p; **c** MLPA (P208-B1), which shows the amplification of the 6p chromosome and its genes.

The newborn presented with atypical reactivity and poor regulation in crying, cyanosis, heart rate more than 100 bpm, generalised hyporeactivity, and respiratory depression, especially during the ceasing of the cry. Due to these events, a nasal fibroendoscopy was performed, which revealed a congenital bilateral choanal atresia. Therefore, she was hospitalised in the neonatal intensive care unit and was immediately subjected to bilateral choanal plastic surgery after sinus CT scans. During the inpatient stay, bilateral renal hypoplasia ($2.5 \times 2.7 \times 1.7$ cm) with mild renal insufficiency (serum creatinine = 101 mg/dl), patent foramen ovale, patent ductus arteriosus, and jaundice were also diagnosed. The brain ultrasound, the neuropsychiatric evaluation and the eye examination were essentially normal. A morphological evaluation remarked the well-known dysmorphic facial features of the partial trisomy 6p: prominent forehead, mild epicanthus, ears slightly rotated with helix facing down, left preauricular pit (this feature is also present in the parents), hypoplastic and bulbous nose, slightly upturned tiny nares, and thin lips. In addition, it reported small angiomas on the face and in the occipital region and cutaneous dyschromias spread

to the trunk and the root of the lower limbs. Psychomotor development was appropriate for age and within normal range. Otoacoustic emissions and auditory brainstem responses testing demonstrated normal hearing. At the patient's discharge, the renal insufficiency, patent foramen ovale, patent ductus arteriosus, and jaundice recovered spontaneously; only a 1–2/6-grade mesocardic heart murmur was detected during the last clinical examination. The genetic investigation on the *CHD7* gene did not identify pathological mutations. Finally, the karyotype carrying a trisomy of the 6p23p25.3 region was described as follows: 46,XX,der(10)(10pte→10qter::6p23→6pter)pat.

The Second Born

The second daughter was born 2 years later at 38 weeks and 4 days of gestational age by caesarean section after a regular pregnancy and chorionic villus sampling for prenatal diagnosis that confirmed the partial trisomy of the short arm of chromosome 6. Maternal serology was negative as in the previous pregnancy, and the vaginal swab was positive for β -haemolytic streptococcus

Fig. 3. **a** A schematic representation of the translocation between chromosomes 6 and 10; **b** the duplicated region 6p23pter (0–13.7 Mb) contains approximately 140 genes; **c** the FISH technique allowed the localisation of the duplicated DNA on 10qter.

group B. The foetus was in a correct cephalic position, and at birth, she presented an atypical cry, mild cyanosis and a cardiac rate of more than 100 bpm. Her Apgar score was 7 at the first minute and 7 at the fifth minute. After a few seconds, she had respiratory distress, and bilateral congenital choanal atresia was diagnosed after nasal fibroendoscopy. Her birth weight was 2,390 g (3 percentile), her length 46 cm (5 percentile) and the head circumference 33.2 cm (28 percentile). Within 48 h, she underwent bilateral choanal plastic surgery after sinus CT scans that confirmed the choanal atresia and showed normality of other anatomical structures (including the middle/inner ear and internal auditory canals). The echocardiographic examination revealed the presence of patent foramen ovale (with a left-right shunt), mild tricuspid regurgitation and right ventricular hypertrophy. During hospitalisation, she was also subjected to phototherapy for jaundice.

The audiological, eye, neurological, and neuropsychiatric examinations were substantially negative as well as the ultrasound brain and kidney, which were all within normal range. At the patient's discharge, she presented a good general condition with a 1–2/6-grade mesocardic heart murmur. Similar to the sister, the karyotype was 46,XX,der(10)(10pter→10qter::6p2→6pter)pat with a duplication of the region 6p23p25.3.

The Proband's Father

The father was a 32-year-old adult male affected by congenital ptosis and congenital progressive hearing loss; the family history was positive for glaucoma, neoplasms, cardiovascular disease, hearing loss, and renal and thyroid dysfunction, especially among ascendants and descendants of the maternal side. At the age of 6, he underwent a right tympanoplasty because of chronic otitis media with a subsequent slight worsening of his hearing.

At the age of 30 years, he referred to the otologist because of left otitis media with effusion, and after subsequent controls and treatments, he underwent a transtympanic ventilation tube insertion. Nonetheless, bilateral hearing aids were prescribed due to difficulty in speech perception. At that time, he presented moderate to severe bilateral mixed, progressive and fluctuating hearing loss that worsened over the following 2 years, until he became a candidate for cochlear implantation (fig. 5a, b). Hearing aids proved insufficient, and the speech audiometry demonstrated a mild dissociation when compared to pure-tone audiometry. He also complained of vestibular symptoms.

To investigate the causes of the hearing loss, we performed a comprehensive audiological evaluation with specific tests. We investigated the aspects of the main suspected causes with specific

Fig. 4. Family tree of the presented cases that resulted in a carrier of the 6p23pter duplication with the characteristic 6p syndrome phenotype. Partially marked circle = hearing loss; black circle = 6p syndrome.

attention to the autoimmune, genetic and vascular causes. We performed a series of blood tests, which all resulted in negative outcomes with the exception of fluctuating D-dimer plasma levels (from 296 to 1,587 ng/ml) and increased activity of coagulation factor FXIII (300%) with a correspondingly enhanced risk for developing thromboembolism. The patient underwent brain/ear MRI, which revealed a slight protrusion of the cerebellar tonsils (Arnold-Chiari malformation type I) (fig. 5d, e) and a simple cyst of the right maxillary sinus. Subsequently, the patient underwent auditory brainstem responses, CT scans of the temporal bone, echography of the supra-aortic trunks, study of the vestibular function, and periodic pure-tone and speech audiometries.

The auditory brainstem responses latency and morphology were broadly consistent with the degree of hearing loss in accordance with the cochlear lesion. The neurological, rheumatological and ophthalmological examinations were all normal. Genetic investigations for *GJB2*, *GJB6* and *SLC26A4* mutations were negative. Finally, a mitochondrial DNA (mtDNA) analysis was performed, which revealed a potentially pathogenic mutation in mtDNA: T961G in the mitochondrial *MTRNR1* (12S rRNA) gene (fig. 5c). Indeed, this mutation could be responsible for progressive and asymmetric sensorineural hearing loss [Li et al., 2004]; to date, the pathogenic nature of T961G has never been confirmed by studies.

The karyotype analysis revealed the presence of the chromosomal abnormalities 46,XY and der(10)(10pte→10qter::6p2→6pter). Based on the clinical history and on the fact that his father (the proband's grandfather) had a normal karyotype 46,XY it was suggested that he most likely inherited the chromosomal translocation and the mtDNA mutation from his mother.

To rule out intellectual disabilities or mental retardation, he underwent the Wechsler Adult Intelligence Scale IQ test, adapted for age and execution time, and a Montreal cognitive assessment test; both results clearly excluded learning disabilities or mental insufficiencies; in fact, he reached an IQ of 101 and a 29/30 Montreal cognitive assessment score (in the normal range). One year later, he underwent cochlear implant surgery with good outcome (fig. 5a, b).

Discussion

In chromosome 6, there are approximately 2,000 genes (<http://www.ncbi.nlm.nih.gov/>, last access April 2013), and approximately 140 of these are located in the distal short arm of chromosome 6 (fig. 3b), which comprises region 6p.23p25.3 (13.7 Mb). Genes that are potentially related to the phenotypes were selected and briefly described in the present research (table 3). At least, 3 genes can be major candidates for further genetic, diagnostic and clinical investigations: *BMP6*, *EDN1* and *F13A1*. In our opinion, these genes were found to have more realistic evidence for contributing to the phenotypes in the case of overexpression during 6p distal trisomy.

The bone morphogenetic proteins (BMPs) are a family of secreted signalling molecules that can induce ectopic bone growth. Many BMPs are part of the transforming growth factor- β superfamily. Based on its expression early in embryogenesis, the BMP encoded by this gene has a proposed role in early development [Mueller and Nickel, 2012]. It is reasonable to think that the *BMP6* gene could be involved in determining craniofacial abnormalities, such as craniosynostosis and choanal atresia, and other mild to severe dysmorphic features. The bilateral congenital choanal atresia urgently requires surgical treatment, as reported in the present study.

The protein encoded by the *EDN1* gene is termed endothelin 1. This peptide is a potent vasoconstrictor and is produced by vascular endothelial cells. Endothelin 1 can also affect the central nervous system. It could be involved in angiogenesis and blood pressure. Even if all of the family members did not show blood pressure alterations, it is quite difficult to evaluate the vasoconstrictive action on the microvessels.

The *F13A1* gene (6p23p25.3) encodes for subunit A of coagulation factor XIII. This molecule is the last zymogen to become activated in the blood coagulation cascade. The plasma factor XIII is a heterotetramer that is composed of 2 A subunits and 2 B subunits (A2B2), while platelets contain only factor XIII A2 homodimer, which is identical to that of plasma origin. The A subunit has a catalytic function, in contrast to the B subunit (which is encoded by a different gene on chromosome 1), which has no enzymatic activity; in fact, the subunit could serve as a plasma carrier molecule. Upon cleavage of the activation peptide by thrombin and in the presence of calcium ions, the plasma factor XIII tetramer dissociates its B subunits, and it yields the same active enzyme (factor XIIIa) as the platelet factor XIII. These enzymes act as a transglutaminase to catalyse the formation of γ -glutamyl- ϵ -

Fig. 5. Clinical data and neuroimaging of the proband's father: **a** tonal audiometry with a right cochlear implant and residual hearing without a cochlear implant (earphones); **b** speech audiometry (open set) with a right cochlear implant; **c** mitochondrial

DNA analysis revealed a potentially pathogenic mutation in the *MTRNR1* gene; **d**, **e** coronal and axial MRI scans that show Arnold-Chiari malformation type 1 and normal inner ear structures.

lysine crosslinking between 2 different fibrin molecules, thus covalently stabilising the fibrin clot. The covalent bond is responsible for the creation of a 'neo-antigen' (D-dimer) in the cross-linked fibrin, and it is considered to be a generic thrombosis indicator. It also cross-links α 2-antiplasmin (fibronectin) and several other important extracellular matrix proteins to the α -chains of fibrin, thus stabilising, in turn, the extracellular matrix. Factor XIII deficiency is classified into 2 categories: type I deficiency, which is characterised by the lack of both the A and B subunits, and type II deficiency, which is characterised by the lack of the A subunit alone. Classically considered as haemorrhagic disorder, it can result in a lifelong bleeding tendency [Komáromi et al., 2011] and defective wound healing and tissue repair [Inbal and Dardik, 2006]. It was recently found to be associated with chronic venous leg ulcers [Zamboni and Gemmati, 2007] and recurrent abortion [Asahina et al., 2007]. High factor XIII circulat-

ing levels can be detected among thrombophilic patients [Muszbek et al., 2010]. An excess of *F13A1* and *EDNI* gene products could be responsible for thrombosis and hypertension in small vessels. An indirect link between hearing loss and FXIII could be the presence of higher mean plasma levels of D-dimer, which suggests activation of the coagulation. In our patient, we found increased levels of both D-dimer and coagulation factor XIII.

Surprisingly, in this study, the father was also a carrier of the T961G mutation in the *MTRNR1* gene. In the Caucasian population, at least 5% of postlingual, nonsyndromic hearing impairment is caused by known mtDNA mutations [Jacobs et al., 2005]. In particular, the mitochondrial genes *MTRNR1* and *MTTS1* have been found to be associated with nonsyndromic hearing loss [Van Camp and Smith, 2000]. The regions of mtDNA that correspond to the genes that are most frequently involved in hearing loss onset were sequenced (611 to 1,400, 1,200 to

2,000, 3,200 to 3,900, and 7,200 to 8,000), thus obtaining the complete sequencing of *MTRNR1* (12SrRNA) and *MTTS1* (tRNA Serine 1). Apart from 2 quite common nonpathological polymorphisms (A750G and A1438G) whose frequencies in the general population are 2,682/2,704 and 2,620/2,704, respectively, based on the mtDataBase (<http://www.mtddb.igp.uu.se/>, updated March 2007, last access April 2013) [Ingman and Gyllenstein, 2006], a mutation at position 961 was detected. The mutation T961G lies in the gene coding region for 12SrRNA, which is considered to be a hotspot for mutations that are associated with nonsyndromic hearing loss and aminoglycoside-induced hearing loss. The mutation at position 961 localises at the C-cluster between loops 21 and 22 of 12SrRNA, a region that is not evolutionarily conserved and whose function is not clearly known. This mutation has been reported in many papers [Li et al., 2004; Lvque et al., 2007], and it appears to be related to hearing impairment, but its precise role has not yet been defined. Li et al. [2004] indicated that the T961G mutation could alter the tertiary or quaternary structure of the rRNA, thus resulting in a mitochondrial translational defect. Deletions, insertions and nucleotide changes between nucleotide position 956 and 965 are often involved in the pathogenesis of mitochondrial dysfunction in individuals who belong to genetically unrelated families [Zhao et al., 2004], which could suggest that mutations at position 961 could be important for the pathogenesis of hearing loss. Furthermore, the maternal inheritance of the mitochondria could partially explain the father's family history and the normal hearing of the 2 children [Lvque et al., 2007].

The chromosomal anomaly der(10)(10pter→10qter::6p23→6pter) in our proband was directly inherited from his father, and the 6p23p25.3 trisomy is thought to be responsible for the signs and symptoms in all of the family carriers. Nevertheless, the distal portion of chromosome 10q could undergo the loss of several functioning genes. Among these could be *FGFR2*, *HMX2* and *HMX3*, even if the cytogenetic investigations did not detect deletions in 10qter. The *FGFR2* gene is a member of the fibroblast growth factor receptor family, and mutations in this gene are known to be responsible for several malformative disorders, such as Crouzon syndrome, Pfeiffer syndrome, Apert syndrome, and craniosynostosis. It is reasonable to believe that the overexpression of this gene product contributes to the genesis of craniofacial abnormalities.

The *HMX2* and *HMX3* genes are involved in hearing and vestibular functions. They are strong candidate genes for human inner ear development, and they could have a

role in sensorineural hearing and vestibular balance disorders [Miller et al., 2009]. The inner ear develops from a placode of ectoderm known as the otic placode. *HMX2* and *HMX3* are coexpressed in the dorsolateral otic epithelium to temporally and spatially signal the embryonic transition of the pars superior of the otocyst to a fully developed vestibular system. These genes are also expressed in the developing central nervous system, including the neural tube and hypothalamus [Miller et al., 2009]. Nevertheless, in the present study, the father's vestibular complaint could be related to Arnold-Chiari malformation type I; additionally, MRI and CT scans showed normal inner ear structures.

To better discuss the clinical and controversial aspects of the aforementioned rare conditions and other similar 6p trisomies, a complete review of the literature was conducted using computer search engines and internet databases; in the end, a total of 60 reports were included in our meta-analysis.

Reviewing the papers revealed a certain similarity with other previously described cases (tables 1, 2). In particular, when pictures are available and patients are comparable in terms of sex and age, a strong physiognomic correlation was noted in cases reported by Mgarban et al. [2002], Giardino et al. [2002], Pierpont et al. [2000], Delatycki et al. [1999], and Ferrando et al. [1981]. All of these cases shared the involvement of the distal tract of 6p25pter with a proximal breakpoint that varies from 6p21.3 to p.25. To the best of our knowledge, there is only a previously reported case of partial 6p trisomy due to balanced translocation t(6;10)(p22;q26), which was directly inherited from the father (table 2) [Ferrando et al., 1981].

Other described cases shared overlapping features even if different regions of chromosome 6p were involved, and they showed a high variability in the concomitant deletions. These findings suggested the definition of the 6p trisomy syndrome [Breuning et al., 1977]. Nevertheless, it could be noted that important features of this syndrome are associated with different partial trisomies that involve different chromosomes [Villa et al., 2000]. In addition, it is quite difficult to clearly evaluate the effects of the concomitant deletions. In most of the cases (table 2), unusual signs and symptoms can find an explanation in genic deletions or monosomies. Even when trisomies are pure, it is quite difficult to identify the genes that are responsible for the phenotypes among the hundreds of genes that were triplicated [Altug-Teber et al., 2007]. Finally, unusual overlapping conditions could influence the clinical aspects of different phenotypes [Mandal et al., 2007].

All of the previously suggested genes are good candidates in sustaining the genotype-phenotype correlation; nevertheless, to date, there is no evidence for defining a unique interpretation in 6p trisomies. *RUNX2* [Varvagiannis et al., 2013] and *BMP5* [Villa et al., 2007] have correctly been proposed to explain craniosynostosis and craniofacial abnormalities; on the other hand, there are cases that have dysmorphic features without the involvement of the *RUNX2* and *BMP5* genes in the triplicated chromosomal segments. Su et al. [2012] suggested 9 other genes: *FOXQ1*, *FOXF2*, *FOXC1*, *NRN1*, *EDN1*, *ATXN1*, *DEK*, *E2F3*, and *NRSN1*. The *FOX* genes belong to the forkhead family of transcription factors, and they are usually considered to be potentially responsible for eye defects in 6p trisomies [Mataftsi et al., 2011]. The *FOXC1* gene is characterised by a distinct DNA-binding forkhead domain. The specific function of this gene has not yet been determined; however, it has been shown to play a role in the regulation of embryonic and ocular development. Mutations in this gene cause various glaucoma phenotypes, including primary congenital glaucoma, autosomal dominant iridogoniodygenesis anomaly and Axenfeld-Rieger anomaly. *FOXQ1* is involved in embryonic development, cell cycle regulation, tissue-specific gene expression, cell signalling, and tumourigenesis [Bieller et al., 2001]. Usually, the transcription factors play an important role during embryogenesis, and in the case of deletions, monosomies or mutations in such genes, the phenotype can be affected severely. Nonetheless, the effects of the overexpression remain unclear.

To explain the overlapping features of different (distal or proximal) 6p trisomies, it could be reasonable to consider genes that have analogous functions and that are present in different tracts of the 6p chromosome. Examples of these gene pairs include the following: (1) *BMP5* (6p12.1) and *BMP6* (6p24); (2) *TUBB2A* (6p25p25.2) and *TUBB2B* (6p25p25.2); and (3) *TFAP2A* (6p22pter) and *TFAP2B* (6p12p13) or *TFAP2D* (6p12.1p12.3).

Other important roles can be attributed to the *SERPINB1*, *SERPINB5* and *SERPINB9* genes, which are located between 6p25 and 6p25.2 [Sprecher et al., 1995; Sirmaci et al., 2010]. The HLA cluster genes on 6p and *IRF4* (6p25.3) could play a crucial role in determining immune-system disorders, including the proliferative disorders [Berger et al., 1979; Andrieux et al., 2006; Shaffer et al., 2009]. In addition, observing the previously reported phenotypes and karyotypes, in particular the cases of Scott et al. [2007] and Stohler et al. [2007], it could also be concluded that genes that are responsible for the partial 6p trisomy syndromes are those located between

6p25.1 and p25.2, and they could be: *ECI2*, *NRN1*, *FARS2*, *TUBB2A*, *TUBB2B*, *SERPINB1*, *SERPINB6*, *SERPINB9*, *NQO2*, *RIPK1*, and/or *BPHL*.

It should be considered that all of the aforementioned genes can have analogues in the deleted regions that are associated with 6p trisomies (table 2). Previously reported cases could be reinterpreted in the light of new discoveries in the field of cytogenetics and molecular biology. The last column of table 2 discusses possible reinterpretations of the clinical findings with a focus on specific features that distinguished one case of partial 6p trisomy from the others.

From a clinical point of view, the 6p trisomies appear to be characterised by mild to severe craniofacial dysmorphisms, developmental delay, neurologic disorders, immunodepression with recurrent respiratory infections, feeding difficulties, congenital heart defects, and renal disorders (tables 1, 2). These aspects could suggest a vicious circle that is composed of craniofacial abnormalities that can lead to feeding difficulties with a consequent development delay, immunodepression and infections (ab ingestis pneumonia). Congenital ptosis is another hallmark, and low set ears or pigmentary anomalies are common findings. Hearing loss is not a constant feature, but a late onset and progression with hearing worsening is possible. In this regard, it is mandatory that the descendants follow continuous monitoring in terms of audiology, cardiology, nephrology, rheumatology, and neurology assessment. Mental retardation is widely described among patients with partial trisomies [Anderlid et al., 2002; Belligni et al., 2009]; nevertheless, a complete investigation and evaluation on this aspect is rarely reported. Among the family members of the present report, there are no signs of mental retardation or cognitive impairment. A reduced life span is possible even if it is obviously related to the entity and quality of clinical pictures, and it could be ameliorated because of new diagnostic and therapeutic approaches.

To date, the treatment of partial 6p trisomy is symptomatic and requires a multidisciplinary approach.

Conclusions

In conclusion, we reported the case of an Italian family with partial trisomy 6p who manifested overlapping features with previously described cases. The phenotypes can vary widely as a result of the involvement of different duplicated or deleted genes on different chromosomes. We discussed the potential role of genes that could be in-

involved, underlining the importance of concomitant deletions. Further studies are needed to assess more realistic rates of incidence and prevalence of the 6p trisomy, and further investigations could elucidate the role of several different conditions (pure trisomies, tetrasomies, inversions, insertions, and subtelomeric rearrangements) [Röthlisberger et al., 1999; Roberts et al., 2004; Wu et al., 2010]. It must be noted that duplication or deletion do not necessarily mean overexpression or underexpression of specific gene products, and in the case of overexpression and underexpression, it could be very difficult to estimate the effects on the embryonic development and the phenotype [López-Gutiérrez et al., 1998; Altug-Teber et al., 2007].

Transcription factors generally play key roles in several cellular activities, and they are reasonably considered to be involved in different genetic disorders; nevertheless, the presence in itself of extrachromosomal material can affect the cellular activities without the contribution of transcription factors; the resulting phenotype can be strictly related to the extension of duplicated material.

Even if chromosomes do not have identical genes, it is thought that the distribution on different chromosomes is the result of a balanced functional assortment rather than of pure randomness [Strippoli et al., 2002]. This evolutionary process has favoured the dislocation of genes with similar functions on different chromosomes with the peculiar aim of reducing the effects of chromosomal abnormalities. The aforementioned processes could explain the similarities among trisomies that involve different chromosomes.

Furthermore, as is the case in other species, it is possible that the distribution and localisation of genes have a spatial and temporal correlation with body 'segments' and embryonic stages during development. To simplify this argument, a specific sequence of genes could exactly reflect the temporal and anatomical order of the development of the phenotype [Klug et al., 2012]. This phenomenon, in addition to the genes' specific functions, may explain the elective localisation of malformations and may differentiate proximal from distal partial trisomies.

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