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Review Articles

X-linked Dominant Inherited Diseases With Lethality in Hemizygous Males

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Summary. X-linked dominant inheritance with lethality in hemizygous males is a rare mode of inheritance. The three best-known disorders which seem to be inherited in this way, are incontinentia pigmenti (IP) Bloch-Sulzberger, oral-facial-digital I (OFD I) syndrome, and focal dermal hypoplasia (FDH syndrome, Goltz syndrome). It is the purpose of this article to give a review of the clinical and genetic aspects of the above-mentioned diseases and to add those disorders in which this mode of inheritance is discussed. These disorders are: X-linked chondrodysplasia punctata (CP), cervico-oculo-acusticus syndrome (Wildervanck syndrome, COA), congenital cataract with microcornea or slight microphthalmia, muscular dystrophy—hemizygous lethal, partial lipodystrophy with lipatrophic diabetes and hyperlipidemia, Aicardi syndrome, coxo-auricular syndrome, and Johanson-Blizzard syndrome. OTC defiency is included in the study, although there is no lethality in utero, only in the neonatal period.

A critical evaluation of the current literature is carried out.

Incontinentia pigmenti (Bloch-Sulzberger) (IP) McKusick's Catalogue No.: 30830

IP (Bloch-Sulzberger) is a relatively rare genodermatosis which is most commonly associated with multiple congenital defects. Eighty per cent of the patients with IP have additional clinical signs: 64.7% dental abnormalities (conical deformity and missing dentition), 37.8% alopecia, 32.5% ocular anomalies (strabismus in 18.2%, cataracts, pseudoglioma, retrolental fibroplasia), 30.5% notable CNS disease (spastic and paralytic disorders, convulsive disorders), 16.4% mental retardation, 7.1% nail dystrophy and 13.7% structural abnormalities like small stature, dwarfism, spina bifida, clubfoot, cleft palate, cleft lip, skull deformities, ear abnormalities, hemiatrophy and congenital dislocated hip—however none of these various structural defects appears to be closely related to the syndrome (Carney Jr 1976).

IP which occurs almost exclusively in females, was first described in 1925 by Bardach. In 1926, Bloch demonstrated a case which was published in greater detail by Sulzberger in 1927. The typical skin changes of the disease show three overlapping stages: In about 90% of these cases (Carney Jr 1976) an erythematous eruption with linear vesiculation, especially on the flexor aspects of the extremities and the lateral parts of the trunk, appears in the first 2 weeks of life. This, the so-called vesico-bullous stage, is followed by the verrucous stage a few months later (second stage) (Fig. 1). With the exception of a few remnants which may persist for several years, the verrucous growths drop off after a few months and leave a mild atrophy or depigmentation behind. The third stage, after which the disease is named, is characterized by irregular macules, streaks and splashes of brown to slate-grey pigmentation on the lateral parts of the trunk, upper arms and upper legs (Figs. 2 and 3). The pigmentary stage remains for a number of years, but usually it disappears sooner or later. Some authors postulate a fourth stage which is characterized by the fading of the preceding three stages, especially of pigmentation, around the age of 20.

Most often the only remaining cutaneous signs of IP in adulthood are atrophy of the skin or depigmentated lesions. It was Wiley (1974), who postulated that these depigmentated lesions are of great diagnostic value. Curth and Warburton (1965)

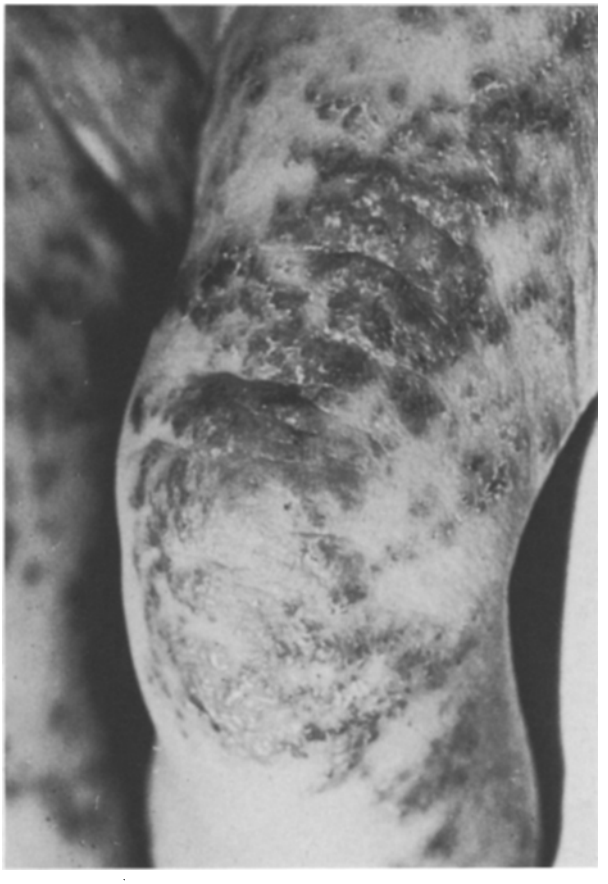

Fig. 1. Lower extremity of a child with IP: verrucous stage (some verrucous growths have already disappeared)

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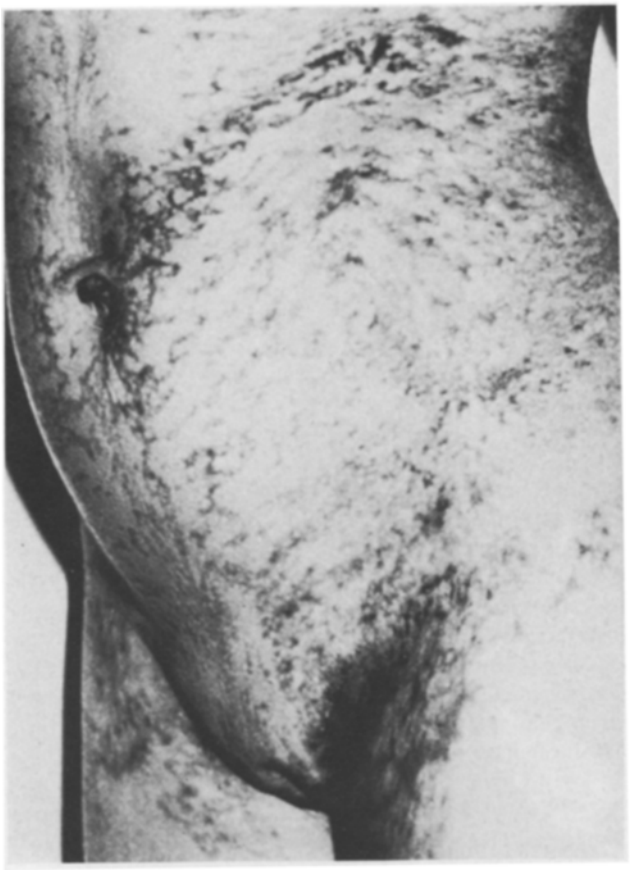


Fig. 2. Trunk of a female patient with IP showing the typical skin changes of the disorder: irregular macules, streaks and splashes of brown to slate-grey pigmentation (photo given by Dr. Tilgen, Dep. of Dermatology, University of Heidelberg)

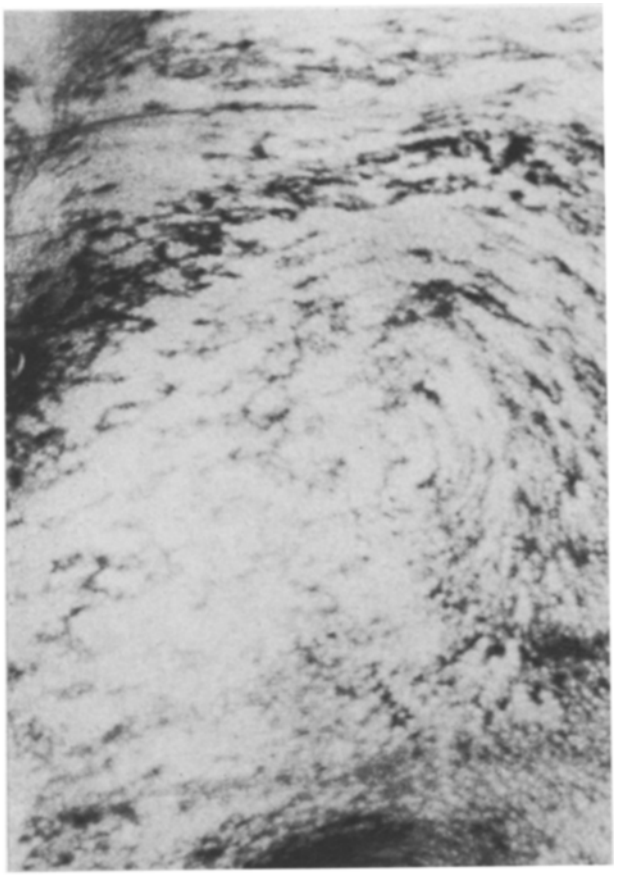


Fig. 3. Typical whorled and blotchy pattern of skin lesions in IP (photo given by Dr. Tilgen)

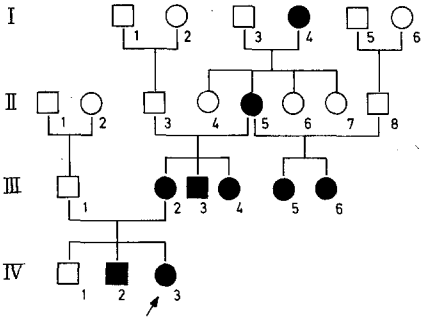


Fig. 4. Pedigree of Wiklund et al. (1980)

stressed the importance of non-cutaneous manifestations as microsymptoms of the syndrome. Furthermore, the observation of increased spontaneous chromosomal aberrations could help in clinical diagnosis (Kelly 1976) if they persist for life. It can be concluded that careful examination of the family members may reveal a significantly higher familial incidence than has been described hitherto.

In 1972, de Grouchy et al. first reported an increased chromosomal instability (breakages and gaps) in IP. The increase of structural chromosomal aberrations was confirmed by several authors (Cantu et al. 1973; Emerit et al. 1977; Iancu et al. 1975; Kelly et al. 1976 and two cases, a female and a male—unpublished, Schroeder and Stahl-Mauge).

An immunologic change in IP was reported twice (Dahl et al. 1976; Jessen et al. 1978). However, an immune defect as part of the syndrome can only be proved after more patients have been investigated immunologically.

In 1980, Wiklund et al. reported a previously undescribed ectodermal defect in IP: wooly hair naevus. Furthermore, they presented a very interesting pedigree with seven affected members in four successive generations (Fig. 4).

Another interesting finding in IP has been reported by Lenz et al. (1982); they described half-sided IP in a male, reviewing the male cases, reported in literature.

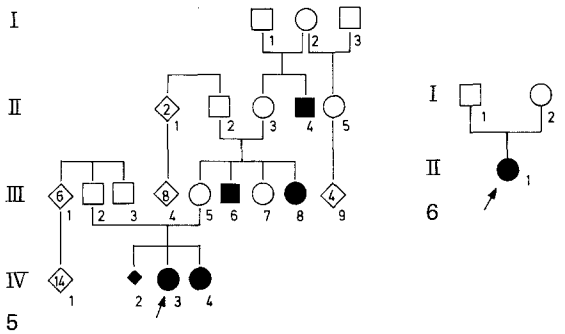
IP should be differentiated from:

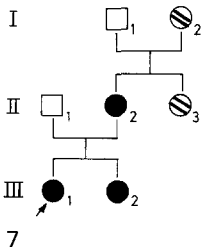
1) *Chromatophore Naevus of Naegeli* (Naegeli 1927) synonymous with Franceschetti-Jadasohn syndrome: skin lesions, resembling those of IP but starting rather later in life (around the 2nd or 3rd year)—no inflammatory phase—hyperkeratosis of the palms and soles—yellow teeth, but no conical malformation—autosomal dominant mode of inheritance.

2) *IP Achromians (Ito-syndrome)* which shows bilateral systematized linear depigmentation and includes a variety of anomalies of the CNS, eyes, musculo-skeletal system. This syndrome can be distinguished from IP Bloch-Sulzberger clinically (no inflammatory, hyperkeratotic stage), histologically (no histologic IP) and genetically (supposed inheritance: autosomal dominant).

In both disorders no reports of chromosomal breakage studies have been made. Differential diagnosis should be possible if chromosomal instability proves to be a constant feature of IP.

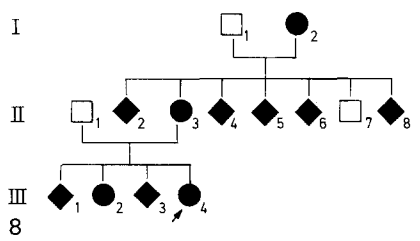
Table 1. Interesting pedigrees of IP in literature





Key to the symbols used in figures

- ○ female, healthy
- □ male, healthy
- ● female, affected
- ■ male, affected
- ▪ abortion, male
- ◆ abortion, sex unknown
- ▨ ⊘ partial expression of the disease
- ◫ ⊙ reported affected



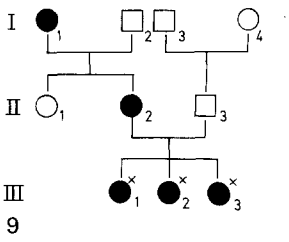


Fig. 5. Pedigree of de Grouchy et al. (1972)

Fig. 6. Pedigree of Iancu et al. (1975)

Fig. 7. Pedigree of Iancu et al. (1975)

Fig. 8. Pedigree of Kelly et al. (1976)

Fig. 9. Pedigree of Siemens et al. (1979)

Genetic Aspects of IP (Table 1)

Carney Jr (1976) in his review of the literature found 653 reports of patients with IP: 593 females, 16 males (37:1) and 44 of whom the sex was unknown. A positive family history was reported in about 55.4%; former authors had found familial occurrence in 15% (Carney and Carney Jr 1970), 15–40% (Morgan 1971). The estimated mutation rate is $0.6–2.0 \times 10^{-5}$ (Essig 1970; Vogel et al. 1975).

Several theories have been put forward to explain the familial occurrence of IP and the almost exclusive affliction of females. The two major hypotheses are those of Pfeiffer (1960) who suggested a female-limited autosomal gene, and Lenz (1961) who suggested a dominant X-linked gene.

At the present time X-chromosomal dominant inheritance with lethality in hemizygous males is regarded as the most likely pattern of inheritance in IP. To strengthen this hypothesis, we add the detailed analysis of Vogel and Dorn (1964), who considered carefully the two hypotheses of Pfeiffer (1960) and Lenz (1961):

I. 1) "In sex-linked manifestation an autosomal dominant gene with limitation of expression in females only and selection of probands (in every sibship only one proband), among the sisters of the probands there must be a 1:1 ratio of affected to unaffected, all the brothers must be healthy. Assuming among all siblings of the affected a sex-ratio of 1:1, there results a sex-ratio of 2♂:1♀ among the healthy siblings.

2) Assuming an X-linked dominant mode of inheritance on the contrary, there also has to be among the sisters a ratio of 1:1 between affected and unaffected, among the brothers, however, the half must have died away before birth having been homozygous for this gene. These zygotes could only be recognized in an increase of abortions. The other half is free of the feature, so that for unaffected siblings results a 1♂:1♀ sex ratio.

II. Assuming autosomal-dominant inheritance and equal chances of marriage for those, possessing the feature, and those, being healthy, the sibship should have received the gene either of an affected mother (50%) or of an unaffected father (50%). Supposing the marriage chances of those, possessing the feature, to be less, even the majority should have inherited the gene of the unaffected fathers.

On the contrary, in dominant X-linked inheritance and lethality of male foetuses, all patients must have received their gene from affected mothers, unless they are new mutants. Except of very unlikely possibilities—for example mosaic mutants of a parent—new mutants must be sporadic cases. It is rather likely that in sibships with at least two carriers the gene must have been transmitted by the affected mother.

III. The next argument is closely related to the preceding and therefore, it does not need any further explanation: in autosomal-dominant inheritance more affected persons have to be found equally within a group of close relatives of father and mother, in X-linked inheritance, however, only in the relationship of the mother.

IV. As another argument the mutation rate can be named: in autosomal-dominant inheritance, the loss of mutant genes in one generation would be relatively small and limited to an eventually decreased reproduction of the female carriers and therefore we would have to expect only a small number of new mutants. On the contrary, in X-linked inheritance the loss of genes by new mutation would be very high (loss of hemizygotes). Accordingly the fraction of new mutations among all cases is expected to be remarkably higher.

Ad 1

Among the healthy siblings of the cases in the table of Lenz (1961) (Table 2) there are 82% male and 62% female (57% male). In autosomal dominance we would expect 67% male, in X-linked inheritance (and if all families show a segregation of the feature) 50% male. χ^2-Comparison in autosomal dominance: $\chi^2 (m-1) = 4{,}375$; $P \approx 0.04$, in X-linked inheritance $\chi^2 (m-1) = 2{,}778$; $P \approx 0.1$, a result which at first sight seems to be in favour of an X-linked trait. We presumed all families to show a segregation of the feature; however, this is not the case. Because of the selection disadvantage of the carriers, there must be a certain number of new mutants among the sporadic cases. Among their siblings the sex-ratio should not differ from the 1:1 ratio, independent the mode of inheritance. The actual number arrived at can be

Table 2a. Enlarged and modified table of Lenz (Table of Lenz: taken from the descriptions of Vogel and Dorn 1964)

I. Sex-ratio among the healthy siblings of probands

Author	Siblings	
	Male	Female
Asboe-Hansen*	1	
Beck*	1	1
Brasin and Calnan*		4
Carney*	1	
Carney*	2	
Carol and Bour*		1
Cramer, Schmidt*	2	
Doornink, Siemens*	1	
Duverne*	1	1
	3	
Elefant*	1	
Elefant*		2
Findlay*	1	
Fleck*	1	
Gasteiger*	1	
Gertler*		2 (1?)
Holtz*	4	1
	2	1
Jeramillo*	1	
Kanste, Paatela*	6	1
Kitamura*		1 (0?)
Küster, Salus*	1	4 (5?)
	1	1
Krümmel*	3	1
Lahiri*	1	
Langer*		1
Levi*	1	
Marty*	3	
Melin*	1	
Moncorps, Seidlmayer*	1	1
Monnet*	1	3
Oldfeldt*		1
Oldfeldt*	1	3
Orozco*	1	1
Pfeiffer*	1	
	1	
Rozehnal, Vodicka*	4 (+3)	
Schulze, Noack*	2	2
Schuermann*	1	
Scott, Friedmann et al.*	1	
	1	3
See, Mingasson*		1
Scott*	1	1
Siemens*	2	
Siemens*	1	1
Siemens*	4	4
Stockholm*	1	
Stinga, Pompariello, Badargo*		1
Sulzberger, Fraser et al.*	1	
	2	
	1	
Undentich*	1	2
Wollensak*	1	
Wodnansky*		4
Lenz own cases*	1	1
	1	
	1	
		1
	1	2
		2
	2	1
	3	3
	1	1
Bargman, Wyse (1975)	1	1
Cantu-Garza, Riz-Barquin (1971)		1
Gordon, Gordon (1970)	1	1
Jackson, Nigam (1962)	4	3
Lenz (1961a)	2	2
Küster, Olbing (1964)	1	2
Kunze et al. (1977)	1	
Morgan (1971)	1	
	1	4
Reed et al. (1967)		2
Shotts, Emery (1966)	1	1

(All authors marked with a * are taken from the table of Lenz; the references for those authors can be found in the descriptions of Vogel and Dorn (1964) — the references for the rest of the authors can be found in the list of references in this paper)

interpreted in calculating autosomal-dominant inheritance with segregation rates among the siblings plus a number of new mutants. The examination of siblings becomes more important in families with several carriers, because there the explanation of new mutations can be disregarded. In those cases the sex-ratio is 21 male : 14 female (16, if one adds two doubtful cases) and the result, 0.6, (0.57) is a number between the expected figures, so that no classification of inheritance is possible.

Ad 2

X-linked dominant inheritance means that all siblings, if these are no new mutants, out of families with more than one affected person, have inherited the gene from an affected mother. Table 2 shows that this does not seem to be so: repeatedly, there are several affected siblings reported without an observed disease of the mother. However, it would be too early to draw a definite conclusion: as we have seen, the skin manifestations have disappeared to a great degree by adulthood, and many investigators may not have regarded the lack of teeth. It is therefore important to ask: what is the proportion in the transmission in the cases of Lenz (1961) (Table 2a, end)? Six of them were sporadic and in the remaining three families the gene was transmitted exclusively by the mother: that seems to favour an X-linked trait.

Table 2b. Enlarged and modified table of Lenz. (Table of Lenz: taken from the descriptions of Vogel and Dorn 1964)

II. Ratio female probands–healthy family members

Author	Probands	Healthy family members
Asboe-Hansen*	2	1
Beck*	1	2
Brasin, Calnan*	2	4
Carney*	1	1
Carney*	1	2
Carol, Bour*	1	1
Cramer, Schmidt*	3	2
Doornink, Siemens	1	1
	1	2
Duverne*	1	3
Elefant*	3	1
Elefant*	3 (1?)	2
Findlay*	2	1
Fleck*	1	1
Gasteiger*	1	1
Gertler*	2	2 (1?)
Holtz*	2	8
Jeramillo*	1	1
Kanste, Paatela*	1	7
Kitamura*	2	1
Küster, Salus*	2	5 (6?)
	1	2
Krümmel*	1	4
Langer*	1	1
Levi*	1	1
Marty*	5	3
Melin*	1	1
Monnet*	1	4
Oldfeldt*	1	4
Orozco*	3 (1?)	2
Pfeiffer*	1	1
	2	1
Rozehnal, Vodicka*	4	4 (+3)
Schulze, Noack*	1	4
Schuermann*	1	1
Scott, Friedmann et al.*	3	5
See, Mingasson*	1	1
Scott*	1	2
Siemens*	1	2
Siemens*	1	2
Siemens*	1	8
Stockholm*	1	1
Stringa, Pompariello, Badargo*	1	1
Sulzberger, Fraser et al.*	4	4
Undentich*	1	3
Wollensak*	1	1
Wodnansky*	1	4
Lenz' own cases*	2	2
	1	1
	1	1
	1	1
	1	0
Lenz own cases*	1	0
	1	0
Cantu-Garza, Riz-Barquin (1971)	2	1
Gordon, Gordon (1970)	2	2
	2	1
Iancu et al. (1975)	1	4 (+2?)
Jackson, Nigam (1962)	3	7
Lenz (1961a)	5	4
Küster, Olbing (1964)	6 (+3?)	2
Morgan (1971)	1	1
	1	5
Müller (1974)	2	0
Reed et al. (1967)	1	2
	1 (+1?)	1
Shotts, Emery (1966)	1 (+1?)	2

(All authors marked with a * are taken from the table of Lenz; the references for those authors can be found in the descriptions of Vogel and Dorn (1964) — the references for the rest of the authors can be found in the list of references in this paper)

Ad 3

In the total material, six sisters and one cousin of the mother have been affected. Assuming autosomal inheritance, the chances of relatives (of the father and the mother) being affected, are equal. Then the affliction of seven relatives of the mother and none of the father has got a probability of $\frac{1}{2^7} = \frac{1}{128}$. This probability is minimal, so that the finding points to an X-linked inheritance. Since in this table all fathers are listed as phenotypically healthy, it is supposed that the search for carriers among their siblings was not conducted as intensively as in the relationship of the affected mothers; thus the result may have been reached by selection.

Ad 4

In X-linked inheritance, the number of new mutations would be very high in relation to the number of carriers, because of the pressure of selection against the gene. Considering the fertility of the hemizygotes f1, the fertility of the heterozygotes f2 (average of the population = 1), the number of dying hemizyogtes x1, the number of heterozygotes x2, the mutation rate in the germ cells of the women μ, the mutation rate in the germ cells of the men γ, then we will find this scheme according to Haldane and X-linked inheritance:

1) $$\frac{x2}{x2} = 1 + \frac{2f1\mu + \gamma}{2\mu + \gamma}$$

in f1 = 0

2) $$\frac{x2}{x1} = 1 + \frac{\gamma}{2\mu+\gamma}$$

Furthermore, it is assumed—probably in this case correctly—that only the fertility not the number of the female carriers is reduced. The selection disadvantage of the gene and therefore the mutation rate is as follows:

3) $$\frac{2\mu+\gamma}{3} = s = x2 \left[\frac{1}{3}\cdot\frac{2\mu+\gamma}{2\mu+2\gamma} + \frac{1}{3}(1-f2)\right]$$

The first term within parenthesis stands for selection by loss of lethal hemizygotes, the second term for the loss of genes by diminished reproduction of the heterozygotes.

On the contrary, in dominant-autosomal inheritance with sex-limitation we have:

4) $$\frac{2\mu+\gamma}{3} = s = \frac{1}{2}(1-f2)\ x2$$

A numerical example should illustrate the difference between the two hypotheses: if $f1 = 0$, $f2 = 0.8$ $\mu = \gamma$, in X-linked inheritance it is:

$$\mu = x2\left(\frac{1}{3}\cdot\frac{1}{1.333} + \frac{1}{3}\cdot 0.2\right) = 0.3167\ x2$$

One third of these new mutants would lead to death of male hemizygotes, two thirds would be found in female zygotes. As the mutation rates are reported in relation to the number of genes (those being twice as large as the number of zygotes in the female sex) among the x2 female carriers, there would be

$$2\cdot\frac{2}{3}\cdot 0.3167 = 0.4223\ x2$$

new mutants.

Therefore the total number of new mutants would be

$2\times 0.05\ x2 = 0.1\ x2.$

Out of these, one half only would appear in female heterozygotes, the other half would remain in male heterozygotes without symptoms, i.e., only a part of the female carriers, namely 0.05 x2 would represent new mutations, whereby the mutation rate in autosomal inheritance is considerably below that of X-linked inheritance. In order to test this argument, much more material would have to be obtained from a large population and thoroughly examined for traces of familial occurrence (teeth of mothers), allowing no influence of selection. But even the present material, with great variation in quality, allows a conclusion of high probability: namely in literature the sporadic cases are predominant. Even if in some of these cases the examination of the family seems to be incomplete, this might not be valid for all sporadic cases. This is particularly true for the cases which were thoroughly examined by Lenz (1961), who found among nine patients where family investigations were possible, six sporadic and only three familial cases which points to a relatively high number of new mutants. Accordingly, the analysis of the fraction of new mutations among all cases are much more in favour of X-linked inheritance with embryonic death of the hemizygotes than in favour of autosomal-dominant inheritance. Together with the findings in close relatives of the mothers, Lenz's (1961) hypothesis of an X-linked trait with lethality in hemizygous males seems very likely, whereas the hypothesis of an autosomal trait with sex-limited manifestation does not seem to be very well established."

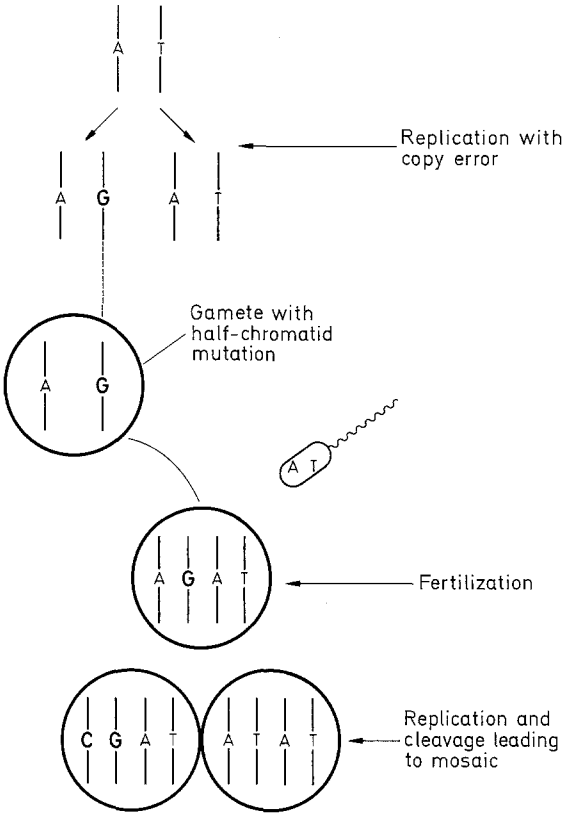


Fig. 10. Principle of half chromatid mutation. (Taken from the descriptions of Vogel and Motulsky 1979)

Carney Jr (1976) in his review of the literature states that X-linked dominant inheritance with lethality in males fits well with the statistics for IP, since most cases have occurred in females (more than 97%), and there is a sex-ratio: one healthy male: one healthy female. Furthermore the abortion rate of 23% (70 miscarriages in 308 pregnancies) found in 74 adequately reported sibships, corresponds approximately with the expected 25%; however, the abortion rate in the general population is already 15% which has to be added. Also the occurrence of IP in a Klinefelter male, reported by Kunze in 1977, is consistent with the hypothesis of an X-linked dominant trait with lethality in hemizygous males.

In this mode of inheritance a sex-linked gene on the X-chromosome acts as a dominant one in females and is lethal in hemizygous males. Females with the mutant gene on one of their X-chromosomes are heterozygous for the condition; this explains the fact that they are usually not severely affected. Hemizygous males are most commonly affected in a manner not compatible with survival. Thus, IP is very uncommon in liveborn males. The males reported in literature were no more severely affected than the heterozygous females. In none of these male cases was a positive family history known. These findings raise the question of how to explain IP in hemizygous males. A possible and reasonable explanation is that IP in hemizygous males may be the result of half chromatid mutations. Gartler and Franke (1975) noted that half chromatid mutations, occurring in gametogenesis, may lead to a mosaicism in the embryo. The mechanism of half chromatid mutation is presented in Fig. 10.

Lenz (1975) suggested that cases of IP in males may be the result of such half chromatid mutations. In his view, the following facts provide evidence for this hypothesis:

Table 3. Analysis of abortions in IP

Author	No sex	Male	Female	Date of abortion
Cantu-Garza, Riz-Barquin (1971)	3			No information
			1	Stillbirth
Abrahams, cited by Curth (1965)	1			No information
		1		8th month stillbirth
Gordon, Gordon (1970)		1		26th week (6th month)
Jackson, Nigam (1962)	5			No information
Küster, Olbing (1964)			2	No information
		1		No information
Lenz (1961a)	6			No information
Reed et al. (1967)	1			7½th month
	1			7th month
	2			No information
Shotts, Emery (1966)		2(1?)		5th month
Wolf, Kopf, Andrade (1964)		4		No information
		3		4th month

1) The pattern of skin changes is like that of the heterozygous state of some X-linked genes in animals (mice, hamsters, cattle);

2) There is no difference in the phenotype of males and females.

Assuming females, who are mosaics due to the Lyon-effect, are affected similarly to males, it is very likely that hemizygous males may also be mosaics and that the mutation took place in an early stage of embryonal development. It is very unlikely that they are mosaics caused by somatic mutations, because in this case one would expect smaller sectorial involvement rather than a generalized pattern (Lenz 1975).

3) As expected, all are sporadic cases.

Recently Hecht et al. (1982) reported the first incidence of mother-to-son transmission and concluded that this finding indicates that a male with an inherited whole chromatid mutation for IP can escape lethality. They interpreted this male as a "Durchbrenner". However, this term which was proposed in 1955 by Hadorn to explain the phenomen of escape from death, does not explain, how this male escaped death before birth. In addition, it does not seem quite clear if the mother indeed had IP (comment of Lenz, personal communication).

The peculiar distribution of the skin changes may be explained by the Lyon hypothesis. Aparently the affected areas of the skin represent those cell populations in which the abnormal gene is active. This functional X-chromosome mosaicism may explain the great variability of expression in IP.

Abortions

Reviewing the literature, we found a remarkable lack of information regarding abortions and stillbirths (Tables 3 and 4). Often the occurrence of abortion is unknown, or there is not enough pedigree information. When abortions are mentioned, the available data are very insufficient: often there is no information regarding the time of abortion or regarding the sex of the aborted child. Furthermore, pathological-anatomical investigations of abortions have never been mentioned.

For further studies we want to stress the importance of careful investigations of abortions (especially pathological-anatomical investigations) as well as accurate pedigree analysis.

Table 4. Analysis of abortions in IP. From a total of 34 abortions in 10 families, there have been 12 in males, 3 in females, 12 have been of unknown sex. The data of abortion were available in 11 cases, not available in 23 cases

Author	Number of cases	Month of gestation
Abrahams, cited by Curth (1965)	1	early pregnancy (1st to 3rd month)
Wolf, Kopf, Andrade (1964)	3	4th month
Shotts, Emery (1966)	2	5th month
Gordon, Gordon (1970)	1	6th month (26th week)
Reed et al. (1967)	1	7th month
	1	7½th month
Abrahams, cited by Curth (1965)	1	8th month (stillbirth)
Cantu-Garza, Riz-Barquin (1971)	1	stillbirth

Oral-Facial-Digital I Syndrome (OFD I Syndrome) McKusick's Catalogue No.: 31120

The second disorder, in which predominantly females are involved is the oral-facial-digital (OFD) I syndrome. This syndrome, consisting of congenital anomalies of the oral, facial and digital structures, was first described as a clearly defined entity by Papillon-Leage and Psaume in 1954. The most common features of the OFD I syndrome, which are fairly well established, are the following: *oral region:* (Figs. 11, 12, 13) numerous hyperplastic frenulas (lingual, buccal, labial) multilobulated tongue with hamartoma, cleft palate, median pseudocleft of the upper lip, dental anomalies. Involvement of the *face*: flatness of the nasion-sella-basion, hypoplasia of the nasal alar cartilages, hypertelorism. Anomalies of the *fingers:* (Fig. 14) usually in form of brachydactyly, syndactyly, clinodactyly and rarely polydactyly.

In 1975 Melnick and Shields postulated multilobulated tongue or hyperplastic frenulas with or without brachydactyly as

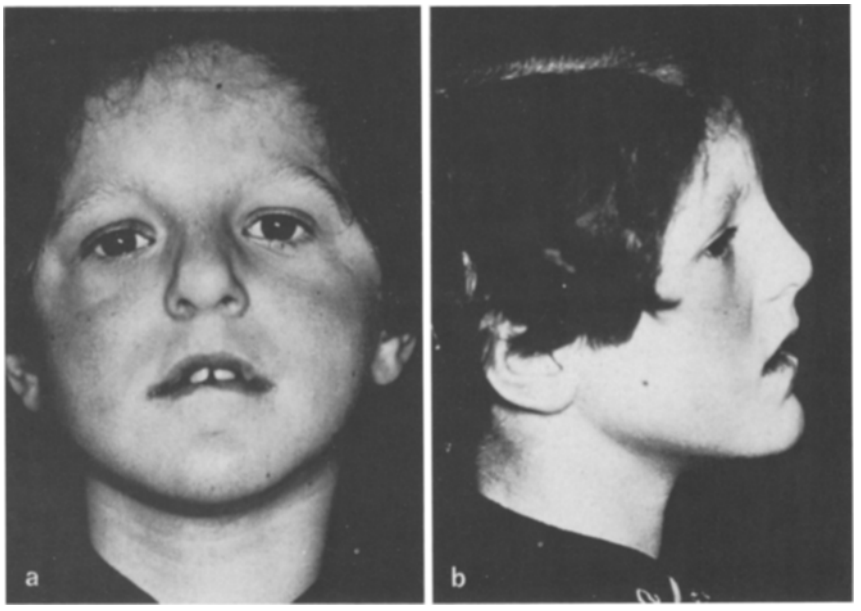


Fig. 11 a, b. OFD 1 syndrome in an 8-year-old female patient seen in our institution: asymmetry of the face, flattened middle face, broad nasal root, short upper lip, irregularity of the lip colour

minimum diagnostic criteria of the OFD I syndrome. Already Fuhrmann et al. (1966) were reporting multiple atypical inserting hyperplastic frenulas and anomalies of the tongue to be the most frequent signs of the syndrome. Less common associated anomalies are: alopecia, skin lesions, trembling, porencephaly, hydrocephalus. A significant number of patients (30–50%) are mentally retarded (Co-Te et al. 1970; Levy et al. 1974; Ruess et al. 1962; Wahrmann et al. 1966).

A new aspect to be mentioned is the finding of renal abnormalities of the OFD I syndrome: Doege et al. (1964) reported two cases with polycystic kidneys; Tucker et al. (1966) reported one case with polycystic kidney disease and Harrod et al. (1976) described a woman with bilateral polycystic kidneys and chronic renal failure. The two cases of Whelan et al. (1975) did not have polycystic disease of the kidneys, but had congenital obstruction of the ureter. The authors suggested that renal abnormalities, especially polycystic kidney disease may be a hitherto unrecognized feature of the OFD I syndrome. In 1978, Mery et al. added two new observations and confirmed polycystic kidneys as a part of the syndrome. Melnick and Shields (1975) agree with this supposition. It were Whelan et al. (1975), who proposed to define the OFD I syndrome by including ear and renal malformations.

Rimoin and Edgerton (1967) coined the terms OFD I syndrome and OFD II (Mohr syndrome). The two syndromes are genetically separate entities and can be distinguished clinically (Table 5).

OFD II (Mohr) Syndrome

The most important signs which allow classification of the OFD II syndrome (Mohr syndrome) are the mode of inheritance (autosomal recessive), the bilateral polysyndactyly of the big toe ("bifid big toe"), and the conductive hearing loss.

Other syndromes, taken into consideration as differential diagnosis, are discussed below.

Dutescu-Grivu-Fleischer-Peters Syndrome (first described in 1966). Microstomia, so-called "bird-face", dental malalignment, vertical frenulas between maxilla and mandible (facultatively), anomaly of the tongue, syndactyly, campto-, clino-, brachy-, polydactyly. Differential diagnosis from the aglossy-adactyly syndrome seems possible by the observation of the extreme microstomia.

Juberg-Hayward Syndrome (first described in 1969). Hypertelorism, broad nasal tip, lateral cleft lip and cleft palate, missing teeth, hypoplasia of the thumb, anomaly of the radius, clinodactyly of the fourth toe.

Aglossy-Adactyly Syndrome (Leiber and Olbrich 1972). Aplasia of the tongue, sometimes microglossia, hypoplasia of the mandible ("bird face"), pseudocleft of the lower lip, adactyly to all degrees; syndactyly may also be present.

C-Syndrome (Opitz-Johnson-McCreadie-Smith Syndrome) (first described in 1969). There are only a few cases reported in the literature. Characteristic facies, dysplasia of the lip (macrostomia with multiple labio-gingival frenulas), high-arched palate, hypoplasia of the mandible, different dsyplasias of the hand and foot (clinodactyly, brachydactyly), multiple anomalies of the visceral organs, congenital heart defects, cutis laxa.

Cleft Palate Lateral Synechia Syndrome (CPLS-Syndrome) (first described in 1961 by Behrends). The term CLPS-syndrome was coined by Fuhrmann et al. in 1972, who observed the syndrome in five members of a family. Cleft palate associated with synechias between the borders of the cleft palate and the lateral, parts of the tongue and the floor of the mouth; additionally moderate hypoplasia of the mandible and the tongue, relatively short upper lip; no other gross malformations.

Several features can be found in other syndromes (Gorlin et al. 1962). In the Ellis-van-Crefeld syndrome, there may also be a mild defect of the mid upper lip. Hypoplasia of the alar cartilages, but to, a higher degree than in the OFD I syndrome, may be a sign of the Waardenburg syndrome. One component of mandibulo-facial dysostosis, hypoplasia of the malar bone, is a feature of the Franceschetti syndrome. However, these last three syndromes have very characteristic other cardinal symptoms, so that differential diagnosis should be possible.

Genetic Aspects of the OFD I Syndrome

In 1966 Fuhrmann and colleagues discussed in detail the following formal genetic hypotheses:

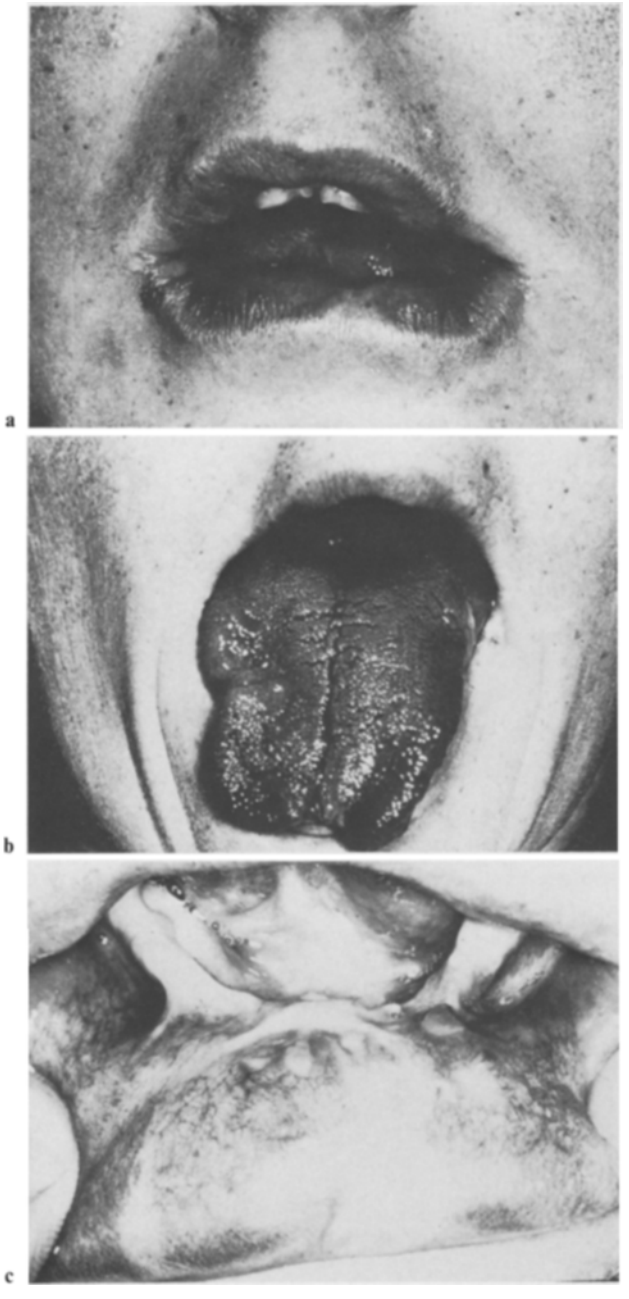


Fig. 12a–c. Oral changes in the same patient. **a** Irregularity of the lip colour; **b** lobulated tongue; **c** atypical inserting frenulas

1. X-linked dominant inheritance with lethality in hemizygous males,
2) autosomal-dominant inheritance with lethality in males,
3) autosomal-dominant inheritance with sex limitation,
4) partial trisomy of a part of a chromosome of the C-group in a chromosome No. 1.

By their detailed segregation analysis, X-linked-dominant and autosomal-dominant inheritance with sex-limitation of manifestation could be excluded. However, autosomal-dominant inheritance with lethality in males remained possible.

They concluded X-linked dominant inheritance with lethality in hemizygous males was the most likely interpretation. Today most authors confirm this suggestion. However, a definite decision for X-linked dominant inheritance with lethality in hemizygous males would only be possible by demonstrating

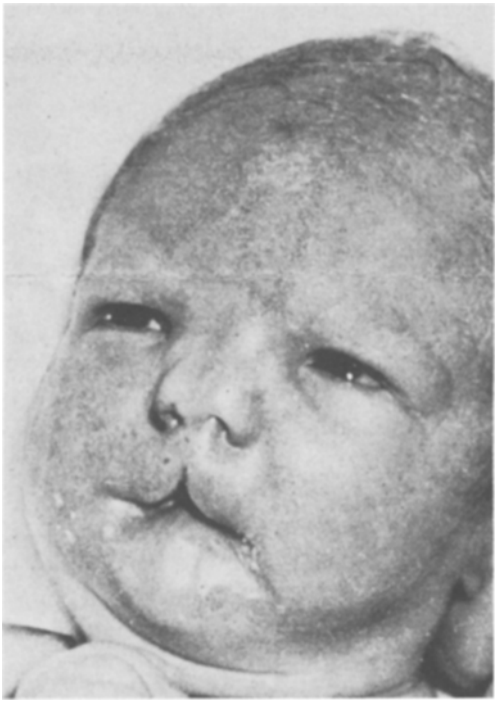


Fig. 13. Patient reported by Fuhrmann and Vogel (1960) with a median cleft of the upper lip

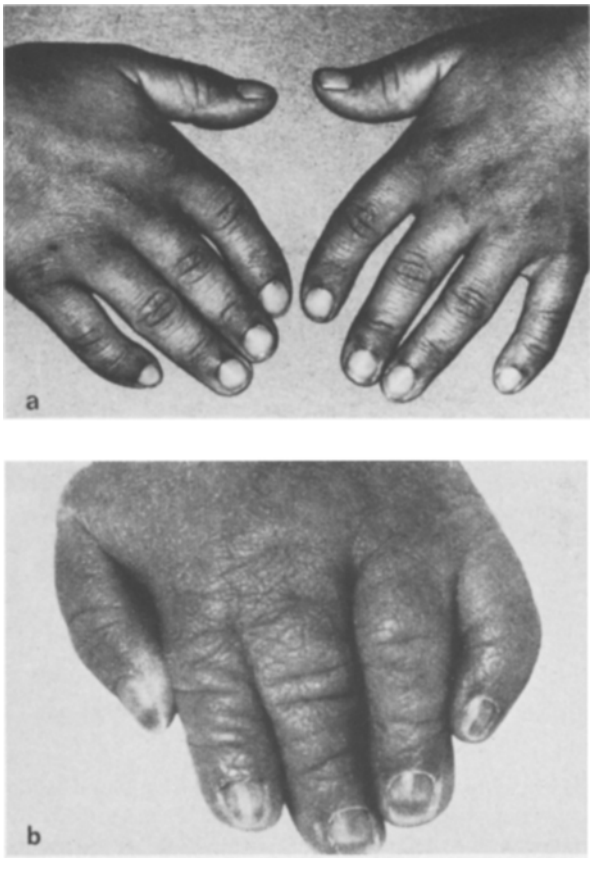


Fig. 14. a Fingers of the patient: brachy-clinodactyly and indicated webs. **b** Left hand of the patient of Fuhrmann and Vogel: syndactyly between the 2nd and 3rd finger as well as between the 4th and 5th finger

Table 5. Characteristics of the OFD I and OFD II (Mohr syndrome) syndrome. Modified table, taken from the descriptions of Gustavson et al. (1971)

	OFD I syndrome	OFD II syndrome (Mohr syndrome)
Inheritance	X-linked dominant	Autosomal recessive
Sex distribution	Only females	Males and females
Height[a]	Normal	Subnormal
Tongue	Partial clefts	Midline cleft and/or Nodules on tongue
Palate	Cleft	Normal, narrow or cleft
Buccal mucous membrane	Multiple hypertrophied labial and lingual frenula	Normal or hypertrophy of normal frenula
Dentition	Lateral incisors absent	Normal or absent central incisors
Mandible	Hypoplasia of ramus	Hypoplasia of corpus; obtuse mandibular angle
Digits	Asymmetric shortening; syndactyly	Bilateral reduplication of great toes; syndactyly
Hair	Alopecia	Normal
Skin	Granular or papular lesions	Normal
CNS	Trembling, hydrocephalus	Hypotonia
Mental development	Normal or mental deficiency	Normal or mental deficiency
Hearing	Normal	Conductive hearing defect
Respiration	Normal	Normal or respiratory distress

[a] Lenz (personal communication) saw at least one patient with extreme growth retardation

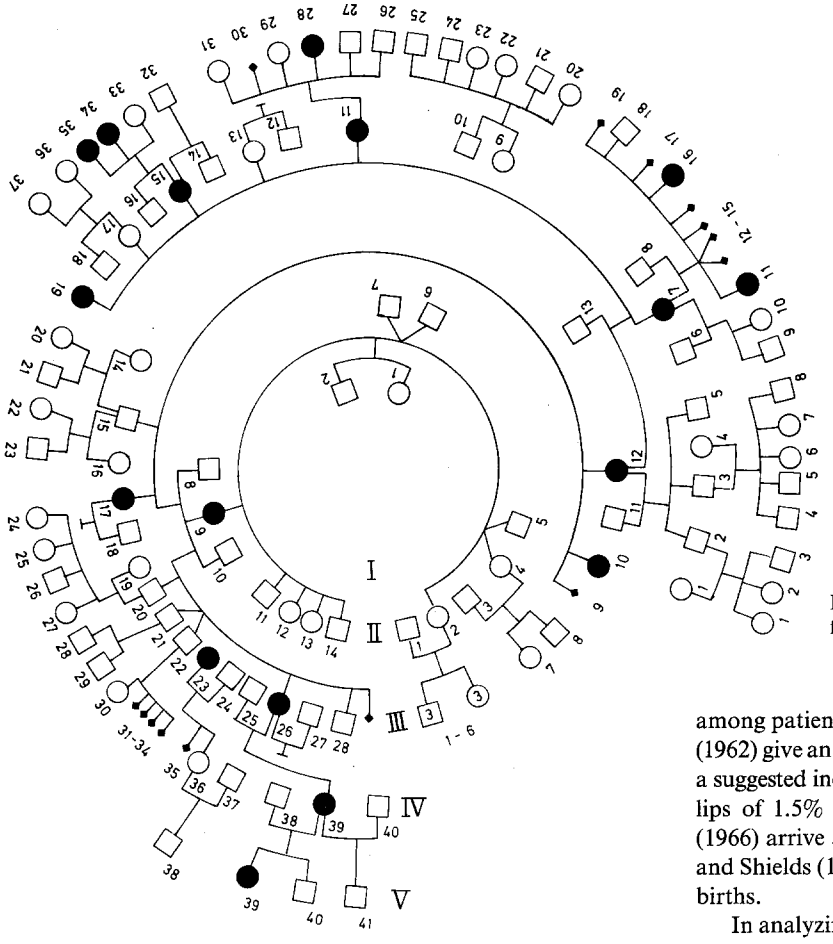


Fig. 15. Pedigree of Doege et al. (1964) with 17 affected females among 87 births in 5 generations

gene-linkage with common X-linked genes like Xg-blood group system, G-6-PD-variants, colour blindness. This was tried by Cantu-Garza and Riz-Barquin (1971) in IP; however the results of this study have not been informative.

About 150 cases are known (Melnick and Shields 1975). The incidence of the OFD I syndrome was suggested to be 1:100 among patients with cleft palate (Gorlin et al. 1962). Ruess et al. (1962) give an estimate of 8–16:1000 cases with cleft palate. From a suggested incidence of 15:1000 cleft lips and an incidence of cleft lips of 1.5% per 1000 Caucasian population, Wahrman et al. (1966) arrive at a frequency of 2.25 per 100,000 births. Melnick and Shields (1975)gave an estimated incidence of 1:250,000 live-births.

In analyzing 14 pedigrees in the literature and one of his own, Melnick reported familial occurrence (Fig. 15) in about 25%. Thus, 75%—the great majority—seem to be sporadic cases. Even if the families of those "sporadic" cases have not been examined thoroughly enough, the percentage of sporadic cases still remains high. The assumption that a certain number of these sporadic cases may represent new mutations would argue in favour of X-linked inheritance with lethality in hemizygous

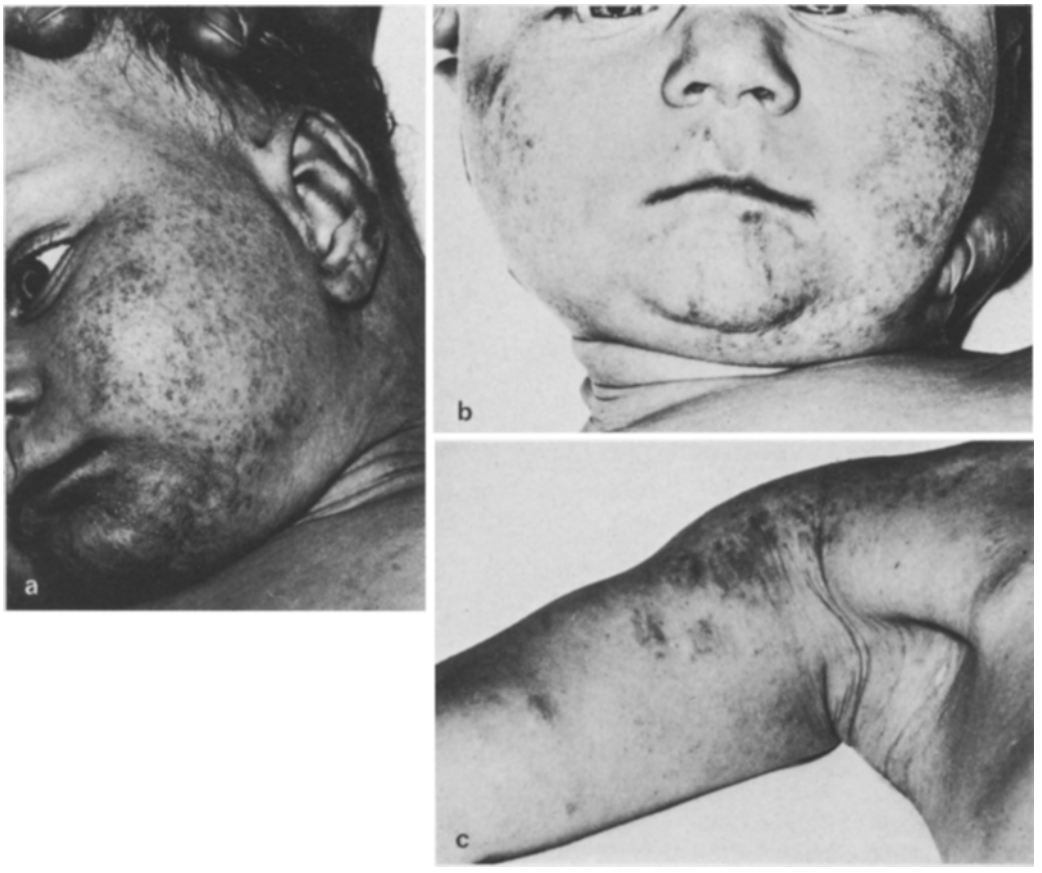


Fig. 16a–c. Patient with FDH showing the typical skin changes: atrophic areas of the skin with herniation of the subcutaneous fat (photos given by Dr. Tilgen)

males. As mentioned earlier, in this mode of inheritance the loss of mutant genes—loss of hemizygotes—is high. In view of the large pressure of selection against the gene, a high fraction of new mutations among the cases will result. Melnick analyzed 31 sibships. From a total of 127 persons, 91 were normal females, none of the males was affected. After eliminating the probands, he found a male:female ratio of 35:76 which approximately corresponds to the 1:2 ratio, expected in an X-linked trait with lethality in males. The results of this pedigree analysis lead Melnick and Shields (1975) to the conclusion that the OFD I syndrome is inherited as an X-linked dominant trait with lethality in hemizygous males. The disorder was recognized by McKusick (1978) in his catalogue under the number 31120.

A chromosomal rearrangement as possible cause of the phenotypic system involved, was discussed in the early sixties by Patau et al. (1961), Ruess et al. (1962) and Gorlin and Psaume (1962). The consistent finding in 3 out of 14 examined patients was a prolonged chromosome No. 1; the interpretation of the authors was such that a fragment of No. 1 was inserted leading to a partial trisomy 1. Never has this finding been checked with banded chromosomes.

A striking feature in the OFD I syndrome is the high phenotypic variability in heterozygous females, varying from mild signs, as for example, skin-lesions or alopecia, to the full picture of the syndrome. This variation in degrees of expression would be explained by the Lyon hypothesis, since affected females, who are heterozygous for the OFD I gene and therefore represent a normal OFD I mosaicism, will have varying percentages of cells in which the mutant gene is active. According to Melnick and colleagues, the case of a female with the OFD I syndrome (Tucker et al. 1966), who died 2 h after birth, may be an example of a nearly complete lyonization for the OFD I gene.

Since hemizygous males have only one X-chromosome, all their cells will carry the active OFD gene, causing lethality. However, the occurrence of OFD I syndrome in liveborn males has been asserted. In 1966, Fuhrmann and co-workers analyzed carefully the male cases known at that time. They found no certain examples in OFD I syndrome in males, because none of the male cases fulfilled the diagnostic requirements.

In evaluating critically the male cases today—so far reported in literature—there is only one male case acceptable: the patient of Wahrmann et al. (1966), who has in addition a Klinefelter syndrome, seems to represent a typical example of the OFD I syndrome. An XXY-male, having the OFD I syndrome, gives further support to the hypothesis of an X-linked dominant trait with lethality in hemizygous XY-males. In this case the additional X-chromosome leads to a functional X-chromosome-mosaicism as in females, preventing from embryonic death. An interesting finding is a woman with an XXX-constitution and typical symptoms of OFD I syndrome (Cohen et al. 1981). This woman, who was pregnant for the sixth time, had had five first-trimester abortions.

Focal Dermal Hypoplasia (FDH) (Goltz-Gorlin Syndrome) McKusick's Catalogue No.: 30560

Focal dermal hypoplasia (FDH) was first described as a separate entity by Goltz et al. (1962) and is characterized by focal areas of hypoplasia (thinning) of the skin with linear pigmentation and

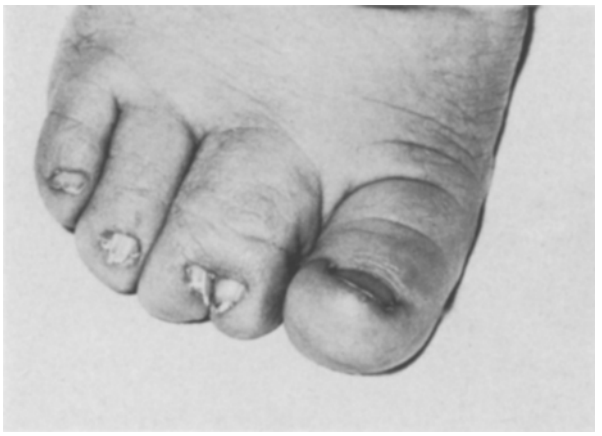


Fig. 17. Toes of a patient with FDH: syndactyly between the 2nd and 3rd toe (photo given by Dr. Tilgen)

teleangiectasia; in some parts of the integument there is almost complete absence of the corium. Herniation of the subcutaneous fat results from the dermal hypoplasia. The areas involved in those characteristic skin lesions, which are most commonly present at birth, are usually the trunk and extremities (Fig. 16). Furthermore, papillomata of the mucosa of lips and of the anal-genital region are found. These papillomatous lesions have a tendency to recur and are prone to neoplastic transformation (Contarini et al. 1977). Besides the cutaneous lesions which represent the hallmark of the syndrome, skeletal defects like syndactyly, hypoplasia of digits and toes (Fig. 17), adactyly, polydactyly, scoliosis and spina bifida are very often found. Other associated anomalies are ocular defects like colobomata, strabismus, nystagmus and microphthalmus, nail dystrophy, sparse hair, short stature, microcephaly; some patients are mentally retarded (Table 6). A new finding, postulated to be highly characteristic of FDH, is osteopathia striata which is characterized by the striation of the metaphyseal regions of the long bones. This was first reported by Larregue et al. (1971), who found in 9 of 11 patients a longitudinal striation in the metaphyses of long bones. This has now been confirmed by several authors. In 1979, Knockaert and Dequeker described the 14th case with osteopathia striata and stressed the importance of a radiological survey of the skeleton in FDH and related syndromes for differential diagnosis.

Recently, the following abnormalities have also been reported in combination with FDH: apocrine naevi (Vakilzadeh and Happle 1976), hemimelia, schisis of the palatum molle, absence of one umbilical artery (Beganovic and Lommen 1977), bilateral cheilo-gnatho-palatoschisis (Valerius 1974), multiple hydrocystomas, bilateral keratokonus, papillomatosis of the oesophagus, hiatus hernia (Zala et al. 1975). Kunze et al. (1979) reported marked right-sided malformations and a right-sided diaphragmatic hernia.

Differential Diagnosis

For differential diagnosis several conditions have to be considered:

Rothmund-Thomson Syndrome. Clinical signs: poikilodermia: atrophy, teleangiectasia, depigmentation, hyperpigmentation; defects of the hair, teeth, nails, skeleton; imune globuline defect; juvenile cataracts. The mode of inheritance is autosomal recessive.

Table 6. Goltz-Gorlin syndrome: distribution of the clinical symptoms (by Ishibashi and Sundhausen). Taken from the descriptions of Braun-Falco and Hofmann (1975)

Symptoms	Number of cases
Skin Changes	**50**
Atrophies	50
Pigmentary anomalies	43
Teleangiectasias	37
Papillomata	36
Nodules, herniation of fat	24
Scars	15
Skeletal Changes	**45**
Syndactyly	38
Hypo- or aplasia of fingers and toes	27
Changes of the vertebral column	19
Anomalies of clavicle and ribs	14
Changes of skull bones	12
Anomalies of the pelvis	11
Radiological changes of the bone structure	11
Anomalies of the Teeth	**29**
Retention or agenesy of teeth	13
Enamel defects	12
Malalignment of teeth	11
Ocular Anomalies	**23**
Colobomata, aniridia	16
Microphthalmia, anophthalmia	10
Changes of the Nails	**14**
Hair Changes	**11**
Physical Retardation	**11**
Mental Retardation	**11**

Other symptoms: omphalocele, rectus diastasis, kidney malformations

The skin lesions starting in the third to sixth month of life, usually involve face, ears, upper extremities.

Though this syndrome is clinically very similar to FDH, it can be distinguished histologically: while in FDH the epidermis is normal and only the corium is involved with almost total replacement of the corium by fat cells, in Rothmund-Thomson syndrome the changes are epidermal (hyper-, parakeratosis, hydropic degeneration of the basal layer cells; later: malignant dyskeratosis).

Naevus Lipomatosus Superficialis Hofman-Zurhelle. Clinical signs: yellow, usually grouped xanthome-like papules, often near the pelvic girdle and thighs, no associated malformations. Histologically, this condition most closely resembles the FDH: there are also fat cells in the corium, but the replacement of the connective tissue by fat cells is by no means as extensive as in FDH. The cause of this disorder is still unknown.

Incontinentia Pigmenti. Many cases of FDH at first have been mistaken for IP, because focal areas of skin atrophy may also be found in this disorder. Although clinically there is a high similarity to FDH, the two diseases can be distinguished histologically.

Atrophoderma of Pasini-Pierini (Pasini-Pierini Syndrome). Clinical signs: this circumscribed skin atrophy, starting in adulthood, i.e. during the second decade of life, is characterized by sharp-edged atrophic plaques, especially on the back; there are no other abnormalities. The cause of this disorder is supposed to be a familiar neurogenic defect. Whether inheritary factors are involved, has not yet been clarified.

Aplasia Cutis Congenita. Clinical signs: localized congenital absence of the skin, most frequently on the scalp, more rarely on the limbs or trunk. Occasionally, large areas and deeper structures may be affected. Most cases show no associated anomalies, however, some cases which seem to be autosomal dominantly inherited, have terminal defects of hands and feet. Genetics: reported in siblings, successive generations—most cases are sporadic.

Lesions of congenital skin aplasia sometimes may also be present in FDH.

Genetic Aspects of FDH (Tables 7 and 8)

Among 175 reported cases in literature (Braun-Falco and Hofmann 1975; Beganovic and Lommen 1977; Happle and Lenz 1977; Toro-Sola et al. 1975; Zala et al. 1975; Contarini et al. 1977; Ishibashi and Kurihara 1972; Vakilzadeh and Happle 1976; Ruiz-Maldonado et al. 1974; Knockaert and Dequeker 1979; Fryns et al. 1978) only 18 cases were male (Toro-Sola et al. 1975; Fryns et al. 1978; Fjellner 1979; Burgdorf et al. 1981). Familial occurrence of FDH is very rare (Freeman 1955; Wodniansky 1957; Goltz et al. 1962; Michel 1971; Ruiz-Maldonado et al. 1974); up to 95% occurred sporadically (Fryns et al. 1978). Under the assumption of an X-linked dominant trait with lethality in hemizygous males, such a high rate of sporadic cases could be interpretated as being due to new mutations.

Due to the preponderance of females (about 90% of the cases) and the increased incidence of miscarriages, Goltz et al. (1970) proposed as mode of inheritance either X-linked dominance or autosomal dominance with sex-limitation and lethality in males. Other authors (Braun-Falco and Hofmann 1975; Contarini et al. 1977; Fryns et al. 1978; Knockaert and Dequeker 1979; Rodermund and Hansmann 1977) express the opinion that a definite conclusion regarding the mode of transmission in this syndrome is not possible. In contrast Toro-Sola et al. (1975) found no evidence for a single gene mode of inheritance. While a few authors (Gorlin et al. 1963; Leiber and Olbrich 1972; Wodniansky 1957) favour autosomal dominance with sex-limitation, the majority (Beganovic and Lommen 1977; Fjellner 1979; Happle and Lenz 1977; Kunze et al. 1979; Ruiz-Maldonado et al. 1974; Vakilzadeh and Happle 1976; Warburg 1970) prefer the hypothesis of X-linked dominant inheritance with lethality in hemizygous males. Happle and Lenz (1977), who also favour X-linked dominance with lethality in males, state that, if this mode of inheritance should hold true, the streaky pattern of skin changes and bone lesions (striation of the metaphyseal regions of long bones) could be explained by the Lyon hypothesis as a functional X-chromosome mosaicism. Furthermore, as in IP, the male cases could be explained as the results of half chromatid mutations.

Two cases of father-daughter-transmission of FDH have been reported in literature (Larrègue et al. 1971; Burgdorf et al. 1981). These findings do not exclude X-chromosomal dominant inheritance with lethality in hemizygous males, since both fathers could have been survivors of a half chromatid mutation of the X-chromosome. However, autosomal dominant inheritance should also be discussed in these families.

To clarify the mode of inheritance in FDH, which is less well established than in IP or OFD I syndrome, more identified cases together with pedigrees for the familial genetic analysis should be published. Furthermore, attention should be paid to the analysis of abortions; in particular, the moment of abortion and the number of abortions should be noted.

Ornithine Transcarbamylase (OTC) Deficiency
McKusick's Catalogue No.: 31125

The mode of inheritance in this inborn error of metabolism has been suggested to be X-linked dominant with lethality in the *neonatal* hemizygous male. The disorder which was first described by Russell et al. (1962) in two female cousins is included in the study, although there is no lethality in utero, only in the neonatal period.

OTC is the second of five enzymes of the urea cycle which catalyze the conversion of ammonia to urea (scheme of conversion see Fig. 31). Campbell et al. (1971, 1973) suggest, that congenital deficiency of OTC is caused by a mutant gene on the X-chromosome and leads to hyperammonemia in infants and children. Due to lyonization, partial OTC deficiency in varying degrees is observed in heterozygotes: it may range from a mere dislike of protein-containing food and feeding difficulties to recurrent episodes of acute hyperammonemia with clinical signs such as vomiting, stupor, spasticity, seizures, lethargy, coma and cerebral atrophy. In severe cases mental and physical retardation may develop. Mildly affected females seem to be intellectually normal; as the only clinical sign, they may show severe intolerance to high-protein foods which may manifest itself in headache, nausea or lethargy. By doing psychometric tests, Batshaw et al. (1980) was able to demonstrate that these protein-intolerant women showed slight intellectual deficits. They suggested that intermittent hyperammonemia might be the cause of this cerebral dysfunction in asymptomatic carriers of OTC deficiency.

In contrast to females with partial deficiency of OTC, the course of the disease in males is much more drastic and usually lethal in the neonates. Hemizygous males nearly always have complete OFD deficiency. While partial deficiency of OTC in females is compatible with long term survival, the almost total absence of this enzyme may be the cause of neonatal death in males. Most males described died within the first 10 days of life. There have been many unsuccesful attempts at treatment: exchange transfusions, peritoneal dialysis, ketoanalogs of essential aminoacids, mixtures of pyrolidone carboxylate and arginine. In 1975, Gelehrter et al. reported another unsuccessful attempt using n-carbamyl-l-glutamate and l-arginine for therapy —they also suggested administration of glucagon or of citrullin; the most drastic possibility, also mentioned, is hepatic transplantation. In 1975, Snyderman et al. reported a male newborn, sib of a girl with OTC deficiency, who was controlled for 54 days by several exchange transfusions, prolonged peritoneal dialysis, adaequate caloric intake and a mixture of essential aminoacids with an excess of aspartic acid and arginine; he died from an infectious complication. Perhaps this new attempt at therapy offers a possibility of successful treatment in the disease; otherwise its outcome has to be considered fatal.

In 1981, Yokoi et al. suggested that mild disease in males could point to the presence of genetic heterogeneity in this disorder.

Table 7. Interesting pedigrees of FDH in literature

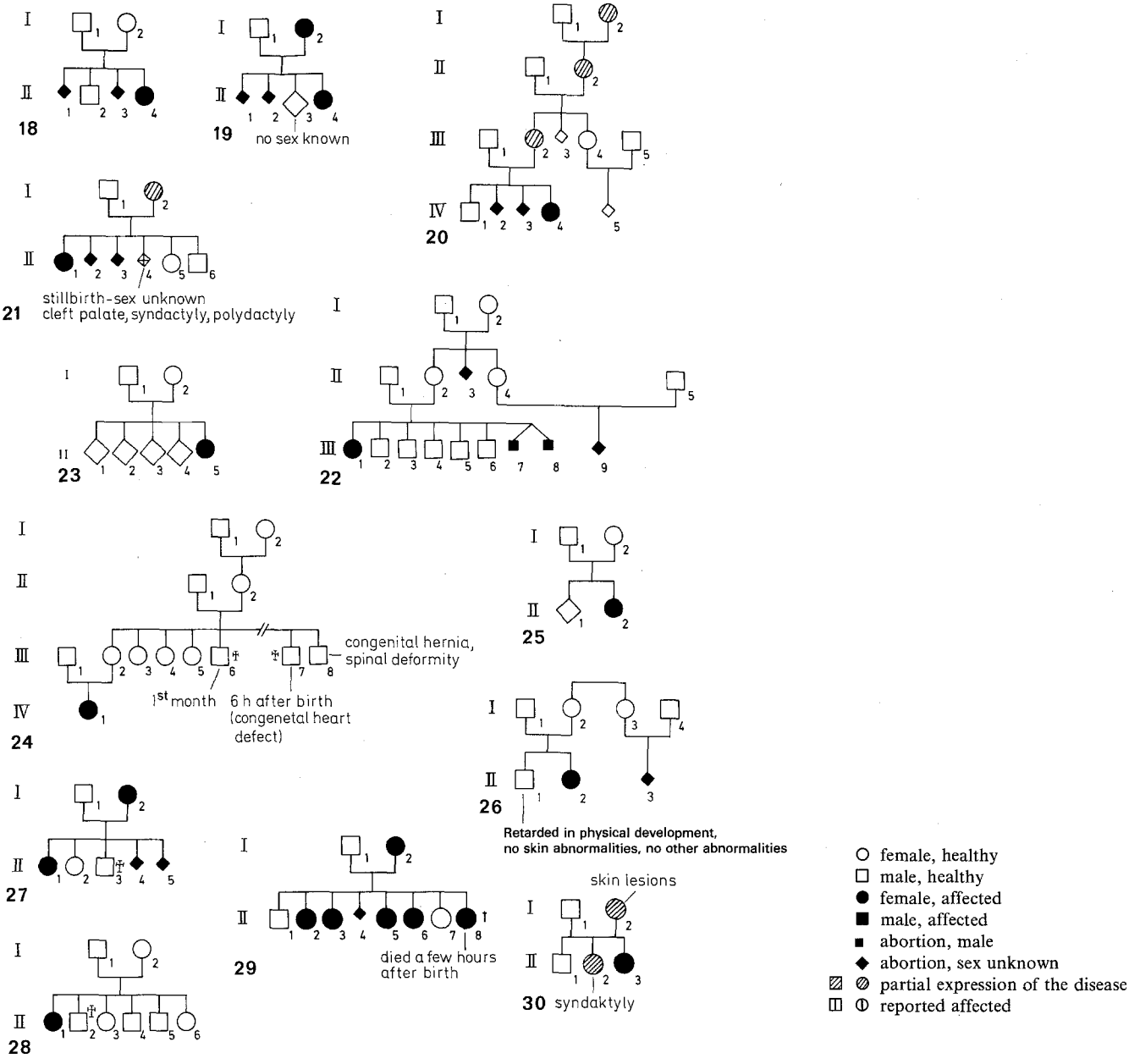


Fig. 18. Pedigree of Braun-Falco and Hofmann (1975). Two abortions in the 4th month, no sex known

Fig. 19. Pedigree of Freeman (1955). Two abortions, no sex known

Fig. 20. Pedigree of Goltz et al. (1962). Four abortions in two generations. ⊘ = show evidence of less severe involvement with the same dystrophy of skin and nails

Fig. 21. Pedigree of Goltz (1962). Two abortions (4th month), 1 stillbirth affected

Fig. 22. Goltz et al. (1962). Also reported by Gorlin (1969). Abortion of male twins

Fig. 23. Pedigree of Goltz et al. (1970). Four younger healthy siblings (no sex known)

Fig. 24. Goltz et al. (1970). Several abortions in two generations

Fig. 25. Pedigree of Hernandez-Perez, cited by Goltz et al. (1970)

Fig. 26. Pedigree of Kunze et al. (1979)

Fig. 27. Pedigree of Michel (1971)

Fig. 28. Pedigree of Michel (1971)

Fig. 29. Pedigree of Ruiz-Maldonado et al. (1974). This pedigree offers strong arguments in favour of X-linked dominant inheritance. The sex ratio 1:6 could be due to an X-linked gene being lethal in hemizygous males

Fig. 30. Pedigree of Wodniansky (1957)

Table 8. Sex-ratio among the healthy siblings of patients with FDH

Author	Patients in one sibship	Healthy siblings		
		Male	Female	No sex
Braun-Falco, Hofmann (1975)	1	1		
Freeman (1955)	1			1
Goltz et al. (1962) a)	1	1		
b)	2	1	1	
c)	1	5		
Goltz et al. (1970) a)	1	No information		
b)	1			4
Hernandez-Perez, cited by Goltz (1970)	1	No information		
Kunze et al. (1979)	1	1—retarded in physical development		
Michel (1971) a)	1	1	1	
b)	1	3	2	
Ruiz-Maldonado et al. (1974)	5(+1)	1	1	
Wodniansky (1957)	2	1		

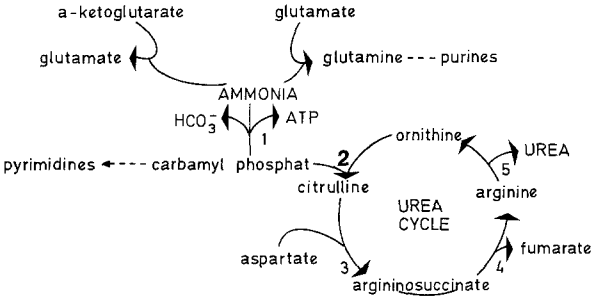


Fig. 31. 1. Carbamyl phosphate synthetase (CPS). **2. Ornithine transcarbamylase (OTC).** 3. Argininosuccinate synthetase (AS). 4. Argininosuccinate lyase (AL). 5. Arginase. Krebs-Henseleit urea cycle and alternate pathways for the detoxification of ammonia. The five urea-cycle enzymes are listed, with their sites of action indicated by numbers. (Taken from the descriptions of Campbell et al. 1973)

In the following, those disorders are included in which X-linked dominace with lethality in hemizygous males has to be discussed thoroughly.

X-linked Chondrodysplasia Punctata (CP)

CP is a congenital defect of bone formation, characterized by the presence of punctate epiphyseal and extra-epiphyseal calcifications (the so-called "stippled epiphyses"). These signs can only be observed in the first years of life. They disappear later, eventually leaving behind severe skeletal changes. Until 1971, CP was regarded as a single nosological entity. However, then Spranger et al. (1971) demonstrated genetic heterogeneity of CP on the grounds of diversities in the clinical picture. He defined two nosological entities with the following cardinal symptoms:

1) Rhizomelic type, which leads to death, usually within the first year of life: severe symmetrical shortening of the extremities and metaphyseal changes, usually bilateral cataracts in $^2/_3$ of the cases; ichthyosiform skin changes in 38% of the cases. This disease is autosomal recessively transmitted.

2) Conradi-Hünermann-type: epiphyseal, often asymmetric calcification and skeletal changes; there are no obvious skin lesions; cataracts have so far not been described in this type (Happle 1981). The mode of inheritance is autosomal dominant. Spranger (1971) subdivided the second type into three subgroups (A, B, C).

Happle et al. (1977) postulated a third distinct type of CP, inherited as a X-linked dominant trait with lethality in hemizygous males. This type, which is of great interest, has some symptoms in common with subgroup B of Conradi-Hünermann-type, but some additional peculiarities are important for differential diagnosis:

1) Skeletal defects: anomalies of the face, limbs, vertebral column with marked asymmetry. The most important finding is the asymmetric shortening of limbs; usually femur and humerus are affected.

2) Ocular anomalies: most frequently unilateral cataracts, being present at birth or developping early in life.

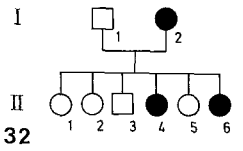
Recently, Happle (1981) suggested using cataracts as a diagnostic marker, allowing differentiation between the three types of CP: a) rhizomelic type: usually bilateral cataracts in $^2/_3$ of the cases; b) X-linked dominant type: often unilateral cataracts in $^2/_3$ of the cases; c) autosomal dominant type: cataracts have not been described so far.

However, Happle stated critically that the lack of cataracts alone does not allow a definite diagnosis, since cataracts may be absent in each of the three types.

3) Cutaneous anomalies, which were described by Happle and Kästner (1979) as follows: "Congenital ichthyosiform erythroderma with thick adherent hyperkeratosis; widespread atrophic skin lesions discernible after the first weeks of life; patchy alopecia; coarse and lusterless hair; onychoschisis. The hyperkeratoses of the newborn as well as the ensuing atrophoderma predominantly involve the hair follicles and are distributed in a bizarre linear or blotchy pattern. In some instances, a linear pattern of pigmentary disturbance has been observed". If present, the pigmentary disturbance may be easily mistaken for IP.

However, Happle states that the cutaneous anomalies might be pathognomic for the condition, thus rendering possible a diagnosis even without X-ray examination.

Manzke (1980) suggested that $^1/_4$ of the cases belong to this third type of CP.



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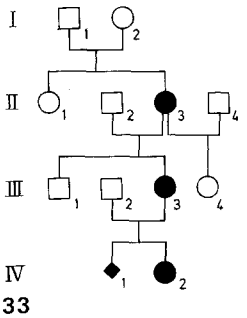

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Fig. 32. Pedigree of Curth (1949)

Fig. 33. Pedigree of Goerttler (1979)

Genetic Aspects of CP

Happle (1979b, 1980) reviewed a total of 40 female cases. Due to the limitation to females so far and the peculiar distribution of skin manifestations, suggesting a functional X-chromosome mosaicism, he postulates X-linked dominant inheritance with lethality in hemizygous males. Furthermore, he states that the marked asymmetry of skeletal and ocular anomalies might also be a manifestation of functional X-chromosome mosaicism. He found familial occurrence in four cases (Curth 1949, Fig. 32; Scott 1971b; Norum et al. 1977; Goerttler 1979, Fig. 33).

Curth (1949) described an affected mother with two affected daughters, three healthy daughters and one healthy son. Goerttler (1979) observed the syndrome in three generations. In a personal communication with Happle, he reported that the affected mother of the proposita had had one abortion in the 2nd month of gestation. The cases of Scott (1971b) and Norum (1977) described mother-daughter transmission (no pedigree available).

The pedigree reported by Bergström et al. (1972) may be of some interest. An affected mother gave birth to a boy with typical signs of CP; the boy died 1 h after birth. Happle suggested that this finding "may represent an example of non-viability of males, carrying the X-linked mutant gene". In addition to Happle, Manzke et al. (1980) also favour X-linked dominant inheritance with lethality in hemizygous males; however, stating that the rate of perceived miscarriages seems not to be increased. Many cases of the X-linked dominant form of CP are sporadic, which might also be indicative for the X-linked dominant form of inheritance. It is also possible that some of these sporadic cases will turn out to be familiar. Happle suggested that there may also exist incomplete forms, not yet recognized. If the linear or blotchy distribution of skin lesions is attributed to functional X-chromosome mosaicism, then this is a good argument for X-linked dominant inheritance with lethality in hemizygous males.

The Cervico-Oculo-Acusticus Syndrome (Wildervanck Syndrome) McKusick's Catalogue No.: 31460

This syndrome was first described as a genetic entity by Wildervanck in 1952; he proposed the term cervico-oculo-acusticus-syndrome. Main clinical features of this syndrome are congenital sensorineural deafness, Klippel-Feil-anomaly, i.e. fusion of the cervical vertebrae resulting in a short neck, and Duane's syndrome, i.e. paralysis of n. abducens, often combined with retractio bulbi. Other anomalies described are: preauricular appendages and fistulae, malformation of the auricle, epibulbar dermoids and lipodermoids, cleft palate, scapula alata—called Sprengel deformity—pseudopapilloedema, heterochromia iridis, kyphoscoliosis, spina bifida, hemivertebrae. Most patients are of normal intelligence, but in some cases, mental retardation has been reported. The estimated frequency of this syndrome among deaf children is about 1–2 per 1000, sometimes higher (Wildervanck 1978). There are 75 females and 7 male known cases (Wildervanck 1978).

A number of isolated cases has been reported without attention to the family history or without further cases in the family. However, Wildervanck (1978) came up to a great number of anomalies by studying thoroughly the family members of patients with the Wildervanck syndrome: deaf-mutism, congenital perceptive deafness, heterochromia iridis, "no neck", Klippel-Feil anomaly, unilateral Duane's syndrome, severe microtia, anencephaly. These findings raise the question whether or not these anomalies may represent a forme fruste of the Wildervanck syndrome.

Nearly all of Wildervanck's patients had normal parents, except one affected female, who was deaf and had retractio bulbi: her father and the father's sister were deaf as well. From literature, there are known only two cases of Wildervanck in which a relative of a patient also showed the syndrome: Waardenburg et al. (1963) reported a girl and paternal aunt affected, and Kirkham (1969) described a girl and paternal aunt affected. If the diagnosis of Widervanck-syndrome in these families was correct, this would be contradictory to the hypothesis of an X-linked dominant trait with lethality in hemizygous males.

All above-mentioned authors agree that genetic factors are involved. Due to the striking preponderance of females, i.e. 75 females : 7 males, McKusick raises the question whether X-linked inheritance with lethality in males could support the Wildervanck syndrome. Wildervanck rather favours polygenic heredity with sex-limitation to females. So does Kirkham (1969), who spoke of "a partly sex-limited gene, acting on a polygenic background which is modified by sex rendering females more susceptible to the action of the gene than males". Konigsmark and Gorlin (1976b) suggested multifactorial inheritance to be the most likely mode of inheritance.

Much more information about the Wildervanck syndrome is needed in order to learn about the formal genetics of the syndrome.

Congenital Cataract with Microcornea or Slight Microphthalmia McKusick's Catalogue No.: 30230

In 1956, Witkop-Oostenrijk described several members in three successive generations of a family having congenital cataract combined with microphthalmia or microcornea. He stated that dominance in transmission seems probable. Since all affected persons had been females, McKusick (1978) suggested X-linked dominance, possibly with lethality in hemizygous males. Waardenburg et al. (1961), in their survey of the literature, came to the conclusion that there is genetic heterogeneity in this eye abnormality which could be inherited either in an autosomal recessive or in a sex-linked way. Furthermore, they stated that cataract with microcornea but without microphthalmia appears to be autosomal dominantly inherited. In 1963, Capella et al. reported two pedigrees demonstrating different modes of inheritance. In one there was sex-linked recessive inheritance, the second pedigree showed autosomal dominant inheritance. These findings of Capella et al. could represent genetic heterogeneity.

Further reports will reveal whether or not this holds true and if there also exists an X-linked dominant form.

Muscular Dystrophy, Hemizygous Lethal
McKusick's Catalogue No.: 30995

In 1967 Henson et al. presented a family in which eight females in two generations showed a limb-girdle form of muscular dystrophy with delayed onset and slow progression. An affected woman, who had three affected daughters, one healthy daughter and one healthy son, had also had one miscarriage. Another woman who had one affected daughter and two healthy sons, had four abortions. One stillbirth was found in a third affected mother. Remarkably, there is a relatively high number of abortions, but unfortunately there is no information about the sex of the aborted fetus and also none about the moment of abortion.

For the limb girdle form of muscular dystrophy with later onset, genetic heterogeneity was observed. Most commonly this type of muscular dystrophy is inherited as an autosomal recessive trait; however, the X-linked Becker-Kiener form also exists. There are many sporadic cases, Henson et al. suppose therefore that the exclusive involvement of females in the family described by him may be explained in the best possible way by an autosomal-dominant pattern of inheritance with limitation of expression in females. In 1969, Heyck and Laudahn reported another family in which two daughters, their mother and their maternal grandmother were affected by the same type of muscular dystrophy. In contrast to Henson et al., Becker (1972) favours the X-linked dominant inheritance with lethality in the hemizygous male. In his opinion, the numerous abortions occurring in the pedigree of Henson are a strong argument in favour of this hypothesis. He further states that the pathoanatomical findings which were described by Henson et al. could be compatible with the Lyon hypothesis. Thus, the hypothesis of X-linked dominant inheritance with lethality in hemizygous males in the family of Henson appears well founded.

Partial Lipodystrophy with Lipatrophic Diabetes and Hyperlipidemia
McKusick's Catalogue, not yet registered

Partial lipodystrophy, confined to the extremities, was first described by Köbberling et al. in 1975. The syndrome consists of partial lipodystrophy, confined to the extremities, lack of heparin releasable lipoprotein lipase activity and is facultatively associated with lipatrophic diabetes, i.e. insulin resistance, lack of ketoacidosis, hyperlipidemia, acanthosis nigrans, hepatomegaly. In 1974, a similar syndrome of partial lipodystrophy of the limbs but also extended to the trunk, was reported by Dunnigan et al. Due to the striking similarities of the two diseases, Köbberling suspected that they would represent a distinct genetic entity which had to be differentiated from the known types of lipodystrophy:

1) congenital total lipodystrophy (Berardinelli-Seip syndrome);

2) acquired total lipodystrophy;

3) partial progressive lipodystrophy limited to trunk and face (cephalo-thoracic lipodystrophy).

Köbberling recently observed a female patient with lipodystrophy as described by Dunnigan. Remarkably, the patient did not have a defect of the heparin releasable lipoprotein lipase,

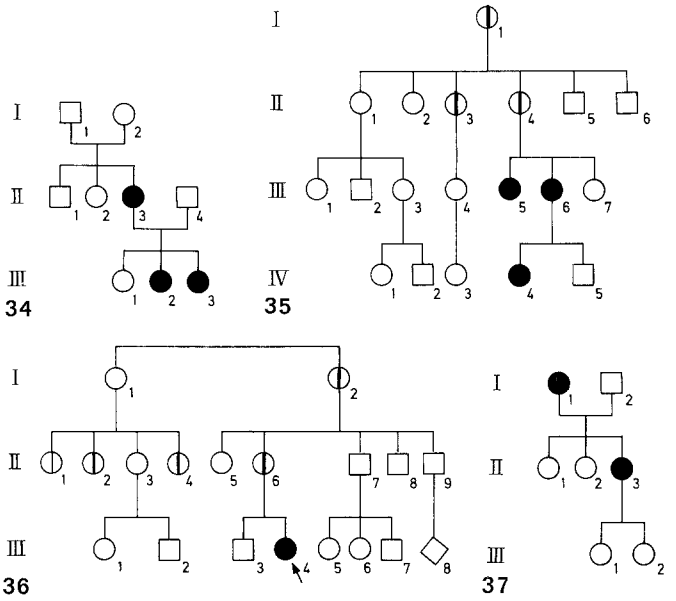

Fig. 34. Pedigree of Köbberling et al. (1975)
Fig. 35. Pedigree of Dunnigan et al. (1975)
Fig. 36. Pedigree of Dunnigan et al. (1975)
Fig. 37. Pedigree of Köbberling (personal communication)

but showed another defect of the lipoprotein pathway, not yet classified. This new finding made Köbberling believe that there might be genetic heterogeneity in the new syndrome of partial lipodystrophy with lipatrophic diabetes and hyperlipidemia.

Köbberling (1975) reported a family in which two female sibs and their mother were affected (Fig. 34) and in addition, two unrelated female patients with unknown family history. Dunnigan et al. (1974) reported two families with several affected persons (Figs. 35, 36). Since these first descriptions of this new type of partial lipodystrophy, further cases were reported (Davidson 1975); Köbberling recently added some more examples of the syndrome (personal communication) (Fig. 37).

The proposed pattern of inheritance is autosomal dominance because affected individuals have been observed in several generations (Köbberling, personal communication). The exclusive involvement of females was explained by the fact that the syndrome has less chance of being detected in males, because of their different anatomy (Köbberling, personal communication). It was Köbberling, who has recently suggested X-linked dominant inheritance with lethality in hemizygous males, because of the unique involvement of females and the sex ratio of 33 females : 19 males in the offspring of affected women. However, no abortions have been reported.

The mode of inheritance is possibly autosomal dominant, but sex limited; however, X-linked dominant inheritance with lethality in hemizygous males is a good alternative. Since there is no occurrence of miscarriages reported, autosomal-dominant sex-limited inheritance seems more likely.

Agenesis of Corpus Callosum with Chorioretinal Abnormality (Aicardi Syndrome)
McKusick's Catalogue No.: 30405

Agenesis of the corpus callosum is an etiologically non-specific anomaly, which may occur as an isolated defect as well as part of a syndrome with multiple congenital anomalies.

In 1969, Aicardi et al. described 16 cases of a disorder which seems to be limited to females. The syndrome consists of infantile spasms, total or partial agenesis of the corpus callosum, characteristic EEG changes, presenting complete asynchrony between the two hemispheres, cortical heterotopias, severe mental retardation, vertebral anomalies and a striking chorioretinopathy—typical punched-out chorioretinal lesions, so-called "retinal lacunae"—which is considered by Aicardi to be pathognomonic of the condition. Never have the patients reproduced.

Aicardi et al. (1969) suggested that the syndrome, which has been described in more than 100 females (Aicardi 1980), may be inherited as an X-linked dominant trait with lethality in hemizygous males. Never has familial occurrence been reported. This finding could be explained by a relatively high fraction of new mutations; Becker (pers. communication with de Jong, 1976) said that the sporadic cases might be new mutations. However, sporadic cases could also have an exogenous etiology, e.g. maternal infection. Bertoni et al. (1979) postulated an unknown intrauterine insult, occurring no later than the first trimester, as a cause of the disorder. In 1981, Musumeci described a case of Aicardi-syndrome combined with cell-mediated immunity deficiency. De Jong et al. (1976) reported two patients with the Aicardi syndrome, who had no pineal gland. He suggested that the absence of the epiphysis cerebri may be incompatible with the development of a viable male child. Ropers and colleagues (1982) described a girl, showing the typical features of the Aicardi syndrome, with a balanced de novo translocation 46,X,t(X;3)(p22;q12).

They agree with the hypothesis of an X-linked dominant trait with male lethality and made the suggestion that the clinical picture in their patient is the consequence of chromosomal breakage, affecting the Aicardi-locus and resulting in a gene mutation or a position effect. Also Dennis and Bower (1972) favour X-linked dominance with lethality in males. In 1979, Hopkins et al. reported the Aicardi syndrome in a Klinefelter male, supporting the hypothesis of X-linked dominant heritance with lethality in hemizygous males. Furthermore, he stated: "An absolute proof would come from an affected mother producing an affected girl, which in view of the severe mental retardation and shortened life expectancy is both unlikely and undesirable." Recently, a second male with normal karyotype was described (Curatolo 1980). Since the pathognomic "retinal lacunae", one of the major diagnostic features, were missing, Hunter (1980) and Aicardi (1980) have doubted that this male case actually represents the Aicardi syndrome.

It remains very likely that this disease belongs to the X-linked dominantly inherited diseases. Thus, the striking predominance of females and the occurrence of the syndrome in an XXY-male give support to the hypothesis of an X-linked dominant trait with male lethality.

Coxo-Auricular Syndrome
McKusick's Catalogue, not yet registered

In 1981, Duca et al. described this new syndrome which is characterized by the following features: shortness of stature, malformation of the middle or external ear (microtia) with corresponding hearing loss, hip dislocation, pelvic and skeletal changes. This syndrome has to be diferentiated from the Beals syndrome which represents auriculo-osteodysplasia.

The fact that a mother and her three daughters were affected, led the authors to the conclusion that the syndrome is autosomal dominantly inherited in this family. Since the mother had one miscarriage and all affected individuals are females, X-linked dominant inheritance with lethality in hemizygous males can be considered also. However, more information is needed.

Nasal Alar Hypoplasia, Hypothyroidism, Pancreatic Achylia, Congenital Deafness (Johanson-Blizzard Syndrome)
McKusick's Catalogue No.: 31048

In 1971, Johanson and Blizzard reported three isolated female cases with a hitherto unrecognized syndrome, consisting of: congenital aplasia of the nasal alae, sensorineural deafness, malabsorption, hypothyroidism, midline ectodermal scalp defect, absent permanent teeth, short stature, mental and motor retardation, urogenital malformations.

The finding of an XXY-male with similar features, but less distinctly expressed which was reported by Grand et al. (1966), was interpreted by Johanson and Blizzard as a "forme fruste" of the same syndrome.

So far, 11 female patients and 8 male patients have been observed (Grand et al. 1966; Morris and Fisher 1967; Townes 1969; Townes et al. 1981; Schussheim et al. 1976; Day and Israel 1978; Mardini et al. 1978; Daentl et al. 1979; Reichart et al. 1979; Bresson et al. 1980; Helin and Jodak 1981).

Genetic aspects of this syndrome which resembles the oculo-dento-digital syndrome, have not been mentioned by Johanson and Blizzard. Konigsmark and Gorlin (1976a) in their survey, stated the possibility of X-linked dominant inheritance with lethality in hemizygous males, because at that time only females and probably one Klinefelter male were known to be affected.

However, Schussheim et al. in 1976 reported a male infant with the Johanson-Blizzard syndrome, whose parents were first cousins, rather suggesting an autosomal recessive trait. Day and Israel (1978) described two male sibs and suggested also autosomal recessive inheritance. This hypothesis was supported by the observation of several affected members in a large family with extensive consanguinity. In 1979, Daentl et al. presented another male case; they also favoured autosomal recessive inheritance. Features strikingly similar to those described by Johanson and Blizzard, were reported by Helin and Jodack (1981) in two siblings, a male and a female. Helin mentioned that if his cases and those collected by Johanson and Blizzard represented the same disorder, the cases of Johanson and Blizzard would be milder forms of the syndrome. He proposed autosomal recessive inheritance.

Thus, the available data from literature offer strong arguments in favour of an autosomal recessive mode of transmission in the Johanson-Blizzard syndrome; the hypothesis of an X-linked dominant trait with lethality in hemizygous males seems very unlikely, unless genetic heterogeneity exists.

CHILD Syndrome = Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects
McKusick's Catalogue No.: 24220;
registered as ascertained autosomal recessive

The term CHILD syndrome was proposed in 1980 by Happle et al. for a syndrome, consisting of unilateral ichthyosiform erythroderma, either present at birth or developing in the first weeks of life, and ipsilateral defects of bones, central nervous system and viscera. Typically, the dermatological changes show

a strict demarcation in the midline of the anterior and posterior trunk.

Happle et al. (1980) reviewed 18 cases, which were previously reported under various designations. The authors were able to add two further cases and suggested that this syndrome may be inherited as an X-linked dominant trait with lethality in hemizygous males. Their arguments in favour of this mode of inheritance are: the sex ratio of 19 females to 1 male, an 11:3 ratio of unaffected sisters to unaffected brothers and the fact that so far five miscarriages and one male stillbirth have been reported. Furthermore, they stated that the linear distribution of the skin alterations, as observed in many patients, could be explained by the Lyon hypothesis. However, the unilateral involvement is not characteristic of the functional X-chromosome mosaicism, so that a further auxiliary hypothesis is necessary for interpretation.

Melnick-Needles Syndrome (MNS) (Osteodysplasty)
McKusick's Catalogue No.: 16610;
registered as ascertained autosomal dominant

This syndrome which was first described in 1966 by Melnick and Needles, is characterized by a severe generalized bone dysplasia with a large variety of skeletal defects and a typical facial appearance with exophthalmus, micrognathia, and full cheeks. In literature there are also reported associated anomalies, especially cardiopulmonary malformations.

Osteodysplasty was first presumed to be inherited as an autosomal dominant trait. However in 1982, Gorlin and Knier reviewed the literature and by cooperation with the authors, who had reported the cases with MNS, they were able to correct the published pedigrees: Melnick reexamined the male cases, especially in the kindred originally reported by him and Needles in 1966, and showed them to be normal. Thus Gorlin and Knier found 23 patients in 15 pedigrees; most cases are sporadic and may represent new mutations, only in 3 pedigrees there is transmission from one generation to another, always female to female. They concluded that X-linked or autosomal dominant inheritance with male lethality are possible explanations for these data. Von Oyen et al. (1982), who found among 24 cases 21 females and 3 males, reported a severely male with multiple congenital anomalies associated with MNS; the boy, who was born to an affected mother, died soon after birth. To their knowledge there is also another case of such a severely affected male child, born to a mother with MNS, reported in the literature (Theander and Ekberg 1981). They suggested that there may be a large clinical variability in the MNS and stated that the sex-ratio of 21:3 may be caused by the more severe affliction of males. They supposed X-linked dominant or autosomal dominant sex-limited inheritance to be most likely interpretations. Ter Haar et al. (1982) reported a family with 3 patients with MNS; because of the fact that two sibs of different sex and one third cousin, whose parents are first cousins, were affected, they postulated an autosomal recessive mode of inheritance of the syndrome in this family.

More data have to be awaited to clarify which mode of inheritance will hold true in this syndrome, or whether there exists genetic heterogeneity.

Concluding Remarks on Genetic Counselling

In Diseases with X-linked Dominant Inheritance with Lethality in Hemizygous Males

In IP, OFD syndrome, FDH and X-linked CP, X-linked dominant inheritance with male lethality is relatively well established. In the Aicardi syndrome also, this mode of inheritance is very likely; however, it is less clearly determined than in the four diseases mentioned above. With regard to these disorders, the following aspects should be considered in genetic counselling.

An affected woman is to be informed about her increased risk of theoretically 25% of having a miscarriage of a male embryo, and her risk of 50% for her female offspring being affected. Assuming that affected hemizygous males usually die early in utero, affected women actually will have a chance of $\frac{1}{3}$ of giving birth to a healthy daughter, $\frac{1}{3}$ to a healthy son and $\frac{1}{3}$ to an affected daughter.

An isolated case in a family most likely will represent a new mutation; however, familial occurrence should be excluded by careful examination of the family members, specifically for microsymptoms in the mother of an affected child.

All male cases should be studied chromosomally in order to find out whether they have a normal karyotype (46,XY) or whether they are Klinefelter males (47,XXY).

Since in OTC deficiency there is also X-linked dominant inheritance, but with lethality in hemizygous newborn males, an affected woman should know that she has a risk of 50% for each female and each male child of being affected and that affected males will usually die in the neonatal period.

In Diseases with Uncertain Mode of Inheritance

Genetic counselling in the remaining disorders, Wildervanck syndrome, congenital cataract with microcornea or slight microphthalmia, limb girdle form of muscular dystrophy with later onset, partial lipodystrophy with lipatrophic diabetes and hyperlipidemia, coxo-auricular syndrome and Johanson-Blizzard syndrome, presents difficulties. In general, there are not yet enough data available for a clarification of the formal genetics in each disease. Today, in most of these diseases genetic heterogeneity is assumed, whereas in the Johanson-Blizzard syndrome evidence for an autosomal recessive mode of inheritance seems to increase.

Finally, it can be concluded that in these above-mentioned diseases no generally valid advices can be given and that genetic counselling has to be carefully adapted to each individual family.

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