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Discordant sex in monozygotic XXY/XX twins: a case report

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ABSTRACT: We report a case of discordant phenotypic sex in monozygotic twins mosaic 47,XXY/46,XX: monozygotic heterokaryotypic twins. The twins presented with cognitive and comprehension delay, behavioural and language disorders, all symptoms frequently reported in Klinefelter syndrome. Molecular zygosity analysis with several markers confirmed that the twins are in effect monozygotic (MZ). Array comparative genomic hybridization found no evidence for the implication of copy number variation in the phenotypes. Ultrasound scans of the reproductive organs revealed no abnormalities. Endocrine tests showed a low testosterone level in Twin 1 (male phenotype) and a low gonadotrophin level in Twin 2 (female phenotype) which, combined with the results from ultrasound examination, provided useful information for potentially predicting the future fertility potential of the twins. Blood karyotypes revealed the presence of a normal 46,XX cell line and an aneuploid 47,XXY cell line in both patients. Examination of the chromosome constitutions of various tissues such as blood, buccal smear and urinary sediment not surprisingly showed different proportions for the 46,XX and 47,XXY cell lines, which most likely explains the discordant phenotypic sex and mild Klinefelter features. The most plausible underlying biological mechanism is a post-zygotic loss of the Y chromosome in an initially 47,XXY zygote. This would result in an embryo with both 46,XX and 47,XXY cells lines which could subsequently divide into two monozygotic embryos through a twinning process. The two cell lines would then be distributed differently between tissues which could result in phenotypic discordances in the twins. These observations emphasize the importance of regular paediatric evaluations to determine the optimal timing for fertility preservation measures and to detect new Klinefelter features which could appear throughout childhood in the two subjects.

Key words: Klinefelter / mosaicism / twin / sex discordance / monozygotic

Introduction

Monozygotic twins are generally believed to share the same genotype and phenotype, but several forms of genetic discordance have been reported in MZ twins (Hall, 1996). A discordant sex between MZ twins was first described by Turpin (Turpin et al., 1961), and has since been reported several times, often in the context of Turner syndrome mosaicism, 45,X/46,XY or 45,X/46,XX (Lespinasse et al., 1998; Wachtel et al., 2000; Gilbert et al., 2002).

More recently, gender-discordant monozygotic twins with mosaicism in the context of presumed Klinefelter syndrome were reported for the first time (Zech et al., 2008). Klinefelter syndrome is the most frequent context for male hypogonadism, and a 47,XXY chromosome

constitution is the most common chromosome aneuploidy detected in males (Lanfranco et al., 2004). Notwithstanding, many cases go undiagnosed because of substantial variation in clinical presentation (Bojesen et al., 2003; Lanfranco et al., 2004). The true prevalence of mosaicism in patients with Klinefelter syndrome may be underestimated, because karyotypes are usually limited to leucocytes. Additional tissues such as skin fibroblasts or testicular biopsy samples for example are rarely studied (Lanfranco et al., 2004). In addition, patients with mosaicism have different phenotypic presentations compared with subjects with complete Klinefelter syndrome.

In the present report, we attempt to predict the reproductive function of MZ twins with 47,XXY/46,XX mosaicism and discuss the underlying mechanism leading to discordant phenotypic sex in the twins.

Clinical report

The twins were referred at 5 years of age to the Genetics Department for behavioural disorders, cognitive difficulties, speech disorders and enuresis. They also presented facial features characterized by arched eyebrows, hypertelorism, smooth philtrum and thin upper lip. Symptoms were more severe for the twin with a male phenotype (Twin 1) than for his sister (Twin 2).

The mother was aged 28 years and the father was 33 years at the time of the spontaneous pregnancy. The pregnancy was uneventful until a risk of premature delivery developed at 28 weeks of gestation (WG). Fetal ultrasound scans showed a dichorionic diamniotic pregnancy with one male and one female fetus without discernible abnormalities. At 32 WG, a Caesarean section was performed in a context of premature rupture of membranes.

Birth parameters for Twin 1, a male, were weight: 1850 g (−1.2 standard deviation, SD), length: 44 cm (−0.5 SD) and OFC (occipital frontal circumference): 30 cm (−1.5 SD). APGAR score was evaluated at 10.

Birth parameters for Twin 2, a female, were weight: 2110 g (−0.5 SD), length: 44 cm (−0.5 SD) and OFC: 30 cm (−1.5 SD). APGAR score was evaluated at 10.

Both newborns were transferred to the intensive care unit for monitoring because of premature birth. The course was satisfactory after a few days. The male twin presented with external hydrocephalus when he was 6-months-old and autoimmune bullous dermatitis at 4 years of age. He had enuresis, bi-coloured hair and cognitive difficulties assessed by the Wechsler Preschool and Primary Scale of Intelligence test (WPPSI). Verbal IQ, performance IQ and processing speed were evaluated at 75, 90 and 57, respectively. At the last physical examination in the Genetics Department at the age of 5 years, growth parameters were in the normal range: height was 111 cm (−0.5 SD), weight was 20 kg (+1 SD) and OFC was 51.5 cm (−0.2 SD).

The female twin had cardiac conduction disorder with a normal heart, detected by ultrasound at the age of 1 month and treated with Amlodipine for 1 year. She also had enuresis, bi-coloured hair and a mild language delay. The WPPSI did not reveal cognitive difficulties: verbal IQ, performance IQ and processing speed were assessed at 87, 92 and 86, respectively. At the last examination at 5 years of age, height was 110 cm (−0.5 SD), weight was 21 kg (+1.5 SD) and OFC was 50.4 cm (Mean). No signs of mosaicism were noticed on the skin of the twins. Physical examination of the external genitalia was normal in both twins.

The mother gave her informed consent for genetic studies for her two children. The study was approved by the ethical board of Montpellier University Hospital.

Ultrasound and endocrine investigations

For Twin 1, a 5-year-old boy, ultrasound examination of testicles was normal. Both the left testis (14 × 9 × 6 mm) and the right testis (14 × 10 × 6 mm) were mobile in the inguinal canal (Fig. 1). Endocrine tests revealed a normal level of anti-Müllerian hormone (AMH) at 974 pmol/l (range: 180–1784 pmol/l). The gonadotrophins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone, were below the normal range: 0.2 UI/l (range: 1–12 UI/l), <0.1 UI/l (range: 1–5 UI/l) and 0.07 ng/ml (range: 3–11 ng/ml), respectively.

For Twin 2, ultrasound examination of the ovaries and uterus showed normal female genitalia (Fig. 1). The left ovary measured 14 × 6 × 4 mm

and the right ovary measured 10 × 7 × 6 mm. The uterus was 29 mm long and had a prepubertal morphology. The AMH concentration was normal at 3.6 pmol/l (range: 0.8–60 pmol/l), as was the testosterone level (0.12 ng/ml, range: 0.1–0.6 ng/ml). FSH and LH levels were below the normal range for a 5-year-old girl, at 1.8 UI/l (range: 3–8 UI/l) and <0.10 UI/l (range: 1.5–6 UI/l), respectively.

Molecular and cytogenetic investigations

Microsatellite studies using 16 different short tandem repeat (STR) markers distributed on different chromosomes (PowerPlex 16 HS System, Promega) were performed according to the manufacturer's recommendations. The size of the allele of each of the 16 microsatellites markers was identical between the twins which strongly supports a monozygotic origin (Table 1). However, the twins were not of the same phenotypic sex and thus further analyses were carried out to explore the discordant sex.

Karyotyping, on cultured peripheral blood lymphocytes according to standard procedures, revealed in Twin 1 with male phenotype a mosaic karyotype 47,XXY[3]/46,XX[13] with two cell lines: 3/16 (19%) cells examined had two X chromosomes and one Y chromosome and 13/16 (81%) cells had a normal female sex chromosome complement (XX). The same mosaic karyotype 47,XXY[3]/46,XX[13] was observed in Twin 2 with a female phenotype. Cytogenetic analysis by fluorescence *in situ* hybridization (FISH) was performed on 200 interphase nuclei from peripheral blood cultures using either CEPX (DXZ1, Xp11.1–q11.1)/LSI SRY (Yp11.3) probes (Vysis) or DXZ1/DYZ1(Yqh)/SRY (Yp11.31) probes (Cytocell), according to the manufacturer's instructions. FISH analysis showed XXY(23%)/XX(77%) mosaicism (nuc ish (DXZ1x2,SRYx1)[46]/(DXZ1x2,SRYx0)[154]) in Twin 1 (Fig. 2) and XXY(25%)/XX(75%) mosaicism (nuc ish (DXZ1x2,SRYx1,DYZ1x1)[50]/(DXZ1x2,SRYx0,DYZ1x0)[175]) in Twin 2. FISH analysis of the buccal smears revealed a different chromosome constitution for the two twins: XXY(78%)/XX(22%) mosaicism in Twin 1 but a non-mosaic normal XX complement in Twin 2. Similar results were found in the urinary sediment samples, namely XXY(55%)/XX(45%) mosaicism in Twin 1 and XXY(5%)/XX(95%) mosaicism in Twin 2.

In an attempt to identify an additional genetic anomaly implicated in the cognitive and comprehension delay and facial features in the twins, array comparative genomic hybridization (array CGH) (60 k, Agilent, Santa Clara, CA, USA) was performed, according to the manufacturer's recommendations, and analysed on an Agilent scanner. For the autosomes, no pathologic copy number variation was discovered at a 300 kb resolution using CytoGenomics 2.7 software (Agilent). For the gonosomes, XXY/XX mosaicism was detected with no additional anomaly at 100 kb resolution.

Discussion

Klinefelter syndrome is often not diagnosed until adulthood. This is due to mild or subtle phenotypes during childhood as well as the extreme variability of clinical presentation and also because males with XXY/XY mosaicism are usually less severely affected than 47,XXY males (Lanfranco *et al.*, 2004). In childhood, the classic cognitive phenotype reflects deficits in specific domains of cognition, mainly language and

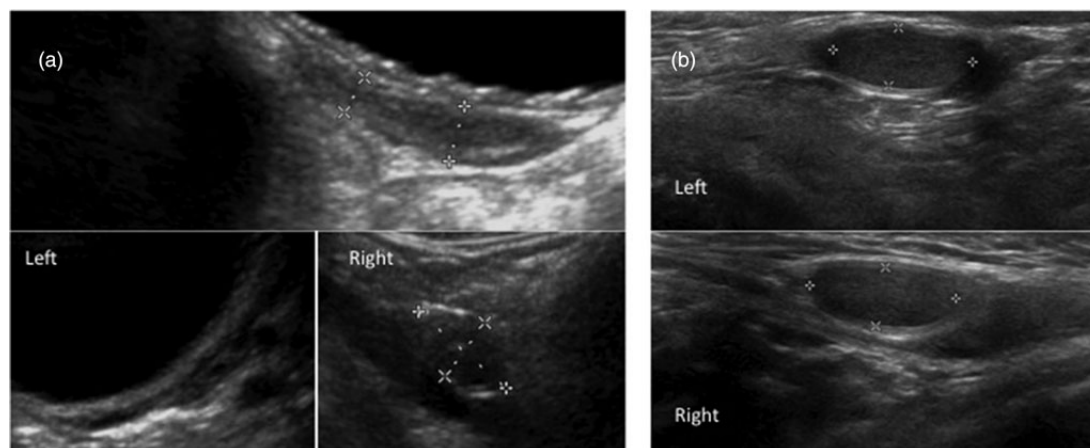


Figure 1 Images of ultrasound scans: (a) Scan of Twin 2, 5 years of age, showing normal uterus and two ovaries. (b) Scan of Twin 1, 5 years of age, showing normal testicles (cross and dotted lines were used for measure).

executive functions (involved in concept formation, problem solving, task switching, inhibitory processes, speed of response and planning) as well as psychological or social problems. Assessment of cognitive ability using the Wechsler intelligence scale for children (WISC) revealed a small but significant lowering of scores for XXY boys (Ratcliffe, 1999). Despite the mosaicism in the twins, we report a speech disorder and psychological behavioural problems were manifest, particularly for the boy, and the facial features were unusual. This association of symptoms could reflect an additional genetic anomaly, which prompted us to perform array CGH studies. The results did not reveal any relevant anomaly.

In addition to the cognitive difficulties, it has been shown that Klinefelter syndrome is one of the most frequent causes of infertility in males, affecting ~11% of azoospermic men and ~3% of all infertile men (Lanfranco *et al.*, 2004). Infertility in males with Klinefelter syndrome is characterized by severe impairment of spermatogenesis associated with hypogonadism and low or normal testosterone levels (Nieschlag *et al.*, 2014). Klinefelter infants present significantly reduced penile and testicular sizes, potentially indicating a testicular degeneration process. Although the reproductive organs of the twins were of normal clinical appearance and size on imaging, it was not possible to predict function.

Normal serum levels of testosterone, FSH and LH characterize pre-pubertal 47,XXY boys until the onset of puberty (Wikström and Dunkel, 2011). From mid-puberty (at about age 13) onwards, there is a gradual increase in FSH and LH concentrations which reach hypergonadotropic levels. On the other hand, inhibin B concentration, which is normal at the beginning of puberty in the majority of children, decreases rapidly. AMH serum levels, a marker of Sertoli cell functional status, remains normal until puberty and slowly decreases afterwards (Lindhardt Johansen *et al.*, 2013). The twins in this report presented different hormonal profiles, showing low levels of gonadotrophins and testosterone for the boy (Twin 1) and low levels of gonadotrophins for the girl (Twin 2). In Klinefelter subjects, the number of spermatogonia is normal in the first year of life and decreases during childhood to a very low or non-existent rate at puberty (Wikström *et al.*, 2004; Wikström and Dunkel, 2011). However, reproductive options exist for Klinefelter patients. Since 1996, intracytoplasmic sperm injection (ICSI) has been

implemented in France for oligospermia. Also, for the last 10 years, testicular sperm extraction coupled with ICSI has allowed biological paternity with similar rates of success for Klinefelter patients with azoospermia (Nicopoullos *et al.*, 2004) as for patients with other non-obstructive azoospermias (Plotton *et al.*, 2014). The success rate seems even better when patients are young, which can be explained by a better sperm extraction rate. In addition, androgen treatment may be often administrated because of hypogonadism which is frequently present at puberty, or even earlier, in Klinefelter subjects. However, as this anti-gonadotrophin treatment can be deleterious for spermatogenesis, androgen administration, before measures are taken to ensure sperm preservation, is much debated. This means that physician should initiate cryopreservation of testicular sperm or pulp before the administration of androgen therapy. Therefore, Twin 1 is recommended to undergo a regular biological monitoring of hormonal markers to determine the optimal age for possible enrolment into a medically assisted reproductive program with testicular biopsy or sperm extraction. Although, the evaluation of hormone levels is considered to be an efficient prognostic tool to assess the outcome of testicular biopsy in men with non-obstructive azoospermia, its prognostic value is not clearly established for Klinefelter patients and must be interpreted with caution, in particular in Klinefelter patients with mosaicism (Bergère *et al.*, 2006). It has been reported that mosaic 47,XXY patients with a high percentage of normal 46,XY lymphocytes are more likely to have sperm in their ejaculates (Lenz *et al.*, 2005). Therefore, it is likely that the mosaicism in itself influences fertility potential.

The extremely low level of gonadotrophins in the girl (Twin 2) could be a sign of impending gonadal function failure. However, the AMH concentration was normal which supports normal ovarian function since low or undetectable AMH is considered as an excellent marker of premature ovarian insufficiency in the paediatric population (Lindhardt Johansen *et al.*, 2013). The high rate of normal 46,XX cells found in the buccal smear and urinary sediment of Twin 2, associated with the hormonal profile and the ultrasound scan images, support the prediction of normal female gonadal function. Monitoring of ovarian function, similar to that performed in girls with Turner syndrome, seems to be the best

Table 1 Similar size of alleles found for the twins for 16 different STRs strongly supporting the monozygotic origin of the twins.

Patient	Marker	Localization	Allele 1 size	Allele 2 size
Twin 1	TPOX	2p24-2pter	281	285
Twin 2	TPOX	2p24-2pter	281	285
Twin 1	D3S1358	3p21.31	124	128
Twin 2	D3S1358	3p21.31	124	128
Twin 1	FGA	4q28	337	342
Twin 2	FGA	4q28	337	342
Twin 1	D5S818	5q23.3–32	126	135
Twin 2	D5S818	5q23.3–32	126	135
Twin 1	CSF1PO	5q33.3–34	333	341
Twin 2	CSF1PO	5q33.3–34	333	341
Twin 1	D7S820	7q11.21–22	228	228
Twin 2	D7S820	7q11.21–22	228	228
Twin 1	D8S1179	8q24.13	214	234
Twin 2	D8S1179	8q24.13	214	234
Twin 1	TH01	11p15.5	174	177
Twin 2	TH01	11p15.5	174	177
Twin 1	vWA	12p13.31	138	154
Twin 2	vWA	12p13.31	138	154
Twin 1	D13S317	13q22–q31	176	188
Twin 2	D13S317	13q22–q31	176	188
Twin 1	Penta_E	15q	377	403
Twin 2	Penta_E	15q	377	403
Twin 1	D16S539	16q24.1	283	295
Twin 2	D16S539	16q24.1	283	295
Twin 1	D18S51	18q21.3	298	321
Twin 2	D18S51	18q21.3	298	321
Twin 1	Penta_D	21q	399	403
Twin 2	Penta_D	21q	399	403
Twin 1	D21S11	21q11–21q21	215	219
Twin 2	D21S11	21q11–21q21	215	219
Twin 1	AMEL	Xp22.1–22.3/Y	104	110
Twin 2	AMEL	Xp22.1–22.3/Y	104	110

strategy to assess the feasibility and, if necessary, optimal timing for cryo-preservation of ovarian cortex or ovary for Twin 2.

On the other hand, for Twin 1 with a male phenotype, despite an encouraging ultrasound scan profile, the high proportion of the two cell lines found in different tissues makes it harder to draw a reliable conclusion regarding his future reproductive capacity.

MZ twins with a different phenotypic sex, deriving from a single 47,XXY zygote, have rarely been described in the literature. Indeed, only a few mechanisms can lead to complete sexual discordance in MZ twins. Monozygotic twins of a different sex have been reported in association with a 45,X cell line but have rarely been associated with a 47,XXY cell line (Gilbert *et al.*, 2002). Different forms of non-disjunction can lead to a 47,XXY karyotype (Lanfranco *et al.*, 2004). In 2012, a study was conducted on 41 Klinefelter twins with different gonadal sex despite monozygosity and revealed only four patients with 47,XXY/46,XX

mosaicism (Rehder *et al.*, 2012). None of the MZ twins in this series showed discordant physical sex. Nonetheless, a case similar to the one we report has been published (Zech *et al.*, 2008). The authors describe a case of discordant sex in MZ twins due to different proportions of the 46,XX and 46,XY cell lines in the gonads and other tissues. The two cell lines are presumed to have resulted from post-zygotic loss of the X or Y chromosome in a primordial 47,XXY zygote. In our patients, it is difficult to determine the timing of the chromosomal accidents. We were not able to complete the zygosity studies by comparing the microsatellite markers in the twins and their parents (due to the father's death) and thus have no information on parental inheritance of different alleles. The maternal or paternal origin of the two X chromosomes, which could have helped clarify the origin of the aneuploidy, is unknown. The simplest mechanism would be that a meiotic accident occurred first, either during spermatogenesis or ovogenesis, and led to a chromosomally

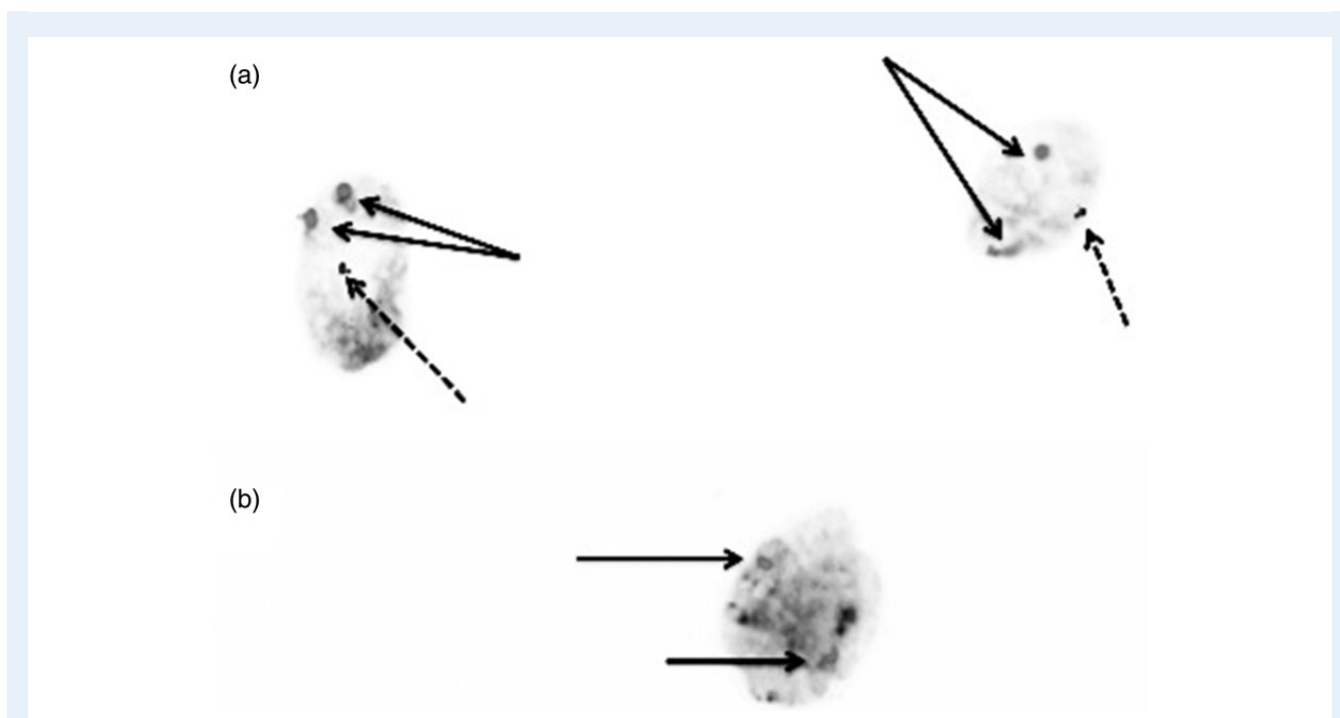


Figure 2 FISH results on the buccal smear sample of Twin I using Vysis probes. Full arrows point to DXZI (Xp11.1q11.1) and dotted arrows point to SRY. **(a)** Two XXXY nuclei. **(b)** One XX nucleus.

aneuploid 47,XXY zygote. During early human embryogenesis, chromosome instability is a well-documented phenomenon (Vanneste *et al.*, 2009). Consequently, during the first embryonic divisions, a distinct second event involving the Y chromosome, such as anaphase lag or mitotic rescue, could very well have occurred (Taylor *et al.*, 2014). The two consecutive accidents would result in an embryo with an aneuploid cell line (47,XXY) and a normal cell line (46,XX). Alternative explanations exist, which could explain the chromosomal constitution found in the twins, but they seem less likely since they require additional chromosomal accidents. In later development, the cells of this 47,XXY/46,XX embryo would have split and formed two embryos, both with the mosaic chromosome constitution (Fig. 3). During embryogenesis, the two cell lines would constitute embryonic tissues with variable chromosome constitutions in the two twins. Gonadal sex determination of the undifferentiated gonad would depend on the different proportions of the cell lines. Then depending on the gonad determined, there would be subsequent sex differentiation of the external genitalia to a male or female phenotype.

In conclusion, it is premature to predict the fertility potential of the 5-year-old children based on the present results. Nonetheless, clinical paediatric evaluation throughout childhood, including size, weight and growth rate measures as well as an annual paediatric endocrine follow-up and ultrasound scans every 2 years, are recommended to optimize future fertility and reproductive options. This strategy should enable clinicians to anticipate the development of features of Klinefelter syndrome which could benefit from early management, such as developmental concerns and hypogonadism.

This case report confirms recent findings that chromosome instability is common in human cleavage-stage embryos (Vanneste *et al.*, 2009).

The type of mosaicism and its clinical consequences are dependent upon a variety of aspects, including when and where the chromosomal malsegregations and subsequent mosaicism are generated during development (Taylor *et al.*, 2014). Therefore, the consequences are always unique for each event and, to our knowledge, this is the first report on monozygotic heterokaryotypic 47,XXY/46,XX twins with complete sex discordance.

Authors' roles

G.T. provided substantial contributions to the study conception and design, acquisition of all data and analysis and interpretation of data, as well as drafting of the article. G.L. provided substantial contributions to revising the manuscript critically for important intellectual content and gave final approval of the version to be published. J.P. and A.S. provided substantial contributions to the analysis and interpretation of CGH array data and FISH data and gave final approval of the version to be published. C.J. provided substantial contributions to analysis and interpretation of endocrine tests and gave final approval of the version to be published. P.B. provided substantial contributions to the acquisition, analysis and interpretation of gynaecologic data during the mother's pregnancy and gave final approval of the version to be published. O.P. provided substantial contributions to the acquisition, analysis and interpretation of ultrasound scan data, contributed to revising the manuscript critically for important intellectual content and gave final approval of the version to be published. P.M. provided substantial contributions to evaluation of neurodevelopment of the twins and gave final approval of the version to be published. I.T. provided substantial contributions to analysis and interpretation of microsatellite analysis and gave final approval of

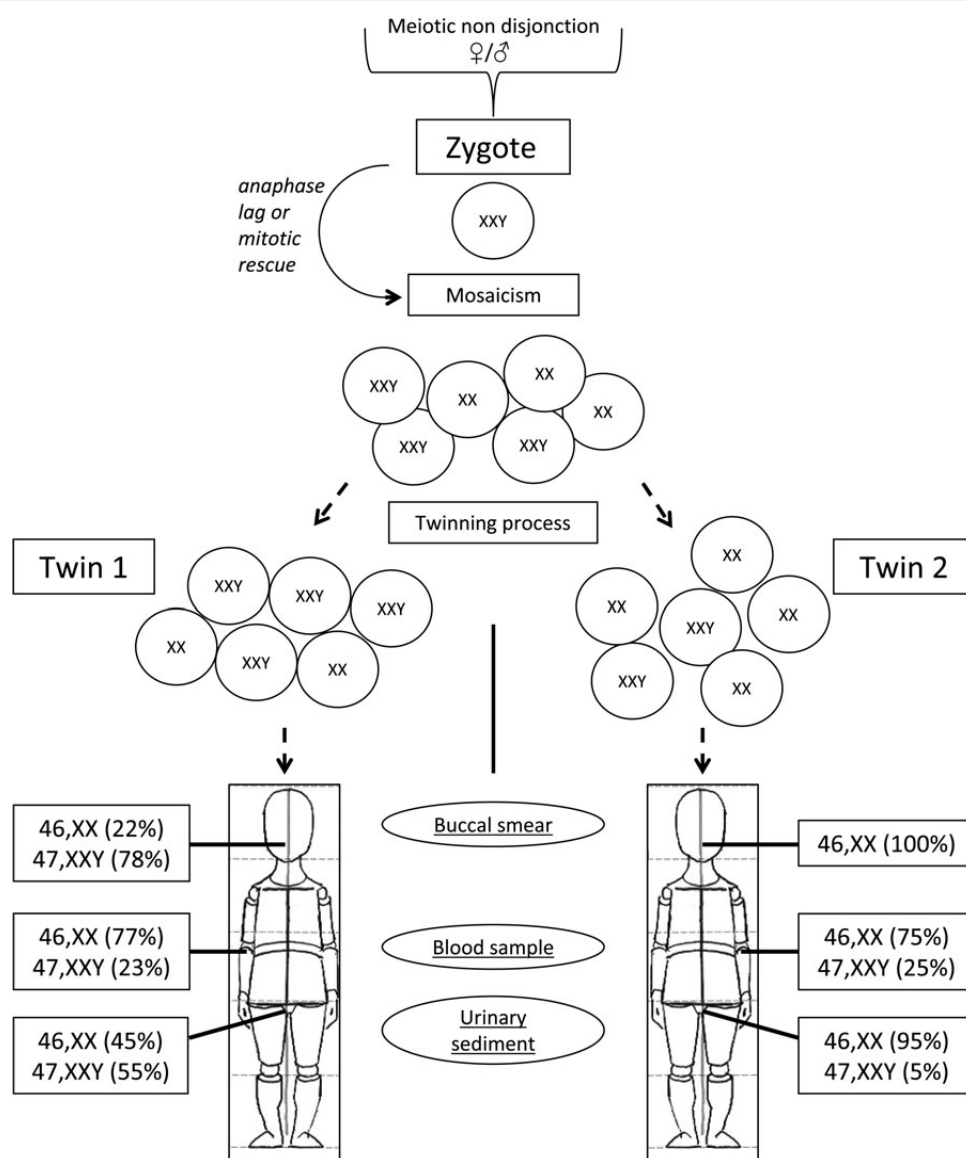


Figure 3 Schematic representation of the drift of the distribution of cell lines of the 47,XXY/46,XX mosaic in the twins during development.

the version to be published. S.T. provided substantial contributions to acquisition analysis, and interpretation of karyotypes and gave final approval of the version to be published. F.P. provided substantial contributions to drafting of the article and to revising it critically for important intellectual content, and gave final approval of the version to be published. D.G. provided substantial contributions to the study conception, design and draft of the article and to revising it critically for important intellectual content, and gave final approval of the version to be published. V.G. provided substantial contributions to the design the article and to interpretation of all types of data, and gave final approval of the version to be published.

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Conflict of interest

The authors have no conflict of interest in relation to this work.

References

- Bergère M, Bailly M, Albert M, Molina-Gomes D, Vialard F, Selva J. Prise en charge actuelle du syndrome de Klinefelter en assistance médicale à la procréation. *MT Méd Reprod* 2006;**8**:218–224.
- Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 2003;**88**:622–626.
- Gilbert B, Yardin C, Briault S, Belin V, Lienhardt A, Aubard Y, Battin J, Servaud M, Philippe HJ, Lacombe D. Prenatal diagnosis of female monozygotic twins discordant for Turner syndrome: implications for prenatal genetic counselling. *Prenat Diagn* 2002;**8**:697–702.

- Hall J. Twins and twinning. *Am J Med Genet* 1996;**61**:202–204.
- Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004;**9430**:273–283.
- Lenz P, Luetjens CM, Kamischke A, Kuhnert B, Kennerknecht I, Nieschlag E. Mosaic status in lymphocytes of infertile men with or without Klinefelter syndrome. *Hum Reprod* 2005;**20**:1248–1255.
- Lespinasse J, Gicquel C, Robert M, Le Bouc Y. Phenotypic and genotypic variability in monozygotic triplets with Turner syndrome. *Clin Genet* 1998;**54**:56–59.
- Lindhardt Johansen M, Hagen CP, Johannsen TH, Katharina M, Picard JY, Jørgensen A, Ewa Rajpert-De Meyts E, Juul A. Anti-Müllerian hormone and its clinical use in pediatrics with special emphasis on disorders of sex development. *Int J Endocrinol* 2013;**2013**:198698.
- Nicopoulos JD, Gilling-Smith C, Almeida PA, Norman-Taylor J, Grace I, Ramsay JW. Use of surgical sperm retrieval in azoospermic men: a meta-analysis. *Fertil Steril* 2004;**82**:691–701.
- Nieschlag E, Werler S, Wistuba J, Zitzmann M. New approaches to the Klinefelter syndrome. *Ann Endocrinol (Paris)* 2014;**75**:88–97.
- Plotton I, Brosse A, Cuzin B, Lejeune H. Klinefelter syndrome and TESE–ICSI. *Ann Endocrinol (Paris)* 2014;**75**:118–125.
- Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. *Arch Dis Child* 1999;**80**:192–195.
- Rehder H, Schoner K, Kluge B, Louwen F, Schwinger E, Neesen J. Klinefelter twins presenting with discordant aneuploidies, acardia, forked umbilical cord and with different gonadal sex despite monozygosity. *Prenat Diagn* 2012;**32**:173–179.
- Taylor TH, Gitlin SA, Patrick JL, Crain JL, Wilson JM, Griffin DK. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. *Hum Reprod Update* 2014; dmu016.
- Turpin R, Lejeune J, Lafourcade J, Chigot P-L, Salmon C. Présomption de monozygotisme en dépit d'un dimorphisme sexuel: Sujet masculin XY et sujet neutre haplo X. *CR Acad Sci (Paris)* 1961;**252**:2946.
- Vanneste E, Voet T, Le Caignec C, Ampe M, Konings P, Melotte C, Debrock S, Amyere M, Vikkula M, Schuit F et al. Chromosome instability is common in human cleavage-stage embryos. *Nat Med* 2009;**15**:577–583.
- Wachtel SS, Somkuti SG, Schinfeld JS. Monozygotic twins of opposite sex. *Cytogenet Cell Genet* 2000;**91**:293–295.
- Wikström AM, Dunkel L. Klinefelter syndrome. *Best Pract Res Clin Endocrinol Metab* 2011;**2**:239–250.
- Wikström AM, Raivio T, Hadziselimovic F, Wikström S, Tuuri T, Dunkel L. Klinefelter syndrome in adolescence: onset of puberty is associated with accelerated germ cell depletion. *J Clin Endocrinol Metab* 2004;**89**:2263–2270.
- Zech NH, Wisser J, Natalucci G, Riegel M, Baumer A, Schinzel A. Monochorionic–diamniotic twins discordant in gender from a naturally conceived pregnancy through postzygotic sex chromosome loss in a 47,XXY zygote. *Prenat Diagn* 2008;**28**:759–763.