Clinical features of nine males with molecularly defined deletions of the Y chromosome long arm

Pia Salo, Jaakko Ignatius, Kalle O J Simola, Esa Tahvanainen, Helena Kääriäinen

Abstract

Deletions of the long arm of the Y chromosome have previously been associated with azoospermia and short stature. We report the results of a detailed clinical and molecular study of nine males with partial deletions of Yq. Special emphasis was laid on congenital anomalies and dysmorphic features. Some of the patients have developmental problems or distinct facial features, namely a small chin and mouth, a high arched or cleft palate, downward slanting palpebral fissures, high nasal bridge, and dysmorphic ears. As far as we know, similar facial dysmorphism has not been previously described in association with del(Yq). These features are not, however, simply correlated to the size of the deletion. In none of these patients could evidence of aberrant Xq-Yq interchange be found.

(J Med Genet 1995;32:711-715)

Deletions of the long arm of the Y chromosome are rare. In a study of 34 910 unselected live-born infants, no Yq deletions were found in any of the 17 872 boys.¹ The incidence of Yq deletions, however, varies largely depending on the criteria used in a particular study. Thus, in another study, at least one in 1000 male infants was classified as del(Yq).² Several case reports on patients with non-mosaic del(Yq) have been published.³⁻²⁴ Many of these reports are old and it is not always clear whether the patient had a deletion of only the fluorescent segment Yq12, which is considered a variant rather than an aberration, or a more proximal deletion involving Yq11. The clinical spectrum of the published patients ranges from a normal male phenotype through azoospermia or short stature to various congenital anomalies or mental retardation. These differences in phenotype apparently reflect different indications for the chromosomal study and thus biased ascertainment.

The association of deletions of the Y chromosome long arm with azoospermia was first suggested by Tiepolo and Zuffardi in 1976.²⁴ Since that time, the azoospermia factor gene (AZF) has been mapped in interval 6²⁵⁻²⁷ and candidate genes in this region have been described.²⁸ In addition, a growth control gene has been tentatively assigned to proximal Yq11²⁹ based on comparison of growth and tooth size in two males with Yq deletions of different

size. Except for these, no clear clinical picture associated with deletions of the Y chromosome long arm has emerged.

The recent detailed mapping of the human Y chromosome has provided a greatly improved tool to delineate deletions of the Y chromosome molecularly.^{30,31} By correlating the height of males with molecularly defined partial deletions of Yq we have located a region whose presence or absence has a marked effect on stature.³² During the study we observed similar facial dysmorphism in some of these males. Therefore we conducted a detailed clinical study of all patients available with special emphasis on congenital anomalies and dysmorphic features. A further molecular study was conducted to test if any of these patients display aberrant Xq-Yq interchange, as recently described.³³

Patients and methods

PATIENTS WITH Y CHROMOSOMAL DELETIONS

All patients with a deletion of the Y chromosome long arm identified in three major chromosome laboratories in Finland were included in this study. Chromosomal investigation of the nine patients thus found disclosed no other chromosomal abnormalities except for the deletion of the Y chromosome long arm. No signs of mosaicism were found. In all cases a sample from the father or brother was available and showed no deletion when studied with STSs or by chromosomal analysis. Hospital files of the patients were studied and eight of the patients were investigated by one of us (JI, KS, or HK). In this study the patients are numbered from 1 to 9 with patient 1 having the smallest deletion and patient 9 the largest. Patients 2 and 9 have been described previously.²⁹ The molecular deletion breakpoints have been reported previously.^{31,32}

SEQUENCE TAGGED SITES DETECTED BY POLYMERASE CHAIN REACTION

The Y chromosomal breakpoints were defined by polymerase chain reaction (PCR) detection of sequence tagged sites (STSs), as previously described.³¹

POLYMERASE CHAIN REACTION ANALYSIS OF POLYMORPHIC MARKERS

Patients and their parents (when available) were typed for CA dinucleotide repeat polymorphisms as previously described.³⁴ The primers used included sDF-1 and sDF-2,³⁵

Department of
Medical Genetics,
University of Helsinki,
PO Box 21,
Haartmaninkatu 3,
SF-00014 Helsinki,
Finland
P Salo
E Tahvanainen

The Finnish
Population and Family
Welfare Federation,
Kalevankatu 16, SF-
00100 Helsinki,
Finland
J Ignatius
H Kääriäinen

Department of
Clinical Genetics,
Tampere University
Hospital, SF-33520
Tampere, Finland
K O J Simola

Correspondence to:
Dr Salo.

Received 28 February 1995
Revised version accepted for
publication 2 May 1995

Table 1 Phenotypes of nine 46,XYq- males. Age refers to the age of the patient at examination

No	Reason for referral	Age	Testes (size and histology)	Dysmorphic features	Height	Other features
1 LGL 5167	Infertility	28	Almost normal sized	None	Normal	Azoospermia
2 LGL 825	Infertility	34	Relatively small, 40 × 25 mm, 30 × 20 mm, Sertoli cell only	Small chin	Normal	Azoospermia
3 LGL 5022	Mild mental retardation	10	Normal	High palate, fingers slightly tapering	Normal	Attended special classes, obesity, fragile X excluded by chromosomal study
4 LGL 5825	Overweight, delayed puberty	15	Small, 15 × 10 mm	Small chin and mouth, downward slanting palpebral fissures, smooth ear lobes, high palate	Retarded growth	Striae on the abdomen, gynecomastia, myopia, ASD, school performance below average, truncal obesity
5 LGL 5019	Retarded growth and development, dysmorphic features	5	Normal, small left hydrocele	As patient 4 plus high bridged nose with small nares, large and posteriorly rotated ears, mild clinodactyly, pes planus	Retarded growth	Walked at 17 months, spoke sentences at 5 years
6 LGL 862	Slow motor development, dysmorphic features	4	Normal	As patient 4 plus triangular face, long nose, submucous cleft palate, epicanthic folds	Normal	Walked at 18 months, speech delayed, special class in school
7 LGL 5860	Undescended testis	9	Undescended testis, normal size and consistency	Small chin and high palate	Normal	Mild mental retardation/low normal intelligence with problems in visual and visuomotor skills, gynecomastia, truncal obesity, inverted nipples
8 LGL 676	Ambiguous genitalia	15	Hypoplasia	Ear lobes poorly folded, high and narrow palate, chest barrel shaped	Short	Aortic coarctation, scrotal hypospadias, very small penis, uterus and abdominal gonads operated on to create as masculine a phenotype as possible, mild or moderate mental retardation
9 LGL 658	Short stature	26	Small, 30 × 22 mm	As patient 4 plus long and high bridged nose	Short	Mild hypothyroidism, normal school performance, normal testosterone levels, frontal baldness

sKK-1 and sKK-4.³⁶ Of these markers sDF-2 and sKK-4 are X specific and sDF-1 and sKK-1 are pseudoautosomal. The physical order of these markers is as follows: cen-sDF-2-sKK-4-sDF-1-sKK-1-tel.

Figure 1 Deletions of nine 46,XYq- males. The exact deletion breakpoints have been reported previously.^{31,32}

Results

The clinical data on patients 1 to 9 are summarised in table 1 and results of CA dinucleotide repeat analysis in table 2. The deletions and facial features of the patients are presented in figs 1 and 2, respectively. Patient 8 refused medical investigation and would not send photographs for this study. Patient 4 refused to be photographed.

CLINICAL FINDINGS

The most common findings among the nine 46,XYq- males in this study were developmental problems and mild facial dysmorphism (table 1). Five patients (patients 3 and 5 to 8) had at least some developmental delay or school problems. Mild facial dysmorphism was found in patients 4, 5, 6, and 9. They all had a small chin, a small mouth, a high arched or cleft palate, downward slanting palpebral fissures, high nasal bridge, and dysmorphic ears.

Table 2 Inheritance of CA dinucleotide repeat polymorphisms in nine XYq- males. Samples from the father were available in patients 3 to 5, 7, and 9, from the mother and brother of patient 1, and from the brother of patients 2 and 8.

Patient	X specific		Pseudoautosomal	
	sDF-2	sKK-4	sDF-1	sKK-1
	Pat/mat	Pat/mat	Pat/mat	Pat/mat
1	-/+	-/+	-/+	-/+
2	-/+	-/+	-/+	-/+
3	-/+	-/+	-/+*	-/+
4	-/+	-/+	-/+	-/+
5	-/+	-/+*	-/+	-/+
6	-/+	-/+	-/+	-/+
7	-/+*	-/+*	-/+	-/+
8	-/+	-/+	-/+	-/+
9	-/+	-/+	-/+*	-/+*

-/+, XYq- male inherited a maternal allele, -/+*, XYq- male inherited a single allele, the size of which is similar to the size of the paternal allele.

Figure 2 (A) Front views of patients 5, 6, and 9 and (B) side views of patients 2, 5 to 7, and 9. Patients 5, 6, and 9 have a long, high bridged nose, small mouth and chin, dysmorphic ears, and narrow or downward slanting palpebral fissures. In addition, patients 2 and 7 have a chin smaller than that of an average Finn.

POLYMERASE CHAIN REACTION ANALYSIS OF POLYMORPHIC MARKERS

All the nine 46,XYq — males had inherited only a single allele for each marker (table 2). Four patients had inherited an allele similar to his father for one or two markers.

Discussion

Patients 1 and 2 had no symptoms apart from azoospermia. They had grown normally. Patient 2 had a small chin, but otherwise their facial features were normal. Patient 1 had the smallest deletion, but the deletion breakpoint in patient 2 fell in the same region as in patients 3 and 4. The physical breakpoints in these patients might differ, however, because the average spacing of STSs is assumed to be about 220 kb between ordered loci.³⁰

Patients 3 and 5 to 8 all had at least some developmental delay or school problems. Also, patient 4, in spite of going to normal school, appeared less intelligent than the other members of his family. However, patient 9 with the largest deletion had normal intelligence. It nevertheless remains possible that there are gene(s) in proximal Yq whose absence predisposes to deficient mental development. On the other hand, as mental retardation is one of the most common reasons for chromosomal investigation, and as it was the main reason for chromosomal study in two of the patients and apparently a secondary reason in two others, the frequent finding of mental retardation in this series may only reflect a bias of ascertainment.

The patients had very few major malformations when compared to other chromosomal syndromes. Congenital heart defect had been present in two patients and ambiguous genitalia in one. In addition, one had undescended testes and the pubertal or adult patients had relatively small testes.

Minor malformations were more common. The facial dysmorphism in patients 4, 5, 6, and 9 was mild but obvious. They all had a small chin, a small mouth, a high arched or cleft palate, downward slanting palpebral fissures, high nasal bridge, and dysmorphic ears. As far as we know, similar facial dysmorphism has not been previously described in association with del(Yq). Truncal obesity was seen in patients 3, 4, and 7. It is possible that patient 8 had the same phenotype as he was stated to have peculiar facies, a high arched palate, and dysmorphic ears. However, patients 1 to 3 and 7 did not show facial dysmorphism.

The occurrence of aberrant Xq-Yq interchange was discovered very recently.³³ In a study of 10 males with 46,XYq — karyotypes three males were shown to be disomic for a portion of distal Xq. These patients exhibited severe mental retardation, generalised hypotonia, and microcephaly; none of our patients displayed a similar phenotype. None of the nine 46,XYq — males in this study showed evidence of Xq-Yq interchange when tested with polymorphic markers; in all cases only a single allele was observed (table 2). Four patients had an allele similar to his father for

one or two markers. Since they had alleles different from their father for other markers tested, occurrence of aberrant Xq-Yq interchange in these patients is unlikely.

The phenotype of the patients cannot be explained simply by the size of the deletion. Possibly some of these patients, particularly patient 8, might have an undetected 45,X mosaic cell line. It is also possible that some patients have other minor chromosomal aberrations, such as Xp;Yq³⁷ or Y;autosome translocations, even though such aberrations were not detected in chromosomal studies. Another explanation, though unlikely, could be variable order of genes in Yq as only the pseudo-autosomal parts of the Y chromosome pair with the X chromosome in male meiosis. On the other hand, del(Yq) might only predispose to facial dysmorphism so that all features are not displayed in every patient owing to multifactorial inheritance. Alternatively Yq deletions could cause chromosomal imbalance leading to non-specific features.

Of the patients with facial dysmorphism, only patients 8 and 9 were short. Patients 4 and 5 were also under their target heights but they are both still growing. Patient 6 was of normal height.

We conclude that the clinical consequences of Yq deletions are variable. Patients with the smallest deletions had azoospermia as the only symptom. In patients with more proximal deletion breakpoints, distinct facial features and developmental problems are a frequent but not a constant finding. It will be of interest to see what underlies this diversity and if any of the common features can be explained by the absence of specific genes on the Y chromosome long arm. Our results also suggest that 46,XYq — males, disomic for distal Xq, form a phenotypically distinct group as in none of the patients studied here could evidence of aberrant Xq-Yq interchange be found.

We thank the patients and their families, several clinical investigators for their help and cooperation, Sinikka Lindh for collecting the samples, Bruce Lahn for providing us with the polymorphic markers, and Professor Albert de la Chapelle for support and critical reading of the manuscript. This study was supported by the Academy of Finland, the Sigrid Juselius Foundation, and the Finnish Cultural Foundation, the Regional Fund of Häme. Part of the work was done at the Folkhälsan Institute of Genetics.

- Nielsen J, Wohler M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Århus, Denmark. *Birth Defects* 1991; 26:209–23.
- Hamerton JL, Canning N, Ray M, Smith S. A cytogenetic survey of 14,069 newborn infants. I. Incidence of chromosome abnormalities. *Clin Genet* 1975;8:223–43.
- Bühler EM. A synopsis of the human Y chromosome. *Hum Genet* 1980;55:145–75.
- Telfer M, Baker D, Rollin I. Probable long-arm deletion of Y chromosome in boy of short stature. *Lancet* 1973;i:608.
- Langmaid H, Laurence KM. Deletion of the long arms of the Y chromosome with normal male development and intelligence. *J Med Genet* 1974;11:208–11.
- Yunis E, García-Conti FL, Torres de Caballero OM, Giraldo A. Yq deletion, aspermatogenesis, and short stature. *Hum Genet* 1977;39:117–22.
- Podruch PE, Yen FS, Dinno ND, Weisskopf B. Yq — in a child with livedo reticularis, snub nose, microcephaly, and profound mental retardation. *J Med Genet* 1982;19: 377–80.
- Kosztolányi G, Trixler M. Yq deletion with short stature, abnormal male development, and schizoid character disorder. *J Med Genet* 1983;20:393–4.
- Skare J, Drwina H, Wyandt H, vanderSpek J, Troxler R, Milunsky A. Interstitial deletion involving most of Yq. *Am J Med Genet* 1990;36:394–7.
- Soudek D, Laraya P. C and Q bands in long arm of Y

- chromosomes; are they identical? *Hum Genet* 1976;32:339-41.
- 11 Meisner LF, Inhorn SL. Normal male development with Y chromosome long arm deletion (Yq-). *J Med Genet* 1972;9:373-7.
 - 12 Chandley AC, Gosden JR, Hargreave TB, Spowart G, Speed RM, McBeath S. Deleted Yq in the sterile son of a man with a satellited Y chromosome (Yqs). *J Med Genet* 1989;26:145-53.
 - 13 Cohen G, Manuel A, Cohen M, Fagan K, Grünstein H. A deletion of heterochromatin only of the Y chromosome in an azoospermic male. *Hum Genet* 1983;64:297-300.
 - 14 Hartung M, Devictor M, Codaccioni JL, Stahl A. Yq deletion and failure of spermatogenesis. *Ann Genet (Paris)* 1988;31:21-6.
 - 15 Kinross J, Fraccaro M, Scappaticci S, et al. Bsu restriction of DNA from cases exhibiting sex-chromosome abnormalities. *Cytogenet Cell Genet* 1978;20:59-69.
 - 16 Martin MJ, Rodriguez MT, Aller V, Abrisqueta JA, Rojo JM. Yq deletion (q11.21) in a H-Y⁺ azoospermic male. *Clin Genet* 1985;28:80-3.
 - 17 Mattei JF, Mattei MG, Lucas C, Giraud F. Les anomalies de structure du chromosome Y. *J Genet Hum* 1979;27:53-66.
 - 18 Neu RL, Barlow MJ, Gardner LI. A 46,XYq- male with aspermia. *Fertil Steril* 1973;24:811-13.
 - 19 Von Tóth A, Gaál M, László J. Der zytogenetische Hintergrund der männlichen Infertilität. *Zbl Gynäkol* 1982;104:1563-77.
 - 20 Crolla JA, Smith M, Docherty Z. Identification and characterisation of a small marker chromosome using non-isotopic in situ hybridisation with X and Y specific probes. *J Med Genet* 1989;26:192-4.
 - 21 Cheng SD, Gasparini R, Müller U. Molecular analysis of aberrations of Xp and Yq. *Hum Genet* 1992;88:379-82.
 - 22 Bardoni B, Zuffardi O, Guioli S, et al. A deletion map of the human Yq11 region; implications for the evolution of the Y chromosome and tentative mapping of a locus involved in spermatogenesis. *Genomics* 1991;11:443-51.
 - 23 Fechner PY, Smith KD, Jabs EW, Migeon CJ, Berkovitz GD. Partial gonadal dysgenesis in a patient with a marker Y chromosome. *Am J Med Genet* 1992;42:807-12.
 - 24 Tiepolo L, Zuffardi O. Localization of factors controlling spermatogenesis in the nonfluorescent portion of the human Y chromosome long arm. *Hum Genet* 1976;34:119-24.
 - 25 Andersson M, Page DC, Pettay D, et al. Y-autosome translocations and mosaicism in the aetiology of 45,X maleness: assignment of fertility factor to distal Yq11. *Hum Genet* 1988;79:2-7.
 - 26 Ma K, Sharkey A, Kirsch S, et al. Towards the molecular localisation of the AZF locus: mapping of microdeletions in azoospermic men within 14 subintervals of interval 6 of the human Y chromosome. *Hum Mol Genet* 1992;1:29-33.
 - 27 Vogt P, Chandley AC, Hargreave TB, Keil R, Ma K, Sharkey A. Microdeletions in interval 6 of the Y chromosome of males with idiopathic sterility point to disruption of AZF, a human spermatogenesis gene. *Hum Genet* 1992;89:491-6.
 - 28 Ma K, Inglis JD, Sharkey A, et al. A Y chromosome gene family with RNA-binding protein homology: candidates for the azoospermia factor AZF controlling human spermatogenesis. *Cell* 1993;75:1287-95.
 - 29 Alvesalo L, de la Chapelle A. Tooth size in two males with deletions of the long arm of the Y-chromosome. *Ann Hum Genet* 1981;45:49-54.
 - 30 Foote S, Vollrath D, Hilton A, Page DC. The human Y chromosome: overlapping DNA clones spanning the euchromatic region. *Science* 1992;258:60-6.
 - 31 Vollrath D, Foote S, Hilton A, et al. The human Y chromosome: a 43-interval map based on naturally occurring deletions. *Science* 1992;258:52-9.
 - 32 Salo P, Kääriäinen H, Page DC, de la Chapelle A. Deletion mapping of stature determinants on the long arm of the Y chromosome. *Hum Genet* 1995;95:283-6.
 - 33 Lahn BT, Ma N, Breg WR, Stratton R, Surti U, Page DC. Xq-Yq interchange resulting in supernormal X-linked gene expression in severely retarded males with 46,XYq-karyotype. *Nature Genet* 1994;8:243-50.
 - 34 Weber JL, May PE. Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am J Hum Genet* 1989;44:388-96.
 - 35 Freije D, Helms C, Watson MS, Donis-Keller H. Identification of a second pseudoautosomal region near the Xq and Yq telomeres. *Science* 1992;258:1784-7.
 - 36 Kvaloy K, Galvagni F, Brown WRA. The sequence organization of the long arm pseudoautosomal region of the human sex chromosomes. *Hum Mol Genet* 1994;3:771-8.
 - 37 Bardoni B, Floridia G, Guioli S, et al. Functional disomy of Xp22-pter in three males carrying a portion of Xp translocated to Yq. *Hum Genet* 1993;91:333-8.