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Cytogenetics of the Mammalian X Chromosome

Part B: X Chromosome Anomalies and Their Clinical Manifestations

Avery A. Sandberg, Editor

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CYTOGENETICS OF THE MAMMALIAN X CHROMOSOME

PART B
X CHROMOSOME ANOMALIES AND THEIR CLINICAL MANIFESTATIONS

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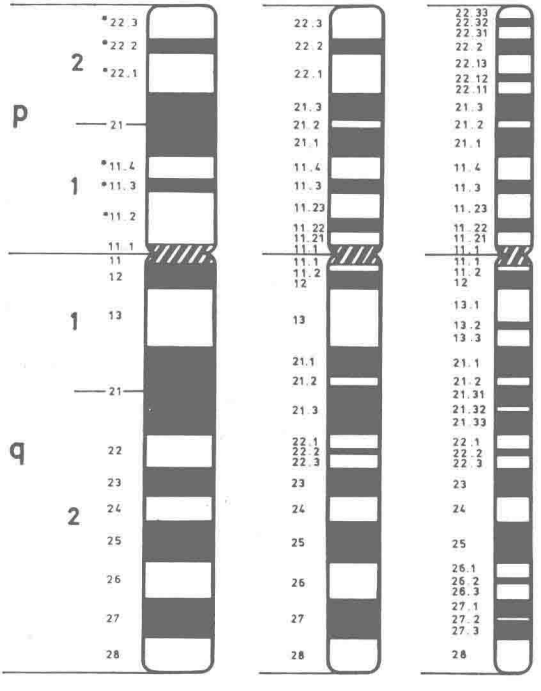

Banding pattern of the human X chromosome at different levels of resolution, the chromosome on the right showing the highest level.

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Preface

Abnormalities of the X chromosome observed cytologically or cytogenetically have as often as not been expressed in or associated with clinical syndromes of variable nature. Not unexpectedly, the role played by the X chromosome in sexual development and behavior manifests itself in a number of conditions in the human (and in animals) in which abnormal sexual development and/or function are associated with numerical and/or morphological changes in the X in both males and females. Part B of this volume addresses itself comprehensively to the clinical consequences of X-chromosome abnormalities; it is thus a logical and indispensable extension of the information presented in Part A, in which the basic mechanisms of X-chromosome behavior were reviewed.

Included in Part B are descriptions of the consequences of abnormalities of the X chromosome manifested prenatally or at birth, their effects on sexual development and other phenotypic aspects, anthropometric consequences, and the X-Y antigen expression. Much attention has also been given to translocations between the X chromosome and either autosomes or gonosomes (X or Y).

Even though an impressive list of gene loci has been mapped on the human X chromosome and this information utilized in a variety of clinical and biochemical aspects covered in Part B, much more work remains to be accomplished in this area. An intriguing finding has been the fragile X and its associated clinical manifestations; a substantial portion of the book is devoted to this unique X-chromosome anomaly. The role played by the X chromosome — whether normal or abnormal in number, morphology, or function — in human neoplasia remains essentially unknown; with this in mind, the value and significance of the sex chromatin body, the incidence of neoplasia in heredity disorders with X-chromosome anomalies, and the various changes in the X in human cancer and leukemia are presented. Hopefully, this material will stimulate further work in the field.

As so often happens, the finding of new chromosomal defects or changes has in some instances depended on methodologic advances, as witness the special conditions required for demonstrating the fragile X. One wonders how many other defects there may be, associated with abnormalities similar to those of the fragile X, that have not yet been demonstrated for lack of the required techniques.

Part B of this volume summarizes existing knowledge and ideas regarding clinical abnormalities associated with X chromosome anomalies: developmental disorders, the X-Y antigen, missing or extra X chromosomes, the fragile X, and changes in neoplasia. Undoubtedly, the future will see the addition of much new knowledge in this field.

I wish to thank Ms. Amy Kramer, Desk Editor of Alan R. Liss, Inc., for her interest in the preparation of this volume, and attention to all of the important details inherent in its editing, and Mr. Alan R. Liss for his cooperation in the publishing of this two-part book.

Avery A. Sandberg, MD

INCIDENCE AND DETECTION OF X-CHROMOSOME ABNORMALITIES

Contents

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Chapter 1

The Incidence of X-Chromosome Anomalies in Abortuses and Stillborn Infants

Vincent M. Riccardi

Sex chromosome aberrations are common in human conceptions. Their relatively high frequencies in surveys of spontaneous abortions and perinatal deaths indicate the potentially adverse consequences of sex chromosome imbalances that may be obscured by surveys of prenatal diagnosis specimens, normal neonates, and other populations. Among spontaneous abortions monosomy-X is seen in about 8%, while polysomy-X is seen very infrequently, or not at all, unless accompanied by autosomal aberrations. Among all stillbirths and neonatal deaths about 1% have sex chromosome aberrations; however, among chromosomally abnormal cases, sex chromosome aneuploidy accounts for about 21%. Moreover, among patients with a sex chromosome abnormality detected at birth, 11% expire in the perinatal period.

INTRODUCTION

The term "sex chromosome abnormalities" can mean many things, but ordinarily it refers to all abnormalities of sex chromosome number and structure, and usually, as well, to discrepancies between karyotype and phenotypic sex. In this presentation the latter will not be discussed, although it must be pointed out that some relevant survey data entail this aspect of sex chromosome abnormalities. In addition, strictly speaking, monosomy-X itself may be due to loss of a Y chromosome or an X chromosome, either of which may be normal or abnormal in structure.

In any case, numerical and structural abnormalities of the X chromosome are both relatively frequent contributions to human pathology and the source of potential insights into the biologic and genetic functions of the X chromosome.

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ABORTUS SURVEYS

Numerous cytogenetic surveys of both spontaneous abortuses and induced abortuses, varying tremendously in quality and the use of banding techniques, have been published. Perhaps the most useful studies include those of Kajii and associates [1], Alberman and Creasy [2], Creasy and associates [3], Boue and associates [4], and Boue and Boue [5]. Table I summarizes the data from a total of 11 studies, including eight previously summarized by Boue and Boue [5]. In the three large studies [1,2,4,5] 2,883 abortuses were included, of which 1,423 (49%) were abnormal. For the entire set of data there were 1,862 chromosomally abnormal abortuses, of which 369 (20%) showed monosomy-X. In one study [2], 1 of 287 (0.3%) was 47,XXX/47,XX, +mar, and 2 (0.7%) had polysomy-X in the presence of autosomal trisomy (48,XXX, +8; 48,XXY, +9). In another study, 3 of 215 (1.4%) showed polysomy-X, but one had a mother with an incompetent cervix (47,XXY), another was 48,XXY, +8, and the third was 48,XXY, +9. Without giving more details Boue and Boue [5] noted that "abortions with trisomy-X have also been observed," and that two cases restudied with quinacrine banding were 47,XXY (though previously considered to be 47,XX, +G).

In any event, whole monosomy-X accounts for about one-fifth of chromosomally abnormal abortuses and about 9% (250/2,883 per Table I) of all spontaneous abortuses, polysomy-X is relatively unusual in that population. Moreover, even when polysomy-X is present, other factors such as autosomal aberrations, maternal anatomic defects, and other coincidental abnormalities must be considered.

Among 121 monosomy-X spontaneous abortuses Boue and Boue [5] noted a mean gestational age of 12.3 weeks and a mean developmental stage of 5.8 weeks (compared to 11.4 weeks and 5.3 weeks, respectively, for chromosomally normal abortuses, and 10.7–13.1 weeks and 2.9–5.0 weeks, respec-

TABLE I. Summary of abortus surveys

Reference	Number studied	Number abnormal	45,X	XXX	XXY	XYY
[5][a]	–	439	119 (27%)	–	–	–
[4,5]	1,498	921	140 (15%)	[b]	[b]	–
[2]	983	287	68 (24%)	1[b]	2[b]	–
[1][c]	402	215	42 (20%)	0	3[b]	0
Total	–	1,862	369 (20%)	–	–	–

[a]Boue and Boue's Table 1, utilizing eight previously published surveys from six countries.
[b]See text.
[c]Unselected cases only.

tively, for other chromosomally abnormal abortuses). However, comparable data from Creasy et al. [3] suggest that chromosomally abnormal products of conception, including a portion of monosomy-X fetuses, may not be expelled until the 20th to the 23rd week of gestation (6%). See also Kajii et al. [1]. Sixty-eight monosomy-X abortuses characterized by Creasy et al. [3] had morphologies ranging from ruptured empty sacs (16%) or a ruptured sac with cord stump (34%) through embryos with encephaloceles (6%) and a fetus with cystic hygromas (1%) to ostensibly normal embryos (24%) and fetuses (3%).

The mean maternal age for monosomy-X abortuses was calculated to be 25.9 years (normals, 26.4 years; trisomics, 30.0 years) by Creasy et al. [3], 27.6 $\pm$ 0.9 years (normals, 27.5 $\pm$ 0.4 years; trisomics, 31.3 $\pm$ 0.6 years) by Boue et al. [4], and 25.8 $\pm$ 4.3 years (normals 28.9 $\pm$ 6.0 years; trisomics, 31.9 $\pm$ 6.5 years) by Kajii et al. [1]. That is, no maternal age effect for 45,X monosomy is apparent. The same is true for paternal age and birth order [4]. Data regarding month of conception for monosomy-X abortuses as an isolated group are not available, though data for all chromosomally abnormal abortuses show no significant monthly variation [1]. While fertilization during or within one cycle of medicinal ovulation stimulation appears to increase the frequency of trisomy and polyploidy, there is no apparent influence on the frequency of monosomy-X [4]. Boue et al. [4] claim that a paternal occupational X-ray exposure increases the frequency of chromosome abnormalities, although neither maternal nor paternal X-ray exposure is claimed to influence the frequency of monosomy-X abortuses.

Whether a monosomy-X abortus increases the risk for the same or different aneuploidy in subsequent conceptions is unclear at present. A precise answer to this query of course will have to take into account the high background of monosomy-X among abortuses and the attendant confounding issue of coincidence. Among 43 women with two consecutive abortions [6], 6 had one abortus with 45,X monosomy: 2 were noted in the second abortus, and one of these followed on a 47,XY, +E abortus whereas the other followed a 46,XY abortus; 2 were noted in the first abortus and were followed by 46,XY abortuses; and 2 were noted in the first abortus and were followed by 47,XX, +D and 69,XXY abortuses, respectively.

The frequencies of monosomy-X and X-chromosome polysomy among induced abortuses are not expected to be the same as seen among spontaneous abortuses, although very early inductions might lead to inclusion of conceptuses that would have aborted spontaneously. In one Japanese study [7], among 300 abortuses induced in women of various ages before 12 menstrual weeks of pregnancy, 22 chromosome abnormalities were found, including 3 with 45,X (3/300 = 1%; 3/22 = 14%), and one each with 47,XXY and 47,XXX (1/300 = 0.3%; 1/22 = 5%). In another Japanese study [8], among 256 abortions induced between 6 and 12 menstrual weeks of pregnancy in women 35 years of age or older only autosomal trisomies were found (13/256

= 5%). In a Swiss study [9] 728 karyotyped abortuses were obtained from women of various ages (mean 28.4 years, range 15–48 years) at various times of gestation (mean 63.4 days from ovulation, range 33–109 days). Twenty-three (3.2%) chromosomally abnormal abortuses were found. There were only two sex chromosome abnormalities (2/728 = 0.3%, 2/23 = 9%): 46,XX/47,XXX (maternal age, 22 years), and 46,X,del(X)(q12) (maternal age, 22 years).

Excepting the immediately preceding notation, structural aberrations of an X chromosome were strikingly absent from the abortus survey material reviewed.

STILLBIRTH SURVEYS

In an important sense the distinction between stillbirth and perinatal death may be a bit arbitrary with regard to chromosome-caused mortality. Thus, a comprehensive survey would include both groups. The data depicted in Table II show that 45,X monosomy does not seem to be a significant cause of stillbirth, but sex chromosome polysomy (primarily 47,XXX and 47,XXY) accounts 1) for 5% of all the tabulated macerated stillbirths and 43% of the detected chromosome aberrations in that group, and 2) for just less than 1% of the tabulated fresh stillbirths and 20% of the detected chromosome aberrations in that group. Among the neonatal deaths, monosomy-X accounts for 0.4% of the total and 6% of those with chromosome aberrations; other sex chromosome aberrations account for 0.5% of the total and 10% of those with chromosome aberrations.

In addition to the data in Table II, Sutherland et al. [10] obtained chromosome analyses on 3 macerated stillbirths, 32 nonmacerated stillbirths, and 98

TABLE II. Summary of perinatal surveys (modified from Alberman and Creasy [2])

	Stillborn							
	Macerated		Fresh		Neonatal death		Livebirth	
	No.	%	No.	%	No.	%	No.	%
Karyotyped	61	100	222	100	551	100	43,558	100
45,X	0	–	0	–	2	0.4	2	0.005
Other sex aneuploidy	3	5	2	0.9	3	0.5	91	0.2
Other chromosome abnormalities	4	7	8	4	26	5	154	0.5

neonatal deaths, with abnormal karyotypes noted in 1, 1, and 7 specimens, respectively. The abnormalities include 5 cases of trisomy 18 and one case each of trisomy 21, triple-X, an unbalanced reciprocal translocation, and mosaicism for an extra C-group chromosome. Thus, at least one (11%) of 9 detected aberrations or one (0.8%) of 133 specimens showed polysomy-X.

The role of sex chromosome abnormalities as a cause of perinatal mortality was emphasized by Robinson [11] when he pointed out that among 66 newborns found to have X-chromosome aneuploidy, 7 (11%) died in the first week of life. Included are 3 with 47,XXY, 3 with 45,X, and one with 47,XXX. Moreover, my personal involvement with several of the cases reported by Robinson [11], and additional experience in consulting on malformed newborns, suggest that X-chromosome aneuploidy is not always anticipated when it is found in this age group. That is, the phenotype may be more abnormal than we usually associate with X-chromosome aneuploidy. Though anecdotal, I believe this observation is worthy of comment because it indicates that the overall morbidity of X-chromosome aneuploidy is greater than might be suggested from incomplete X-chromosome surveys and our syndrome (e.g., Klinefelter and Turner syndrome) stereotypes.

Mosaicism for X-chromosome aneuploidy as well as X-chromosome structural rearrangements, including isochromosomes and X/autosome translocations, are also more likely to be seen at or near term for the obvious reason that they are not associated with spontaneous abortions as is 45,X monosomy. However, I am unaware of survey data establishing relative frequencies among either stillbirths or liveborns.

DISCUSSION

The combined information on X-chromosome aneuploidy in spontaneous abortions and stillbirths indicates, first, that these cytogenetic aberrations can impose a severe pathologic burden on their respective bearers. These genetic distortions must not be presumed to be trivial merely because the patient can survive to and beyond term. Second, this survey information raises intriguing questions about X-chromosome behavior and function. Why is monosomy-X so frequent at conception? What determines survival of 45,X embryos through fetal life to term? What accounts for the tremendous variation in phenotypes among X-chromosome aneuploid patients that survive to the newborn period?

The answers to these questions will not be forthcoming promptly, and in any case not without a comprehensive investigation of the X chromosome as detailed in this volume. At the least, data regarding the incidence and consequences of X-chromosome aberrations in liveborns (Chapter 2) and fetuses at prenatal diagnosis (Chapter 4) are needed to provide additional context. And