Prenatal diagnosis of de novo proximal interstitial deletion of 14q associated with cebocephaly

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Abstract

We report on the prenatal diagnosis of a case of cebocephaly, alobar holoprosencephaly, and microcephaly associated with a de novo proximal interstitial deletion of the long arm of chromosome 14: del(14)(q13q21.1) or (q13q21.2). This is the third case of holoprosencephaly in association with a deletion in this region. The present report concerns the association between prenatal craniofacial development, a holoprosencephaly locus, and the chromosomal segment 14q13.

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Isolated de novo proximal interstitial deletions of 14q are rare. We present a case of a de novo proximal interstitial deletion of chromosome 14 with the karyotype 46,XY,del(14)(q13q21.1) or (q13q21.2) in a fetus with cebocephaly, alobar holoprosencephaly (HPE), and microcephaly. Comparison of this proband's phenotype with seven previously reported patients[1–5] associated with proximal interstitial deletion of 14q suggests that the chromosomal segment 14q13 is possibly associated with fetal craniofacial development and holoprosencephaly.

Case report

A 29 year old primigravida came to our clinic for confirmation of fetal craniofacial malformations during the late second trimester. Ultrasonography at 26 weeks' gestation showed a single fetus with microcephaly, alobar HPE, centrally fused thalami surrounded by a single ventricle, hypotelorism, and a single nostril. A tentative diagnosis of cebocephaly was made. Cordocentesis of the fetus showed an interstitial deletion of a small segment within bands 14q13 and 14q21. The karyotype was 46,XY,del(14)(q13q21.1) or (q13q21.2) (fig 1). Whole chromosome painting using a digoxigenin labelled whole painting probe for chromosome 14 in fluorescence in situ hybridisation excluded the possibility of translocation or insertion. Chromosome studies on the parents showed a 46,XY karyotype in the father and 46,XX karyotype in the mother. The parents were Chinese, non-consanguineous, and healthy. The paternal age was 28 years. There was no family history of diabetes mellitus or congenital malformations. Maternal urine throughout the pregnancy did not contain glucose. The mother denied any exposure to alcohol, teratogenic agents, irradiation, or infectious diseases during this pregnancy. She elected to terminate the pregnancy at 27 gestational weeks. A male infant was delivered with a weight of 1006 g and a length of 36.5 cm. On gross examination, the infant showed microcephaly, cebocephaly, ocular hypotelorism, a single nostril, low set ears, micrognathia, a short neck, and cryptorchidism (fig 2). At necropsy, the proband was found to have microcephaly, alobar HPE, arrhinencephaly, agenesis of the corpus callosum, a single ventricle of the brain, left testicular agenesis, right undescended testis, and right adrenal hypoplasia. Other internal organs such as liver, lungs, kidneys, and heart were normal.

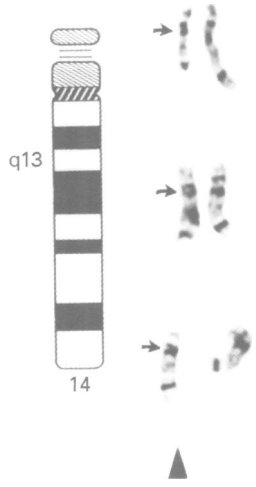

Figure 1 Partial karyotype of the proband showing the abnormal chromosome 14, which is indicated by an arrowhead. Arrows indicate the proximal interstitial deletion of the long arm of chromosome 14.

Discussion

HPE is associated with teratogens, familial factors with autosomal dominant and recessive inheritance, and chromosomal anomalies. Cytogenetic abnormalities have been reported in 50% of all HPE patients.[6] The specific chromosome aberrations include trisomy 13, trisomy 18, triploidy, del(13q), dup(13q), del(18p), del(7)(q36), dup(3)(p24-pter), del(2)(p21), and del(21)(q22.3).[6] At least four putative loci for HPE have been identified through the analysis of chromosomal rearrangements in HPE patients: HPE 1 on chromosome 21q22.3; HPE 2 on 2p21; HPE 3 on 7q36-qter; and HPE 4 on 18pter-q11.[7] Recently, the human Sonic Hedgehog (SHH) gene has been identified as HPE 3.[8] Mutations

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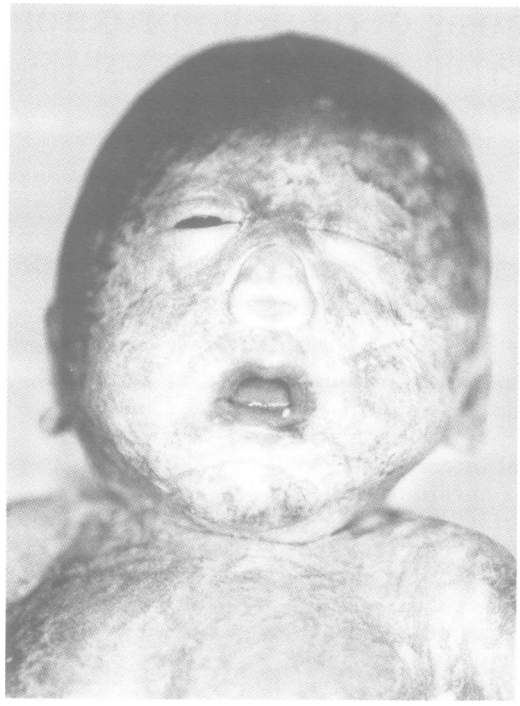

Figure 2 Anterior view of cebocephaly in the proband.

in the SHH gene causing HPE have been reported.[9] Other chromosomal abnormalities described in HPE include trisomy 21,[10] isochromosome 18q,[11] del(X)(q22),[12] del(11)(q21) mosaicism,[13] dup(1q),[14] and del(14)(q11.1q13) or (q11.2q21).[1 5]

Seven previous 14q deletion case reports have described a variety of proximal interstitial deletions encompassing band 14q13. Kodoma *et al*[2] reported two sibs with proximal interstitial deletion of chromosome 14, del(14)(q12q13.3). Clinical features of the two sisters included failure to thrive, severe mental retardation, microcephaly, round face, hypertelorism, micrognathia, and high arched palate. Grammatico *et al*[3] presented the first case of deletion 14q11.2q13 with clinical phenotypic findings of microcephaly, right plagiocephaly, bilateral cryptorchidism, and left hip subluxation. Shapira *et al*[4] described investigations in one patient with novel proximal deletion 14q11.2q21.1 and in another patient with deletion 14q12q22. The two patients shared phenotypic similarities of failure to thrive, micrognathia, and hypoplasia of the corpus callosum, which can be part of the holoprosencephaly sequence. Levin and Surana[1] reported the first case of HPE associated with proximal interstitial deletion of 14q, del(14)(q11.1q13). Bruyere *et al*[5] reported the second case of HPE associated with proximal interstitial deletion of 14q, del(14)(q11.1q13) or (q11.2q21). Our case was a further example of HPE with proximal interstitial deletion of 14q. Comparing the craniofacial malformations in this proband with those of seven previously reported cases associated with proximal interstitial deletion of 14q, our case suggests that chromosomal segment 14q13 may play a role in fetal craniofacial development. We suggest a holoprosencephaly locus within this region. Such an association will require more clinical reports as well as further pathological, cytogenetic, and molecular data to be proven.

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