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Association of Pigmentary Anomalies with Chromosomal and Genetic Mosaicism and Chimerism

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Summary

We have evaluated eight patients with pigmentary anomalies reminiscent of incontinentia pigmenti or hypomelanosis of Ito. All demonstrated abnormal lymphocyte karyotypes with chromosomal mosaicism in lymphocytes and/or skin fibroblasts. In seven the skin was darkly pigmented, and in all of these seven cases the abnormal pigmentation followed Blaschko lines. The literature contains at least 36 similar examples of an association between pigmentary anomalies and chromosomal mosaicism, as well as five examples of an association with chimerism. The pigmentary anomalies are pleomorphic, and the chromosomal anomalies involve autosomes and sex chromosomes. The pigmentation patterns are reminiscent of the archetypal paradigm seen in allophenic mice and demonstrate the clonal origin of melanoblasts from neural crest precursors. Patients with anomalous skin pigmentation, particularly when it follows a pattern of Blaschko lines, should be appropriately evaluated for a possible association with chromosomal or genetic mosaicism or chimerism.

Introduction

Pigmentary anomalies of the skin, particularly those which are extensive or associated with significant multisystem involvement, often present interesting diagnostic dilemmas.

While patients with Bloch-Sulzberger incontinentia pigmenti form a relatively well-defined group (Bloch 1926), other patients are often loosely categorized as suffering from either hypomelanosis of Ito (Ito 1951) or one of the "neurocutaneous syndromes."

The observation of chromosomal mosaicism in a 7-year-old black girl with skin pigmentation reminiscent of incontinentia pigmenti led us to investigate seven other patients with abnormal skin pigmentation (table 1). Most of them had, in addition, various patterns of multiple congenital anomalies and mental retardation, and they all demonstrated chromosomal mosaicism in lymphocytes and/or in skin fibroblasts (Thomas and Frias 1986; Thomas et al. 1987*a*, 1987*b*; Cantu et al., in press). A literature review identified 41 other examples of an association between pigmentary anomalies and either chromosomal mosaicism or chimerism (Ferrier et al. 1964; Zuelzer et al. 1964; Teplitz et al. 1967; Varela and Sternberg 1969; Atnip and Summitt 1971; Fulton et al. 1977; Pallister et al. 1977; Abe et al. 1978; Corey et al. 1978; Bernstein et al. 1979; Fitzgerald et al. 1979; Johnson et al. 1979; Findlay and Moores 1980; Schmidt et al. 1981; Chemke et al. 1983; Hersh et al. 1983; Neri et al. 1983; Tharapel et al. 1983; Wilson et al. 1983; DeLozier and Guenin 1984; Fujimoto et al. 1985; Hall 1985; Hunter et al. 1985; Carey et al. 1986; Donnai et al. 1986; Rott et al. 1986; Turleau et al. 1986; Wertelecki et al. 1986; Reynolds et al. 1987; Warburton et al. 1987). Flannery et al. (1985) were the first to report an association between hypomelanosis of Ito and chromosomal mosaicism.

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Table 1

Cytogenetic Characteristics of Patients in Present Series

Case and Tissue Source	No. of Cells Examined	Karyotype	%
1:			
Lymphocytes	106	46,XX, − 14, + rob(14;14)	64
		45,XX, − 14,21ph +	23
		46,XX,r(14),21ph +	12
		46,XX,21ph +	1
Lymphocytes	101	46,XX, − 14, + rob(14;14)	75
		46,XX,r(14),21ph +	19
		45,XX, − 14,21ph +	4
		46,XX,21ph +	2
Skin:			
Unspecified color	20	46,XX,r(14)	90
		45,XX, − 14	10
Dark	103	46,XX,r(14),21ph +	79
		46,XX, − 14, + rob(14;14),21ph +	18
		45,XX, − 14,21ph +	1
		46,XX,21ph +	2
Light	104	46,XX,r(14),21ph +	83
		46,XX, − 14, + rob(14;14),21ph +	7
		45,XX, − 14,21ph +	7
		46,XX,21ph +	3
2:			
Lymphocytes	20	45,X,inv(9)(p13q12)	100
		45,X	?
		45,X, + acentric fragment	?
Skin (unspecified color)	22	45,X,inv(9)(p13q21)	77
		46,X,del(X)(q21),inv(9)	23
3:			
Lymphocytes	110	48,XYY, + 8	80
		47,XYY	20
Skin (unspecified color)	50	48,XYY, + 8	100
4:			
Lymphocytes	100	46,XX,4p +	56
		46,XX	44
Skin:			
Unspecified color	60	46,XX	83
		46,XX,4p +	17
Dark	100	46,XX	84
		46,XX,4p +	16
Light	100	46,XX	92
		46,XX,4p +	8
5:			
Lymphocytes	50	46,XX,18p −	73
		46,XX	27
Skin (light-dark interface)	50	46,XX,18p −	100
6:			
Lymphocytes	50	45,X	94
		46,X,r(Y)	6
Skin (unspecified color)	50	45,X	56
		46,X,r(Y)	44
7:			
Lymphocytes	50	45X	100
Skin (light)		45,X	66
		46,XY	34
8:			
Lymphocytes	?	45,X	?
		46,XY	?
Skin (unspecified color)	50	46,XY	72
		45,X	28

Material and Methods

Case 1, TF, was a 7-year-old black female with generalized linear skin pigmentation resembling incontinentia pigmenti, microcephaly, and severe mental retardation (fig. 1*A*).

She was the firstborn child of a 22-year-old American black female and a 25-year-old black male. The pregnancy was normal, and her delivery was uneventful. Birth weight was 2,320 g, and length was 47 cm. At birth she was noted to have extensive, unusual skin pigmentation, including linear streaks and whorls. She was also noted to have right-sided choanal stenosis, left congenital hip dislocation, and a left talipes equinovarus deformity.

Developmental delay was evident by the age of 1 year. She was unable to sit unaided until age 2 years and at 4 years was functioning at an 8-mo level. At the age

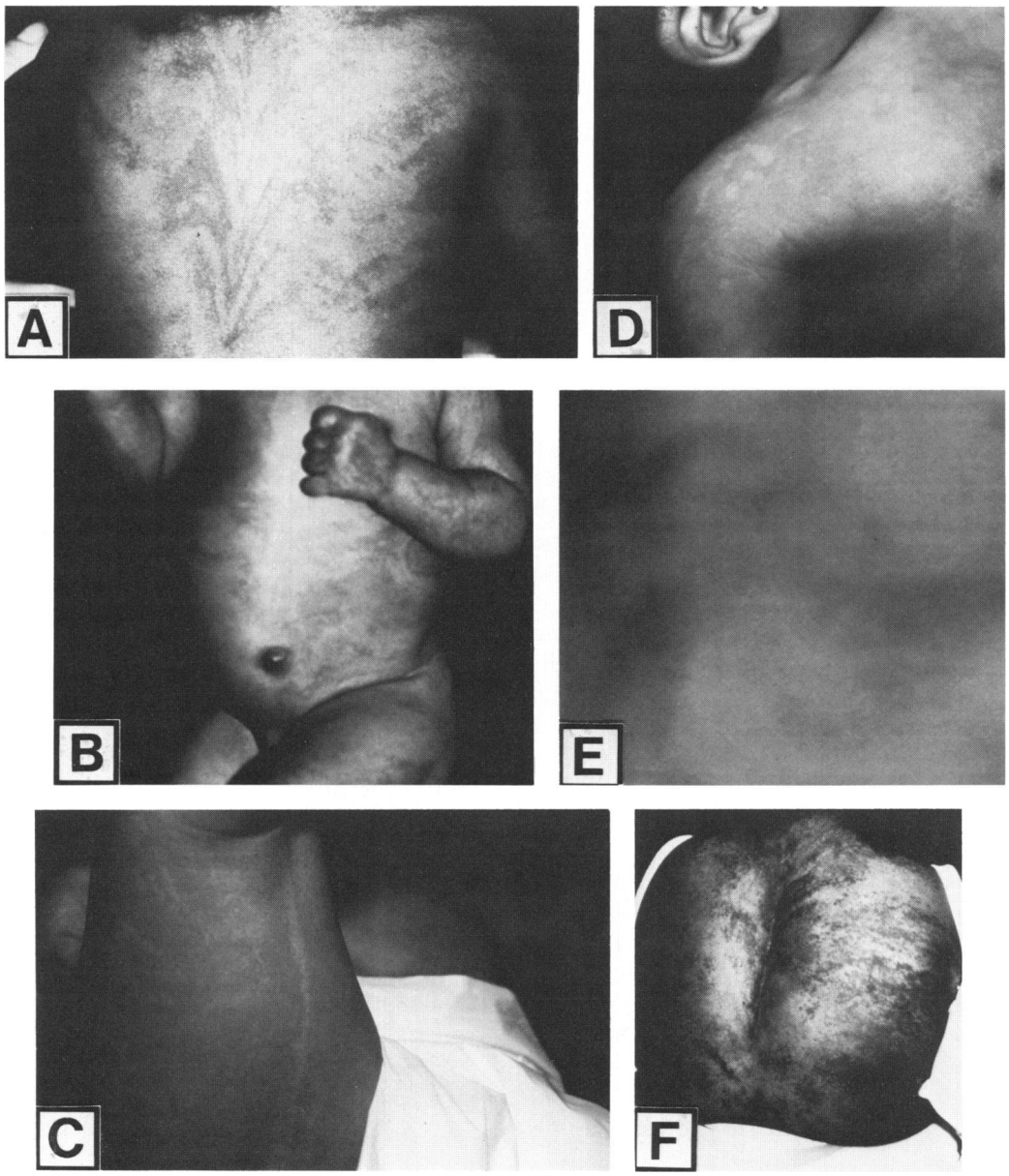

Figure 1 Demonstration of the pigmentary anomalies associated with chromosomal mosaicism. *A, B,* and *F:* Generalized pigmentation following Blaschko lines—cases 1, 2, and 7, respectively. *C:* Linear hypopigmented streaks on the posterior aspect of right thigh—case 3. *D:* Hypopigmented streaks and spots on left shoulder—case 4. *E:* Hypopigmented areas over abdomen—case 5.

of 4 years she developed seizures which required long-term phenobarbital therapy.

At the age of 7 years she could walk unaided, had no intelligible speech, and had signs of a spastic diplegia.

Her karyotype showed four cell lines: a normal 46,XX female line and three abnormal lines containing, respectively, monosomy 14, a pseudoisodicentic 14q, and a ring 14. All four lines were represented in lymphocytes and in skin fibroblasts.

Case 2, KiH, was a 2-year-old black female with linear pigmentation of trunk and limbs that was reminiscent of incontinentia pigmenti and with short stature, microcephaly, and psychomotor delay (fig. 1*B*). She was, unfortunately, lost to follow-up after her first clinic visit.

Her lymphocyte karyotype, performed at an outside laboratory, demonstrated a 45,X constitution with an acentric fragment, while our laboratory found it to be 45,X. Skin fibroblasts showed 45,X/46,X,del(X) mosaicism.

Case 3, KH, was an 11-mo-old black male who presented with developmental delay, multiple congenital anomalies, and linear hypopigmentation (fig. 1*C*).

He was born following a full-term pregnancy, the fourth offspring of a 34-year-old American black female and the first that she had by this 36-year-old black male. At birth he weighed 2,636 g, measured 50 cm in length, and was noted to have a left talipes. His subsequent development was delayed. He smiled at 4 mo, rolled over at 8 mo, and by 11 mo was unable to sit unaided but had begun to babble.

At 11 mo his height, weight, and head circumference were within the normal range. His inner canthal distance was 3 cm (above the 97th percentile), and he had a depressed nasal bridge, epicanthal folds, a prominent metopic ridge, and unusual ears with absence of the upper part of the helix. His palms and soles showed deep linear creases, with syndactyly of toes 4 and 5 on the right and of toes 2 and 3 on the left. His left foot was in a cast for a talipes equinovarus. Both lower limbs demonstrated increased tone, with brisk reflexes. He had linear hypopigmented streaks on the posterior surfaces of all four limbs. Roentgenographic assessment demonstrated butterfly vertebra in his thoracic spine, and a cranial CT scan was normal. Renal ultrasound showed right-sided renal agenesis.

His lymphocytes demonstrated 47,XYY/48,XYY,+8 mosaicism, while skin fibroblasts showed only the 48,XYY,+8 line.

Case 4, CM, was an 8-year-old black female who presented with mental retardation and multiple congenital anomalies (fig. 1*D*).

She was born 2 mo prematurely of the first pregnancy of a 25-year-old black female and a 28-yr-old black male. Birth weight was 2,400 g. She began to walk at the age of 2 years and by that time had developed a single-word vocabulary. At 3 or 4 years her mother felt that she was "slow" and that the responded rather poorly to social stimulation. At some time during the first few years of life it was noted that she had a pigmentary anomaly consisting of linear hypopigmented streaks and punctate hypopigmented lesions, most noticeable on her lower extremities and including the soles of her feet.

At her first visit to the genetic clinic, at the age of 8 years, her height was 115 cm, weight was 19 kg (both below the fifth percentile), and head circumference was 52 cm (50th percentile). In addition to the linear pigmentation of her lower limbs, she was noted to have marked limitation of extension and flexion at the knees and elbows, as well as decreased supination and pronation at the left elbow.

She had marked bilateral tightness of the heel cords, with hypertonia, hyperreflexia, and obvious mental retardation.

Lymphocytes and skin fibroblasts demonstrated 46,XX/46,XX,4p+ mosaicism.

Case 5, HO, was a white female who presented at the age of 4½ years for evaluation of weakness (fig. 1*E*).

She was delivered at term and had an appropriate birth weight. She fed poorly for the first few months and was developmentally delayed, sitting alone by 22 mo of age, crawling at 26 mo, and walking alone by 28 mo. She was "floppy" as an infant and continued to be weaker than all of her normal siblings and displayed poor fine-motor coordination. She developed single-word speech by the age of 3½ years. Over the left side of her abdomen and lower thorax, she was noted to have whorled pigmentation which did not cross the midline; in addition, she had a few hypopigmented areas on her abdomen. She had generalized hypotonia and hyporeflexia, with poor fine- and gross-motor coordination. Her height was 94 cm (third percentile), weight was 24 kg (third–10th percentile), and head circumference was 60 cm (50th percentile). Her teeth were carious, and microscopic examination after extraction showed flattening of the dentino-enamel junction. She was thought to have hypomelanosis of Ito.

Her lymphocytes demonstrated 46,XX/46,XX,18p- mosaicism, while skin fibroblasts showed only the 46,XX,18p- line. The karyotype of her mother was normal.

Case 6, KSP, was an 8-year-old black female who presented for evaluation of hypertension which had been discovered on routine physical examination.

She was hyperactive with some developmental delay.

Her face was dysmorphic, with hypertelorism and a broad nasal bridge. She was noted to have whorled hypopigmentation of her trunk and extremities and was thought to have hypomelanosis of Ito. Her height was 116 cm (below the fifth percentile), and weight was 24.5 kg (50th percentile). Further evaluation revealed a horseshoe kidney which was thought to be the cause of her hypertension. Soon after her initial evaluation she was, unfortunately, lost to follow up.

Lymphocytes and skin fibroblasts demonstrated 45,X/46,r(Y) mosaicism.

Case 7, LW, was an 18-year-old black female with mental retardation, short stature, obesity, a seizure disorder, and generalized linear and whorled pigmentation involving her trunk and extremities (fig. 1*F*).

She was born of a normal pregnancy and was found at birth to have a lumbo-sacral meningomyelocele which was repaired. When first seen at the genetic clinic, at the age of 18 years, she was enrolled in special education classes at the 12th-grade level and was able to read and write. She was treated with phenobarbital with good seizure control, but, unfortunately, soon after her initial assessment she died, following a seizure at home.

Lymphocytes demonstrated a 45,X karyotype, while skin fibroblasts showed 45,X/46,XY mosaicism.

Case 8, BJW, was a 6-year-old black male who had been previously assessed because of first-degree hypospadias and linear hypopigmented lesions on the posterior aspects of his lower limbs. He was of normal intelligence and stature, and by 6 years the hypopigmentation visible in infancy had disappeared.

Lymphocytes and skin fibroblasts demonstrated 45,X/46,XY mosaicism.

Cases 1–4, 7, and 8 were seen at the Genetic Clinics of the University of Florida College of Medicine, case 5 was seen at the Clinical Genetic Clinic of the Dartmouth Hitchcock Medical Center, and case 6 was seen at the Genetic Clinic of the Medical College of Georgia. Case 6 has been reported in abstract form (Flannery et al. 1985), and all eight cases have been previously reported in a letter to *The Lancet* and in two abstracts (Thomas and Frias 1986; Thomas et al. 1987*a*, 1987*b*).

Discussion

Some of the common clinical features seen in our eight patients are as follows: Seven of them had darkly pigmented skin, and all seven were mentally retarded. Five were of short stature, and five had other congenital anomalies—unilateral renal agenesis with vertebral anomalies; choanal stenosis, congenital hip dysplasia and talipes; hypertelorism and horseshoe kidney; spina bifida; and hypospadias. In five of the patients the pigmentary anomalies were extensive and commonly followed Blaschko lines (fig. 2). In one patient there were merely a few hypopigmented streaks on the limbs, in another patient there were hypopigmented patches on the abdomen, and in a third patient linear hypopigmentation seen on the posterior aspects of the limbs in early infancy had disappeared by age 6 years.

None of our patients had a normal peripheral blood karyotype. Seven of the eight cases demonstrated mosaicism in peripheral blood and skin fibroblasts. The exception, case 7, was a phenotypic male with a 45,X chromosome complement in lymphocytes and with 45,X/46,XY mosaicism in skin fibroblasts. In some cases, we biopsied skin from a dark area on one side of the midline and from a light area on the other side of the midline. We did this because the literature contains two case reports of unilateral mosaicism in skin fibroblasts (Chemke et al. 1983; Fujimoto et al. 1985) and also to attempt to correlate differences in pigmentation with karyotypic differences. We found neither any examples of unilateral mosaicism in our series nor significant differences in the degree or type of mosaicism from skin areas with different pigmentation.

We initially conducted a computer-based literature search for cases with pigmentary anomalies and chro-

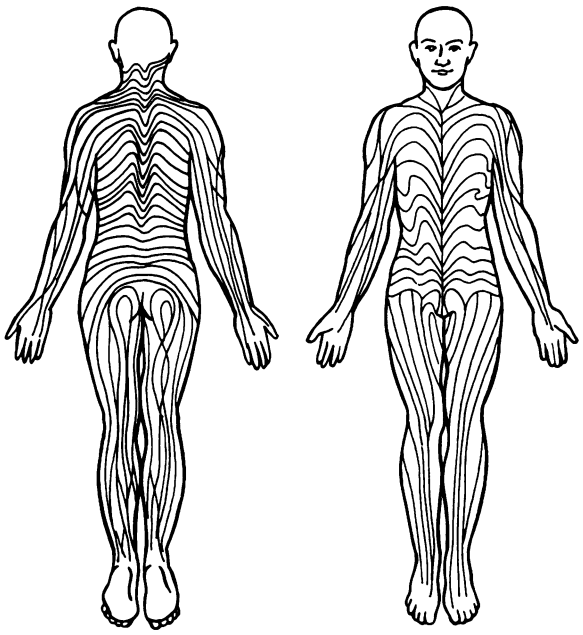

Figure 2 Blaschko lines, modified to represent a simplified pattern and to illustrate the lack of information concerning the pattern over the head and face.

Table 2

Clinical and Cytogenetic Characteristics of Chromosomal Mosaics from the Literature

Reference	Clinical Features and Ethnic Origin	Cytogenetics		
		Tissue	Karyotype	%
Abe 1978	Linear pigmentation on arms and chest, two irregular vitiligos on chest, mental retardation, seizure disorder, Japanese	Lymphocytes	46,XX,r(13)	?
			46,XX,t(13;14)(p12;q24)	?
Atnip and Summitt 1971	Diffusely scattered minute areas of hypopigmentation, mental retardation, growth retardation, American black	Lymphocytes	Diploid	?
			Triploid	?
		Skin	47,XY + 18	?
			Diploid	?
			Triploid	?
Bernstein et al. 1979	Mental retardation, small stature, pigmentary anomaly like incontinentia pigmenti, Tswana-Caucasian	Lymphocytes	45,X, − 15, + t(X;15)	87
			45,X	13
Carey et al. 1986	Mental retardation, seizures, hypopigmented macules, hyperpigmented streaks on legs	Lymphocytes	46,XX	100
		Skin	47,XX,i(12p)	80
			46,XX	20
Carey et al. 1986	Mental retardation, congenital heart disease, hip dislocation, hypopigmented macules, hyperpigmented streaks on legs	Lymphocytes	46,XX	100
		Skin	47,XX,i(12p)	100
Chemke et al. 1983	Hyperpigmented areas limited to right side, mental retardation, Arab	Lymphocytes	46,XY	50
			47,XY, + 18	50
		Skin–right arm	47,XY, + 18	100
		Left arm	46,XY	100
		Right thorax	46,XY	100
DeLozier-Blanchet and Guenin 1984	Numerous pigmented nevi, normal intelligence, dysmorphic facies, Swiss	Lymphocytes	46,XX,r(7)	98
			46,XX	2
		Nevi + normal skin	45,XX, − 7	86
			46,XX,r(7)	14
Donnai et al. 1988	Hypomelanosis of Ito, mental retardation, facial and body asymmetry, unusual hands and feet, English	Lymphocytes	46,XX	100
		Skin	69,XXX	84
			46,XX	16
	Hypomelanosis of Ito, unusually pigmented retinas, body asymmetry, unusual feet, English	Lymphocytes	46,XX	100
		Skin	46,XX	59
			69,XXX	41
Ferrier et al. 1964	Body asymmetry (R<L), mental retardation, down-slanted fissures, syndactyly, large serrated, pigmented spots, on right trunk and right thigh, small penis, cryptocorchidism	Lymphocytes	46,XY	100
		Skin–right-side fascia lata	46,XY	79
			69,XXY	21
		Right forearm	46,XY	93.8
			69,XXY	6.2
		Left forearm	46,XY	91
			69,XXY	9
		Left forearm	46,XY	92.5
			69,XXY	6.5

Fujimoto et al. 1985	Reticular pigmentation sometimes in linear whorls, mental retardation, growth retardation, facial and body asymmetry (R<L), thought to have incontinentia pigmenti, Mexican	Lymphocytes	46,XX	80
			46,XX, − 15, + t(14;15)(q11;p11)	20
		Skin–right arm	46,XX	98
			46,XX, − 15, + t(14;15)(q11;p11)	2
		Skin–left arm	46,XX	100
Fulton et al. 1977	Mental retardation, seizures, asymmetry (L<R), syndactyly, kyphoscoliosis, pigmentation on legs consistent with incontinentia pigmenti, Caucasian	Lymphocytes	46,XX	100
		Skin–5 years	46,XX	50
			69,XXX	50
		Skin–11 years	46,XX	80
			69,XXX	20
Hall 1985	Teschler-Nichola/Killian syndrome, hypopigmented lesion on forehead and anterior scalp, mental retardation	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	100
Hersh et al. 1983	Teschler-Nichola/Killian syndrome, mild hyperpigmented and hypopigmented areas, mental retardation, Caucasian	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	86
			46,XY	14
Hunter et al. 1985	Teschler-Nichola/Killian syndrome, mottled hyperpigmentation over right knee, mental retardation	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	100
Johnson et al. 1979	Mental retardation, failure to thrive, dysmorphic facies, tetralogy of Fallot, body asymmetry (L>R), hypo- and hyperpigmentation, American Indian	Lymphocytes	46,XX	59
			47,XX, + 14	41
Neri et al. 1983	Achromic spots, unusual facies, apparently normal intelligence, Italian	Lymphocytes	46,XX,r(15)	98
			46,XY	2
Pallister et al. 1977	Teschler-Nichola/Killian syndrome, both patients have a widespread dysplasia best seen under UV light	Lymphocytes	46,XX	100
		Skin	46,XX	70
			47,XX, + i(12p)	30
	Teschler-Nichola/Killian syndrome, coarse facial features, cataracts, mental retardation	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	50
			46,XY	50
Reynolds et al. 1987	Previously reported by Pallister (1977), mental retardation, coarse face, joint contractures, pigmentary dysplasia visible under UV light, marbling like incontinentia pigmenti	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	50
			46,XY	50
	Mental retardation, prognathism, chest asymmetry (L<R), areas of hypopigmentation over body, previous diagnosis of hypomelanosis of Ito	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	75
			46,XY	25
	Mental retardation, coarse face, seizures, bilateral accessory nipples, large areas of alternating hypo- and hyperpigmentation on left upper arm and right flank	Lymphocytes	46,XX	100
		Skin-normal	47,XX, + i(12)p	80
			47,XX, + 12p	12
			46,XX	8
		Marbled	47,XX, + 12p	100
	Mental retardation, coarse face, seizures, faint areas of hyper- and hypopigmentation over trunk	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	100
	Mental retardation, coarse face, blindness, seizures, hyperpigmented streak back of left thigh and leg	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	80
			46,XY	20

(*continued*)

Table 2 (continued)

Reference	Clinical Features and Ethnic Origin	Cytogenetics		
		Tissue	Karyotype	%
	Mental retardation, hypotonia, macrostomia, hypopigmentation on forehead, including hair	Lymphocytes	46,XY	100
		Skin	47,XY, + i(12p)	90
			46,XY	10
	Mental retardation, hypertelorism, flat nasal bridge, hypopigmented areas on forehead and left eyelid, American black	Lymphocytes	46,XY	88
			47,XY, + i(12p)	12
		Skin	47,XY, + i(12p)	90
			46,XY	10
Rott et al. 1986	Linear patchy hypopigmented areas demonstrated under UV light, mental retardation	Lymphocytes	46,XX	100
		Normal skin	46,XX	100
		Hypopigmented skin	46,X,r(X)	41
			45,X	33
			46,XX	26
Schmidt et al. 1981	Mental retardation, hypertelorism, seizures, café au lait patches, multiple depigmented spots (abdomen, thighs, right leg, left buttock), thought to have tuberous sclerosis, Puerto Rican	Lymphocytes	46,XX,r(14)	?
		Skin	46,XX,r(14)	?
			45,XX, − 14	?
Teplitz et al. 1967	Mental retardation, microcephaly, hypospadias, recurrent pneumonia, café au lait patches, Caucasian	Lymphocytes	46,XX,r(13)	83
			45,XY, − 13	11
			46,XY	6
Tharapel et al. 1983	Up-slanted and palpebral fissures, micrognathia, camptodactyly, rocker-bottom feet, large café au lait spot right leg, asymmetry, seizure disorder, Caucasian	Lymphocytes	46,XX	100
		Skin	69,XXX	60
			46,XX	40
Turleau et al. 1986	Sacrococcygeal tumor, body asymmetry, seizures, acromicria, agenesis of corpus callosum, linear acrhomic patches on trunk and four limbs, hypomelanosis of Ito, Algerian-Moroccan	Lymphocytes	46,XX	50
			46,XX,del(15)(q11)	50
Varela and Sternberg 1969	Mental retardation, microcephaly, short stature, café au lait spots over back and ankles, American black	Lymphocytes	46,XX,r(14)	82
			45,XX, − 14,r(14)	18
		Skin	46,XX,r(14)	84
			45,XX, − 14,r(14)	18
Warburton et al. 1987	Delayed development, scoliosis, hypertelorism, diffuse lesions over back, thighs, upper arms	Lymphocytes	46,XX	88
		Skin	47,XX, + i(12p)	12
			47,XX, + i(12p)	86
			46,XX	14
Wertelecki et al. 1986	Streaks of brown pigmentation on flexor surface of left limbs, mental retardation	Lymphocytes	46,XX	100
		Skin–right arm	47,XX + 22	100
		Skin–left arm	47,XX, + 22	78
			46,XX	22

	Linear pigmentation on limbs, mental retardation, Mexican	Lymphocytes	46,XX	100
		Skin	47,XX,+22	100
	Small and pigmented nevi, short stature, webbed neck, low hairline, facial and body asymmetry (L<R)	Lymphocytes	46,XX	100
		Skin–right and left arms	46,XX	65
			47,XX,+22	35
Wilson et al. 1983	Streaky hyperpigmentation thought to represent incontinentia pigmenti, mental retardation, small stature, dysmorphic facies, microtia, postaxial polydactyly of hands, probable ventricular septal defect	Lymphocytes	47,XX,+18	98
			46,XX	2
		Skin–right arm	47,XX,+13	92
			47,XX,+18	8
		Skin–left arm	47,XX,+18	93
			47,XX,+13	4
			46,XX	3

mosomal abnormalities, but we found very few such cases. We subsequently mounted an extremely laborious manual search, including chromosomal abnormalities, Turner syndrome, pigmentary anomalies including incontinentia pigmenti and hypomelanosis of Ito, mosaicism, and chimerism. We found 36 examples in which pigmentary anomaly was associated with chromosomal mosaicism (table 2), five examples in which it was associated with dispermic chimerism (table 3), and at least 200 examples of mosaicism with no pigmentary anomaly.

The pigmentary anomalies were pleomorphic and consisted of achromic spots or vitiligos (tables 2, 3), pigmented nevi, unilateral pigmentation, bilateral lines and whorls, and block pigmentation. Fifteen of 41 cases were of racial or ethnic groups in which pigmented skin is common. In some cases, the pigmentary anomaly was not evident under usual lighting conditions but was clearly demonstrated under UV light.

The chromosomal abnormalities were characterized by the presence of mosaicism in peripheral blood lymphocyte and/or skin fibroblast cultures and were not restricted to diploid/triploid mixoploidy as has been suggested elsewhere (Donnai et al. 1986) (tables 2, 3). The anomalies included 34 examples involving only autosomes and two examples in which sex chromosomes were involved (Bernstein et al. 1979; Rott et al. 1986).

A normal peripheral blood karyotype was found in 22 of 36 cases of chromosomal mosaicism, including 14 cases of the Pallister mosaic syndrome, and in two of five chimeras (Findlay and Moores 1980). Further, patients with the same mosaic chromosomal abnormality sometimes showed a totally different pigmentation pattern (Wertelecki et al. 1986).

Pigmentation patterns analogous to those seen in our cases and to those reported in the literature have been described in experimentally derived mouse chimeras known as allophenic mice (Mintz 1970). When inbred strains of different colors are manipulated in this way, mice are produced that show a variety of coat patterns depending on the proportion and distribution of each parental type in the embryo. Those that are completely striped are said to carry the "archetypal" or "standard" pattern, consisting of transverse bands repeated down the length of the body and showing a demarcation at the midline. It is this archetypal paradigm alone that demonstrates the basic mechanism responsible for coat color patterning.

Each band represents a single clone descended from one melanoblast. In the mouse there are, on each side,

Table 3

Clinical and Cytogenetic Characteristics of Chimeras from the Literature

Reference	Clinical Features and Ethnic Origin	Cytogenetics		
		Tissue	Karyotype	%
Corey et al. 1978	Patchiness of skin color, block pigmentation on abdomen, upper left and lower right quadrants darker than alternate areas, phenotypic male, extreme hypospadias, bifid scrotum, right ovary/tube/uterus, left testis descended, dispermic chimera, normal intelligence	Lymphocytes	46,XX	60
			46,XY	40
		Dark skin	46,XX	60
			46,XY	60
		Light skin	46,XX	94
			46,XY	6
		Ovary and fallopian tube	46,XX	100
Findlay and Moores 1980	Pigmentation more marked on right, speckled/mottled/reticulate areas with streaks and blocks, followed Blaschko lines, normal fertile female, dispermic chimera, Indian	Lymphocytes	46,XX	100
	More heavily pigmented right side, spraylike pigmentation and dark café au lait patches, confluent areas meeting at midline, normal fertile female, dispermic chimera, Zulu	Lymphocytes	46,XX	100
		Dark and light skin	46,XX	100
Fitzgerald et al. 1979	Alternating blocks of light and dark pigmentation meeting at midline abdomen, phenotypic male, gynecomastia, hypospadias, right ovary/tube/uterus, left testis descended, dispermic chimera, normal intelligence	Lymphocytes	46,XX	70
			46,XY	30
		Dark and light skin	46,XX	100
		Laparotomy site	46,XX	64
			46,XY	34
Zuelzer et al. 1964	Pigmentation in irregular patches on face, symmetrical wedges and bands on trunk and abdomen, phenotypic male, gynecomastia, dispermic chimera, black-Amerindian-Caucasian	Lymphocytes	46,XX	89
			46,XY	7
			Tetraploidy	3
		Light skin	46,XY	100
		Dark skin	46,XY	92
			46,XX	8

three clones on the head, six on the body, and eight on the tail, so that the entire melanoblast precursor population of the coat appears to arise from 34 clonal initiator cells. Each melanoblast clone is associated with a number of hair-follicle clones, resulting in the final production of approximately 266 narrower transverse bands (Mintz 1967). The patterns on each side are independent of one another and are established at some stage before the closure of the neural tube—before day 8 in the mouse (Mintz 1967), which is equivalent to day 22 in the human (Moore 1973).

The archetypal paradigm is produced when, by chance, clonal initiator cells of different parental types become arranged in an alternating fashion along the neural crest and undergo equal proliferation and cell migration. Since the clonal arrangement of melanoblast precursors is random, the great variability in the coat color of allophenic mice may be due to different proportions of the two parental types in the melanoblast population, to permutations of their positions along the length of the neural crest, to their relative proliferative capacity, and to their relative migration potential (Mintz 1970).

This allophenic mouse model is thought to be applicable to the situation in other mammals (Mintz 1974). It offers a satisfactory explanation for the skin pigmentation patterns seen in patients such as ours, who have chromosomal mosaicism, in those with chimerism, and in female carriers of certain X-linked conditions, such as Menkes syndrome and chondrodysplasia punctata (Happle 1987).

In 1901 Blaschko published details of 83 cases of such linear nevi as nevus unius lateris and of 63 examples of such acquired linear skin diseases as psoriasis and scleroderma. In this publication he produced a composite drawing of the patterns that he saw (Blaschko 1901). These patterns consisted of transverse bands on the trunk, following a sigmoid curve over the abdomen, a V-shaped curve over the back, and showing a marked midline effect; the pattern on the left and right sides being independent of each other. On the limbs they followed a linear pattern. These lines are currently known as Blaschko lines (fig. 2). Jackson's review of this work was published in 1976 and reproduced some of the original drawings, including one showing "a system of lines on the human body which the linear nevi and dermatoses follow" (Jackson 1976). The author commented on other linear systems—the system of dermatomes, Voight lines, and Langer lines—and noted that they seemed to differ from the lines Blaschko described. Jackson stated that he did not know the cause of the distribution pattern, but he suggested that it might be due to chromosomal mosaicism.

Transverse bands following Blaschko lines have been reported in female heterozygotes for such X-linked conditions as incontinentia pigmenti, focal dermal hypoplasia, X-linked dominant chondrodysplasia punctata, X-linked ectodermal dysplasia, Menkes syndrome, CHILD syndrome, and the oral-facial-digital syndrome (Happle 1987). Happle's interpretation is that the pattern seen in these women represents mosaicism for the X-linked genes responsible for the respective conditions and that it demonstrates the effect of lyonization on the distribution of maternal and paternal X chromosomes. We suggest that he is correct in his assertion, but we note that this form of mosaicism for parental X chromosomes is not limited to heterozygous carriers of genetic mutations; it is present in all 46,XX females.

Although we agree with Happle's interpretations of many of the examples that he quotes in the literature (Happle 1985*a*, 1985*b*), we disagree on two points.

First, we suggest that the pattern seen in these mosaics need not always be the narrow linear streaks of Blaschko lines. Indeed, if Mintz's work on allophenic mice is applicable to humans, then the archetypal paradigm of narrow bands is one of the many patterns that human mosaics and chimeras may demonstrate (Mintz 1970). Since the pattern is caused by the random arrangement of melanoblast precursors along the length of the neural crest and by such parameters as their relative proliferative capacity and relative migration potential, heterozygous human females should be as variously patterned as the allophenic mice. Some should demonstrate no patterning at all, while others should demonstrate patches and blotches, all variations on the basic paradigm represented in humans by Blaschko lines.

If there is random distribution of cells in the morula, then there may develop an alternating arrangement in the melanocyte precursors along the length of the neural crest. The proliferation and migration of these cells will then produce the striped pattern of Blaschko lines. Nonrandom cell distribution and differences in proliferative and migration potential will produce patterns different from the archetypal paradigm.

Second, the pattern outlined by Blaschko lines is not restricted to a representation of lyonization (Lyon 1961). It demonstrates genetic mosaicism or chimerism that has arisen in the embryo before the development of neural folds—and, therefore, will be seen in conditions other than those which are X linked. This is exemplified by its presence in chimerism with XY cell lines and in chromosomal mosaicism in which the two populations of

cells have autosomal rather than X-chromosome differences.

Our cases and those we have culled from the literature firmly establish the relationship between chromosomal mosaicism and chimerism and anomalous pigmentation. We suggest that anomalous pigmentation, especially when it follows a pattern reminiscent of Blaschko lines, should be carefully evaluated to exclude chromosomal mosaicism or chimerism. The evaluation should include a lymphocyte karyotype and karyotypes from two skin biopsies representing different sides of the midline, one from dark skin and the other from light skin, and the count should be at least 100 cells in each preparation. This plan would help verify the presence or absence of a positive correlation between the skin fibroblast karyotype and the pigmentary abnormalities, a correlation that we did not discover in our cases. It would also produce valuable data on the distribution of mosaicism. Such careful evaluation will provide useful information regarding the frequency of this association and will contribute to a better understanding of anomalies of pigmentation.

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