CASE REPORT

Short Man with 46,X, Del (Yp) Del (Yq) Karyotype and More Distal Yq Deletion

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- **Abstract**

Deletion mapping studies suggest that genes on the long arm of the Y-chromosome (Yq) may play a pathogenetic role in a group of short males. Although recent researchers have postulated that growth genes are located on the most proximal portion of the long arm of the chromosome, the precise location has not been determined. We report a case of an adult male with a short stature and 46,X, del (Yp) del (Yq) karyotype. The deletion breakpoint on Yq was determined by the use of sequence-tagged site markers and was found between sY182 (5E) and sY151 (5F). This case suggests that the growth determinant gene(s) is/are located distal to sY182 and is/are more distal from the regions, which were previously reported.

Keywords • Short stature • Y-chromosome deletion • GCY • STS markers • tooth size

Introduction

Height represents a multifactorial trait, influenced by both environmental and genetic factors.[1]

Several cytogenetic studies have shown that deleted or morphologically altered long arm of the Y-chromosome is found in patients with short stature[2-5], proposing that there is a gene on the long arm of Y-chromosome which has an effect on stature. This putative gene was named growth control Y, (GCY).[3,6] The hypothesis that the gene related to tooth size is identical to the one related to the height was under investigation.[3]

Salo et al, correlating the height of the 15 males with their deletion breakpoints suggested that the critical region is the most proximal portion of the long arm of Y-chromosome, extending from markers sY78 in interval 4B to marker sY94 in interval 5G of the proximal long arm.[7] The study carried out by Barbaux et al, led to the result that the regions defined by sY78 at interval 4B and by sY90 at interval 5E, may be the critical regions for the Y-specific growth gene(s).[8] Ogata et al, analyzing 13 Japanese and 4 European non-mosaic adult male patients with a partial Yq deletion, localized the growth gene(s) to a more limited region than other studies, i.e. the region extending from marker sY83 in interval 5C to marker sY87 in interval 5D.[9] A recent study conducted by Kirsch et al and using FISH deletion mapping established the proximal interval between markers sY78 and sY83 as the only GCY critical interval.[16]

Here we report the case of short and azoospermic patient with 46,X, del (Yp) del (Yq) karyotype. Deletion breakpoint of Yq is more distal to the previously reported region.

Case Report

A 35-year-old male attended in our center with azoospermia. On physical examination, he was found to be 145cm (<1° centile) in height, with small chin, mouth and teeth. Examination of the genitalia revealed reduced volume of the testes and normal phallus. Semen analysis revealed complete azoospermia. Physical obstruction of the seminiferous pathways was ruled out.

Hormonal evaluation showed an increased level of serum LH and normal serum FSH and testosterone. Serum thyroid hormones and TSH levels were normal. The bilateral testicular biopsy showed incomplete maturation arrest.

Peripheral blood lymphocytes were used to determine karyotype by analysis of metaphasic chromosomes; banding GTG, according to ISCN 1995.[11] One hundred cells were examined. Chromosomal study revealed 46,X, del (Yp) del (Yq) karyotype in all of the studies cells.

The Y-chromosomal breakpoints were defined by polymerase chain reaction (PCR) detection of sequence-tagged sites (STS). Twenty STSs (Research Genetics, Alabama, USA), used to map Y-chromosome deletions, were selected from the STS map of Vollrath et al[12], Foote et al[13] and the recent map of DAZ region.[14] Of these markers (none of which were pseudoautosomal), 10 were on the short arm, one was in the centromeric region and 9 were in the euchromatic q11 band of the long arm (Table 1). PCR was performed under the condition previously described by Salo et al.[7] The breakpoint of deletion in the long arm of the Y-chromosome was located between sY 182 and sY 151, at the boundary between intervals 5E and 5F. Table 1 shows the results of deletion mapping with STS markers.

Discussion

The gene that is contributing to human growth has been tentatively mapped to the long arm of the Y-chromosome. As mentioned before, using the sequence-tagged site (STS) markers, the critical region is mapped in proximal Yq; from marker sY 78 in interval 4B to marker sY 94 in interval 5G[7]; from marker sY 78 in interval 4B to marker sY 182 in interval 5E[8]; from marker sY 78 in interval 4B to marker sY 83 in interval 5C[10]; or from marker sY 83 in interval 5C to marker sY 165 in interval 5D.[9]

Deletion breakpoint of the long arm of Y- chromosome in our patient is more distal than the previously reported cases, including those by Ogata, Salo, and others.[15,16] However, it still remains in the distal part of the region, which is postulated by Salo et al.[7] This analysis indicates that the GCY is located distal to STS marker sY 182.

Deletions of the pseudoautosomal region (PAR1) of the short arm of sex chromosomes have recently been reported in patients with short stature. Rao et al, have identified a novel homeobox containing gene, SHOX(short stature homeobox containing gene), with the size of 270-kb which is located in the distal part of PARI.[17,18] SHOX escapes X-inactivation and is expressed from an inactive X-chromosome, as well as an active X and a normal Y-chromosome. Mutational analysis of SHOX in 400 patients with idiopathic short stature has identified three types of heterozygous nonsense and missense mutations. SHOX has an important role in bone growth and development.[19] The possibility that another Y- specific growth gene(s) is present on the proximal Yp has not been excluded and the short stature of our patient may be partially due to the deletion of the genes located in proximal Yq. We cannot however, rule out the possible role of autosomal chromosomes.

Tooth size is another parameter of growth. It has been suggested that tooth size is closely correlated with height. However, it is yet to be determined whether the gene for tooth size is identical to the one related to height.[7] The small chin and mouth that were present in our patient had also been reported

before.[20]

Considering the hormonal profile of this patient, it can thus be hypothesized that the deletion of GCY gene(s) causes short stature independent to the effect of testosterone.

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