CHARGE Syndrome with del(3)(p13p21): Expanding the Genotype

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Known specific genetic loci responsible for the CHARGE syndrome are very rare. *CHD7*, encoding for the chromodomain helicase DNA binding protein, is the only gene currently known to be associated with the CHARGE syndrome [1-3]. Individuals with both chromosomal abnormalities and CHARGE are also rare. Hence, the diagnosis of CHARGE syndrome is still based on clinical features [4].

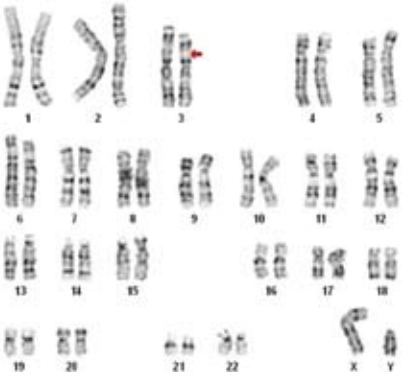
A search revealed only seven previously reported individuals with CHARGE association and chromosomal abnormalities: balanced t(2;7)(p14;q21.11) translocation; balanced whole arm translocation involving chromosomes 6 and 8; a partial monosomy 21q; a de novo chromosomal aberration 46, X,der(X)t(X;2)(p22.1;q33); a de novo interstitial deletion involving bands 8q11.2 to 8q13; unbalanced translocations involving chromosomes 2 and 18 in one family, and chromosomes 3 and 22 in the other; and a de novo interstitial deletion of the short arm of chromosome 3 (p12 to p21.2) (5). We describe here a second infant with phenotypic CHARGE syndrome and a deletion of the short arm of chromosome 3: del(3) (p13 to p21).

PATIENT DESCRIPTION

The male infant was born at 38 weeks gestation to healthy non-consanguineous parents (mother 26 and father 30 years old) with an unremarkable family history and three healthy daughters. Prenatal ultrasound raised suspicion for fetal heart anomaly, but the parents declined fetal karyotype examination. At birth, physical examination revealed a symmetrical small-for-gestational age infant with a low birth weight of 2035 g (< 3rd percentile) and microcephaly with a head circumference of 30 cm (< 3rd percentile). Also noted were congenital malformations compatible with CHARGE syndrome according to Blake's four major criteria [4]: bilateral iridial colobomata, unilateral choanal atresia, small cup-shaped ears, and cranial nerve dysfunction (bilateral sensorineural deafness and swallowing problems). Minor criteria included genital hypoplasia (micropenis and cryptorchidism), severe developmental delay, severe growth deficiency (prenatal and postnatal), cardiac malformation (pulmonary valve stenosis and patent ductus arteriosus), and a distinctive dysmorphic face. Additional findings in our patient included horse-shoe kidney, microcephaly, partial agenesis of corpus callosum, unilateral extra rib, posteriorly located anus and pilonidal sinus.

Complete blood count, serum glucose, electrolytes, hepatic and renal functional biochemical tests were normal. Specific immunoglobulin M titers of Toxoplasma, rubella, cytomegalovirus and herpes simplex were negative, with no evidence of cytomegalovirus in urine. Serum levels of free thyroxine and thyroid-stimulating hormone were normal. Serum levels of 17-OH progesterone and of cortisol before and after ACTH stimulation were normal. Serum levels of cholesterol and of 7 dehydro-cholesterol were normal. Karyotype examination revealed an interstitial deletion in the proximal short arm of chromosome 3:46,XY, del(3)(p13p21) [Figure]. Maternal and paternal karyotypes were normal. CHD7 mutation was not tested.

Infant's karyotype showing 46XY, del(3)(p13p21) (arrow)



Follow-up at age 14 months revealed swallowing problems, poor feeding and severe growth deficiency with a weight of 6.2 kg, height 69.8 cm and head circumference 43.5 cm, all below the third percentile.

COMMENT

Based on the clinical features and findings of our infant, the diagnosis of CHARGE

syndrome was made according to Blake's criteria [4]. The patient had a de novo interstitial deletion involving bands 3p13 to 3p21. Absence of one or more of the expressed genes within the deleted region could potentially contribute to the manifestations of CHARGE association.

Known specific genetic loci responsible for CHARGE syndrome are very rare. *CHD7*, encoding for the chromodomain helicase DNA binding protein, is the only gene currently known to be associated with this syndrome [1]. Sequence analysis of the *CHD7* coding region detected mutations in 58% of 110 individuals with CHARGE syndrome [1].

CHARGE syndrome, caused by mostly de novo mutations in *CHD7*, is inherited as an autosomal dominant trait [1]. CHARGE individuals with CHD7 mutations more commonly have ocular colobomas, temporal bone anomalies, and facial nerve paralysis as compared with mutation-negative individuals [2]. There was wide phenotypic variability, even among family members with the same mutation. Wincent et al. [3] identified CHD7 mutations in 18 (64%) of 28 index patients with CHARGE syndrome.

So far, only seven previous reports of individuals with CHARGE association and chromosomal abnormalities have been reported. In one of these reports, Wieczorek and colleagues [5] described a boy with a de novo interstitial deletion of the short arm of chromosome 3 (p12 to p21.2) and clinical findings typical of proximal 3p deletion together with coloboma of iris, heart defect, choanal atresia, retardation of growth and development, genital hypoplasia and ear anomalies [5]. These clinical findings were compatible with CHARGE syndrome. Parental chromosomes were normal. The findings of this patient and of our patient overlap both clinically (CHARGE syndrome) and cytogenetically: del(3)(p12-p21.2) and del(3)(p13-p21), respectively.

We report an infant with CHARGE syndrome and a concomitant deletion in the proximal short arm of chromosome 3. To the best of our knowledge, this is the second report of such a chromosomal aberration together with typical CHARGE syndrome which can now be added to the already known chromosomal aberrations in association with this syndrome.

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Capsule

Interactions between cancer stem cells and their niche govern metastatic colonization

Metastatic growth in distant organs is the major cause of cancer mortality. The development of metastasis is a multistage process with several rate-limiting steps. Although dissemination of tumor cells seems to be an early and frequent event, the successful initiation of metastatic growth, a process termed 'metastatic colonization', is inefficient for many cancer types and is accomplished only by a minority of cancer cells that reach distant sites. Prevalent target sites are characteristic of many tumor entities, suggesting that inadequate support by distant tissues contributes to the inefficiency of the metastatic process. Malanchi et al. show that a small population of cancer stem cells is critical for metastatic colonization, that is, the initial expansion of cancer cells at the secondary site, and that stromal niche signals are crucial to this expansion process. The authors find that periostin (POSTN), a component of the extracellular matrix, is expressed by fibroblasts in the normal tissue and in the stroma of the primary tumor. Infiltrating tumor cells need to induce stromal POSTN expression in the secondary target organ (in this case lung) to initiate colonization. POSTN is required to allow cancer stem cell maintenance, and blocking its function prevents metastasis. POSTN recruits Wnt ligands and thereby increases Wnt signaling in cancer stem cells. They suggest that the education of stromal cells by infiltrating tumor cells is an important step in metastatic colonization and that preventing *de novo* niche formation may be a novel strategy for the treatment of metastatic disease.

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"Most people think that shadows follow, precede, or surround beings or objects. The truth is that they also surround words, ideas, desires, deeds, impulses and memories"

Elie Wiesel (b. 1928), Romanian-born Jewish-American writer, political activist, Nobel Laureate, and Holocaust survivor