Evidence for high breakpoint variability in 46, XX, SRY-positive testicular disorder and frequent ARSE deletion that may be associated with short stature

Céline Capron, Louis Januel, Gaëlle Vieville, Sylvie Jaillard, Paul Kuentz, Gaëlle Salaun, Gwenaël Nadeau, Patrice Clement, Marie Pierre Brechard, Bérénice Herve, et al.

▶ **To cite this version:**

Céline Capron, Louis Januel, Gaëlle Vieville, Sylvie Jaillard, Paul Kuentz, et al.. Evidence for high breakpoint variability in 46, XX, SRY-positive testicular disorder and frequent ARSE deletion that may be associated with short stature. Andrology, 2022, 10 (8), pp. 1625-1631. 10.1111/andr.13279 . hal-03768973

HAL Id: hal-03768973
https://hal.inrae.fr/hal-03768973

Submitted on 16 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Accepted Article

Title: Evidence for high breakpoint variability in 46, XX, SRY-positive testicular disorder and frequent ARSE deletion that may be associated with short stature.

Running title: 46, XX, SRY-positive, breakpoint variability and *ARSE*

Céline Capron[1], Louis Januel[2], Gaëlle Vieville[3,4], Sylvie Jaillard[5,6], Paul Kuentz[7], Gaëlle Salaun[8], Gwenaël Nadeau[9], Patrice Clement[10], Marie Pierre Brechard[11], Bérénice Herve[1], Jean Michel Dupont[12], Nicolas Gruchy[13,14], Pascal Chambon[15,16], Fatma Abdelhedi[17,18], Eric Dahlen[7], Philippe Vago[8], Radu Harbuz[3], Ingrid Plotton[19,20,21], Charles Coutton[3,4], Marc-Antoine Belaud-Rotureau[5,6], Caroline Schluth-Bolard[2,22], François Vialard[1,23*]

1: Département de Génétique, CHI de Poissy St Germain en Laye, Poissy, France

2: Service de Génétique, Hospices Civils de Lyon, Lyon, France

3: Département de Génétique et Procréation, Hôpital Couple Enfant, CHU Grenoble, 38043 Grenoble Cedex, France

4 : INSERM U1209, CNRS UMR 5309, Institute for Advanced Biosciences, Team Genetics Epigenetics and Therapies of Infertility, Université Grenoble Alpes, Grenoble, France

5; Cytogénétique et Biologie cellulaire, CHU de Rennes, France

6 : IRSET - INSERM UMR1085 – Equipe Physiologie et physiopathologie du tractus uro-génital, Faculté de Médecine, Université de Rennes 1, Rennes, France

7: Oncobiologie Génétique Bioinformatique, PCBio, CHU Besançon, Besançon, France

8: CHU Clermont-Ferrand, Cytogénétique Médicale, Clermont-Ferrand, France

9: Laboratoire de Cytogénétique, CH de Chambéry, Chambéry, France

10: Laboratoire Clément, Le Blanc Mesnil, France

11: Laboratoire, Hôpital Saint Joseph, Marseille, France

12: APHP Centre Université de Paris - site Cochin, Paris, France

13 : Service de Génétique - CHU de Caen - Site Clémenceau, Caen, France

14 : EA7450, Université Caen Normandie, Caen, France

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/andr.13279.

Accepted Article

15: UNIROUEN, Inserm U1245, Université de Normandie, Rouen, France

16 : Département de Génétique, CHU Rouen, Rouen, France17 : Service de Génétique Médicale, CHU Hédi Chaker, Sfax, Tunisie

18 : Laboratoire de Génétique Moléculaire Humaine, Faculté de Médecine de Sfax, Tunisie

19: Service de Médecine de la Reproduction, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

20 : Laboratoire d'hormonologie et endocrinologie Moléculaire, Hospices Civils de Lyon, Bron, France

21 : Unité INSERM 1208, Université Lyon 1, Lyon, France.

22 : Institut Neuromyogène, Equipe Métabolisme énergétique et développement neuronal, CNRS UMR 5310, INSERM U1217, Université Lyon 1, Lyon, France.

23 : UMR-BREED, INRAE, ENVA, UVSQ, UFR SVS, Montigny le Bretonneux, France

*Corresponding author:

François Vialard: francois.vialard@uvsq.fr, ORCID: https://orcid.org/0000-0002-5774-2756

Abstract:

Background: The translocation of *SRY* onto one of the two X chromosomes results in a 46,XX testicular disorder of sex development; this is supposedly due to non-allelic homologous recombination between the protein kinase X gene (*PRKX*) and the inverted protein kinase Y pseudogene (*PRKY*). Although 46,XX *SRY*-positive men are infertile, the literature data indicate that some of these individuals are of short stature (relative to the general population). We sought to determine whether short stature was linked to additional, more complex chromosomal rearrangements.

Methods: Twelve laboratories gathered detailed clinical, anthropomorphic, cytogenetic and genetic data (including chromosome microarray (CMA) data) on patients with 46,XX *SRY*-positive male syndrome.

Results: *SRY* was present (suggesting a der(X)t(X;Y)) in 34 of the 38 cases (89.5%). When considering only the 20 patients with CMA data, we identified several chromosomal rearrangements and breakpoints – especially on the X chromosome. In the five cases for whom the X chromosome breakpoint was located in the pseudoautosomal (PAR) region, there was partial duplication of the derivate X chromosome. In contrast, in the 15 cases for whom the breakpoint was located downstream of the pseudoautosomal region, part of the derivate X chromosome had been deleted (included the arylsulfatase E (*ARSE*) gene in 11 patients). For patients with vs. without *ARSE* deletion,

Accepted Article

the mean height was respectively 167.7 ± 4.5 and 173.1 ± 4.0 cm; this difference was not statistically significant (p=0.1005).

Conclusion: Although 46,XX *SRY*-positive male syndromes were mainly due to imbalanced crossover between the X and Y chromosome during meiosis, the breakpoints differed markedly from one patient to another (especially on the X chromosome); this suggests the presence of a replication-based mechanism for recombination between non-homologous sequences. In some patients, the translocation of *SRY* to the X chromosome was associated with *ARSE* gene deletion, which might have led to short stature. With a view to explaining this disorder of sex development, whole exome sequencing could be suggested for *SRY*-negative patients.

Keywords: 46,XX *SRY*-positive male syndrome, replication-based mechanisms, *PRKX*, chromosomal rearrangement, short stature, arylsulfatase E gene

Introduction

de la Chapelle et al. first described "46,XX male syndrome" in 1964 [1]. This rare disorder affects approximately one in 20,000 male infants [2,3]. As there are three phenotypes (depending on the development of male genitalia), the entity was subsequently renamed as "46,XX testicular disorder of sex development" [4]. According to the literature data, an unbalanced translocation between the X and Y chromosome during paternal meiosis [5] means that 80 to 90% of the individuals with this disorder have Y chromosomal material - particularly the sex-determining region of Y chromosome (*SRY*: chrY:2654896-2655792) gene [6]. The karyotype is then 46,X,der(X)t(X;Y)(p22.3;p11.2). Chromosome microarray (CMA) studies have shown that most breakpoints involve the protein kinase X-linked gene (*PRKX*; chrX:3522384-3631675) and the protein kinase Y-linked pseudogene (*PRKY*; chrY:7142013-7249588) [7]; these results are in line with previous studies of Y chromosome polymorphisms [8]. It has been hypothesized that the translocation results from non-allelic homologous recombination between *PRKX* and *PRKY*. In rare cases, *SRY* is located on the short arm of an acrocentric chromosome, rather than on the short arm of the X chromosome [9].

The presence of two pseudoautosomal regions (PAR1 and PAR2, located respectively at the tip of the short arm (Xp/Yp) and the tip of the long arm (Xq/Yq)) is observed in humans but not in other mammals [10,11]. Although the 2.7 Mb PAR1 region is found in most eutherian mammals and was incorporated into the sex chromosome within the last 105 million years, the 330 kb-sized PAR2

Accepted Article

emerged after the divergence of humans and chimpanzees (i.e. approximately 6 million years ago) [12]. In PAR1, crossing-over (CO) is essential for the full disjunction of the X and Y chromosomes during male meiosis [13]. PAR1 deletion is associated with total male sterility in humans [14], and a low recombination frequency can produce aneuploid sperm [15]. Pedigree analysis has revealed that one CO per male meiosis in the PAR1 is obligatory [16]. A study of male mice showed that homologous chromosomes pair significantly later in the PAR than in the autosomes, and that this processes is mediated by a different isoform of a key recombination protein (Spo11) [13]. Lastly, it has been postulated that the t(X;Y)(p22.3;p11.2) karyotype results from extension of the CO to X-specific and Y-specific regions, leading to unequal Y-to-X interchange during male meiosis. As *SRY* is the first gene downstream of PAR1 on the Y chromosome, this process leads to the translocation of *SRY* onto the X chromosome [17].

46,XX men are sterile (due to azoospermia) and can present a variety of particular physical and developmental characteristics: abnormal hair distribution, gynecomastia, low testes volume, abnormal penis size, abnormal pubic hair development, erectile function disorders, and hypergonadotropic hypogonadism. All these characteristics are associated with the X chromosome disomy and the absence of most of the Y chromosome [18]. Surprising, a nonnegligible proportion of "46,XX" men have short stature, relative to healthy controls and patients with Klinefelter syndrome (mean ± standard deviation (SD) height: 170.6 ± 6.0 cm, 180.7 ± 6.7 cm, and 183.4 ± 9.4 cm, respectively [19]) – even though the short stature homeobox (*SHOX)* gene has not been deleted (the cause of Léri-Well syndrome [20]). Similarly, with reference to both the male and female standard height curves and the target height (based on the parents' measurements), 46,XX-males are shorter and grow more slowly than expected [21]. The same study found that 47,XXY and 47,XYY individuals are taller than expected. The fact that 47,XYY boys grew slightly faster and were taller than 47,XXY boys has prompted researchers to suggest the existence of an additional, Y-specific growth gene. However, to the best of our knowledge, no such candidate genes have been identified.

We therefore hypothesized that chromosomal rearrangements leading to short statute would be more complex than expected and would affect a contiguous gene. To evaluate the putative relationship with short statute, we invited the members of a network of French cytogenetics laboratories (www.eaclf.org) to collate their data on "46,XX" men and to characterize their patients' chromosomal rearrangements (using a CMA).

Accepted Article

Materials and Methods

The 37 member laboratories of the *Association des Cytogénéticiens de Langue Française* (www.eaclf.org) who used CMAs were invited to provide all the available data (the karyotyping results, the indication for karyotyping, the age at diagnosis, height, weight, hormone levels, the presence or absence of the *SRY* gene, and the CMA results) on individuals with 46,XX male syndrome. Detailed information on each case was extracted from the corresponding medical records. We only considered "46,XX" patients for whom the karyotype indication was available and who had been tested for the presence or absence of the *SRY* gene. The CMA resolution and format varied from one laboratory to another and changed over time. All statistical analyses were performed using Statview software (version 5.0, SAS Institute Inc, Cary, NC, USA). In line with the French legislation on retrospective studies of routine clinical practice, the study protocol was approved by a hospital committee with competency for research not requiring approval by an institutional review board. All patient data were anonymized prior to analysis.

Results

General information: Twelve laboratories accepted our invitation and supplied data on a total of 38 cases of 46,XX male syndrome diagnosed between 2001 and 2021. Karyotyping had been prompted by infertility (azoospermia) in 29 cases (76.3%), by a urogenital malformation in 6 cases (15.8%), and by another indication in 3 cases (7.9%). When considering solely adult patients with data, the mean follicle stimulating hormone and luteinizing hormone levels were respectively 34.4 ± 13.0 and 19.6 ± 7.7 IU/L. The *SRY* gene was detected in 34 of the 38 cases (89.5%).

CMA analysis: A CMA analysis was performed in 20 of the 34 *SRY*+ patients. We observed 14 unbalanced translocations with breakpoints on Xp22.3 and Yp11.2 (46,X,der(X)t(X;Y)(p22.3;p11.2)), one unbalanced translocation leading to a dicentric chromosome with breakpoints on Xp22.3 and Yq11.2 (46,X,dic(X;Y)(p22.3;q11.2)), two unbalanced chromosomal insertions (46,X,der(X)ins(Y;X)(p11.2;p11.2;p22.3)), and three complex chromosomal rearrangements that combined an unbalanced translocation (46,X,der(X)t(X;Y)(p22.3;p11.1)) with a deletion on Yp11.2. CMA analysis was performed in only one of the *SRY*-negative patients, and the result was normal. When taking account of the various CMA resolutions and formats, at least eight different X chromosome breakpoints were observed (Table1 and Figure 1); they ranged from the 5' region of SHOX to the 3'

Accepted Article

region of NLGN4. The breakpoint was in or close to *PRKX* in 9 of the 20 patients (Figure 1 and 2). No detailed conclusions could be drawn for the Y chromosome, since the CMA was not designed to evaluate the region between *ZFY* (chrY:2,803,518-2,850,547) and *PCDH11Y* (chrY:4,924,131-5,610,264). All the breakpoints occurred downstream of *ZFY* in a 2 Mb region that lacked coding genes (Figure 3); however, none were close to *PRKY*. The breakpoint was 2,656,461 bp from the telomere in 2 cases, 2,905,059 bp from the telomere in 6 cases, 3,163,585 bp from the telomere in 9 cases, and 5,246,319 bp from the telomere in 2 cases (Table1 and Figure 3). In the latter case, the breakpoint was located on the long arm of the Y chromosome.

X chromosome deletion and duplication: All 15 patients, with an X chromosome breakpoint outside the PAR1 region, had a del(X)(p22.3) on the derivate chromosome. The deletion included 1 to 7 genes. The deleted genes considered to be morbid in the OMIM database (https://omim.org/) were *ARSE* (coding for arylsulfatase E) in 10 cases and *NLGN4* (coding for neuroligin 4) in one case. The remaining five patients had a breakpoint in PAR1; none of these partial duplications of the X chromosome included *SHOX*.

ARSE and height: Given that *ARSE* inactivation in humans is associated with the X-linked recessive disease brachytelephalangic chondrodysplasia punctata (MIM #302950, CDPX1, associated with shortened long bones and short stature), we compared the patients' height as a function of *ARSE* deletion. Patients lacking *ARSE* (n=8) were shorter (mean height: 168.0 ± 4.7 cm) than patients bearing *ARSE* (n=7; mean height: 173.3 ± 3.8 cm) but the difference was not statistically significant (p=0.1005).

Discussion

In line with the literature data, *SRY* was present in 80% of our cases; this observation confirmed that rearrangements between the X and Y chromosomes are the most common cause of a 46,XX testicular disorder of sex development. However, our CMA findings confirmed that although the most common rearrangement is an unbalanced translocation with breakpoints on Xp22.3 and Yp11.2, translocation breakpoints on Yq11.2 and two insertions of the Y chromosome are also possible. An additional copy number variation on Yp11.2 was identified in three cases. According to conventional karyotyping, (i) the breakpoints appeared to be similar in 17 of the 20 patients, and (ii) the X breakpoint was always on Xp22.3, regardless of the Y chromosome breakpoint. Although these findings have no implications for clinical practice, they indicate that CMA should be preferred to *SRY*-spanning FISH when seeking to better define the karyotype and chromosomal rearrangement in

Accepted Article

male patients with a 46,XX karyotype; to avoid any incidental findings, the analysis must focus on the X and Y chromosomes only.

Unexpectedly, our CMA results demonstrated that Xp22.3 breakpoints are heterogeneous (Figure 1) – even though they were close to *PRKX* in 9 of the 20 cases. After taking account of variability in the CMA design, we identified eight different breakpoints on the X chromosome. The Y chromosome breakpoints (Figure 3) appeared to be far from *PRKY* (chrY:7142013-7249588); this finding contradicts previous reports [7,8]. Three hot spots were identified: the first close to *ZFY*, the second close to *AGPAT5P1*, and the third close to *PCDH11Y*. This result prompted us to hypothesize that a replication-based mechanism (i.e. recombination between nonhomologous sequences) is more likely than non-allelic recombination between the homologous sequences of the short arms of the X- and Y chromosomes.

In males, the CO rate in the 2.7 Mb PAR1 is approximately 17-fold greater than in the genome as a whole and over four times greater than in the next most recombinogenic genomic region of a similar size. In females, the recombination rate in PAR1 is similar to the mean genome-wide rate [22]. In contrast to PAR1 (with at least one recombination per male meiosis), it has been estimated that recombination within PAR2 occurs in just 1% of male meioses and is extremely rare in female gametogenesis [22,23]. In male PAR1, the main recombination hotspot is located within the *SHOX* gene and even constitutes one of the hottest spots in the genome [24]. However, CO activity is intense throughout PAR1, with a high frequencies close to the pseudoautosomal boundary. In females, the highest recombination rate is found near this boundary [25]. According to a study of genetic diversity in PAR1, recombination spans the pseudoautosomal boundary [23]; this would explain the occurrence of the 46,XX testicular disorder of sex development and then the breakpoint variability observed in the present series.

Twelve of the 20 patients had an X chromosome deletion, and eleven of the 15 deletions including *ARSE* (Figures 1 and 2). As mentioned above, *ARSE* inactivation can lead to CDPX1. Given that *ARSE* is the only OMIM-listed gene recurrently deleted from the X chromosome, we hypothesize that *ARSE* deletion is associated with the short stature in “46,XX” males. Females lacking *ARSE* have not been described clinically but some women are of short stature [26]. For a few X-linked diseases, female carriers are expected to have skewed X-chromosome inactivation (sXCI) and clinical findings [27][28]. No data are available for female carriers of CDPX1, since the prognosis for men with CDPX1 is quite good; however, some affected men have significant medical problems, including respiratory compromise, cervical spine stenosis and instability, mixed conductive and sensorineural hearing loss, and intellectual disability [26]. We therefore hypothesize that stature depends on sXCI in female carriers. Some of the patients in our series probably had sXCI, since the rearranged X chromosome

Accepted Article

had been predominantly activated and the male phenotype was still normal. The mean height in our study population (170.4 ± 6.1 cm) is quite similar to a value of 170.6 ± 6.0 cm reported previously for 46,XX males [19]. In our series, the patients with *ARSE* deletion were shorter than those still bearing *ARSE* (mean ± SD height: 168.0 ± 4.7 vs. 173.3 ± 3.8 cm, respectively) but the difference was not statistically significant (p=0.1005). However, no firm conclusions can be drawn for the 15 patients (including 8 without the *ARSE* deletion), even though they were shorter (on average) than the French male population in 2019 (mean height: 177.8) [29]. Regardless of the real impact of the *ARSE* deletion, 46,XX testicular disorder of sex development should be considered as a particular type of contiguous genetic syndrome that combines sex reversal and short stature. The sex reversal is due to the *SRY* translocation on the X chromosome, and the short stature is probably due to the *ARSE* deletion.

Conclusion

Chromosomal rearrangements in 46,XX,SRY+ male patients appear to be more complex than originally thought; in particular, they are highly variable with regard to the X chromosome breakpoint. Moreover, many of these chromosomal rearrangements are combined with *ARSE* deletion, which might explain the short stature observed in some patients and correlate the phenotype to the genotype. Further characterization of 46,XX males is required to confirm this hypothesis and thus to establish whether the 46,XX testicular disorder of sex development is a contiguous gene syndrome in some cases. A major limitation of efforts to correlate *ARSE* deletion with the patient's height is the absence of data from whole genome sequencing, whole exome sequencing, and/or RNA sequencing. If pathologic variants cannot be ruled out, no clear conclusions can be drawn.

Data Availability Statement : Yes

Author contribution statement

Patient inclusion: SJ, PK, GS, GN, PC, MPB, BH, JMD, NG, PC, FA, ED, PV, IP, CC, MABR, CSB, FV

CMA analysis: LJ, GV, SJ, PK, GS, BH, JMD, RH, CSB, FV

Study design: FV

Writing: CC and FV

Proofreading: LJ, GV, SJ, PK, GS, IP, CC, CSB

References:

1. de la Chapelle A, Hortling H, Niemi M, Wennstroem J. XX SEX CHROMOSOMES IN A HUMAN MALE. FIRST CASE. Acta Med Scand. 1964;175:SUPPL 412:25-28.

Accepted Article

2. de la Chapelle A. The etiology of maleness in XX men. Hum Genet. 1981;58:105–16.

3. Berglund A, Johannsen TH, Stochholm K, Aksglaede L, Fedder J, Viuff MH, et al. Incidence, prevalence, diagnostic delay, morbidity, mortality and socioeconomic status in males with 46,XX disorders of sex development: a nationwide study. Hum Reprod Oxf Engl. 2017;32:1751–60.

4. Hughes IA, Houk C, Ahmed SF, Lee PA, Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology Consensus Group. Consensus statement on management of intersex disorders. J Pediatr Urol. 2006;2:148–62.

5. Ferguson-Smith MA. X-Y chromosomal interchange in the aetiology of true hermaphroditism and of XX Klinefelter's syndrome. Lancet Lond Engl. 1966;2:475–6.

6. Terribile M, Stizzo M, Manfredi C, Quattrone C, Bottone F, Giordano DR, et al. 46,XX Testicular Disorder of Sex Development (DSD): A Case Report and Systematic Review. Med Kaunas Lith. 2019;55.

7. Akar OS, Gunes S, Abur U, Altundag E, Asci R, Onat OE, et al. Multiscale analysis of SRY-positive 46,XX testicular disorder of sex development: Presentation of nine cases. Andrologia. 2020;52:e13739.

8. Jobling MA, Williams GA, Schiebel GA, Pandya GA, McElreavey GA, Salas GA, et al. A selective difference between human Y-chromosomal DNA haplotypes. Curr Biol CB. 1998;8:1391–4.

9. Brisset S, Izard V, Misrahi M, Aboura A, Madoux S, Ferlicot S, et al. Cytogenetic, molecular and testicular tissue studies in an infertile 45,X male carrying an unbalanced (Y;22) translocation: case report. Hum Reprod Oxf Engl. 2005;20:2168–72.

10. Freije D, Helms C, Watson MS, Donis-Keller H. Identification of a second pseudoautosomal region near the Xq and Yq telomeres. Science. American Association for the Advancement of Science; 1992;258:1784–7.

11. Graves JAM, Wakefield MJ, Toder R. The Origin and Evolution of the Pseudoautosomal Regions of Human Sex Chromosomes. Hum Mol Genet. 1998;7:1991–6.

12. Otto SP, Pannell JR, Peichel CL, Ashman T-L, Charlesworth D, Chippindale AK, et al. About PAR: The distinct evolutionary dynamics of the pseudoautosomal region. Trends Genet. 2011;27:358–67.

13. Kauppi L, Jasin M, Keeney S. The tricky path to recombining X and Y chromosomes in meiosis. Ann N Y Acad Sci. 2012;1267:18–23.

14. Gabriel-Robez O, Rumpler Y, Ratomponirina C, Petit C, Levilliers J, Croquette MF, et al. Deletion of the pseudoautosomal region and lack of sex-chromosome pairing at pachytene in two infertile men carrying an X;Y translocation. Cytogenet Cell Genet. 1990;54:38–42.

15. Hassold TJ, Sherman SL, Pettay D, Page DC, Jacobs PA. XY chromosome nondisjunction in man is associated with diminished recombination in the pseudoautosomal region. Am J Hum Genet. 1991;49:253–60.

Accepted Article

16. Schmitt K, Lazzeroni LC, Foote S, Vollrath D, Fisher EM, Goradia TM, et al. Multipoint linkage map of the human pseudoautosomal region, based on single-sperm typing: do double crossovers occur during male meiosis? Am J Hum Genet. 1994;55:423–30.

17. Délot EC, Vilain EJ. Nonsyndromic 46,XX Testicular Disorders of Sex Development. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2021 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1416/

18. Li J-H, Huang T-H, Jiang X-W, Xie Q-D. 46, XX male sex reversal syndrome. Asian J Androl. 2004;6:165–7.

19. Vorona E, Zitzmann M, Gromoll J, Schüring AN, Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46,XX male syndrome, compared with 47,XXY Klinefelter patients. J Clin Endocrinol Metab. 2007;92:3458–65.

20. Binder G, Rappold GA. SHOX Deficiency Disorders. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2021 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1215/

21. Aksglaede L, Skakkebaek NE, Juul A. Abnormal sex chromosome constitution and longitudinal growth: serum levels of insulin-like growth factor (IGF)-I, IGF binding protein-3, luteinizing hormone, and testosterone in 109 males with 47,XXY, 47,XYY, or sex-determining region of the Y chromosome (SRY)-positive 46,XX karyotypes. J Clin Endocrinol Metab. 2008;93:169–76.

22. Flaquer A, Fischer C, Wienker TF. A new sex-specific genetic map of the human pseudoautosomal regions (PAR1 and PAR2). Hum Hered. 2009;68:192–200.

23. Monteiro B, Arenas M, Prata MJ, Amorim A. Evolutionary dynamics of the human pseudoautosomal regions. PLoS Genet. 2021;17:e1009532.

24. May CA, Shone AC, Kalaydjieva L, Sajantila A, Jeffreys AJ. Crossover clustering and rapid decay of linkage disequilibrium in the Xp/Yp pseudoautosomal gene SHOX. Nat Genet. 2002;31:272–5.

25. Hinch AG, Altemose N, Noor N, Donnelly P, Myers SR. Recombination in the human Pseudoautosomal region PAR1. PLoS Genet. 2014;10:e1004503.

26. Braverman NE, Bober MB, Brunetti-Pierri N, Suchy SF. Chondrodysplasia Punctata 1, X-Linked. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2021 Apr 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1544/

27. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, et al. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016;89:44–54.

Accepted Article

28. Viggiano E, Ergoli M, Picillo E, Politano L. Determining the role of skewed X-chromosome inactivation in developing muscle symptoms in carriers of Duchenne muscular dystrophy. Hum Genet. 2016;135:685–98.

29. Santé publique France. https://www.santepubliquefrance.fr/determinants-de-sante/nutrition-et-activite-physique/articles/enns-etude-nationale-nutrition-sante/anthropometrie-adultes-tableaux-de-distribution-enns [Internet]. 2019. Available from: https://www.santepubliquefrance.fr/determinants-de-sante/nutrition-et-activite-physique/articles/enns-etude-nationale-nutrition-sante/anthropometrie-adultes-tableaux-de-distribution-enns

Figure legends:

Figure 1: X chromosome rearrangements with the location of *ARSE* in light blue. A to C: the blue line corresponds to partial duplication. D to H: the red line corresponds to partial deletion. Specific breakpoint locations are given in Table 1.

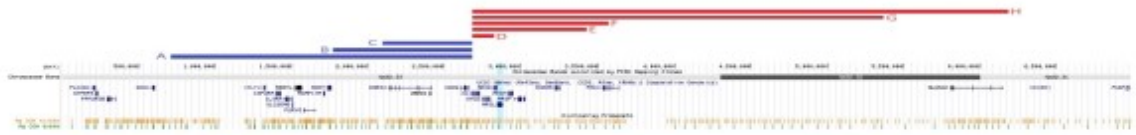
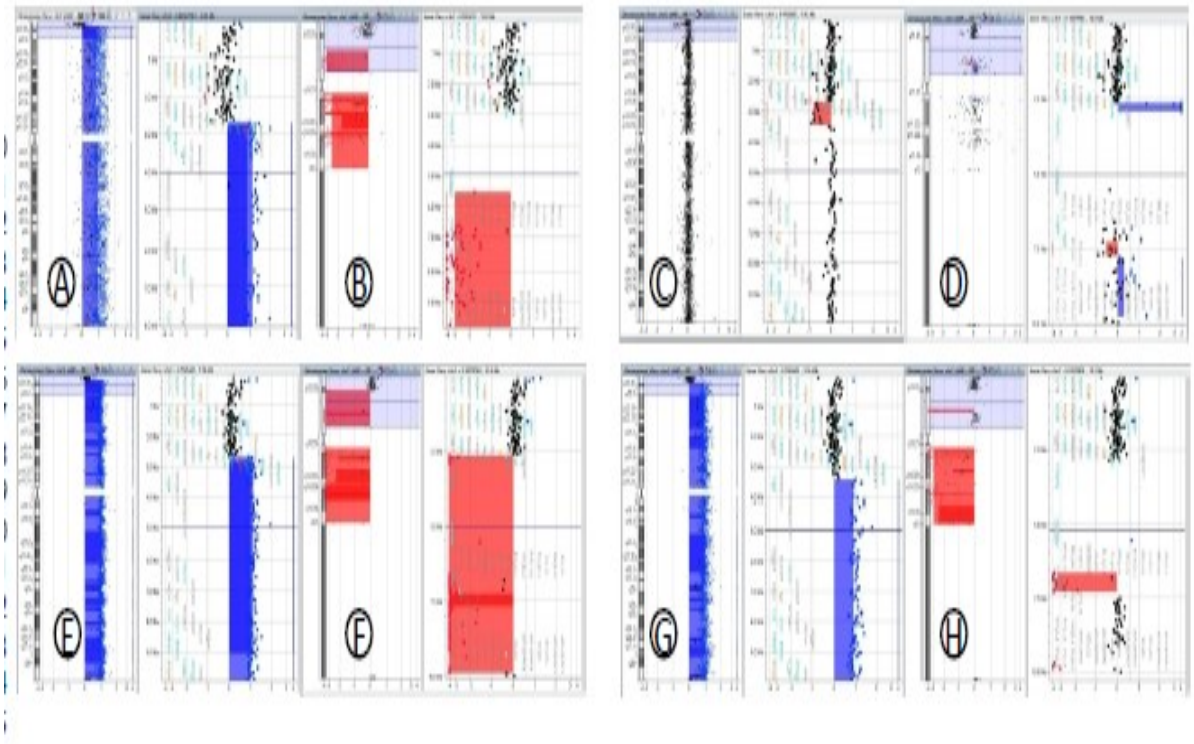


Figure 2: CMA results, using male (A/B, E/F and G/H) or female (C/D) DNA references.



Accepted Article

Figure 3: Y chromosome rearrangements. A to C; the blue line corresponds to partial duplication. Specific breakpoint locations are given in Table 1.

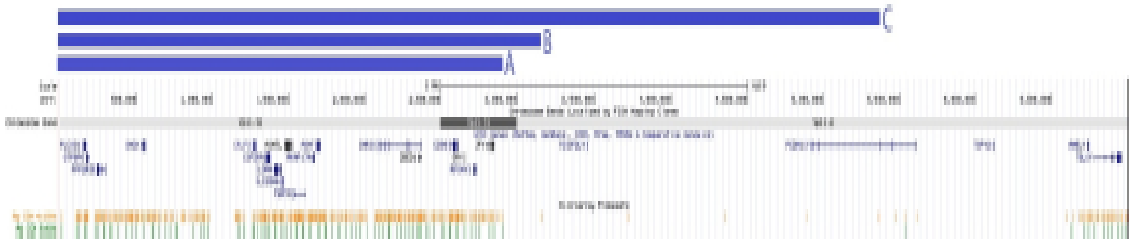


Table legend:

Table 1: Detailed chromosome microarray data for the 20 "46,XX,SRY positive" patients.

Patient number	Karyotype interpretation	Agilent array format	Chromosome X abnormality	X chromosome breakpoint	X Chromosome rearrangement type	Chromosome Y short arm abnormality	Y chromosome short arm breakpoint	Y Chromosome rearrangement type
1	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(1,838,587–2,689,408)x3	1,838,587	B	(1-3,163,585)x1	3,163,585	B
2	46,X,der(X)t(X;Y)(p22,3;p11,1),del(Y)(p11,1)	180k	(2,701,273–3,590,348)x1	3,590,348	F	(1-3,163,585)x1,(7,184,216–9,458,094)x1	3,163,585	B
3	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,120,345–2,689,408)x3	2,120,345	C	(1-3,163,585)x1	3,163,585	B
4	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273–3,548,012)x1	3,548,012	F	(1-3,163,585)x1	3,163,585	B
5	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273–3,469,500)x1	3,469,500	E	(1-3,163,585)x1	3,163,585	B
6	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(1,789,694-2,689,408)x3	1,789,694	B	(1-2,905,059)x1	2,905,059	A
7	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273–	6,182,748	H	(1-2,905,059)x1	2,905,059	A

Accepted Article

			6,182,748)x1					
8	46,X,dic(X;Y)(p22,3;q11,2)	180k	(2,701,273-3,524,184)x1	3,524,184	F	(1-9,650,194)x1	/	/
9	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273-2,716,319)x1	2,716,319	D	(1-3,163,585)x1	3,163,585	B
10	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273-3,351,301)x1	3,351,301	E	(1-5,246,319)x1	5,246,319	C
11	46,XX,ins(Y;X)(p11,2p11,2;p22,3)	180k	(697,227-2,689,408)x3	697.227	A	(1-3,163,585)x1	3,163,585	B
12	46,X,der(X)t(X;Y)(p22,3;p11,2)	60k	(2,709,027-3,469,559)x1	3,469,500	E	(1-2,905,059)x1	2,905,059	A
13	46,X,der(X)t(X;Y)(p22,3;p11,2)	60k	/	/	/	(1-2,905,059)x1	2,905,059	A
14	46,X,der(X)t(X;Y)(p22,3;p11,1),del(Y)(p11,1)	60k	(2,709,027-3,376,702)x1	3,376,702	E	(1-2,905,059)x1,(7,512,591-9,394,173)x1	2,905,059	A
15	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273–5,395,569)x1	5,395,569	G	(1-3,163,585)x1	3,163,585	B
16	46,XX,ins(Y;X)(p11,2p11,2;p22,3)	180k	(1,755,742-2,689,408)x3	1,755,742	B	(1-2,905,059)x1	2,905,059	A
17	46,X,der(X)t(X;Y)(p22,3;p11,1),del(Y)(p11,1)	180k	(2,701,273-3,351,301)x1	3,351,301	E	(1-5,246,319)x1,(7,530,569-9,458,094)x1	5,246,319	C
18	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273-2,716,319)x1	2,716,319	D	(1-2,905,059)x1	2,656,461	A
19	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273-2,716,319)x1	2,716,319	D	(1-2,905,059)x1	2,656,461	A
20	46,X,der(X)t(X;Y)(p22,3;p11,2)	180k	(2,701,273-3,524,184)x1	3,524,184	F	(1-3,163,585)x1	3,163,585	B

Accepted Article

X chromosome abnormality: only partial duplications of the pseudoautosomal region are shown (cases 1, 3, 6, 11 and 16), or deletions after the pseudoautosomal region.

The types of X chromosome breakpoints are linked to Figure 1

Y chromosome abnormality: The complete sequence of the Y chromosome included in the derivative chromosome is described, including the pseudoautosomal region.

The types of Y chromosome breakpoints are linked to Figure 3