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A Girl with del(4)(q33) and Occipital Encephalocele: Clinical Description and Molecular Genetic Characterization of a Rare Patient

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ABSTRACT

We present clinical and developmental data on a girl with a *de novo* terminal deletion of the long arm of chromosome 4, del(4)(q33). The patient was evaluated at birth and followed up until 5 years of age. She showed facial and digital dysmorphism, a complex congenital heart defect, a large occipital encephalocele, and postnatal growth deficiency. Her neuropsychomotor milestones were delayed, and she developed learning difficulties. Apart from standard Giemsa banding, a molecular genetic analysis was performed using a comparative genomic hybridization (CGH) array. This revealed a terminal deletion at the band 4q32.3, which is directly adjacent to 4q33. The clinical findings in our patient differ from those described previously in patients with del(4)(q33) and del(4)(q32), respectively. In particular, the prominent occipital encephalocele has not been observed before in a terminal 4q deletion.

INTRODUCTION

CHROMOSOME 4Q DELETIONS are rare, with an estimated incidence of 1/100,000 (Strehle and Bantock 2003). Deletions of the terminal region of the long arm of chromosome 4 have been characterized as a distinct syndrome based on a number of common clinical features shared by previously reported cases (Townes *et al*. 1979; Strehle *et al*. 2001). Common characteristics are mild facial and digital stigmata (especially of the fifth finger), cardiac, skeletal, gastrointestinal, and renal anomalies, developmental delay, learning difficulties, growth failure, and a significant mortality (Mitchell *et al*. 1981; Yu *et al*. 1981; Lin *et al*. 1988; Strehle and Bantock 2003).

Patients with large terminal deletions (4q31) are more severely affected with the characteristic facial, skeletal, and developmental anomalies (Giuffrè *et al*. 2004). The region 4q31q34 may be critical for most of the clinical phenotype (Lin *et al*. 1988). Some authors propose that the critical region for the 4q terminal deletion syndrome is 4q33, and that genes involved in facial, limb, cardiac, and central nervous system development must reside on 4q33 (Keeling *et al*. 2001). Most deletions occurred *de novo* and therefore carried a low recurrence risk (Strehle *et al*. 2001).

The deletion 4q33 has been described in 15 patients; most of these cases presented with developmental delay and learning difficulties, facial and digital dysmorphisms, and congenital heart disease (Strehle and Bantock 2003). There are only 4 published cases of del(4)(q32), which will be discussed below (Lin *et al*. 1988).

Here, we describe a patient evaluated repeatedly until the age of 5 years with a terminal deletion of chromosome 4, del(4)(q33), who in addition to the clinical features previously reported in patients with terminal 4q33 deletion, showed a prominent occipital encephalocele.

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MATERIALS AND METHODS

Patient

The patient was born at a gestational age of 38 weeks by caesarian section as the first offspring of healthy, nonconsanguineous parents. Her mother and father were 23 years old at the time of her birth. Vaginal bleeding was reported in the second trimester of pregnancy. Birth weight was 2.9 kg ($< 50^{th}$ centile) and her head circumference was 34 cm ($> 50^{th}$ centile). The newborn had Apgar scores of 8 at 1 min and 9 at 5 min. She was noted to have dysmorphic craniofacial features, including hypoplastic supraorbital ridges, large fontanelles, upwards slanting, short palpebral fissures, hypertelorism, glabellar haemangioma, over-folded ear helix, microstomia, and micrognathia (Fig. 1A). An occipital encephalocele was also present, which was surgically removed at the second day of life (Fig. 2). Magnetic resonance imaging of the brain performed at 3 months showed an Arnold–Chiari malformation type II, neuronal migration defects, and a supratentorial hydrocephalus. The patient was also noted to have hand and foot deformities: overlapping fingers and clinodactyly of the 5^{th} digits, bilateral isodactyly of the toes, an overlap of the hypoplastic 5^{th} toe over the 4^{th} toe, and proximal implantation of the 2^{nd} toes (Fig. 1C). Additional findings included abnormal labia minora, a prominent clitoris, and a sacrolumbar hemangioma. Chest X ray, echocardiogram, and cardiac catheterization revealed a complex cardiac defect with cardiomegaly, preductal coarctation of the aorta, patent ductus arteriosus, and a perimembranous ventricular septal defect. Corrective heart surgery was performed on day 5 of life. The girl developed secondary pulmonary hypertension, which was controlled with medication.

On follow up she showed postnatal onset growth deficiency and feeding difficulties until 4 months of age. She displayed good head control at 5 months and sat alone at 1 year. At that time she had evidence of growth retardation with a weight of 5.9 kg ($< 3^{rd}$ centile) and a length of 70 cm ($< 10^{th}$ centile). The clinical features remained unchanged (Fig. 1B,C).

She was re-evaluated at aged 4 years (Fig. 3); weight was 14.2 kg (10^{th} centile), length was 92 cm ($< 3^{rd}$ centile), and head circumference was 47 cm ($< 3^{rd}$ centile). Her neurodevelopmental milestones were significantly delayed. Unaided walking was possible from the age of 2.5 years. She was eating using her fingers and a spoon, but had problems with toilet training. She could say single words and carry out simple orders. Vision and hearing were normal. She did not attend nursery, but enjoyed playing by herself or with other children.

Cytogenetic and molecular analyses

Chromosome analysis was performed on peripheral blood lymphocytes from the patient and her parents. GTG-banding was performed using standard protocols. A total of 20 GTG-banded metaphases were examined with the complete analysis of four karyotypes. For molecular analysis, the Agilent Human Genome CGH microarray kit 44B (Agilent Technologies, Inc.) was used. The microarray contains approximately 43,000 60-mer oligonucleotide probes, which provide genome-wide coverage for >30,000 mapped genes with a spatial resolution of

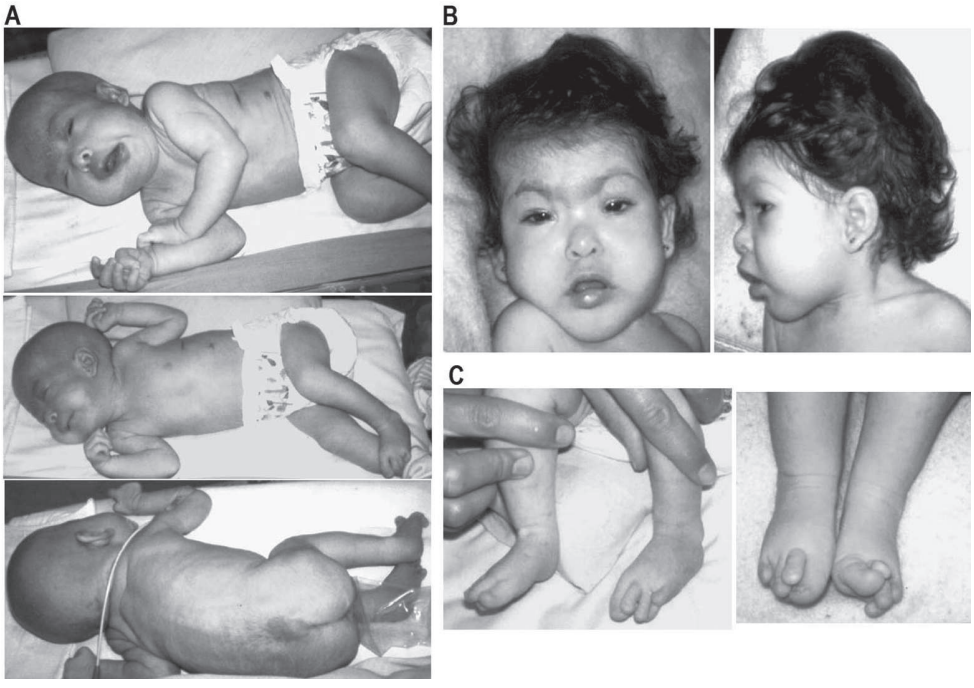

FIG. 1. Facial features of the patient in the neonatal period (**A**) and at 1 year of life (**B**). Note the dysmorphic craniofacial features described in the text. **C:** Details of her feet at birth and at 1 year of life, respectively.

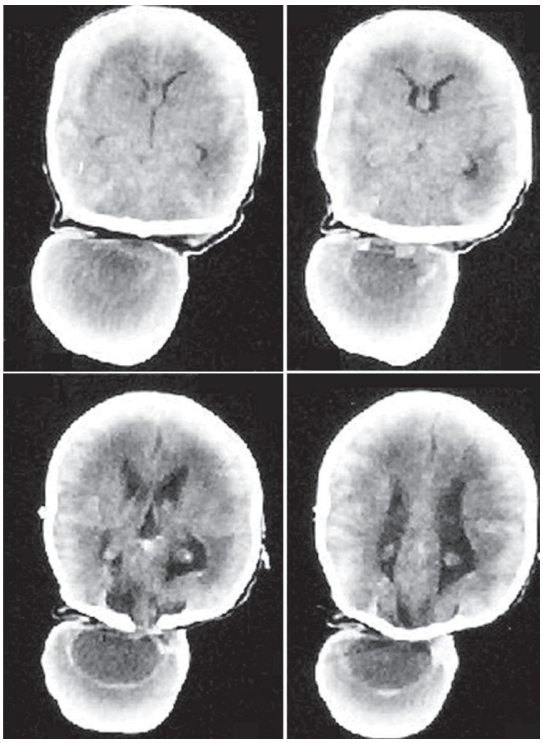

FIG. 2. Computerized tomogram of the patient's head showing a prominent occipital encephalocele.

30–35 kb (calculated using the nonrepeated sequences of the genome). The experiment was performed as recommended by the manufacturer. Briefly, patient genomic DNA was extracted from peripheral blood using the Pure Gene kit (Gentra Systems, Minneapolis, MN). Both reference DNA (Promega, Madison, WI) and test DNA were digested with *Rsa*I and *Alu*I (Invitrogen, Carlsbad, CA), and then purified using a Clean and Concentrator™ kit (Zymo Research, Orange, CA). Purified test and reference DNA samples were labeled with Cy5- and Cy3-labeled dCTPs (GE Healthcare Bio-Sciences Corp. Piscataway, NJ), respectively, using a BioPrime random labeling kit (Invitrogen, Carlsbad, CA). The labeled test and reference DNA samples were combined and hybridized to the microarray slide. After hybridization and washing, the slide was scanned on an Agilent Microarray Scanner and captured images were analyzed with Feature Extraction Software v8.1 and CGH Analytics 3.1 (Agilent Technologies, Inc.).

RESULTS

Figure 4 shows a G-banded metaphase from peripheral blood lymphocytes. The normal and deleted chromosomes 4 are shown with their corresponding ideogram. A *de novo* terminal deletion with breakpoints at 4q33 was found. Parental chromosomes were normal, indicating that the deletion had arisen *de novo* and carried a low recurrence risk. Molecular analysis using an array CGH kit revealed a terminal 25.7-MB deletion at the breakpoint 4q32.3 (Fig. 5). The bands 4q33 and 4q32.3

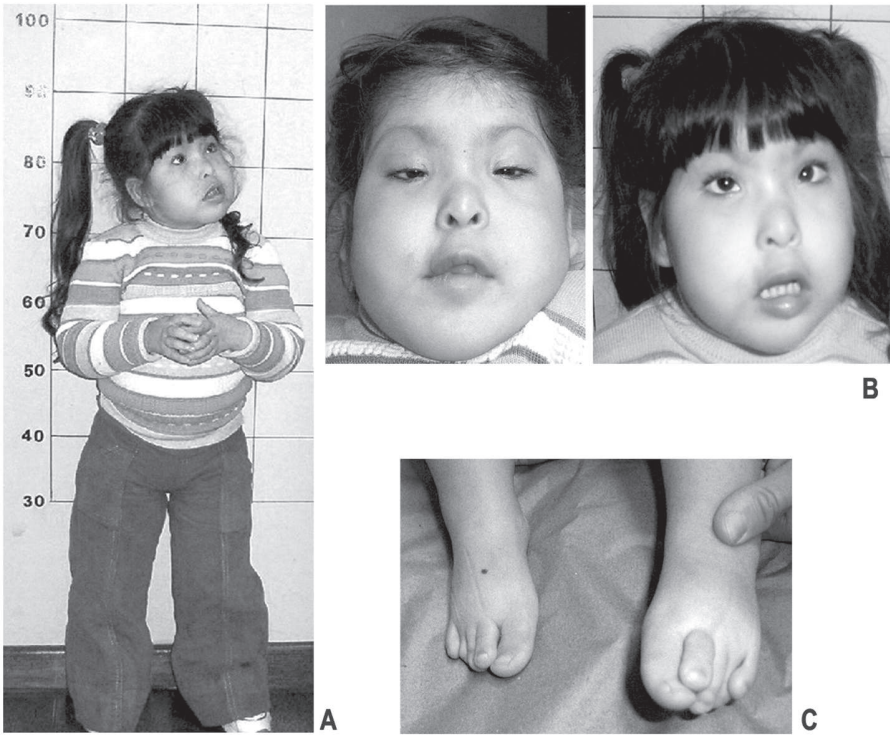

FIG. 3. **A:** Full-body view of patient at the age of 4 years. **B:** Facial feature show persistence of the supraciliar and interciliar frontal hemangioma. **C:** A close-up view of her feet.

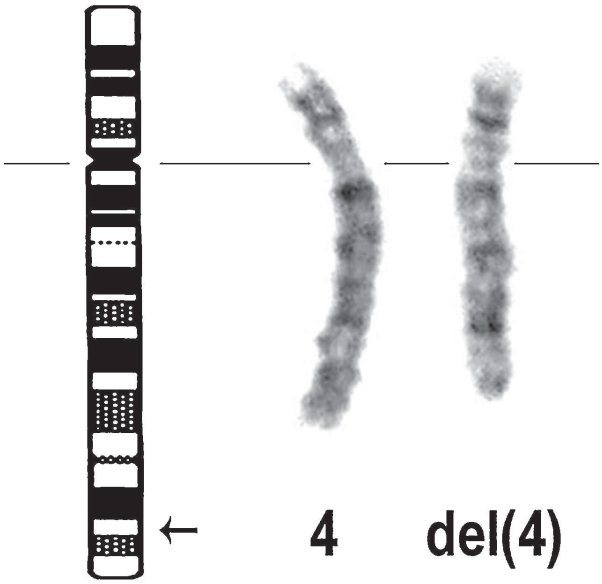

FIG. 4. G-banded partial karyotype of the patient.

could not be differentiated from each other by light microscopy alone.

DISCUSSION

So far more than 100 patients have been reported with terminal or interstitial deletions of chromosome 4q. According to Strehle and Bantock, the 4q deletion syndrome falls under the category of multiple congenital anomalies and mental retardation syndromes and has growth failure as a leading phenotypical characteristic (Strehle and Bantock 2003). The phenotype and the severity of clinical manifestations are variable and depend on the exact site and extension of the deleted 4q segment (Giuffrè *et al*. 2004). Comparison of the clinical signs in our patient with those published by other research groups showed that our patient has the key features present in the 15 patients described with 4q33 deletion (Strehle and Bantock 2003). She had most of the manifestations like facial and digital anomalies, congenital heart defect, and postnatal onset growth deficiency. She did not have gastrointestinal or renal anomalies. Pediatric reviews until 5 years of age revealed growth failure and delayed neuropsychomotor milestones. Our patient also had a cardiovascular abnormality similar to those described in 4q deletions with identical breakpoints (Evers *et al*. 1993; Grammatico *et al*. 1997).

In their literature review of 101 children with interstitial and terminal 4q deletion syndrome, Strehle and Bantock reported central nervous system involvement in 34% of cases. Brain anomalies were more common in interstitial than in terminal deletions of 4q (Strehle and Bantock 2003). Epilepsy was a frequent feature (Kempen 1975; Raczenbeck *et al*. 1991; Suwa *et al*. 1998) and several children had structural abnormalities, for instance an absent or hypoplastic corpus callosum (Fagan and Gill 1989; Fukushima *et al*. 1992), cerebral or cerebellar atrophy (Hoo *et al*. 1986; Koppitch *et al*. 1990; Slavotinek *et al*. 1997; Strehle *et al*. 2001) or dilated ventricles/macrocephaly (Frappaz *et al*. 1983; Beall *et al*. 1998; Rose *et al*. 1991; Kulharya *et al*. 1995). The only published case of a 4q deletion associated with an encephalocele was described by Nowaczyk *et al*. (1997). Their patient of Italian origin was born with a high occipital encephalocele, which was excised at 7 days of age, cerebellar hypoplasia, and a ventricular septal defect. Karyotype analysis revealed an interstitial deletion of chromosome 4, del(4)(q13.2q23). The boy died following a respiratory arrest at the age of 7 months.

Occipital encephalocele and ocular abnormalities are characteristic for patients with Knobloch syndrome. This syndrome is caused by mutations of the gene *COL18A1*, which maps to chromosome 21q22.3. *COL18A1* encodes collagen XVIII, which is a component of basement membranes. Various cell types use basement membranes as a structure to which they can adhere and for the transport of nutrients. It is possible that other genes responsible for collagen production reside on chro-

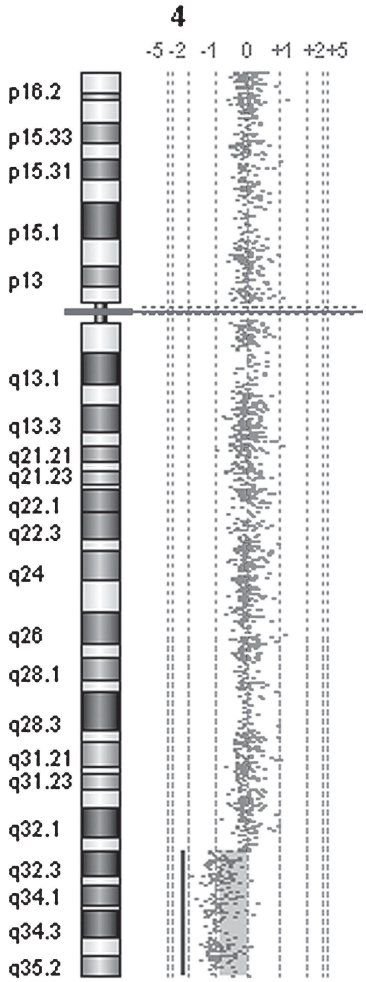

FIG. 5. Chromosome 4 ideogram and plot as obtained by array CGH. The 25.7 MB deletion is indicated by a vertical gray bar.

mosome 4q (Marneros and Olsen 2005; Passos-Bueno *et al*. 2006).

Chromosomal deletion syndromes with slightly differing breakpoints and different phenotypes contribute to the localization of genes with specific functions. A review of the features reported in patients with del(4)(q32), del(4)(q33), and del(4)(q34) showed that there was a clear difference in the frequency and severity of anomalies in children with either of these deletions (Keeling *et al*. 2001). In their review of 4q deletions, Lin and co-workers (1988) compared 2 new patients with del(4)(q32) with 2 cases of del(4)(q32) described by Rethore *et al*. (1979) and Fryns *et al*. (1981). All 4 patients had the Pierre–Robin sequence, were hypotonic at birth, and developed moderate to severe learning difficulties. Three of them had a congenital heart defect and absent digital flexion creases, and 1 died at the age of 3 months. Other reports of patients with interstitial deletions inside the terminal region 4q may contribute to an understanding of genotype–phenotype correlations and to an identification of the critical region and the genes responsible for the main manifestations (Sarda *et al*. 1992; Calabrese *et al*. 1997; Robertson *et al*. 1998; Keeling *et al*. 2001; Strehle *et al*. 2001; Giuffrè *et al*. 2004).

In less than 10% of published cases with 4q syndrome, molecular genetic techniques have been applied, for instance fluorescent *in situ* hybridization (FISH), comparative genomic hybridization (CGH), representational oligonucleotide microarray analysis (ROMA), or multiplex amplifiable probe hybridization (MAPH) (Armour *et al*. 2004; Jain 2004; Jobanputra *et al*. 2005; Ylstra *et al*. 2006). These relatively new techniques have enabled researchers to determine the chromosomal breakpoints in 4q deletions more accurately than previously possible with Giemsa banding (Becker *et al*. 2003; Pickard *et al*. 2004; Van Buggenhout *et al*. 2004; Eggermann *et al*. 2005). In addition, they have resulted in the mapping of the genes for piebaldism and Rieger syndrome to chromosome 4q (Spritz *et al*. 1992; Flomen *et al*. 1997; Schinzel *et al*. 1997) and to the identification of a candidate gene for autism (Ramanathan *et al*. 2004). More than 200 genes were deleted in our patient as shown in our array CGH study, including 34 genes with well-known function (a list of deleted genes can be obtained from the author). Many of them are important for embryo development. For example, *dHAND* is a basic helix–loop–helix transcription factor. It is expressed in the developing heart and may play an important role in cardiogenesis (Srivastava *et al*. 1995). Thus far, there is no definitive correlation between *dHAND* deletion and congenital heart disease (Huang *et al*. 2002; Vogt *et al*. 2006). In mouse models, knockout of *dHAND* causes cardiac defects (Firulli *et al*. 1998). Another gene associated with cardiovascular development is *VEGF-C*, which is active in angiogenesis and cell growth (Cao *et al*. 1998).

Previously, it was reported that chromosome 4q deletions are associated with cervical cancer (Backsch *et al*. 2005), sporadic basal cell carcinomas (Sironi *et al*. 2004), and hepatocarcinoma (Bluteau *et al*. 2002). Several tumor suppressor genes reside in this region. The inhibitor of growth family member-1 is able to modify the function of histone acetylase and histone deacetylase (*HDAC*) and functions in DNA repair and cellular apoptosis (Wang *et al*. 2006). This raises the question whether patients with 4q deletion syndrome should be surveyed for cancer. *Caspase 3* is also deleted in our patients. This protein plays a central role in apoptosis, which is an essential process for embryological development. Another gene deleted in our patient is the *FAT* tumor suppressor homologue 1. This gene is highly expressed in fetal epithelia and plays an important role in the developmental process (Dunne *et al*. 1995). We would like to point out that coagulation factor XI is also deleted in our patients. However, patients with 4q deletion syndrome have never been reported in association with a coagulopathy.

In conclusion, the findings in our patient differ from those previously found in patients with 46,XX,del(4)(q33) and del(4)(q32), respectively. To our knowledge, this is the first description of a patient with a terminal 4q deletion associated with an encephalocele. It could be more than coincidence that two cases of 4q deletions were associated with an occipital encephalocele, and therefore detailed research should be performed to establish a possible link. We recommend that molecular genetic analyses be performed in all future case reports of children with 4q deletion syndrome.

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REFERENCES

Armour JA, Rad IA, Hollox EJ, Akrami SM, Cross GS (2004) Gene dosage analysis by multiplex amplifiable probe hybridization. Methods Mol Med 92:125–139.

Backsch C, Rudolph B, Kuhne-Heid R, Kalscheuer V, Bartsch O, Jansen L, Beer K, Meyer B, Schneider A, Durst M (2005) A region on human chromosome 4 (q35.1 → qter) induces senescence in cell hybrids and is involved in cervical carcinogenesis. Genes Chromosomes Cancer 43:260–272.

Beall HM, Falk RE, Ying KL (1988) A patient with an interstitial deletion of the proximal portion of the long arm of chromosome 4. Am J Med Genet 31:553–557.

Becker SA, Popp S, Rager K, Jauch A (2003) A new case of an interstitial deletion (4)(q25q27) characterized by molecular cytogenetic techniques and review of the literature. Eur J Pediatr 162:267–270.

Bluteau O, Beaudoin JC, Pasturaud P, Belghiti J, Franco D, Bioulac-Sage P, Laurent-Puig P, Zucman-Rossi J (2002) Specific association between alcohol intake, high grade of differentiation and 4q34–q35 deletions in hepatocellular carcinomas identified by high resolution allelotyping. Oncogene 21:1225–1232.

Calabrese G, Giannotti A, Mingarelli R, Digilio MC, Piemontese MR, Palka G (1997) Two newborns with chromosome 4 imbalances: Deletion 4q33–q35 and ring r(4)(pter-q35.2-qter). Clin Genet 51:264–267.

Cao Y, Linden P, Farnebo J, Cao R, Eriksson A, Kumar V, Qi JH, Claesson-Welsh L, Alitalo K (1998) Vascular endothelial growth factor C induces angiogenesis in vivo. Proc Natl Acad Sci USA 95:14389–14394.

Dunne J, Hanby AM, Poulsom R, Jones TA, Sheer D, Chin WG, Da SM, Zhao Q, Beverley PC, Owen MJ (1995) Molecular cloning and tissue expression of FAT, the human homologue of the Drosophila fat gene that is located on chromosome 4q34–q35 and encodes a putative adhesion molecule. Genomics 30:207–223.

Eggermann K, Bergmann C, Heil I, Eggermann T, Zerres K, Schüler HM (2005) Rare proximal interstitial deletion of chromosome 4q,

del(4)(q13.2q21.22): new case and comparison with the literature. Am J Med Genet 134A:226–228.

Evers LJM, Schrander-Stumpel CTRM, Engelen JJM, Mulder H, Borghgraef M, Fryns JP (1993) Terminal deletion of long arm of chromosome 4. Genet Couns 4:139–145.

Fagan K, Gill A (1989) A new interstitial deletion of 4q(q21.1::q22.1). J Med Genet 26:644–647.

Firulli AB, McFadden DG, Lin Q, Srivastava D, Olson EN (1998) Heart and extra-embryonic mesodermal defects in mouse embryos lacking the bHLH transcription factor Hand1. Nature Genet 18:266–270.

Flomen RH, Gorman PA, Vatechva R, Groet J, Barisic I, Ligutic I, Sheer D, Nizetic D (1997) Rieger syndrome locus: a new reciprocal translocation t(4;12)(q25;q15) and a deletion del(4)(q25q27) both break between markers D4S2945 and D4S193. J Med Genet 34:191–195.

Frappaz D, Bourgeois J, Berthier JC, Laurent C, Bethenod M (1983) [Syndrome of terminal deletion of the long arm of chromosome 4. Apropos of a personal case with a review of the literature] [Review in French] Pediatrie 38:261–270.

Fryns JP, Timmermans J, Hoedemaekers J, Emmery L, Van den Berghe H (1981) Pierre-Robin anomalad, moderate mental retardation and distal 4q deletion. Ann Genet 24:187–188.

Fukushima Y, Ohashi H, Wakui K, Nishida T, Nakamura Y, Hoshino K, Ogawa K, Ohishi T (1992) DiGeorge syndrome with del(4)(q21.3q25): possibility of the fourth chromosome region responsible for DiGeorge syndrome. Am J Hum Genet 51:A80.

Giuffrè M, La Placa S, Carta M, Cataliotti A, Marino M, Piccione M, Pusateri F, Meli F, Corsello G (2004) Hypercalciuria and kidney calcifications in terminal 4q deletion syndrome. Am J Med Genet 126A:186–190.

Grammatico P, Spaccini L, DiRosa C, Cupilari F, Del Porto G (1997) Del(4)(pter → q33:) case report and review of the literature. Genet Couns 8:39–42.

Hoo JJ, Haslam RHA, Van Orman C (1986) Tentative assignment of piebald trait gene to chromosome band 4q12. Hum Genet 73: 230–231.

Huang T, Lin AE, Cox GF, Golden WL, Feldman GL, Ute M, Schrander-Stumpel CT, Kamisago M, Vermeulen SJ (2002) Cardiac phenotypes in chromosome 4q− syndrome with and without a deletion of the dHAND gene. Genet Med 4:464–467.

Jain KK (2004) Current status of fluorescent in-situ hybridization. Med Device Technol 15:14–17.

Jobanputra V, Sebat J, Troge J, Chung W, Anyane-Yeboa K, Wigler M, Warburton D (2005) Application of ROMA (representational oligonucleotide microarray analysis) to patients with cytogenetic rearrangements. Genet Med 7:111–118.

Keeling SL, Lee-Jones L, Thompson P (2001) Interstitial deletion 4q32-34 with ulnar deficiency: 4q33 may be the critical region in 4q terminal deletion syndrome. Am J Med Genet 99:94–98.

Kempen C (1975) A patient with congenital anomalies and a deletion of the long arm of chromosome 4 (46,XY,del(4)(q31)). J Med Genet 12:204–212.

Koppitch FC, Ramashi A, Quereshi F, Budev H, Perrin E, Evans MI (1990) Prenatal diagnosis of and midtrimester pathology with karyotype 46,XY,del(4)(q22q26). A case report. J Reprod Med 35:182–186.

Kulharya AS, Maberry M, Kukolich MK, Day DW, Schneider NR, Wilson GN, Tonk V (1995) Interstitial deletions 4q21.1q25 and 4q25q27: phenotypic variability and relation to Rieger anomaly. Am J Med Genet 55:165–170.

Lin AE, Garver KL, Diggans G, Clemens M, Wenger SL, Steele MW, Jones MC, Israel J (1988) Interstitial and terminal deletions of the long arm of chromosome 4: further delineation of phenotypes. Am J Med Genet 31:533-548.

Marneros AG, Olsen BR (2005) Physiological role of collagen XVIII and endostatin. FASEB J 19:716–728.

Mitchell JA, Packman S, Loughman WD, Fineman RM, Zackai E, Patil SR, Emanuel B, Bartley JA, Hanson JW (1981) Deletions of different segments of the long arm of chromosome 4. Am J Med Genet 8:73–89.

Nowaczyk MJM, Teshima IE, Siegel-Bartelt J, Clarke JTR (1997) Deletion 4q21/4q22 syndrome: two patients with de novo 4q21.3q23 and 4q13.2q23 deletions. Am J Med Genet 69:400–405.

Passos-Bueno MR, Suzuki OT, Armelin-Correa LM, Sertie AL, Errera FI, Bagatini K, Kok F, Leite KR (2006) Mutations in collagen 18A1 and their relevance to the human phenotype. An Acad Bras Cienc 78:123–131.

Pickard BS, Hollox EJ, Malloy MP, Porteous DJ, Blackwood DH, Armour JA, Muir WJ (2004) A 4q35.2 subtelomeric deletion identified in a screen of patients with co-morbid psychiatric illness and mental retardation. BMC Med Genet 5:21.

Raczenbeck C, Krassikoff N, Cosper P (1991) Second case report of del(4)(q25q27) and review of the literature. Clin Genet 39:463–466.

Ramanathan S, Woodroffe A, Flodman PL, Mays LZ, Hanouni M, Modahl CB, Steinberg-Epstein R, Bocian ME, Spence MA, Smith M (2004) A case of autism with an interstitial deletion on 4q leading to hemizygosity for genes encoding for glutamine and glycine neurotransmitter receptor sub-units (AMPA 2, GLRA 3, GLRB) and neuropeptide receptors NPY1R, NPY5R. BMC Med Genet 5:10.

Rethore MO, Couturier J, Mselati JC, Cochois B, Lavaud J, Lejeune J (1979) [De novo monosomy 4q32.1 leads to 4qter in a newborn with multiple malformations (authorís transl)] [French] Ann Genet 22:214–216.

Robertson SP, OíDay K, Bankier A (1998) The 4q-syndrome: delineation of the minimal critical region to within band 4q31. Clin Genet 53:70–73.

Rose NC, Schneider A, McDonald-McGinn DM, Caserta C, Emanuel BS, Zackai EH. (1991) Interstitial deletion of 4(q21q25) in a liveborn male. Am J Med Genet 40:77–79

Sarda P, Lefort G, Fryns JP, Humeau C, Rieu D (1992) Interstitial deletion of the distal long arm of chromosome 4. J Med Genet 29:259–261.

Schinzel A, Braegger CP, Brecevic L, Dutly F, Binkert F (1997) Interstitial deletion, del(4)(q12q21.1), owing to de novo unbalanced translocation in a 2 year old girl: further evidence that the piebald trait maps to proximal 4q12. J Med Genet 34:692–695.

Sironi E, Cerri A, Tomasini D, Sirchia SM, Porta G, Rossella F, Grati FR, Simoni G (2004) Loss of heterozygosity on chromosome 4q32-35 in sporadic basal cell carcinomas: evidence for the involvement of p33ING2/ING1L and SAP30 genes. J Cutan Pathol 31:318–322.

Slavotinek A, Kingston H (1997) Interstitial deletion of bands 4q12 → q13.1: case report and review of proximal 4q deletions. J Med Genet 34:862–865.

Spritz RA, Droetto S, Fukushima Y (1992) Deletion of the KIT and PDGFRA genes in a patient with piebaldism. Am J Med Genet 44:492–495.

Srivastava D, Cserjesi P, Olson EN (1995) A subclass of bHLH proteins required for cardiac morphogenesis. Science 270:1995–1999.

Strehle EM, Bantock HM (2003) The phenotype of patients with 4q-syndrome. Genet Couns 14:195–205.

Strehle EM, Ahmed OA, Hameed M, Russell A (2001) The 4q-syndrome. Genet Couns 12:327–339.

Suwa K, Momoi MY, Yamagata T, Mori Y (1998) Interstitial deletion of the long arm of chromosome 4(del(4)(q21.22q23)) and a liver tumour. Am J Med Genet 78:291–293.

Townes PL, White M, Di Marzo SV (1979) 4q-syndrome. Am J Dis Child 133:383–385.

Van Buggenhout G, Maas NM, Fryns JP, Vermeesch JR (2004) A dysmorphic boy with 4qter deletion and 4q32.3-34.3 duplication: clinical, cytogenetic, and molecular findings. Am J Med Genet 131A:186–189.

Vogt J, Ryan E, Tischkowitz MD, Reardon W, Brueton LA (2006) The tale of a nail sign in chromosome 4q34 deletion syndrome. Clin Dysmorphol 15(3):127–132.

Wang J, Chin MY, Li G (2006) The novel tumor suppressor p33ING2 enhances nucleotide excision repair via inducement of histone H4 acetylation and chromatin relaxation. Cancer Res 66:1906–1911.

Ylstra B, Van den Ijssel P, Carvalho B, Brakenhoff RH, Meijer GA (2006) BAC to the future! or oligonucleotides: a perspective for micro array comparative genomic hybridization (array CGH). Nucleic Acids Res 34:445–450.

Yu CW, Chen H, Baucum RW, Hand AM (1981) Terminal deletion of the long arm of chromosome 4. Report of a case of 46,XY,del(4)(q31) and review of 4q-syndrome. Ann Génét 24:158–161.

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