45,X male – rare case of unbalanced translocation of Y chromosome to chromosome 2 presenting with developmental delay, learning difficulty and obesity

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Summary

A male phenotype accompanied by a 45,X karyotype is rare. It may occur due to Y chromosomal translocation or insertion to X/autosome. Clinical presentation may vary depending on the presence of the Y chromosomal locus and the degree of loss of autosome material. 45,X males can present with short stature and Turner syndrome phenotype due to haploinsufficiency of genes which are normally expressed in both X and Y chromosomes. The presence of the sex-determining region Y (SRY) gene leads to the differentiation of bipotential gonads to testis. Most individuals go through puberty normally, but some may need pubertal induction for delayed puberty. Rarely some can have a pubertal arrest. The risk of gonadoblastoma is minimal in these individuals due to functioning testicular tissue. The azoospermia factor (AZF) region is found on the long arm of the Yq chromosome and is needed for spermatogenesis. In a 45,X male with unbalanced translocation of Y chromosome, spermatogenesis can be affected due to the lack of AZF leading to Sertoli cell-only syndrome. This will have an implication on fertility in adult life. We present a 14-year-old boy with developmental delay, learning difficulties and subtle dysmorphic features who was diagnosed with 45,X,der(2)t(Y;2)(?:p25). Fluorescence in situ hybridisation analysis revealed translocation of SRY (Yp11.3) to the terminal part of the short arm of chromosome 2 resulting in the deletion of most of the Y chromosome (Yp11.2-q12) and part of chromosome 2(2p25.3). This is the first case where SRY translocation to chromosome 2 presents with the above clinical presentation.

Learning points

• 45,X karyotype is rare in male.
• It may occur due to SRY translocation or an insertion to X/autosome.
• SRY gene translocation to chromosome 2 has been not reported in the literature.
• Clinical presentation can be varied due to degree of loss of chromosomal material.
• Due to loss of AZF region found on the long arm of the Yq, spermatogenesis can be affected. Loss of 2p25 leads to learning difficulty and obesity.
Introduction

A male phenotype with testicular differences in sex development (DSD) in the presence of a 45,X karyotype is rare. This may result from a Y chromosomal translocation or an insertion to X/autosome (1). Clinical presentation can be varied depending on the presence of the Y chromosomal locus and the degree of loss of autosome material. Children can have a typical male phenotype or present with stature abnormality and/or infertility in adult life (2, 3, 4). Detailed molecular genetics will often reveal 45,X/46,XY mosaic cell line. Very rarely it can be noted that the Y chromosome has been translocated to the X chromosome or autosome (5, 6, 7). The frequency of Y/autosome translocations in the general population is low occurring in approximately 1 in 2000 individuals (8).

The majority of individuals with a 45,X karyotype are phenotypically female with features of Turner syndrome (TS), which include short stature, ovarian failure, heart and renal structural abnormalities, and autoimmune disorders. These clinical features are due to the haploinsufficiency of genes which do not undergo inactivation in the second X chromosome. The short-stature homeobox (SHOX) gene is located in the pseudoautosomal region 1 (PAR1) of X and Y chromosomes (9). Haploinsufficiency of the SHOX gene is associated with idiopathic growth retardation and in the short stature phenotype of TS patients. SHOX-deficient 45,X males can present with short stature and milder Turner phenotype.

The SRY, located in the short arm of the Y chromosome, is responsible for the testis determination and differentiation in the bipotential gonads during early embryogenesis (10, 11). Genes located in the AZF region, found on the long arm of the Yq chromosome, are needed for spermatogenesis. Loss of AZF locus is associated with infertility in males (12, 13).

We describe a 45,X male with Y chromosomal translocation to chromosome 2. Chromosomal translocation has resulted in the deletion of most of the Y chromosome (Yp11.2-q12) and a small part of chromosome 2(2p25.3). This has resulted from a translocation of the tip of Yp onto the tip of 2p. To our knowledge, this is the first case of SRY translocation to chromosome 2, leading to 45,X male phenotype associated with obesity and intellectual disability due to lack of 2p25.3.

Case report

A 14-year-old male was born at term with a birth weight of 2.6 kg (−1.67 SDS). His antenatal and postnatal periods were uncomplicated, and developmental delay and poor attention span were identified during late infancy. His blood sample was sent for the diagnosis of Fragile X syndrome. CGG expansion in the FRAX A gene (FMR1) by fluorescent PCR analysis reveals CGG repeat within the normal range. Conventional cytogenetics revealed 45,X,der(2)t(Y:2)(?:p25). Chromosome analysis conducted on cultured cells from peripheral blood sample from this male child has indicated an abnormal karyotype with 45 chromosomes and no Y chromosome.

Figure 1

Karyotype. Chromosome analysis conducted on cultured cells from peripheral blood sample indicated an abnormal karyotype with 45 chromosomes and no Y chromosome visible cytogenetically. An equivocal banding pattern was evident on the distal short arm of one copy of chromosome 2.

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visible cytogenetically (Fig. 1). Additionally, an equivocal banding pattern was evident on the distal short arm of one copy of chromosome 2. Microarray analysis of the DNA sample from our patient has shown deletion of chromosome Y between Yp11.2 and Yq12, encompassing 74 BAC clones. These deletions are estimated to be between 2.69–3.08 Mb and 51.5–52.2 Mb in size using the Ensembl database, respectively. Fluorescence in situ hybridisation investigation carried out using the Vysis probe for the SRY gene (Yp11.3) showed the SRY gene was present on the terminal part of the short arm of chromosome 2 (Fig. 2). The use of sub telomeric probes for chromosome 2 also demonstrated partial monosomy for the short arm from 2pter to 2p25 (Fig. 2).

He was initially referred to endocrinology at the age of 5 years due to short stature. On examination, there were no facial dysmorphic features. He was noted to have short and wide feet without short fourth metatarsal bones. No upper limb deformities or mesomelia were noted. His height was 101 cm (−2.2 SDS), which was below the mid parental height (169.4 cm; −0.98 SDS), and his weight was 21.1 kg (+0.95 SDS). His BMI was high, which was 20.7 kg/m² (+3.21 SDS), and marked central adiposity was noted on examination. His stretched penile length was 2 cm with a palpable left testis and undescended right testis, which was not palpable in the scrotal sac.

He was commenced on daily growth hormone (GH) treatment at this stage at a starting dose of 40 µg/kg/day. After 6 months, the GH therapy was discontinued due to poor compliance, and he was unfortunately lost to follow-up.

He was later referred to the endocrinology team at the age of 10 years. At that point, he was diagnosed with pervasive developmental disorder (motor delay and speech delay) and behavioural problems including significant oppositional behaviour at school, hyperactivity and attention problems. Due to the behavioural problems and learning difficulties, he attended a special needs school. At that point, his height was 128.8 cm (−1.26 SDS), which had improved from his previous height SDS of −2.2. His weight was 44.7 kg (+2.2 SDS) and BMI was 26.9 kg/m² (+3.2 SDS) (Fig. 3). His genital examination revealed stretched penile length of 3 cm. His left testis was 2 mL with an palpable right testis in the scrotum.

Hormonal investigations at 10 years of age revealed prepubertal levels (Table 1). An ultrasound of the abdomen and pelvis revealed no renal abnormalities or Mullerian structures. Echocardiography revealed a structurally normal heart. His anti-Mullerian hormone (AMH) level was 611.9 pmol/L (84–976) which is suggestive of preserved Sertoli cell function. He underwent right orchidopexy for his undescended right testis at the age of 10 years. Subsequently, he developed secondary sexual characteristics and went into puberty spontaneously. At 14 years of age, his pubertal examination revealed axillary, pubic hair and genitalia Tanner stage 2. Both his testes were palpable in the scrotal sac. His left testicular volume was 6 mL, and his right testicular volume was 8 mL. At this stage, his serum testosterone, inhibin B and AMH levels showed normal testicular function (Table 1).

Investigations in view of his obesity revealed impaired glucose tolerance with elevated fasting insulin and C-peptide. He also had evidence of elevated liver enzymes and dyslipidaemia (Table 2). An abdominal ultrasound scan revealed normal liver parenchyma. Extensive investigations by the gastroenterology team were normal and the team concluded that the elevated liver enzymes were due to non-alcoholic steatohepatitis due to metabolic syndrome considering the background history of chromosomal abnormality and obesity. He was regularly followed up in the clinic with growth and pubertal monitoring. His tumour markers were monitored annually. Lifestyle modification advice was given and metformin was started for his obesity and insulin resistance.

**Discussion**

Most males who have testicular DSD with Y chromosomal abnormality will have Y cell line mosaicism, but rarely it may be a result of a Y chromosomal translocation. Y chromosomal mosaicism containing SRY has a broad phenotype ranging from a female with TS to a complete male phenotype including atypical genitalia at neonatal period or gonads with mixed gonadal dysgenesis (14, 15). The majority (95%) of Y chromosomal mosaicism are

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**Figure 2**

Fluorescence in situ hybridisation (FISH) analysis. (Left) FISH investigation using the Vysis probe for the SRY gene (Yp11.3) showed SRY gene was present on the terminal part of the short arm of chromosome 2. (Right) The use of sub telomeric probes for chromosome 2 demonstrated partial monosomy for the short arm from 2pter to 2p25.
typically male and rarely come to medical attention except in the case of short stature or infertility (14).

Both X and Y chromosomes are derived from the same ancestral autosome. With human evolution, most of the genes are lost in the Y chromosome. To compensate the gene dosage problem, one X undergoes inactivation in females (9). However, several genes in the X chromosome do not undergo inactivation. These genes are expressed in the Y chromosome to produce the homologous effect of the X chromosome (9). Genes in PAR 1, in the short arm of X (Xp22.23) and Y chromosome (Yp11.3), do not undergo inactivation. The SHOX in the PAR 1 region is present in both the X and Y chromosome, which belongs to the homeobox gene family (16). It is a transcriptional regulator and key controller of multiple processes during embryonic development. Haploinsufficiency of SHOX expression manifests phenotypic features of TS. It intervenes in the development of the elbow and knee by affecting the chondrogenesis and resulting in skeletal abnormality, slow growth and short stature (16). The presence of Yp11.3 in chromosome 2 in our patient demonstrates no haploinsufficiency in SHOX which has contributed to achieve reasonable height.

SRY in Yp11.3 is needed for specific sex and differentiation from bipotential gonads. Sex determination and differentiation of gonads to testicular Sertoli cells is initiated by SRY along with other genes, which include GATA4, WT1 and SF1. These are active during the critical period of sex differentiation (17). Activation of SOX9, which is the target gene of SRY, maintains the testicular development and Sertoli cell lineage (17). Germ cells derived from the embryonic yolk sack migrate to gonadal ridge and differentiate into spermatogonia, a result of factors secreted by the Sertoli cells (12). Spermaggonia have a dual responsibility. They undergo meiosis to produce the male gamete and mitosis to self-renew, which maintains the continuous production of spermatozoa (12). In general, structural abnormalities of the Y chromosome do not cause severe abnormalities but impact primarily on pathways of sexual development and spermatogenesis. The large deletion of the Y chromosome seen in our patient does not extend to the SRY at Yp11.3 and thus male sex determination was initiated. The AZF located in the Yq is necessary for spermatogenesis. Loss of Yq or microdeletion in the AZF locus leads to interruption of spermatogenesis and may cause male infertility (18). Clinical presentation can be varied depending on the degree of the deletion. The presentation can range from azoospermia to oligozoospermia and histologically manifest as Sertoli cell-only syndrome to varying stages of spermatid maturational arrest (12). The azoospermia

| Table 1 | Sex hormones and testicular volume at 10 and 14 years of age |
|-----------------|------------------|-----------------|
| **Biochemistry** | **At 10 years** | **At 14 years** |
| LH, IU/L | <0.1 | 5 |
| FSH, IU/L | 1.2 | 3.2 |
| Testosterone, nmol/L | <0.7 | 4.5 |
| AMH, pmol/L | 611.9 (84–976) | 262 (9.43–331.80) |
| Inhibin B (74–470) pg/mL | 228 |
| aFP (0–7) IU/mL | 1.7 |
| βhCG (0–10) IU/L | <1 |
| Testicular volume, left/right | 2 mL/2 mL | 6 mL/8 mL |

αFP, alpha fetoprotein; AMH, anti-Mullerian hormone; βhCG, beta human chorionic gonadotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
Deletions involving chromosome band 2p25.3 have been described in patients presenting with a non-specific clinical phenotype that includes intellectual disability (ID), obesity/overweight and dysmorphic features (21). MYT1L belongs to the myelin transcription factor 1 (MYT1) family, which is located in the 2p25.3. It is a neural-specific transcription factor involved in brain development and function along with other neural-specific transcription factors. SNTG2 located in 2p25.3 region is encompassed in copy number variants associated with autism spectrum disorders (22). Haploinsufficiency of MYT1L and SNTG2 have been observed in children with ID (21, 22, 23).

Deletion in ACP1 and TMEM18 located in the 2p25.3 region is associated with being overweight or having obesity (22). ACP1 is expressed in adipocytes. Polymorphisms in this gene have been linked with severe obesity and increased total cholesterol and triglyceride levels (24). TMEM18 has been associated with children with early-onset obesity and intellectual dysfunction (25, 26). It is likely that the deletion of chromosome 2 at 2p25.3 seen in our patient has contributed to his learning difficulties, obesity and related metabolic abnormalities.

### Conclusion

45,X males need surveillance for TS due to haploinsufficiency of genetic material from Y chromosome which is normally expressed. Due to the presence of SRY in the X/autosome, secondary to translocation or insertion, bipotential gonads differentiate into testes. However, spermatogenesis can be affected due to the lack of AZF gene in the long arm of Y chromosome. Clinical presentation can be greatly varied depending on the loss of autosomal material.

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**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case.

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**Patient consent**
Written consent has been obtained from parents and patient for publication.

**Author contribution statement**
JS collected information, wrote, and revised the manuscript; LA revised the manuscript; SS critically reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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**Table 2** Biochemical investigations at the age of 14 years.

| Investigations                                      | Result | Reference range         |
|-----------------------------------------------------|--------|-------------------------|
| Oral Glucose Tolerance Test, mmol/L                 |        |                         |
| 0 minute                                            | 5      | > 6.1                   |
| Normal                                             |        | 6.1–6.9                 |
| Impaired fasting glucose tolerance                 |        |                         |
| Diabetes mellitus                                   |        | > 7                     |
| 120 minutes                                         | 8.7    | < 7.8                   |
| Normal                                             |        | 7.8–11.1                |
| Impaired glucose tolerance                          |        |                         |
| Diabetes                                           |        | > 11.1                  |
| Fasting Insulin, pmol/L                             | 269    | <105                    |
| C-Peptide, pmol/L                                   | 2052   | 190–990                 |
| AST, IU/L                                           | 48     | 1–37                    |
| ALT, IU/L                                           | 82     | 1–40                    |
| Fasting lipid profile, mmol/L                       |        |                         |
| Triglyceride                                        | 2.6    | 0.4–1.4                 |
| Cholesterol                                         | 6      | 3.1–6.5                 |
| LDL cholesterol                                     | 3.76   | 0–2.85                  |
| HDL cholesterol                                     | 1.06   | >1.17                   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

factor genes (AZFa, AZFb and AZFc) located along Yq are included in the deleted region and it is therefore likely our patient will be infertile (12, 13).

Risk of gonadoblastoma is found in dysgenetic gonads where there is a disturbance in the germ cell migration and/or their correct organisation in the fetal gonad (19). Gonadal dysgenesis is caused by structural or numerical anomalies of the sex chromosomes or mutations in one of the genes involved in sex determination and differentiation of the bipotential gonad (19, 20). Our patient had functional testicular tissue indicated by a pubertal level of testosterone, normal AMH and Inhibin B. He has not undergone any testicular biopsy. His tumour markers have remained normal during his follow-up. He will need routine follow-up with monitoring of serial tumour markers to look for developing gonadoblastoma due to Y chromosomal structural abnormality.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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