

# A Case of del(13)(q22) with Multiple Major Congenital Anomalies, Imperforate Anus and Penoscrotal Transposition

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"13q-" syndrome is known to have widely variable manifestations, including retinoblastoma, mental & growth retardation, malformation of brain & heart, anal atresia, and anomalies of the face and limbs. Here we report a case of del(13)(q22) with multiple major congenital anomalies for the first time in Korea. The patient was born at 36<sup>+4</sup> weeks of pregnancy by caesarian section. Birth weight was 1490g. On examination the following features were noted: - imperforate anus, ambiguous genitalia (bifid scrotum, penoscrotal transposition, hypospadias), syndactyly of toes, absence of thumbs, abnormal facies (dolichocephaly, telecanthus, large low set ears, saddle nose, high arched palate, micrognathia). Neurocranial ultrasonography showed atrophy of the corpus callosum and multiple calcifications. He died at 14 days. Post-mortem autopsy findings showed cholestasis and fatty metamorphosis of liver, abnormal lobulation (Rt:2, Lt:1) and lymphangiectasis of the lung, VSD, ASD, PDA of heart, and acute tubular necrosis of kidney. Cytogenetic studies was confirmed to 46,XY,del(13)(q22) by Giemsa banded chromosomes from peripheral blood lymphocytes.

**Key Words:** Chromosomes 13, deletion, imperforate anus, penoscrotal transposition

## INTRODUCTION

Various phenotypic abnormalities have been associated with deletions of the long arm of chromosome 13. The most common clinical features of this 13q- syndrome are mental & growth retardation, facial abnormalities, limb & digital abnormal-

ities, retinoblastoma, colobomata, microcephaly, and intestinal atresia.<sup>1</sup> Proximal deletions of 13q tend to have fewer major anomalies except for retinoblastoma, but distal deletions are closely related to multiple major malformations.<sup>2</sup> Here we report a case of del(13)(q22) with multiple major congenital anomalies for the first time in Korea.

## CASE REPORT

The proband, a male infant, was born after 36<sup>+4</sup> weeks of gestation by caesarian section delivery. At the time of his birth the father and mother were both 34-year-old. There was no evidence the mother being exposed to known teratogens during the pregnancy. Birth weight was 1,490g due to fetal distress, which was below the 3rd percentile. On first day of life the infant was transferred to the neonatal intensive care unit of Yonsei University Yongdong Severance Hospital for the evaluation of multiple anomalies.

On physical examination the following features were observed. Facial anomalies included dolichocephaly, telecanthus, large low set ears, saddle nose, high-arched palate and micrognathia (Fig. 1). No major eye abnormalities such as retinoblastoma, cataract, colobomata, microphthalmia were observed. Hand and feet anomalies showed oligodactyly (absence of thumbs) (Fig. 2) and foot syndactyly of 4th-5th toes (Fig. 3). He had imperforate anus with anocutaneous fistula and ambiguous genitalia including bifid scrotum, cephalad transposition of small penis relative to the position of scrotum and hypospadias (Fig. 4).

Neurocranial ultrasonography showed atrophy

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Fig. 1. Frontal & lateral view of the face. Anomalies included dolichocephaly, telecanthus, large low set ears, saddle nose, high-arched palate and micrognathia.



Fig. 2. Hand anomaly showing oligodactyly (absence of thumbs).



Fig. 3. Foot anomalies showing syndactyly of 4th-5th toes.

of the corpus callosum and multiple parenchymal calcifications. Cardiac echocardiography showed paradoxical septal motion and multiple congenital heart anomalies including ventricular septal defect type I (large, 4 mm), atrial septal defect secundum (large, 5 mm) and patent ductus arteriosus (large, right to left).

During the first week of life he showed intermittent hypotension, bradycardia, tachypnea and hypoxia. Nasal oxygen was applied, and dopamine & dobutamine were started. During the second week he developed congestive heart failure because of his heart anomalies. He was given digoxin and lasix, but heart failure increased rapidly. He eventually died after 14th days of life.

The post-mortem autopsy finding showed abnormal lobulation (Rt:2, Lt:1) and lymphangiectasis of lung. The liver was grossly malformed and showed cholestasis & mild fatty metamorphosis. Heart anomalies were confirmed to ventricular septal defect, atrial septal defect and patent ductus arteriosus. Acute tubular necrosis of



Fig. 4. Perineal region showing imperforate anus with anocutaneous fistula and ambiguous genitalia including bifid scrotum, penoscrotal transposition and hypospadias.

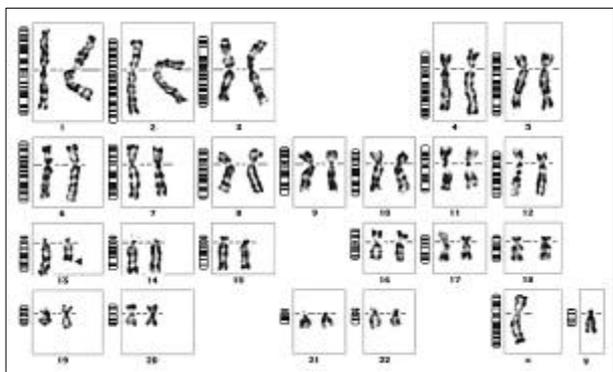


Fig. 5. Karyotype of patient showing 46,XY,del(13)(q22), by Giemsa banding.

the kidney was also noted.

Cytogenetic analysis of phytohemagglutinin stimulated peripheral lymphocytes by Giemsa banding revealed a deletion in a segment of the long arm of chromosome 13 (Fig. 5). The karyotype was interpreted as 46,XY,del(13)(q22). Band 13q22 was consistently missing in all 21 cells examined. Parental karyotypes were normal.

## DISCUSSION

"13q" syndrome is caused by the absence of a portion of the long arm of chromosome No.13, as first reported by Allderdice et al.<sup>3</sup> The majority of cases have involved ring chromosome formation, terminal and interstitial deletions are less common. Specific diagnostic criteria are difficult

to define because there are widely variable manifestations in 13q deletion patients. Common clinical findings have included retinoblastoma, mental retardation, growth retardation, brain malformations, renal malformations, heart malformations, anal atresia and other malformations of the gastrointestinal system, various minor anomalies of the face, and several limb and digital malformations.<sup>1-3</sup> With the advent of chromosomal banding techniques, several attempts have been made to correlate the region of deletion with phenotype.<sup>1,2,4-6</sup>

Niebuhr proposed four categories associated with deletions of different portions of chromosome 13.<sup>2</sup> Category 1 included patients with monosomy of the distal long arm, most often having a ring chromosome with a breakpoint at q33 or q34. Frequently observed features were microcephaly, trigonocephaly, hypertelorism, epicanthic folds, large ears, and protruding maxilla. Category 2 included patients with a deletion involving the segment distal to 13q22. In addition to category 1 features, most of these patients had absent or fused metacarpals, absent or fused toes, and many showed intrauterine growth retardation and early death. Category 3 included patients with a deletion encompassing q14, the main distinguishing feature of which was retinoblastoma. According to factor of host resistance and degree of carcinogenic potential of deletion of 13q, it was calculated that some 13% to 20% of de novo deletion 13q14 cases remain unaffected with retinoblastoma.<sup>7</sup> So high-resolution cytogenetic analysis may be recommended in such patients in order to diagnose those with the 13q14 deletion and at risk of developing retinoblastoma. Category 4 was tentatively associated with the deletion of q21. Although these patients were defined primarily by the absence of thumb defects and retinoblastoma, they also shared a group of abnormalities, including; microcephaly, hypertelorism, large ears, abnormal dermatoglyphics and cardiac defects. In summary, Niebuhr observed that those patients with distal deletions of 13q were the most severely affected, and that those with more proximal deletions tended to have fewer major anomalies except for retinoblastoma. According to the Niebuhrs categorization our case corresponds well to category 2.

Another approach to 13q deletion is described in the report of Brown et al.<sup>1</sup> They proposed that 13q deletion patients fall into three separate groups. According to this scheme Group 1 is comprised of those with proximal deletions, usually not extending into q32, and with mild or moderate mental retardation, variable dysmorphic features, and growth retardation. Depending on the deleted segment, retinoblastoma may or may not be present. Group 2 is comprised of those with more distal deletions, including at least a part of q32, and one or more major malformations. These are most frequently severe microcephaly and brain malformations, such as, posterior encephalocele and holoprosencephaly, absent thumbs or other distal limb abnormalities, eye malformations such as severe microphthalmia and retinal colobomata, and genitourinary and gastrointestinal tract malformations. Severe mental retardation and growth retardation are also usually present. Group 3 is comprised of those with the most distal deletions, involving q33-q34, with severe mental retardation but without major malformations and usually without growth retardation. According to Browns classification our case would fall into group 2.

Brown et al also postulated that there is a critical region in 13q32 where deletion leads to a syndrome of severe major malformations including digital and brain anomalies.<sup>6</sup> Using molecular analysis, they undertook deletion mapping in 17 patient cell lines with the 13q deletion. As a result the 13q32 region was found to be deleted in all of the severely affected patients but not deleted in more than one mildly affected patient. The weak point of this postulate is that there are many reports upon cases with no major anomaly in which q32 is completely or partially deleted,<sup>5,8-10</sup> and there are also a few reports about major anomaly cases with no q32 deletion.<sup>11</sup> Therefore, it is difficult to correlate clinical features with the deletion of specific chromosome regions. There are many possible causes. It might be because subjective evaluation of physical findings and cytogenetic analysis, nonpenetration of causative genes, and developmental complexities and redundancies that permit normal development when crucial genes are present in abnormal doses.<sup>12</sup>

This patient showed complete penoscrotal transposition with bifid scrotum and hypospadias. This is explained by an embryological hypothesis. At four months gestation there is a caudal shift of the scrotal swellings with fusion to form a definitive scrotal sac posterior to the penis. A failure of this shift produces the aforementioned anatomic arrangement.<sup>13</sup> It has been also associated with mosaic trisomy 18 karyotype and other chromosomal anomalies.<sup>14,15</sup>

In conclusion, this case gives additional information about the deletion of chromosome 13. Its manifestations are so variable that further studies, such as the high-resolution banding technique, fluorescent in-situ hybridization (FISH), and molecular mapping may be needed to clarify the correlation between 13q deletion and clinical features.

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