Two male patients with ring Y: definition of an interval in Yq contributing to Turner syndrome

Maria Tzancheva, Radka Kaneva, Philip Kumanov, Gareth Williams, Chris Tyler-Smith

Abstract

Turner syndrome is thought to result from the haploinsufficiency of genes on the sex chromosomes, but these genes have not been identified yet. We describe two males with deleted ring Y chromosomes, one (TS) with full Turner syndrome and one (DM) without. TS has short stature, skeletal anomalies, lymphogenenic obstruction, cardiovascular abnormalities, and miscellaneous features including pigmented naevi, antimongoloid slanting of the palpebral fissures, and widely spaced nipples. In contrast, DM has short stature but no other specific Turner stigmata except high arched palate and a few pigmented naevi. Since little chromosomal mosaicism was detected, the different segments of the Y chromosome retained by these two males identify the location of one or more “anti-Turner” genes. Most of the Yp pseudoautosomal region and Yq were deleted from both patients during the formation of the ring chromosome, while the Y specific portion of Yp and the centromere were retained. The major difference detected was an interval of proximal Yq present in DM and deleted in TS. None of the previously identified genes, DFFRY, DBY, UTY, or TB4Y, lies entirely within this interval, although DFFRY was truncated by DM’s breakpoint. These data suggest that one or more additional “anti-Turner” gene(s) remains to be identified in the region of Yq proximal to DFFRY.

Turner syndrome is a comparatively frequent genetic disorder affecting 4 in 10 000 newborn girls. The full clinical picture includes short stature, gonadal dysgenesis, and a number of dysmorphic stigmata (Turner stigmata), such as slanting of palpebral fissures, pterygium colli, low posterior hair line, lymphoedema, skeletal abnormalities like micrognathia, high arched palate, short neck, shield-like chest, cubitus valgus, short metacarpals/metatarsals, scoliosis, cardiovascular and renal abnormalities, and pigmented naevi. The sex is usually female, but sometimes males are affected. Mental development is not impaired. The clinical picture is variable; most of the patients present some, but not all, of the dysmorphic features and anomalies.

About half of the patients with Turner phenotype have the karyotype 45,X0. In the remaining cases, mosaicism or rearrangement of the sex chromosome is seen. Structural aberrations can affect one of the X chromosomes (deletions of Xp or Xq, ring X, isoXq) or the Y (deletion of Yp or Yq, ring Y). The variability in the cytogenetic findings could explain some of the phenotypic differences. Karyotype/phenotype correlations in such patients indicate that many genes are involved in the formation of the full Turner phenotype. The pertinent factors have not been determined so far. It has been suggested that Turner syndrome is the result of monosity of loci on the short arm of the X chromosome, which have homologues on the Y chromosome. The haploid dosage, rather than a complete lack of the gene product, leads to the Turner phenotype. The hypothetical “anti-Turner” genes, repressors of the Turner phenotype, should have the following characteristics: expression in “double dosage”, escape from inactivation on the inactive X, and the existence of homologous genes on the Y.

Several genes that escape X inactivation and have functional Y chromosome homologues have been identified. The importance of these candidate anti-Turner genes needs to be evaluated. Patients with Turner syndrome associated with “pure” Y deletions are particularly informative in this respect. In this paper we present two male patients with the karyotype 46,X,r(Y), but with different phenotypes: one displays the full Turner phenotype, while the other shows only short stature, high arched palate, and a few pigmented naevi.

Case reports

CASE 1

TS was the product of an uneventful pregnancy and birth. His birth weight was 2800 g and length 49 cm. He failed to thrive. As a child he has always been shorter than his classmates, but the growth retardation became more obvious after 12 years of age. Mental development is not impaired. He presents almost all of the Turner stigmata (fig 1): short stature (height 140 cm, weight 50 kg at 19 years of age), antimongoloid slanting of palpebral fissures, rotated auricles, low posterior hair line, short neck, shield-like chest, widely spaced nipples, pigmented naevi, hypoplastic nails, cubitus valgus bilaterally, short left fourth metacarpal bone, short right fourth toe and metatarsal bone, and congenital heart disease (atrioseptal defect type II). External genitalia were well developed: penile length 9 cm, penile circumference 8.5 cm, pubic hair Tanner stage IV, but testes were small for his age (right 6 ml, left 5 ml), measured with a Prader orchidometer. He...
has regular ejaculations with azoospermia. The normal serum level of testosterone (26.2 nmol/l, normal range 9-35 nmol/l) correlates well with good androgenisation. He has normal function of the pituitary, thyroid, and adrenals. Growth hormone response to insulin is normal. He has an exaggerated response of gonadotrophic hormones LH and FSH to stimulation with gonadotrophin releasing hormone (100 µg).

Cytogenetic examination of peripheral blood lymphocytes after conventional (fig 2A) and GTG staining (fig 2B) was performed. The karyotype was 46,X,r(Y) in 92/100 cells, with a very small dot-like ring Y chromosome. In three cells (3%), a double sized Y ring was found (fig 2C). Five cells (5%) had a 45,X0 karyotype.

CASE 2
DM was born after the third normal pregnancy and delivery. His parents and first degree relatives are of short stature. His prenatal development was delayed: his birth weight was 2200 g and length 48 cm. He has always lagged behind his classmates. His height is now 131 cm (<−2 SD) and weight 30 kg at the age of 13 years. The bone age correlates well with his chronological age. No other specific Turner stigmata exist except a high arched palate and a few pigmented naevi. He lacks facial, body, and axillary hair, but pubic hair has started to develop (Tanner stage III). The penile length is normal (6 cm) and testicular volume is 2 ml on each side. There is evidence for anticipation of pubarche before gonadarche, which might suggest testicular hypoplasia and azoospermia in the future. Serum testosterone level is 5.9 nmol/l and the β-17 oestradiol level is in the normal range (0.017 nmol/l). Growth hormone response to insulin is quite good (14-fold increase of the basal level). Normal functioning of the pituitary, thyroid, and adrenal glands was found. Intellectual level is normal. Cytogenetic examination of GTG stained chromosomes from short term lymphocyte cultures showed a
The possible location of a gene protecting against Turner skeletal stigmata in this region is

Discussion

Patients TS and DM have strikingly different phenotypes: TS has full Turner syndrome, while DM has few Turner stigmata (table 1). Potential explanations for these differences are mosaicism and the different regions of the Y chromosome retained. DM showed no loss of the r(Y) in the peripheral blood lymphocytes examined, while TS had a low level of mosaicism, 5% 45,XO cells in lymphocytes. The level of mosaicism in other tissues is unknown, but his normal male genitalia and high testosterone levels (above the normal male average values) suggest it is also low. Thus mosaicism is unlikely to account for the different phenotypes.

The two patients both have r(Y) chromosomes, which have each been generated by a break in Yp and a break in Yq. The Yp breakpoints lie proximally within the pseudoautosomal region and so delete SHOX/PHOG,14 15 thus accounting for the short stature of the patients. The Yq breakpoints are distinct, with that of DM being the more distal. In the terminology of Vollrath et al,16 the breakpoint of TS lies between sY78 (DYZ3, interval 4B) and sY81 (interval 5A). That of DM is more difficult to assign in this terminology, but GMGY6 has been placed in interval 5D17 and RBF5 can be placed using its presence or absence from yOX YACs.16 It is present in yOX92 and yOX215, but absent from yOX219, yOX116, yOX84, and yOX186 (unpublished observations), and so must lie in interval 5C. Therefore the Yq breakpoint of DM lies within interval 5C or 5D. One or more “anti-Turner” genes providing protection against the skeletal, lymphogenic, and cardiovascular anomalies may lie within the additional sequences carried by DM in intervals 4B-5D.
Table 1 Patients harbouring Y deletions: clinical description and breakpoints

<table>
<thead>
<tr>
<th>Breakpoint localisation</th>
<th>Present patients</th>
<th>Barbaux et al18</th>
<th>Salo et al19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS (PAR) Yq (4B/5A)</td>
<td>DM (PAR) Yq (5D)</td>
<td>PP (PAR) Yq (4B/5A)</td>
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<tr>
<td>Phenotype</td>
<td></td>
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<td></td>
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<tr>
<td>Azoospermia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Short stature</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Skeletal</td>
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<tr>
<td>Short neck</td>
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<td>-</td>
<td>+</td>
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<tr>
<td>Cubitus valgus</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Short metacarpals/metatarsals</td>
<td>+</td>
<td>-</td>
<td>+ ?</td>
</tr>
<tr>
<td>Shield-like chest</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Lymphogenic obstruction</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High arched palate</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Low posterior hair line</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td></td>
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</tr>
<tr>
<td>Atrioseptal defects</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Pigmented naevi</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antimongoloid slanting of palpebral fissures</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Widely spaced nipples</td>
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</table>

from the TS/DM comparison alone, it could be suggested that such a gene lies in proximal Yq. However, other reports are not consistent with this: both patients of Barbaux et al18 with Turner stigmata and proximal Yq deletions (PP and PA) have skeletal defects only. Alternatively, gene(s) protecting against lymphatic obstruction could be situated in Yp. This possibility is supported by the finding that some patients with Yq intact but Yp deletions show lymphogenic stigmata: Ferguson-Smith1 and Ogata et al20 assign the putative lymphogenic gene(s) to the Y specific 1A1A-2B region, where ZFY provides a candidate gene. The observation that TS has apparently intact Y specific Yp sequences (including ZFY) but nevertheless several features resulting from lymphatic obstruction (low posterior hairline, rotated auricles, and hypoplastic nails) calls into question the role of ZFY in protecting against these Turner stigmata and could be explained in several ways. He could have an undetected defect in ZFY or another Y encoded gene from this region; alternatively, the relevant gene could be in the proximal part of the pseudoautosomal region, which DM possesses, instead of the Y specific portion of the chromosome, or these features of his phenotype could be caused by a gene on a different chromosome.

It is also difficult to locate precisely the cardiovascular and pigmented naevi gene(s) from our patients’ phenotypes. TS has atrioseptal defect type II (ASD2) that is not a characteristic feature of Turner syndrome. Instead, ASD2 is described as a monogenic entity occurring in a sporadic or autosomal dominant form (McKusick No 108800). Thus, ADS2 observed in TS could be due to a separate gene, not connected with the r(Y) aberration. Pigmented naevi are found in both patients, although TS has multiple pigmented naevi, while DM has only a few. This could perhaps be because of their polygenic determination; the role of the anti-Turner gene(s) in these cases is difficult to assess.

The ring Y of TS also provides some insights into the sequence requirements for a human chromosome in vivo. It is so small that it can be...
detected as a broad band on a pulsed field gel after linearisation by 60Co irradiation, although its size cannot be determined accurately because of the lack of size markers in this range (unpublished observations). It contains the smallest centromeric alphoid array discovered so far, and shows that 100 kb of Y alphoid DNA is sufficient for mitotic centromere function. The low level of mosaicism it shows may indicate that the overall chromosome size or alphoid array size are at the lower limit tolerated by a human chromosome in vivo, but the ring topology may also contribute to the mosaicism.

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