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The Phenotype of 45,X/46,XY Mosaicism: An Analysis of 92 Prenatally Diagnosed Cases

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Summary

We undertook an international survey of prenatally diagnosed 45,X/46,XY mosaicism to ascertain the phenotypic spectrum of this condition. Ninety-two cases were obtained by means of a questionnaire sent to over 730 cytogenetic laboratories. Seventy-six cases (75 males and 1 female) had physical examinations after delivery or termination of pregnancy. Among these, there were four significant genital anomalies: three hypospadias and one female with clitoromegaly. Gonadal histology was abnormal in three (27%) of 11 cases, all of whom had normal male external genitalia. Other anomalies were noted in five cases: one cystic hygroma in a male, two cardiac anomalies, one spina bifida with multiple other defects, and one intrauterine growth retardation. There was no relationship between the percent mosaicism and the presence or degree of abnormalities. We conclude that 95% of 45,X/46,XY fetuses will have normal male genitalia, although there will also be a significant risk (27%) for abnormal gonadal histology. Long-term follow-up studies of prenatally diagnosed cases of 45,X/46,XY mosaicism are needed to study, without ascertainment bias, stature, pubertal development, tumor risk, and fertility.

Introduction

The prenatal diagnosis of 45,X/46,XY mosaicism is a genetic counseling dilemma. The literature on this condition is primarily retrospective, consisting of postnatally diagnosed cases which reflect an ascertainment bias toward the phenotypically or functionally abnormal. These reports indicate an extreme diversity of presentation, encompassing phenotypic females with or without virilizing features or elements of Turner syndrome, to ambiguous genitalia, to phenotypic males who vary with respect to phallic size, hypospadias, scrotal fusion, and descent of the testes. Conversely, anecdotal reports of prenatally diagnosed cases do not support a high rate of abnormality. In order to provide more appropriate genetic counseling and to evaluate both the range and magnitude of abnormalities associated with 45,X/46,XY, we undertook the following collaborative study.

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Material and Methods

A questionnaire was designed to address the cytogenic findings and clinical outcome of prenatally diagnosed 45,X/46,XY mosaicism. Background information on each laboratory noted the population base from which its sampling was derived. Cytogenetic details included both the indication for the prenatal evaluation and the specific cell or colony count in each case. Only cases of "true mosaicism," defined as the identical chromosomal abnormality detected in two or more flasks or colonies of cultured amniotic fluid cells (Bui et al. 1984; Hsu and Perlis 1984), were included. Identical chromosomal abnormalities involving multiple cells or clones but restricted to one culture vessel were excluded, as were isolated abnormal cells or clones. Details of Y-chromosome banding and postnatal confirmatory cell counts were requested. Areas of clinical inquiry included ultrasound studies and additional prenatal evaluation, outcome of pregnancy, general phenotype of the neonate, external genitalia, internal examination (when available), and any follow-up information. As no single classification of ambiguous genitalia is universally accepted, diagrams of the external genitalia were designed to facilitate international communication.

Over 730 questionnaires were sent to cytogenetic laboratories in 51 countries. The mailing list was derived from the International Directory of Genetic Services of the March of Dimes (8th ed., July 1986) and supplemented by the mailing list of Comprehensive Clinical Genetic Service Centers. We asked cytogeneticists to forward the questionnaire to the appropriate clinician for clinical information. Further telephone contact was made when necessary to complete or clarify the information.

Results

We received 176 questionnaires, for a response rate of 25%. Of these respondents, 25 laboratories did not perform prenatal diagnosis and 109 other institutions had not encountered 45,X/46,XY mosaicism in their amniotic fluid samples. The 42 remaining institutions provided a total of 92 true-mosaic prenatally diagnosed cases of 45,X/46,XY, including two cases (cases 67 and 68) from our own institution. In over 548,000 amniotic fluid samples, the incidence of 45,X/46,XY mosaicism in this series is 1.7/10,000.

The indication for amniocentesis most often was advanced maternal age (66%) but also included abnormal maternal serum alpha-fetoprotein, parental anxiety, and a family history of various genetic disorders.

The chromosomal analysis of each case is summarized in table 1. In addition to the 83 cases of pure 45,X/46,XY mosaicism, there were two cases of 45,X/46,XY/47,XYY (cases 61 and 92), four cases of 45,X/47,XYY (cases 5, 19, 52, and 57), and three cases with other variations on the mosaicism (45,X/46,X+mar/46,XY, case 15; 45,X,21p+/46XY, case 65; and 45,X/46,XY,t(12;18), case 82). Postnatal confirmatory cytogenetic studies were available in 59 cases: seven were 46,XY, two were 45,X, 46 were 45,X/46,XY, two were 45,X/47,XYY, and two were 45,X/46,XY/47,XYY.

There were seven cases of documented Y abnormalities, including isodicentric Y (cases 42, 49, and 56), Yq- (cases 8, 47, and 78), and three cells with Yq- or metacentric Y in case 60.

Additional prenatal evaluation was undertaken in 45 of the 92 pregnancies, including 11 repeat amniocenteses (eight with 45,X/46,XY and three with 46,XY) and 35 ultrasound studies (33 normal, one unspecified, and one (case 92) with intrauterine growth retardation and mild oligohydramnios). The outcome of pregnancy was 39 elective terminations (42%), three spontaneous abortions, one stillbirth, one fetal demise, 44 live births (48%), and four continuing pregnancies.

Of the total 92 cases, 76 had clinical examinations after delivery and were therefore considered clinically informative. Of these cases, two were abnormal in general appearance. One live-born male had a unilateral cystic hygroma of the neck which was surgically removed (case 88); no other stigmata of Turner syndrome were noted. A stillborn male had spina bifida with meningomyelocele, polymicrogyria, and malformed hands, feet, and ears (case 2).

There were no cases in which the sex could not be assigned. There were 75 phenotypic males and one phenotypic female (case 85). Normal male genitalia were found in 72 cases (95%). Only four significant genital abnormalities were detected. Three males had hypospadias: one penile (case 84), one total (case 92), and one perineal associated with a micropenis and an abnormal scrotum (case 55). The only female had clitoromegaly.

Gonadal histology was available in 11 of 14 autopsies but in no live borns. The three gonadal abnormalities were found in abortuses with normal male external genitalia, though one did have multiple congenital abnormalities (case 2). These three included two cases of bilateral ovatestes (cases 2 and 27) and one case with a testicular lesion described only as "precancerous" (case 13). Internal exam on one of the cases of ovatestes revealed an epididymis on one side with a fallopian tube on the other (case 27). Gonadoblastoma was not identified in any of the gonads examined.

Other anomalies included two common cardiac malformations: an atrial septal defect (case 9) and a small ventricular septal defect (case 69). Meckel diverticulum (case 30), bilateral inguinal hernias (case 41), unilateral cryptorchidism (case 42), and scrotal hydrocele (case 63) were also noted. A summary of the major abnormalities is found in table 2.

The average percent mosaicism—i.e., the number of 45,X cells relative to the total number of cells—was 35.8% with an SD of 24.3. In calculating this percent mosaicism, tetraploid cells, CVS data, and repeat amniocentesis data were not included; in situ cultures were used preferentially over flask cultures when the criteria for true mosaicism were fulfilled by the in situ data alone. Statistical analysis was undertaken using the runs tests and the *t*-test with LOGIT transformation of the percent mosaicism values ($\log\{[1-\%mos]/\%mos\}$). The group with genital abnormalities and the group with gonadal abnormalities were reviewed separately, and the percent mosaicism was not significantly higher in any of the anomalous groups than in the normals; nor was there a difference in the distribution of the percent mosaicism (see fig. 1).

Table I

Cytogenetic Findings in 45,X/46,XY Mosaicism

Case	Prenatal Cell Count				Postnatal Confirmation			Pregnancy Outcome[b]
	Source (no. of cultures)[a]	45,X	46,XY	%45,X	Source (no. of cultures)[a]	45,X	46,XY	
1.....	AF (3)	50	26	65.8	AF,FB	45,X/46,XY		TAB
2.....	AF (6)	26	39	40.0	AF,C,FB,FS	9	34	Stillbirth
3.....	AF	25	25	50.0	None			SAB
4.....	AF	50%	50%	50.0	P,FS	49	101	TAB
5.....	AF (4)	11	0	68.8	P	23	0	TAB
		5 Cells 47,XYY				27 Cells 47,XYY		
6.....	AF (4)	25	31	44.6	Abortion AF	15	35	TAB
7.....	AF (2)	16	38	29.6	None			LB
8.....	AF (2)[c]	16	14	53.3	None			LB
	Repeat AF	16	4					
9.....	AF (2)	23	8	74.2	None			TAB
10....	AF (2)	8	20	28.6	F	14	36	TAB
	Repeat AF	5	10					
11....	AF (2)	12	28	30.0	P,F	76	344	TAB
	CVS(2)	5	14					
12....	AF (2)	4	66	5.7	None			LB
	Repeat AF	0	29					
13....	AF (2)	37	15	71.2	P,F	72	360	TAB
14....	AF (2)	6	67	8.2	N/A			CP
15....	AF (3)	18	63	18.0	P,CB,FB	5	80	TAB
		15 Cells 46,X + mar						
16....	AF (3)	16	44	26.7	NB	5	10	LB
17....	AF (3)	18	36	33.3	F	24	25	TAB
18....	AF (3)	10	15	40.0	None			SAB
19....	AF (3)	15	0	51.7	NB	3	0	LB
		14 Cells 47,XYY				28 Cells 47,XYY		
20....	AF (3)	22	48	31.4	FG	6	5	TAB
21....	AF (3)	35	25	58.3	N/A			CP
22....	AF (3)	14	66	17.5	CB	0	16	LB
23....	AF (3)	12	28	30.0	None			TAB
24....	AF	16	1	80.0	FS	45,X/46,XY		TAB
25....	AF	11	8	57.8	NB	9	77	LB
	CVS	0	7					
26....	AF	4	26	13.3	None			TAB
27....	AF (2)	14	16	46.7	None			TAB
28....	AF (2)	8	37	17.8	FS	3	42	TAB
29....	AF (7)	86	19	68.8	None			TAB
30....	AF (3)	14	72	16.3	None			TAB
31....	AF (3)	10	48	17.2	FS	16	82	TAB
32....	AF (3)	8	89	8.2	None			TAB
	Repeat AF	3	8					
33....	AF (2)	47	15	74.6	NB	13	37	LB
34....	AF (2)	9	41	18.0	None			TAB
35....	AF (3)	14	19	30.0	FS	7	43	TAB
36....	AF	1	0	80.0	None			TAB
	Repeat AF	11	3					
37....	AF (3)	13	28	34.9	None			TAB
38....	AF	10	35	22.2	NB	6	194	LB
39....	AF	5	14	26.3	NS	5	45	LB
	PUBS	4	56					
40....	AF in situ (10)	8	58	12.1	CB,NS	1	121	LB
	AF flask	1	241					
41....	AF in situ (6)	2	24	7.7	NB	2	98	LB
	AF flask(2)	3	197					

(*continued*)

Table 1 (continued)

Case	Prenatal Cell Count				Postnatal Confirmation			Pregnancy Outcome[b]
	Source (no. of cultures)[a]	45,X	46,XY	%45,X	Source (no. of cultures)[a]	45,X	46,XY	
42....	AF (6)[c]	12	8	60.0	NB	17	33	LB
43....	AF in situ (4)	1	13	7.1	None			LB
	AF flask (2)	3	86					
44....	AF (4)	12	25	43.2	F	2	4	TAB
45....	AF (4)	3	49	7.5	NB	1	103	LB
46....	AF (4)	5	37	15.9	NB	1	99	LB
47....	AF (2)[c]	26	41	38.8	CB,F	14	32	TAB
48....	AF (2)	19	52	26.8	NB	"Same" as AF		LB
49....	AF (2)[c]	42	21	66.7	NB	4	23	LB
50....	AF (2)	12	19	38.7	NB	30	88	LB
51....	AF (2)	25	19	56.8	None			LB
52....	AF (2)	308	0	94.8	None			LB
		17 Cells 47,XYY						
53....	AF (2)	39	64	37.9	NB	"Same" as AF		LB
54....	AF (2)	30	9	76.9	None			LB
55....	AF	23	17	56.3	NB	15	21	LB
	AF	90%	10%					
56....	AF (2)[c]	82	31	71.9	NB	15	31	LB
	PUBS	13	18					
57....	AF (2)	30	0	34.1	N/A			CP
		58 Cells 47,XYY						
58....	AF (2)	13	47	21.7	FS	3	3	TAB
59....	AF (4)	10	139	6.7	P,F	17	43	TAB
	Repeat AF (2)	0	29					
60....	AF (4)[c]	15	139	9.6	P,F,NB	19	45	LB
61....	AF (4)	5	6	2.9	P,F,FS	11	9	TAB
		163 Cells 47,XYY				102 Cells 47,XYY		
62....	AF (3)	12	28	31.0	F,FS,FG	8	190	TAB
63....	AF (4)	11	120	8.3	NB	4	96	LB
64....	AF (2)	12	8	60	F	50	0	TAB
65....	AF	67%	33%	66.7	NB	18 Cells 45,X,21p-	8	LB
66....	AF (4)	15	9	62.5	None			SAB
67....	AF (3)	19	281	6.3	NB	0	18	LB
68....	AF (3)	3	297	1.0	CB,NS	0	85	LB
69....	AF (3)	8	37	17.8	NB	3	17	LB
70....	AF (3)	15	57	20.8	N/A			CP
71....	AF (3)	4	58	6.5	None			LB
72....	AF (3)	9	19	32.1	None			LB
73....	AF (3)	11	49	18.3	C,F,FS	8	47	TAB
74....	AF	4	5	44.4	None			LB
75....	AF (3)	4	45	8.0	None			LB
76....	AF (2)	9	21	30.0	None			TAB
77....	AF (3)	4	90	4.2	CB,FS	0	200	LB
78....	AF[c]	18	31	36.7	F,FB	1	49	TAB
79....	AF (3)	88	2	97.7	NB	38	62	LB
		7 Cells 90,XX; 3 cells 92,XXYY						
80....	AF (3)	24	37	39.3	CB	2	38	LB
81....	AF (2)	4	40	9.1	NB	1	99	LB
82....	AF	11	19	36.7	F	8	22	TAB
		All cells t(12;18)				All cells t(12;18)		
83....	AF (2)	31	10	75.6	NB	30	0	LB
84....	AF (2)	11	54	16.9	N	0	17	LB
	CVS direct	7	3					

(*continued*)

Table 1 (continued)

Case	Prenatal Cell Count				Postnatal Confirmation			Pregnancy Outcome[b]
	Source (no. of cultures)[a]	45,X	46,XY	%45,X	Source (no. of cultures)[a]	45,X	46,XY	
85....	AF (2)	7	58	10.8	None			TAB
86....	AF (3)	5	26	16.1	NB	0	51	LB
	Repeat AF (3)	0	25					
87....	AF (3)	3	8	27.3	None			TAB
88....	AF (2)	1	15	17.1	C,NB	17	108	LB
	Repeat AF (2)	6	19					
89....	AF (3)	37	17	68.5	FB	10	90	TAB
90....	AF (3)	4	55	6.8	NB	0	50	LB
91....	AF (2)	8	42	16.0	None			Fetal demise
92....	AF	22	11	63.0	NB,NS	45,X/46,XY/47,XYY		TAB
		2 Cells 47,XYY						

Note.—N/A = no answer or not applicable.

[a] AF = amniotic fluid; P = placenta; C = cord; F = fetus; N = neonate; B = blood; S = skin; G = gonad. Numbers in parentheses are number of cultures.

[b] TAB = elective termination; SAB = spontaneous abortion; LB = liveborn; CP = continuing pregnancy.

[c] Abnormal Y.

Follow-up information was available for 23 patients. The longest follow-up time was 4 years. Mental status and stature were normal, except for the one male whose height was less than the fifth percentile at 3.5 years after follow-up (case 79). No information was available on endocrine function, puberty, or sexual maturation or function.

Discussion

These 92 cases represent the largest group of prenatally diagnosed cases of 45,X/46,XY mosaicism studied. The incidence of 1.7/10,000 amniotic fluid samples is consistent with previous prenatal reports of 0.7–2.8/10,000 (Benn et al. 1984; Bui et al. 1984; Hsu and Perlis 1984; Worton and Stern 1984) and with the reported incidence of 1.5/10,000 consecutively born neonates (Hamerton et al. 1975).

The literature on postnatally diagnosed cases of 45,X/46,XY mosaicism indicates a high rate of abnormality, reflecting bias in ascertainment. In Lippe's (1982) series on Turner syndrome, five of 80 subjects had 45,X/46,XY. Similarly, 22 of 287 of gonadal dysgenesis patients (Ferguson-Smith 1965), 45 of 81 mixed gonadal dysgenesis patients (Zah et al. 1975), 10 of 30 gonadoblastoma patients (Scully 1970), and three of 100 hypospadic males (Aarskog 1971) also had this mosaic condition. Furthermore, postnatally ascertained case reports on 45,X/46,XY mosaics emphasize the spectrum of anomalies, such as short stature, delayed sexual development, Turner syndrome, ambiguous genitalia, pseudohermaphroditism, true hermaphroditism, hypospadias, dysgenetic streak ovaries, mixed gonadal dysgenesis, gonadoblastoma, as well as other anomalies (Hirschhorn et al. 1960*a*, 1960*b*; Willemse et al. 1962; Borghi et al. 1965; Edwards et al. 1966; Jackson et al. 1966; Russel et al. 1966; Ferrier et al. 1970; Karp et al. 1975; Boczkowski et al. 1976; Schmidt et al. 1976; Gantt et al. 1980; Kofman et al. 1981; Muller et al. 1983; Ayuso et al. 1984; Knudtzon and Aarskog 1987; Reindollar et al. 1987; Rosenberg et al. 1987).

None of these aforementioned abnormalities or the female phenotype was commonly encountered in published reports of prenatally ascertained cases. A review of the literature revealed 33 cases of 45,X/46,XY mosaicism diagnosed prenatally: 26 were normal males (85%) (Sutherland et al. 1975; Hsu et al. 1976; Zabel et al. 1981; Hecht and Hecht 1982; Benn et al. 1984; Bui et al. 1984; Hsu and Perlis 1984; Watson et al. 1984; Lieber et al. 1986; Wheeler et al. 1986; Kirkilionis et al. 1987). Twenty-three of the cases were collected incidentally as part of large general investigations of prenatal diagnosis; the details provided are accordingly restricted. In the four individual case reports extensive information was provided. Significant findings noted by these authors included two case of hypospadias, one of whom also had a horseshoe kidney and asymmetric gonadal dysgenesis. Unfortunately, much of the infor-

Table 2

Congenital Anomalies in Prenatally Diagnosed 45,X/46,XY Mosaicism

Case	Symptom(s)
Abnormal male external genitalia:	
55	Microphallus; perineal hypospadias; prepuce with dorsal hood only and chordee; both tests descended into an abnormal scrotum
84	Penile hypospadias in an otherwise normal male
85	Phenotypic female with normal labia and clitoromegaly
92	Short spherical penis and total hypospadias
Abnormal internal genitalia/gonadal histology	
2	Bilateral ovatestes
13	Precancerous testicular lesion
27	Bilateral ovatestes with left epididymis + vas deferens and right fallopian tube
Other abnormalities	
2	L2–L4 spina bifida with meningomyelocele; polymicrogyric brain; malformed ears, hands, feet
9	Cardiac malformation with atrial septal defect
69	Small ventricular septal defect
88	Cystic hygroma of the left neck
91	Mild oligohydramnios; intrauterine growth retardation shown by ultrasound (maternal systemic lupus erythematosis and heavy smoking)

mation on prenatally diagnosed cases is incomplete, and there may still be biased reporting of those with phenotypic abnormalities in single case reports. Nevertheless, the data from these 33 cases support our conclusion that the most likely product of a 45,X/46,XY pregnancy is a phenotypically normal male.

During the preparation of the manuscript of the present paper, Hsu (1989) published a collection of 54 cases, several of which had been previously reported. She found a similar rate of abnormality; 42 cases (89%) were associated with a normal male phenotype. Some of our respondents also participated in Hsu's study; our cases 6, 37, 70, 76, 78, 81, 82, and 86–88 correspond, respectively, to Hsu's cases I-26, II-10, I-1, VII-1, II-4, I-14, II-12, IV-1, II-2, and II-1. Our case 37 has also been published by Hecht and Hecht (1982) as a single case report, and our case 70 has been reported by Watson et al (1984) as case 18 of their survey of fetal blood sampling. We caution readers to note duplicate reporting and the possibility of data inflation. To the best of our knowledge, no other case has been previously published.

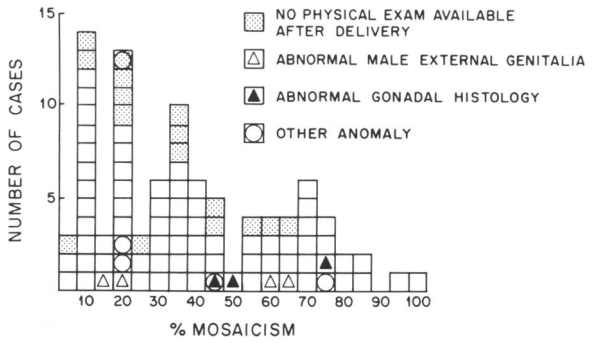

Figure 1 Distribution of percent mosaicism in prenatally diagnosed 45,X/46,XY mosaicism.

In our prenatally ascertained series, 95% had normal male genitalia, and there was no instance of severe genital ambiguity. The large discrepancy between data ascertained after postnatal and prenatal diagnosis, as presented here, must be emphasized. In addition, the abortion rate of 42% in our study contrasts with the much lower rate of abnormality found. The frequent decision to terminate 45,X/46,XY pregnancies may reflect the overrepresentation, in the literature, of the abnormal minority.

In our sample of 11 cases with gonadal histology, 27% had gonadal abnormalities, all in the presence of normal external genitalia. We encourage pathological examination of the gonads on all 45,X/46,XY abortuses, to increase these data. Although we did not identify any cases of gonadoblastoma, the increased risk of this and other tumors in dysgenetic gonads is well documented and occurs primarily near the age of puberty (Teter and Boczkowski 1967; Scully 1970; Manuel et al. 1976; Simpson 1976). Quoting only studies in which cases were ascertained on the basis of tumor or dysgenetic gonads, Simpson (1976; Simpson and Photopulos 1976) may have overestimated when he put the risk of gonadoblastoma or dysgerminoma in 45,X/46,XY mosaicism at approximately 15%–20%. Without a prospective follow-up study of prenatally ascertained cases into adulthood, the risk of gonadoblastoma cannot be accurately stated but must be considered significant in the 45,X/46,XY individual. In view of this risk, close regular follow-up is mandatory. Unfortunately, there is no consensus regarding what optimum management would entail. Some authors favor gonadal biopsy (Muller et al. 1985). Prophylactic orchiectomy prior to puberty has also been recommended (Manuel et al. 1976; Muller et al. 1983, 1985). At a minimum, noninvasive procedures such as pelvic ultrasound and endocrine studies should be considered.

In our series, we could find no association between the degree of mosaicism and the occurrence of genital, gonadal, or somatic abnormality. Most authors who have addressed this question support this conclusion (Gantt et al. 1980; Kofman et al. 1981; Ayuso et al. 1984; Knudtzon and Aarskog 1987; Rosenberg et al. 1987). In fact, 21 of 23 of our examined cases with >50% 45,X cells had a normal male phenotype, while the only phenotypic female (case 86) had a relatively low rate of mosaicism of 11%. For purposes of genetic counseling and clinical decision making, the percent mosaicism found in amniotic fluid samples should be considered a poor predictor of phenotype.

None of the cases with a genital abnormality had a prenatal ultrasound following diagnosis. We were unable to gather sufficient data on repeat amniocentesis, ultrasound, or other prenatal evaluations to comment on their usefulness for diagnosis or decision making. Nonetheless, the benefit of ultrasound for parental reassurance may be significant.

In conclusion, we want to stress the following points: (1) Ninety-five percent of 45,X/46,XY mosaics have normal male genitalia. (2) Information from a subgroup of 11 abortuses showed that 27% have abnormal gonadal histology. Dysgenetic gonads can occur in the presence of normal male external genitalia; therefore, the risk of gonadal pathology is not limited to individuals with hypospadias or ambiguous genitalia. (3) 45,X/46,XY individuals are at risk for gonadoblastoma and should be followed closely for signs of the development of gonadal tumors. Long-term follow-up studies of prenatally diagnosed cases of 45,X/46,XY are needed to evaluate the lifetime risk for both tumor formation and sexual dysfunction, infertility, short stature, etc. (4) The degree of amniotic fluid mosaicism does not predict the degree of genital or gonadal abnormality. (5) Data derived from postnatally ascertained cases exaggerate the extent of genital and other abnormalities by overrepresenting the phenotypically abnormal minority. In counseling of families with a 45,X/46,XY pregnancy, unbiased data from prenatally diagnosed cases should be emphasized.

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Respondent	*Institution*
U.S. respondents:	
Hecht, B. K.	Southwest Biomedical Research Inst, Scottsdale (cases 36–38)
Tsai, Joseph	Valley Children's Hospital, Fresno
Ying, Tuang Lin	Children's Hospital of Los Angeles, Los Angeles
Bass, Harold	Kaiser Permanente Medical Program, Los Angeles (case 40)
Carr, Daisy	King/Drew Medical Center, Los Angeles
	Vivigen, Los Angeles (case 39)
Conte, W.	Prenatal Diagnostics, Mountain View, CA (cases 41–46)
Wassman, E. R.	Genetics Institute, Pasadena (cases 47–58)
Mascasella, James	Children's Hospital, San Diego
Stephens, John	California Prenatal Diagnosis Institute, San Jose
Mann, John	Kaiser Permanente Northern California, San Jose (cases 59–65)
Sandlin, Connie	Memorial Med Center of Long Beach, Signal Hill, CA (case 66)
Mohandas, T. K.	Harbor-UCLA Medical Center, Torrance CA (cases 67 and 68)
Whiteman, David	University of Connecticut Health Center, Framington
Yang-Feng, Teresa	Yale University School of Medicine, New Haven, CT (cases 69 and 70)
Borgaonkar, D. S.	Medical Center of Delaware, Inc., Newark
Cantu, Eduardo	University of Florida (R. C. Phillips Research Lab), Gainesville
Maniken, Carl	Nemours Children's Clinic, Jacksonville
Falek, Arthur	Georgia Mental Health Institute, Atlanta
Arakaki, David	Kapiolani Medical Center, Honolulu (cases 71–73)
Webb, Mary	Idaho Department of Health and Welfare, Boise
Chmura, Mark	Illinois Masonic Hospital, Chicago

(continued)

Respondent	*Institution*
Hoo, Joe	University of Illinois at Chicago, Chicago
Zunich, Janice	Indiana University School of Medicine, Gary
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Palmer, Catherine	Indiana University School of Medicine, Indianapolis (case 75)
Patil, Shivanand	University of Iowa Hospitals and Clinics, Iowa City (case 76)
Kior, Charles	University of Kansas Medical Center, Kansas City
Cho, Sechin	University of Kansas School of Medicine, Wichita
Beauregard, L.	Eastern Maine Medical Center, Bangor
Stetten, Gail	John Hopkins University, Baltimore (case 77)
Saxe, Debra	Molecular Medicine, Inc., Bethesda, MD
White, Beverly	National Institutes of Health, Bethesda, MD
Tishler, Peter	Brockton–West Roxbury VA Medical Center, Brockton, MA
Spina, Frank	Berkshire Medical Center, Pittsfield, MA
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Terry, Kelland	State of Nevada, Division of Mental Hygiene, Sparks
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	SUNY Health Science Center, Syracuse
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Carpenter, Nancy	Children's Medical Center, Tulsa
Soukup, Shirley	Cincinnati Children's Hospital, Cincinnati
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Mennuti, Michael	Hospital University of Pennsylvania, Philadelphia
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Ming, Pen-Ming	Temple University School of Medicine, Philadelphia
Wenger, Sharon	Children's Hospital of Pittsburgh, Pittsburgh
Richardson, Ann	Women and Infants Hospital, Providence (cases 82 and 83)
Young, S. R.	University of South Carolina School of Medicine, Columbia (case 84)
Phelan, Mary	Greenwood Genetic Center, Greenwood, SC
Johnson, Virginia	University of South Dakota School of Medicine, Vermillion
Myers, Terry	East Tennessee State University, Johnson City
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Strong, Louise	University of Texas System Cancer Center, Houston
Khudr, Gabriel	Southwest Genetics, PA, San Antonio (case 85)
Dobin, Sheila	Scott and White Clinic, Temple, TX
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Vamos, Esther	Université Libre de Bruxelles, Brussels
Gillerot, Yves	Institut de Morphologie Pathologique, Loverval, Belgium (cases 1 and 2)
Santos, Rita	Instituto Betautau, Brazil
Salzano, Francisco	Instituto de Biociencias, UFRGS, Porto Alegre, Brazil
Pinto, Walter	Universitas of Campinas, Sao Paulo
Farah, Leila	Servicia Genetica Materuidade, Sao Paulo (case 3)
Cox, David	Alberta Children's Hospital, Calgary
Lin, C. C.	University Hospitals, Edmonton
Klousek, D. K.	British Columbia Children's Hospital, Vancouver (cases 4 and 5)
McGillivray, B.	Grace Hospital, UBC, Vancouver
Pantzar, Tapio	Vancouver General Hospital, Vancouver
Vekemens, M.	Montreal Children's Hospital, Montreal (case 6)
Duncan, Alessandra	Kingston General Hospital, Kingston, Canada (case 7)
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Subrt, Ivan	Institute for the Care of Mother and Child, Prague
Steensmidt-Jensen	Cromosome Lab Rigshospitlalet, Copenhagen (cases 8–14)
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Williams, Jeffrey	St. James Hospital, Leeds (case 16)
Berry, Caroline	Southeast Thames Regional Genetics Centre, London (cases 17–21)
Fennell, S. J.	Royal Manchester Children's Hospital, Manchester, England
Andrew, Tony	St. Mary's Hospital, Manchester, England
	Kennedy Galton Centre, Middlesex, England (case 22)
Roberts, D. F.	University of Newcastle-upon-Tyne, New Castle-upon-Tyne, England
Freemantle, Mike	South Trent Regional Cytogenetics Unit, Nottingham (case 23)
Jonasson, Jon	Churchill Hospital, Oxford (cases 24–26)
Barnes, Islay	Centre for Human Genetics, Sheffield (cases 27 and 28)
Jalbert, P.	Centre Hospitalier Universitaire, Cedex, France
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Stanyon, Roscoe	Instituto di Antropoligia, Florence
Lamberti, Laura	Università di Torino, Turin
Nikawa, Norio	Nagasaki University School of Medicine, Nagasaki
Utsumi, Kazuhiko	Aichi Cancer Center Research Institute, Nagoya, Japan
Suzumori, Kaoru	Nagoya City University Medical School, Nagoya, Japan
Abe, Kyohko	Hokkaido University School of Medicine, Sapporo, Japan
Arima, Masataka	National Center Hospital, Tokyo
Nakagome, Yasuo	National Children's Medical Research Center, Tokyo
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Boman, Helge	University of Bergen, Haukeland Hospital, Bergen
Brogger, Anton	IFK/Radiumhospitalet, Oslo
Hansteen, I. L.	Telemark Central Hospital, Porsgrunn, Norway
Bocian, Ewa	National Research Institute of Mother and Child, Warsaw
Krzykwa, B.	Medical Academy Krakow, Krakow
Boon, Wong	National University of Singapore, Singapore
Smart, Ronald	Medical School, Cape Town
Bernstein, Renee	South African Institute for Medical Research, Johannesburg
Venter, P. A.	Department of National Health and Population Development, Pretoria
Pieto, Felix	Hospital "La Fe", Valencia
Kristoffersson, U.	University Hospital, Lund (cases 33 and 34)
Nordenson, Ingrid	University Hospital, Umeå, Sweden
Buhler, Erica	University Children's Hospital, Basel (case 35)
Pescia, Graziano	Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
Hammond, Frank	Universidad de Genetica Medicina, Lora, Venezuela
Gregory, Peter	Institute of Medical Genetics for Wales, Cardiff (case 92)

References

Aarskog, D (1971) Intersex conditions masquerading as simple hypospadias. Birth Defects 7:122–130

Ayuso MC, Ramos MC, Bello MC, Jiminez A, Sanchez Cascos A, Herrera JL (1984) Cytogenic and clinical findings in ten 45,X/46,XY patients. Clin Genet 25:336–340

Benn P, Hsu LYF, Perlis T, Schonhaut A (1984) Prenatal diagnosis of chromosome mosaicism. Prenat Diagn 4:1–9

Boczkowski K, Teter J, Tomaszewska H, Philip J (1967) Gonadoblastoma (gonocytoma III) in a boy with XO/XY mosaicism: case report with a survey of literature. Acta Pathol Microbiol Scand 71:46–58

Borghi A, Montali, Bigozzi U, Giusti G (1965) XO/XY mosaicism in a phenotypic female with gonadoblastoma: attempt of classification of the clinical picture of the XO/XY mosaics. Helv Paediatr Acta 20:185–192

Bui TH, Iselius L, Lindstein J (1984) European collaborative study on prenatal diagnosis: mosaicism, pseudomosaicism and single abnormal cells in amniotic fluid cell cultures. Prenat Diagn 4:145–162

Edwards JH, Dent T, Kahn J (1966) Monozygotic twins of different sex. J Med Genet 3:117–123

Ferguson-Smith MA (1965) Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. J Med Genet 2:142–155

Ferrier PE, Ferrier SA, Kelley VC (1970) Sex chromosome mosaicism in male pseudohermaphrodism. Am J Dis Child 120:566–577

Gantt PA, Byrd JR, Greenblatt RB, McDonough PG (1980) A clinical and cytogenetic study of fifteen patients with 45,X/46,XY gonadal dysgenesis. Fertil Steril 34:216–221

Hamerton JL, Canning N, Ray M, Smith S (1975) A cytogenic survey of 14,069 newborn infants. Clin Genet 8: 223–243

Hecht F, Hecht BK (1982) 45,X/46,XY chromosome mosaicism detected by midtrimester amniocentesis in amniocyte clones. Prenat Diagn 2:233–235

Hirschhorn K, Decker WH, Cooper HL (1960*a*) Human intersex with chromosome mosaicism of type XY/XO. N Engl J Med 263:1044–1048

——— (1960*b*) True hermaphroditism with XY/XO mosaicism. Lancet 2:319–320

Hsu LYF (1989) Prenatal diagnosis of 45,X/46,XY mosaicism—a review and update. Prenat Diagn 9:31–48

Hsu LYF, Kim HY, Hausdnecht R, Hirschhorn K (1976) Prenatal diagnosis of 45,X/46,XY mosaicism with postnatal confirmation in a phenotypically normal male infant. Clin Genet 10:232–238

Hsu LYF, Perlis TE (1984) United States survey on chromosome mosaicism and pseudomasaicism in prenatal diagnosis. Prenat Diagn 4:97–103

Jackson WPU, Hoffman M, Makda H (1966) A 45XO/46XY mosaic intersex syndrome. J Med Genet 3:23–32

Karp L, Bryant JI, Tagatz G, Giblett E, Fialkow PJ (1975) The occurrence of gonadal dysgenesis in association with monozygotic twinning. J Med Genet 12:70–78

Kirkilionis AJ, Rodney P, Sergovich FR, Armstrong R (1987) Prenatal diagnosis of 45,X/46,XY mosaicism in a fetus with asymmetric gonadal dysgenesis. Prenat Daign 7:521–524

Knudtzon J, Aarskog D (1987) 45,X/46,XY mosaicism: a clinical review and report of ten cases. Eur J Pediatr 146: 266–271

Kofman S, Perez-Palacios G, Medina M, Escobar N, Garcia M, Ruz L, Mutchinick O, et al (1981) Clinical and endocrine spectrum in patient with the 45,X/46,XY karyotype. Hum Genet 58:373–376

Lieber E, Wachtel SS, Aftalion B, Zaslav A (1986) Diagnostic applications of H-Y serology: H-Y negative phenotype in cells from 45,X/46,XY fetus with testes. Clin Genet 30: 366–373

Lippe B (1982) Turner's syndrome. In: Kaplan SA (ed) Clinical pediatric and adolescent endocrinology. WB Saunders, Philadelphia, pp 272–292

Manuel M, Katayama KP, Jones HW (1976) The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol 124:293–300

Muller J, Skakkebaek NE, Ritzen M, Ploen L, Petersen KE (1985) Carcinoma in situ of the testis in children with 45,X/46,XY gonadal dysgenesis. J Pediatr 106:431–436

Muller U, Mayerova A, Fraccaro M, Zuffardi O, Mikelsen M, Prader A (1983) Presence of H-Y antigen in female patients with sex-chromosome mosaics and absence of testicular tissue. Am J Med Genet 15:315–321

Reindollar RH, Byrd JR, Hahn DH, Hasseltine FP, McDonough PG (1987) A cytogenetic and endocrinologic study of a set of monozygotic isokaryotic 45,X/46,XY twins dicordant for phenotypic sex: mosaicism versus chimerism. Fertil Steril 47:626–633

Rosenberg C, Frota-Pessoa O, Vianna-Morgante AM, Chu TH (1987) Phenotypic spectrum of 45,X/46,XY individuals. Am J Med Genet 27:553–559

Russel A, Moschos A, Butler LJ, Abraham JM (1966) Gonadal dysgenesis and its unilateral variant with testis in monozygous twins: related to discordance in sex chromosomal status. J Clin Endocrinol 26:1282–1292

Schmidt R, Sobel EH, Nitowsky HM, Dar H, Allen FH (1976) Monozygotic twins discordant for sex. J Med Genet 13: 64–79

Scully RE (1970) Gonadoblastoma: a review of 74 cases. Cancer 25:1340–1356

Simpson JL (1976) 45,X/46,XY. In: Disorders of sexual differentiation: etiology and clinical delineation. Academic Press, New York, pp 184–189

Simpson JL, Photopulos G (1976) The relationship of neoplasia to disorders of abnormal sexual differentiation. Birth Defects 12:15–50

Sutherland GR, Bowser-Riley SM, Bain AD (1975) Chromosomal mosaicism in amniotic fluid cell cultures. Clin Genet 7:400–404

Teter J, Boczkowski K (1967) Occurrence of tumors in dysgenetic gonads. Cancer 20:1301–1310

Watson MS, Breg WR, Hobbins JC, Mahoney MJ (1984)

Cytogenetic diagnosis using midtrimester fetal blood samples: application to suspected mosaicism and other diagnostic problems. Am J Med Genet 19:805–813

Wheeler M, Peakman D, Robinson A, Henry G (1986) 45,X/46,XY mosaicism: contrast of prenatal and postnatal diagnosis. Am J Hum Genet 39:A268

Willemse CH, Van Brink JM, Los PL (1962) XY/XO mosaicism. Lancet 1:488–489

Worton RG, Stern R (1984) A Canadian collaborative study of mosaicism in amniotic fluid cell cultures. Prenat Diagn 4:131–144

Zabel B, Baumann W, Gehler J, Hoffmann G (1981) Different chromosomal aberrations in prenatal cytogenetic diagnosis. Clin Genet 20:401–402

Zah W, Kalderon AE, Tucci JR (1975) Mixed gonadal dysgenesis: a case report and review of the world literature. Acta Endocrinol (Suppl) 79:1–39