

# Popliteal pterygium syndrome

## A phenotypic and genetic analysis

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**SUMMARY** Two additional families with popliteal pterygium syndrome are presented. Using previously published pedigrees, as well as the ones reported here, evidence is presented that supports an autosomal dominant mode of inheritance for this syndrome. Analysis of previous familial cases showed a large degree of between and within-family variation. The segregation analysis supports the dominant hypothesis ( $P = 0.5$ ).

The finding of cleft lip and/or palate, congenital sinuses of the lower lip, popliteal pterygium, and genital anomalies in any combination was first termed popliteal pterygium syndrome by Gorlin and Pindborg in 1964. Rintala and Lahti (1970), on the basis of the term not being fully descriptive, suggested the eponym facio-genito-popliteal syndrome. Nevertheless, it is the original term which is commonly used. The pathogenesis of the syndrome is obscure, though it has been suggested (Rintala and Lahti, 1970) that the hereditary factor involved predisposes to developmental arrest (Pashayan *et al.*, 1974).

The first description of the syndrome seems to be that of Trélat in 1869. Since that time approximately 45 cases have been published. Though most cases have been sporadic, the condition has been transmitted from affected parents to one or more children (Lewis, 1948; Klein, 1962; Hecht and Jarvine, 1967; Kind, 1970; Pfeiffer, 1970; Frohlic *et al.*, 1977). In a few other families, the parents have been normal but several sibs have been affected (Kopits, 1937; Champion and Cregan, 1959; Rosselli and Gulienetti, 1961; Bixler *et al.*, 1973). A thorough pedigree analysis has never been performed; nevertheless, the mode of inheritance of the popliteal pterygium syndrome is commonly thought of as an autosomal dominant (Hecht and Jarvine, 1967; Gorlin *et al.*, 1976) though recessive inheritance (Bartsocas and Papas, 1972) and even multifactorial inheritance have been suggested (Kind, 1970). It is the purpose of this paper (1) to describe two additional families with the popliteal pterygium syndrome; (2) to review the published familial cases and show the large intra- and

inter-familial variation seen in this syndrome, and (3) using segregation analysis, to present data supporting an autosomal dominant mode of inheritance.

### Subjects and methods

#### (A) CASE REPORTS

A 4-month-old white boy (family no. 23269) was seen in the Department of Medical Genetics because of his numerous congenital anomalies including bilateral cleft lip and palate and popliteal webbing. He was the product of a full-term pregnancy which was complicated by a urinary tract infection in the first trimester. The mother was Caucasian, 18-years-old and  $G_1P_1A_0$  at the time of delivery. The father was 24 years old and unrelated to the mother. Physical examination of the boy disclosed typical findings of the popliteal pterygium syndrome including: prominent occiput, low set hypoplastic left ear, ankyloblepharon filiforme, bilateral cleft lip and palate, congenital sinuses of the lower lip, and syngnathia (Fig. 1). In addition, the sternum was short, the umbilicus was low in the abdomen, and phimosis was present, as well as right inguinal hernia. The arms and legs showed limitation to full extension. A distinct popliteal webbing, particularly on the left side, can be seen extending from the upper thigh to the heel (Fig. 2). Partial cutaneous syndactyly of the 4th and 5th toes was present bilaterally. The nails were dysplastic with a skin bridge over the great toe. Family studies showed that the father had a bifid uvula and a paternal aunt had polydactyly in one foot.

Clinical findings of the popliteal pterygium syndrome were also seen in another medical genetics

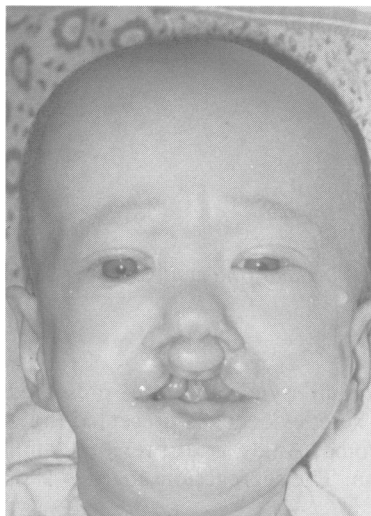


Fig. 1 *Proband family 23269. Notice ankyloblepharon filiforme, bilateral cleft lip, and congenital sinuses of the lower lip.*



Fig. 2 *Leg of proband in family 23269. Notice popliteal webbing.*

clinic patient, MC (family number 896), a 6-year-old white boy (Fig. 3). He was the product of a 36-week-old uncomplicated pregnancy. His development had been normal, though he had had asthma since the age of 3. At the time of delivery the mother was 20 years old and had had a previous pregnancy which aborted. She has subsequently had 4 more pregnancies which resulted in a boy, 2 miscarriages, and a girl. The father was also 20 years old and was unrelated to the mother. The patient (MC) presented with flat occiput,

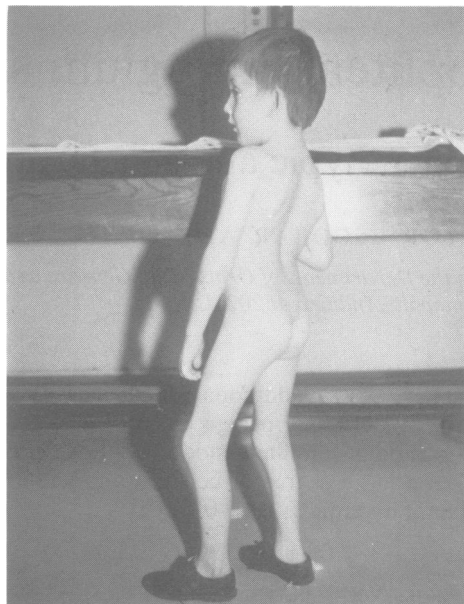


Fig. 3 *Proband in family 896. Notice popliteal webbing.*

facial asymmetry, cleft palate, low set-hypoplastic ears, thoracic kyphoscoliosis, and lumbar lordosis. The hands were small with bilateral simian creases and normally located axial triradii. The genitalia were male, with left undescended testis and inguinal hernia. Popliteal webbing and syndactyly of the 4th and 5th toes bilaterally were also present. Radiological examination showed bifid ribs and anomalies of the thoracic and lumbar vertebrae suggestive of occult spinal disraphism. Further study of family 896 disclosed that the mother, one of her sisters, and one of her sister's daughters also had bilateral syndactyly of 4 and 5 toes.

#### (B) PHENOTYPIC AND SEGREGATION ANALYSES

In an attempt to understand the apparent intra- and interfamilial phenotypic variation we analysed all the positive family histories that could be ascertained from the published material which provided detailed description of the affected individuals (Table 1). It was assumed that if a trait was not mentioned by the investigator, it was not present. In order to determine if there were any recognisable differences between familial and nonfamilial cases of popliteal pterygium syndrome, a group of isolated patients with this condition, who had been fully described, was collected from the literature (Table 2).

Since the available evidence suggests a dominant mode of inheritance for the popliteal pterygium

Table 1\* Between and within-family phenotypic variation

	Family number†											Percentage of all affected individuals
	1	2	3	4	5	6	7	8	9	10	11	
No. of affected in family	3	3	2	2	3	3	2	3	2	2	3	
<i>Orofacial</i>												
Ankyloblepharon filiforme	0	0	2	1	0	1	0	0	1	0	0	17.9
Cleft lip ± palate	3	3	2	1	3	3	2	3	2	2	3	96.4
Lower lip pits	3	3	2	2	1	3	2	1	1	1	0	67.9
Ankyloglossia	2	0	0	0	0	0	0	0	0	0	0	7.1
Syngnathia	2	3	3	1	0	2	0	0	2	2	2	53.6
Micrognathia	0	0	0	0	0	0	0	0	0	0	0	—
Epicanthal folds	0	1	0	0	0	0	0	3	0	0	0	14.3
Hypoplastic ear lobes	0	0	0	0	0	0	0	0	1	0	0	3.6
<i>Cutaneous and musculoskeletal</i>												
Popliteal pterygium	2	2	2	1	2	3	2	3	2	2	2	82.1
Spina bifida occulta	0	0	0	1	0	0	0	2	2	0	0	17.9
Scoliosis/lordosis	0	0	0	1	0	0	0	2	0	0	0	10.7
Hypoplastic/absent digits	0	0	0	0	0	0	2	0	2	0	0	14.3
Hand syndactyly	0	0	0	0	0	0	0	3	0	0	0	10.7
Bipartite/absent patella	0	0	0	0	0	0	0	0	0	0	0	—
Varus/valgus deformity of feet	1	0	1	1	0	0	0	3	1	0	0	25.0
Syndactyly of toes	1	1	2	2	0	0	2	3	0	2	0	46.4
Pyramidal skin bridge over great toe	1	2	2	1	0	0	1	1	2	2	2	50.0
Hypoplastic toe nails	2	2	2	2	0	0	2	0	2	0	1	46.4
Brachydactyly of toes	1	0	2	0	0	0	2	0	0	0	2	25.0
Metatarsal fusion	1	0	0	0	0	0	0	0	0	0	0	3.6
Hypoplastic/supernumerary nipples	0	1	0	0	0	0	0	0	1	0	0	7.1
Oligohydramnios	0	0	0	0	0	0	0	0	1	0	0	3.6
Arthrogriposis	0	0	0	0	0	0	0	0	2	0	0	7.1
<i>Genitourinary</i>												
Cryptorchidism	1	0	0	0	0	0	0	1	1	0	0	23.1*
Absent/cleft/ectopic hypoplastic scrotum	1	1	0	0	0	0	0	0	1	0	0	23.1*
Small penis	0	1	0	0	0	0	0	0	1	0	0	15.4*
Inguinal hernia	0	0	0	0	0	0	0	0	0	0	0	—
Hypoplastic/absent labia majora	0	1	2	0	0	0	0	0	1	1	2	53.3 <sup>b</sup>
Clitoromegaly	1	0	1	0	0	0	0	0	1	0	1	26.7 <sup>b</sup>
Intercrural pterygium	1	1	2	0	0	0	2	0	2	1	0	32.1
Mental retardation	0	0	0	0	0	0	0	0	0	1	0	—

\*Numbers in this Table represent affected persons who show the trait in each family.

<sup>a</sup> = % based on males only.

<sup>b</sup> = % based on females only.

†The family numbers represent reference numbers as follows: 1 and 2 = Hecht and Jarvine (1967), 3 = Kind (1970), 4 = Klein (1962), 5 = Lewis (1948), 6 = Pfeiffer (1970), 7 = Champion and Cregan (1959), 8 = Kopits (1937), 9 = Rosselli and Gulienetti (1961), 10 = Bixler *et al.* (1973), and 11 = Frohlic *et al.* (1977).

syndrome (Lewis, 1948; Klein, 1962; Hecht and Jarvine, 1967; Kind, 1970; Pfeiffer, 1970; Frohlic *et al.*, 1977) we decided to test the hypothesis of dominance ( $P = 0.5$ ). To accomplish this, segregation analysis on the data using the Weinberg proband method (Weinberg, 1927) under the assumption of single selection with probability of ascertainment ( $\pi$ ) equal to zero ( $\pi = 0$ ) was performed. Therefore, the estimate of  $p(\hat{p})$  was computed as  $\hat{p} = \sum (r - 1) / \sum (s - 1)$  where  $r$  is the number of affected persons in a sibship of size  $s$  and where summation is over all sibships. Since  $\pi = 0$ , this estimate ( $\hat{p}$ ) is a maximum likelihood which is fully efficient and whose variance is:  $V\hat{p} = \hat{p}\hat{q} / \sum (s - 1)$  (Crow, 1973).

## Results

The basic data for the analysis are derived from patients described in the literature (Tables 1 and 2) who presented typical findings of popliteal pterygium syndrome. The combined data indicate that the most consistent malformations in this syndrome, both within and between families (Table 3) are popliteal pterygium (96%), cleft lip and/or palate (93%), lower lip congenital sinuses (56%), genital anomalies (57.1%), and syndactyly of the toes (51%). Other malformations like intraoral connective tissue bands, pyramidal skin bridge over the great toe-nail, and hypoplastic toe-nails are present in about a third of the patients but their within-family variation is very high.

Table 2 Phenotypic variation of popliteal pterygium syndrome among sporadic patients from literature

	Individual number*																	Percentage of occurrence
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Sex	M	F	F	M	M	F	F	F	F	F	M	M	F	F	M	M	F	
<i>Orofacial</i>																		
Ankyloblepharon filiforme	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	+	+	29.4
Cleft lip ± palate	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	88.2
Lower lip pits	-	+	+	-	-	-	-	+	-	-	-	-	-	-	+	+	+	35.3
Ankyloglossia	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	17.6
Syngnathia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Micrognathia	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	5.9
Epicanthal folds	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypoplastic ear lobes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Cutaneous and musculoskeletal</i>																		
Popliteal pterygium	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100.0
Spina bifida occulta	+	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	17.6
Scoliosis/lordosis	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.9
Hypoplastic/absent digits	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	11.8
Syndactyly of the fingers	-	-	+	+	+	+	+	+	+	+	-	-	+	-	-	-	-	41.2
Bipartite/absent patella	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.9
Varus/valgus deformity of feet	-	+	+	-	+	-	-	+	-	-	-	+	-	-	-	-	-	29.4
Syndactyly of toes	-	-	+	+	-	-	+	+	-	-	-	+	+	+	+	-	+	58.8
Pyramidal skin bridge over great toe	-	+	-	+	-	-	+	+	+	-	-	-	-	-	-	-	+	35.3
Hypoplastic toe nails	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	11.8
Brachydactyly of toes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metatarsal fusion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypoplastic/supernumerary nipples	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oligohydramnios	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	5.9
Arthrogriposis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Genitourinary</i>																		
Cryptorchidism	-	-	-	-	-	-	-	-	-	-	+	+	-	-	+	+	-	57.9 <sup>a</sup>
Absent/cleft/ectopic hypoplastic scrotum	-	-	-	-	+	-	-	-	-	-	+	+	-	-	-	-	-	42.8 <sup>a</sup>
Small penis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inguinal hernia	-	-	-	+	-	-	-	-	-	-	+	+	-	-	-	+	-	23.5 <sup>a</sup>
Hypoplastic/absent labia majora	-	+	-	-	-	+	+	+	+	-	-	-	+	-	-	+	-	70.0 <sup>b</sup>
Clitoromegaly	-	-	-	-	-	-	+	+	+	-	-	+	-	-	-	-	-	20.0 <sup>b</sup>
Intercrural pterygium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	11.8
Mental Retardation	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.9

\*Individual numbers represent the references as follows: 1 = Kopits (1937), 2 = Trélat (1869), 3 = Wolff (1889), 4 = Rydgier (1891), 5 = Basch (1890), 6 = Basch (1892), 7 = Fisher (1893), 8 = Hackenbroch (1924), 9 and 10 = Aberle-Horsteneegg (1937), 11 = Marquandt (1937), 12 = Schramm (1940), 13 = Schönenberg (1955), 14 = Dahmen (1961), 15 = Fèvre and Languépin (1962), 16 = Gorlin *et al.* (1868), 17 = Pashayan *et al.* (1974).

<sup>a</sup> = % based only on males.

<sup>b</sup> = % based only on females.

+ = present.

- = absent.

The rest of listed malformations were present in less than 25% of the affected individuals and show a random occurrence among the two groups (Tables 1 and 2). From this series, it seems that genital anomalies are a relatively frequent complication of this syndrome. Mental retardation has not been considered a part of this disorder before; however, 6.7% of our patients presented with this complication. From the analysis of the pedigrees and description of the affected patients we concluded that the minimum diagnostic criteria for popliteal pterygium syndrome should include at least, in the absence of a positive family history, any three of the following: cleft lip ± palate, popliteal pterygium, lower lip congenital sinuses, genital anomalies, or toe anomalies. This of course, does not mean, though it would be unlikely, that a single isolated case with some features of this

condition but without the above anomalies does not have the popliteal pterygium syndrome. In the kinships analysed (Fig. 4), there were 59 individuals, 28 of whom were affected. The female-to-male ratio (15/13) is not significantly different from the 1:1 ratio ( $P > 0.05$ ) which is expected if there is no sex influence or linkage.

If the popliteal pterygium syndrome is inherited as an autosomal recessive trait, approximately one-fourth of the offspring in matings in which both parents are heterozygotes will be affected. Using the binomial probability distribution, the probability of observing at least 8 affected children (twins are MZ, therefore counted as one) in the pedigrees with normal parents (Fig. 4) is 0.00106, a rare event. If the popliteal pterygium syndrome is autosomal dominant, the probability of observing at least 8 affected children in

Table 3 Comparison of our patients with those reported in literature

	Case 1 (BM)	Case 2 (MC)	Combined percentage of isolated and familial cases
<i>Orofacial</i>			
Ankyloblepharon filiforme	+	—	22.2
Cleft lip ± palate	+	+	93.3
Lower lip pits	+	—	55.6
Ankyloglossia	—	—	4.4
Syngnathia	+	—	40.4
Micrognathia	—	—	2.2
Epicanthal folds	—	—	8.9
Hypoplastic ear lobes	+	+	2.2
<i>Cutaneous and musculoskeletal</i>			
Popliteal pterygium	+	+	95.6
Spina bifida occulta	—	+	17.8
Scoliosis/lordosis	—	+	11.1
Hypoplastic/absent digits	—	—	13.3
Syndactyly of fingers	—	—	24.4
Bipartite/absent patella	—	—	2.2
Varus/valgus deformity of feet	—	—	26.6
Syndactyly of toes	—	+	51.1
Pyramidal skin bridge over great toe	+	+	44.4
Hypoplastic toe nails	+	—	33.3
Brachydactyly of toes	—	—	15.6
Metatarsal fusion	—	—	2.2
Hypoplastic/supernumerary nipples	—	—	4.4
Oligohydramnios	—	—	4.4
Arthrogriposis	+	+	4.4
<i>Genitourinary</i>			
Cryptorchidism	—	+	35.0 <sup>a</sup>
Absent/cleft/ectopic hypoplastic scrotum	—	—	30.0 <sup>a</sup>
Small penis	+	—	40.0 <sup>a</sup>
Inguinal hernia	+	+	8.9
Hypoplastic/absent labia majora	—	—	60.1 <sup>b</sup>
Clitoromegaly	—	—	24.0 <sup>b</sup>
Intercrural pterygium	—	—	24.4
Mental retardation	—	—	6.7

<sup>a</sup> = % of males.

<sup>b</sup> = % of females.

the same pedigrees becomes 0.113, a more likely event. A careful inspection of the pedigrees (Fig. 4) also suggests that the popliteal pterygium syndrome is transmitted as an autosomal dominant. A segregation analysis of the data supports that hypothesis ( $P = 0.5$ ). The maximum likelihood estimate of ( $\hat{p}$ ) was found to be 0.45. When inappropriately applied, this method tends to underestimate the value of 'p'. However, in this case the value obtained has wide 95% confidence limits because the numbers are small (i.e.  $0.45 \pm (1.96)(0.106)$  or 0.252 to 0.658), which would accommodate the theoretical value for p of 0.50. Thus, in this series the popliteal pterygium syndrome behaves as an autosomal dominant trait with variable expressivity and incomplete penetrance (90%).

## Discussion

The clinical findings of the two patients described here were most suggestive of the popliteal pterygium syndrome. Though no similar abnormalities were present in the parents it is interesting that in family 23269 the father had a cleft uvula and in family 896 the mother and two other relatives also had syndactyly

of the toes. We acknowledge that it is somewhat presumptive to suggest that these individuals are mildly affected, since toe syndactyly may be by itself an autosomal dominant trait (McKusick, 1975); nevertheless, non-penetrance of the dominant gene for popliteal pterygium syndrome in these people cannot be ruled out. To this end, it is important to notice that the few documented familial cases (Table 2) show a wide variation in gene expression in the affected relatives. Frohlic *et al.* (1977) observed a father whose only manifestation was cleft lip and palate but who had two children with the full syndrome. Hecht and Jarvine (1967) also observed two families with dominant transmission; in one, the affected parent had a cleft lip and palate with bilateral lip pits. Lewis (1948) described a father who also had cleft lip and palate as the only stigmata of the syndrome but whose two children exhibited the full expression of the gene. On the other hand, a very severely affected individual gave birth to a daughter whose only indication of being affected were lip pits and nail dysplasia (Klein, 1962). Though with all probability these individuals all had the same genetic disorder they differed significantly in the malformations they presented. Many other examples of such within-family variation could be

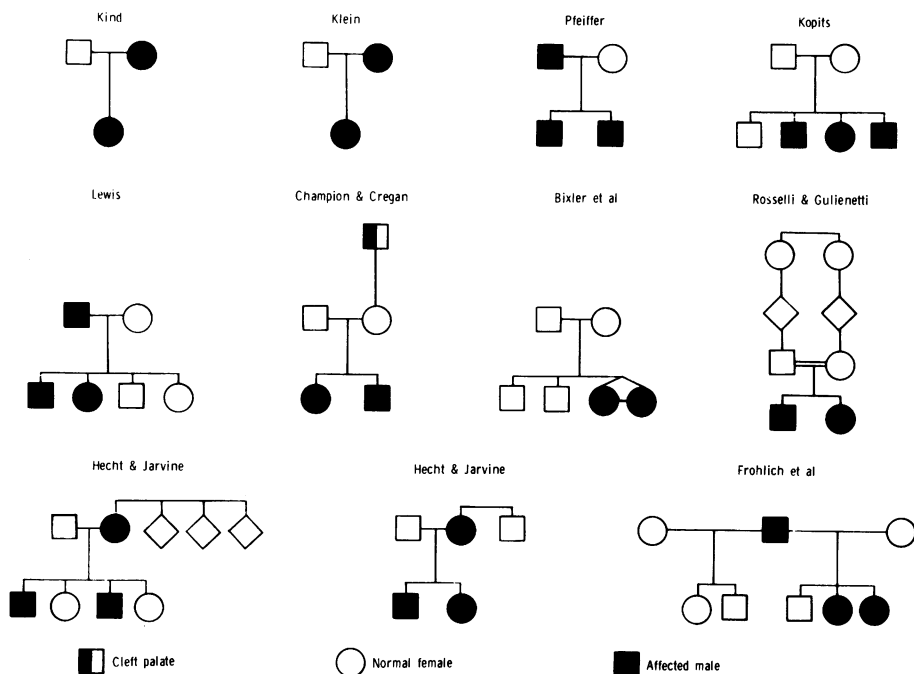


Fig. 4 Published pedigrees of patients with popliteal pterygium syndrome.

cited as examples of gene pleiotropic effect. By recognising the existence of pleiotropy in families with the popliteal pterygium syndrome, one may make the diagnosis in a mildly affected kinsperson. On the other hand, if one suspects this condition in an individual who lacks the major features, the diagnosis can be comfortably made by finding a typically affected relative. A case in point is the one reported by Newman and Shulman (1961) who presented with cleft palate, lip pits, intraoral bands, and ankyloblepharon filiforme but lacked pterygia. In our opinion, this patient probably represents a mild expression of the popliteal pterygium syndrome.

The syndrome appears to be rare though numerous examples have been reported in the German literature and in the patients whose chromosomes have been investigated no abnormalities have been reported (Hecht and Jarvine, 1967; Gorlin *et al.*, 1968; Bajaj and Bailey, 1969; Rintala and Lahti, 1970). The relatively frequent occurrence of affected sibs with normal parents and the consanguinity present in one family (Rosselli and Gulienetti, 1961) suggested to Bartsocas and Papas (1972) that two forms of the syndrome might exist, a mild autosomal dominant and a more severe autosomal recessive form with multiple additional anomalies. In their family (Bartsocas and Papas, 1972) 4 out of 7 sibs, the products of a consanguineous mating, were affected. The anomalies

noted included those of the popliteal pterygium syndrome along with corneal aplasia, microcephaly, and aplasia of thumbs. We believe that their report, indeed, represents a recessively inherited syndrome which is not the popliteal pterygium syndrome. The same authors included in their study the family reported by Matolcsy (1936) in which a brother and a sister, born to normal parents, were affected with multiple pterygia of the popliteal space, axilla, elbow, and neck but who lacked other commonly observed features of the popliteal pterygium. This family may actually be the first description of the multiple pterygium syndrome, a separate disorder.

Bixler *et al.* (1973) have suggested that the family reported by Rosselli and Gulienetti (1961) represented the same syndrome reported by Bartsocas and Papas (1972). However, Gorlin *et al.* (1968) believe it to be the popliteal pterygium syndrome, and we agree with the latter authors.

Older paternal age has been implicated in the production of fresh mutations in several autosomal dominant malformation syndromes, for example Apert syndrome (Erickson and Cohen, 1974) and achondroplasia (Murdock *et al.*, 1970). In the majority of the cases, however, insufficient data have been available for analysis, primarily because of the rarity of the disorders involved; nevertheless, fresh mutations or phenocopies are usually suspected to be responsible

for most of the sporadic cases seen. In the popliteal pterygium syndrome, 17 of the patients reported in this series were sporadic. Since paternal age information is not available to us we cannot complete the analysis but there is the possibility that these cases actually represent new mutations of an autosomal dominant gene. Since genital anomalies occur in this syndrome, we suspect that the fitness of affected individuals is reduced, accounting for the rarity of familial cases.

The differential diagnosis of the popliteal pterygium syndrome should include isolated occurrences of cleft lip and/or palate, the Van der Woude syndrome, and the multiple pterygium syndrome. However, in the latter pterygium of the axilla, neck, elbows, and popliteal areas are also present without lip pits and in the Van der Woude syndrome no pterygium, syngnathia, or ankyloblepharon are seen.

In summary, here we have presented data supporting the variable expression of an autosomal dominant gene that produces a spectrum of facial, genital, and musculoskeletal abnormalities—the popliteal pterygium syndrome. We are not, however, in the position of completely ruling out genetic heterogeneity but on the basis of the data presented here we feel very confident in stating that the popliteal pterygium syndrome, in most cases, is inherited as an autosomal dominant trait with variable expressivity and incomplete penetrance.

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