Different Karyotypes, Same Disease?

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Daniele Gianfrilli, Francesco Carlomagno, Francesca Sciarra, and Francesco Lombardo

Not very long after the original description by Harry F. Klinefelter Jr. et al. in 1942 of the eponymous syndrome (KS) [1], characterized by an additional X chromosome in six male individuals, came the first reports by Ford et al. of a man harboring 48 chromosomes (possibly a 48,XXYY karyotype) [2] and by Fraccaro et al. of a child with a 49,XXXXY karyotype (although originally believed to possess an additional X chromosome plus a trisomy of both chromosomes 8 and 11), manifesting with ambiguous genitalia, congenital heart disease, and cognitive deficit [3].

Although specific signs and symptoms pertaining to conditions other than the classical KS were originally recognized, as well as their increased overall severity, it came to widespread use by many authors [4–11] to label every male patient with at least one supernumerary X chromosome as being affected by KS or a variant thereof. This association was mostly justified by the common findings of tall stature and hypergonadotropic hypogonadism in all these patients. Nonetheless, others have advocated these conditions to substantially differ from KS [12–15], and as such should be best referred to as high-grade aneuploidies of the sex chromosomes (HGA) presenting with a male phenotype.

A number of different karyotypes have been described to belong to the HGA family, namely, 48,XXXY, 48,XXYY, 48,XYYY, 49,XXXXY, 49,XXXYY, and 49XYYYY, each possibly presenting as pure or mosaic forms, which contributes to their phenotype heterogeneity. HGA are characterized by elevated, although variable, rarity, ranging in prevalence from 1:17,000 to 1:100,000 males [16–18], with some having only few cases reported in the literature, as compared to approximately 1:650 males for KS [19], although correct estimates are lacking.

D. Gianfrilli (✉) · F. Carlomagno · F. Sciarra · F. Lombardo
Department of Experimental Medicine, "Sapienza" University of Rome, Policlinico "Umberto I" of Rome, Rome, Italy
e-mail: daniele.gianfrilli@uniroma1.it; francesco.carlomagno@uniroma1.it; francesca.sciarra@uniroma1.it; francesco.lombardo@uniroma1.it

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The 47,XYY syndrome, also known as Jacobs syndrome, in our opinion should not be regarded as a HGA for its higher prevalence, milder phenotype, and substantially different clinical picture, and therefore we will not discuss it; interested readers can refer to other specific works [20–25].

A feature invariably observed in patients affected by HGA is the development of a hypergonadotropic hypogonadism, in which testicular damage occurs earlier and in a more severe form than that in KS. Testicular dysfunction often manifests as impaired genital development (e.g., micropenis and cryptorchidism) and otherwise becomes apparent by pubertal age, while testicular histology in adults with 48,XXYY, 48,XXXY, and 49,XXXXY syndromes shows a similar, yet more diffuse, hyalinization and fibrosis of the seminiferous tubules, loss of germ cells, and Leydig cell hyperplasia as in KS [2, 3, 26].

To date, the only study evaluating the endocrine and metabolic phenotype of HGA in comparison with KS [12] showed an earlier increase in follicle-stimulating hormone (FSH) values in patients younger than 12 years, and higher gonadotropin values in the 12–20 years age range accompanied by lower total testosterone and inhibin B and higher sex hormone-binding globulin (SHBG) values, seemingly indicating an earlier testicular damage; these differences, however, were no longer present in adulthood. Prolactin values were also higher than those in KS in the age range 12–20 years and in adulthood, while a normal thyroid function was observed, although with an altered free triiodothyronine/free thyroxine ratio (fT3/fT4). The study of the metabolic profile showed higher total and LDL cholesterol in HGA patients compared with KS at all ages and lower, although not significantly, HDL cholesterol; no differences were observed in triglyceride levels and in the glucose metabolism of HGA patients.

Currently, there is no specific treatment protocol or consensus for testosterone replacement therapy in HGA, and therefore patients usually begin testosterone therapy when delayed puberty is evident by late pubertal onset or pubertal arrest or, more rarely, in adult life following a finding of reduced testosterone levels. Treatment regimens do not currently differ based on the specific genetic diagnosis. More research is needed to determine whether an earlier therapy start or a "priming" during infancy or pre-pubertally could be beneficial in ameliorating brain development and/or body composition, similarly to what is recently being evidenced in KS [27, 28].

HGA are generally associated with more pronounced phenotypic *abnormalities compared to KS and are* characterized by mild craniofacial dysmorphism, skeletal anomalies, significant developmental delays, neurological symptoms, and poor dentition [29, 30]. The more significant cognitive and behavioral differences observed in HGA when compared to KS may be explained by the increased gene expression [14]. The phenotype of all HGA is proposed to result from gene dosage effects, in which genes on the additional X and Y chromosomes that are not X inactivated are therefore expressed at higher levels than those in typical 46,XY males. For example, genes that are expressed from both the X and Y chromosomes, in HGA would be expressed twofold to threefold in comparison with a 46,XY male. Microarray studies in 47,XXY have identified genes that are differentially expressed compared with 46,XY [31], and differentially expressed genes were correlated with verbal cognitive skills in one study. However, the behavioral characteristics of individuals with

Table 4.1 Comparison of the characteristics of the three main HGA syndromes

	48, XXYY	48, XXXY	49, XXXXY
Prevalence	1:18.000–40.000 males	1:17.000–50.000 males	1:85.000–100.000 males
Origin	Paternal	Maternal or paternal	Maternal
Facial dysmorphism	Hypertelorism Epicanthus Cleft palate Taurodontism	Hypertelorism Flat nasal bridge	Hypertelorism Microcephaly Flat nasal bridge Cleft palate Bifid uvula
Skeletal malformation	Clinodactyly Radioulnar synostosis Pes planus Joint laxity	Clinodactyly Radioulnar synostosis	Clinodactyly Radioulnar synostosis Pes cavum Genu valgum
Visceral involvement	Cardiac malformations Renal dysplasia Inguinal hernias	Cardiac malformations Renal dysplasia Inguinal hernias	Cardiac malformations Inguinal hernias
FSIQ	60–80	40–75	20–60

FSIQ full scale intelligence quotient

sex chromosome tetrasomy and pentasomy are limited to case studies and usually lack standardized normative measures.

Effects on physical and mental development increase with the number of extra Xs, and each X is roughly estimated to reduce the overall intelligence quotient (IQ) by 15 points, with the language domain being the most affected one [32], and the behavioral phenotype frequently highlights attention problems, impulsivity/aggression, and mood instability [29].

Data from epidemiological studies have evidenced an important increase in mortality in HGA for all causes, with a standardized mortality ratio (SMR) of 2.1, specifically from chronic lower respiratory disease and congenital anomalies. An increased standardized incidence ratio (SIR = 32.6) and SMR (36.7) have been specifically reported in 48,XXYY patients for non-Hodgkin lymphoma [33], although the authors admit that these data need confirmation from future studies.

The real complete spectrum of different HGA remains to be fully elucidated in detail and their phenotype possibly depends on the severity of the expression of the genetic defect, androgen deficiency, and androgen receptor sensitivity [34, 35].

Table 4.1 compares the principal findings of the three better known and more frequent HGA, namely, 48,XXYY, 48,XXXY, and 49,XXXXY syndromes, which are discussed in greater detail below.

4.1 48,XXYY

The first patient affected by a 48,XXYY karyotype was possibly described by Ford [2] and the syndrome was then correctly identified by Muldal and Ockey [36]. Its prevalence is estimated at 1:18<000–40,000 males [16].

Three possible mechanisms explain the formation of the 48,XXYY karyotype: (1) two consecutive non-disjunctive events in meiosis I and II in a normal man that fertilize a normal oocyte [37–40], (2) a single non-disjunctive event in meiosis I in a man harboring a 47,XYY karyotype [41], and (3) non-disjunction during mitosis of a normal fertilized egg. Although 1–2% of spermatozoa contain aneuploid sex chromosomes, as compared to more than 20% in oocytes [42], only the paternal origin of the 48,XXYY syndrome via a triploid gamete ($X_pY_pY_p$) has been actually documented.

Mean age at diagnosis has been reported to be 7.7 ± 5.6 years in a cohort of 95 patients [43], later than more complex HGA syndromes (see below) and much earlier than the median age at diagnosis of KS (27 years), after exclusion of prenatal diagnoses [19].

Males with 48,XXYY show a mean adult height of 193 cm [43], typically exceeding males with KS. They have an eunuchoid habitus characterized by long legs, abdominal adiposity, micropenis, and very small and cryptorchid testes or ambiguous genitalia [44]. Patient's body weight can vary from underweight to obese and approximately 30% show gynecomastia [14].

Facial dysmorphism is present in all HGA syndromes; however, it is variable in degree and most frequent features include hypertelorism, epicanthus, and upslanting palpebral fissures. The most frequently reported characteristics include clinodactyly of the fifth finger (up to 70% of patients), pes planus and clubfoot, joint laxity and radioulnar synostosis, renal dysplasia and cardiac malformations, inguinal hernias, cleft palate, and short nail beds [45–48]. Taurodontism, frequent caries, thin enamel, and malocclusion are among the most frequent dental problems [49]. Similar to KS, a tremor with features reminiscent of essential tremor is present in some patients [50].

48,XXYY is typically associated with a higher degree of neuropsychiatric symptoms compared to KS. The full scale intelligence quotient (FSIQ) ranges from 60 to 80, with 10% of patients having an IQ above 80 [16]. Global developmental delay and severe expressive language disability are common, and verbal IQ is usually lower than performance IQ. Speech and motor delays vary from 75% to 92% and the latter usually associates with hypotonia and a mean age at independent ambulation of 18 months. Behavioral features range from shyness to aggressiveness based on several case reports [32].

Attention deficit–hyperactivity disorder (ADHD) is present in over 70% of patients, according to a study based on parent- and teacher-reported symptoms (Diagnostic and Statistical Manual of Mental Disorders, DSM IV criteria), while the prevalence of autism spectrum disorders is estimated at 34%, with most patients only mildly affected and showing difficulties in social skills and social interactions [51].

These patients are azoospermic and are considered infertile. Nowadays, modern surgical techniques in combination with the assisted reproduction technology (ART) offer the possibility of fatherhood even to patients with azoospermia, where spermatozoa can be recovered using (microdissection) testicular sperm extraction (TESE/micro-TESE). This approach, combined with Intra-Cytoplasmatic Sperm Injection

(ICSI), is already frequently employed in KS patients [52]. The ability of different factors in predicting the success of TESE have been evaluated, including testicular size, Y chromosome microdeletions, genetic abnormalities, gonadotropin, and sex hormone levels [53]; however, none have been shown to be useful in clinical practice [54, 55]. Recently, a case report has been published of a successful micro-TESE performed in a 30 year-old man non-mosaic 48,XXYY and his spouse was successfully pregnant with a normal karyotype embryo [56].

4.2 48,XXXY

Among HGA, the prevalence for 48,XXXY is estimated at 1:17,000–50,000 males [17, 18].

The possible mechanisms that explain the formation of the 48,XXXY karyotype have been reported in five cases: in two of these cases, the origin was successive non-disjunction in formation of the sperm fertilizing a normal female oocyte. The other three cases indicated double non-disjunction events during oogenesis [39].

Mean age at diagnosis has been reported from available case reports to vary from infancy to early adulthood [57]. Males with 48,XXXY show a mean adult height of 190 cm [43], typically exceeding males with KS. Phenotypically, these patients resemble those with 48,XXYY, although with a somewhat more severe phenotype. Frequent physical findings include ocular hypertelorism, flat nasal bridge, radioulnar synostosis, fifth finger clinodactyly, micropenis, and severe testicular hypotrophy (and cryptorchidism) with classic hypergonadotropic hypogonadism, while congenital malformations are similar to that of 48,XXYY and 49,XXXXY [4].

Their IQ is typically between 40 and 75 and all show some degree of learning disability, with severe verbal retardation in more than half of the patients. The assessment of mental capacities itself can be quite challenging because of the invariable presence of some language impairment in these patients. Behaviorally, patients frequently show immaturity consistent with their IQ level and are described as passive and pleasant, although aggressive outbursts are frequent as a result of mental deficits [8, 32, 58, 59].

4.3 49,XXXXY

Among HGA, the prevalence for this condition has been estimated at 1:85,000–100,000 males [17, 18]. Mean age at diagnosis was 4 months in a cohort of 20 patients [9] and this is coherent with the inherent gravity of this syndrome.

Genetically, 49,XXXXY seems to results from non-disjunction of the X chromosome during both meiosis I and II, that is, an aneuploid oocyte being fertilized with a normal male sperm [39, 60]. Although stature of these patients has been described in some case reports to be lower than other HGA tetrasomies, this is not always the case in our experience.

Clinical features of the syndrome include microcephaly, ocular hypertelorism, flat nasal bridge, upslanting palpebral fissures, bifid uvula, and cleft palate; skeletal abnormalities are frequently present, in particular radioulnar synostosis, genu valgum, pes cavum and clinodactyly, hypotonia and hyperextensible joints. Underdeveloped genitalia with classic hypergonadotropic hypogonadism are almost always present at diagnosis [61]. These patients have been reported to possess an increased risk for immunodeficiency and immune-mediated conditions, such as asthma and atopic dermatitis, possibly explained by antibody deficiency and impaired immune response to polysaccharide antigens [62].

The behavior of affected people is described as timid, shy, or friendly, with some patients showing bouts of frustration that can lead to irritability [32], while the IQs of the patients range between 20 and 60 points, significantly lower than the other HGA [57, 63].

In conclusion, HGA syndromes encompass a number of very rare conditions, once considered as variants of KS, although characterized by an earlier and more severe hypergonadotropic hypogonadism and a broad spectrum of peculiar physical malformations and neurodevelopmental and behavioral disorders. Different karyotypes are associated with peculiar phenotypes, although significant overlap is observed. Age at diagnosis ranges from infancy to adolescence, owing to evidence of facial, skeletal, and genitourinary malformations. Testosterone replacement therapy is usually necessary to start or complete pubertal development, although the appropriate timing is currently unknown. Owing to their inherent complexity, HGA syndromes benefit from a multidisciplinary team management.

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