Popliteal pterygium syndrome: a clinical study of three families and report of linkage to the Van der Woude syndrome locus on 1q32

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Abstract

Popliteal pterygium syndrome (PPS) is a rare autosomal dominant disorder, thought to occur with an incidence of approximately 1 in 300 000 live births. The main clinical manifestations are popliteal webbing, cleft lip, cleft palate, lower lip pits, syndactyly, and genital and nail anomalies. This report describes the clinical features in two families with PPS and one isolated case, showing the range of anomalies found both within and between the families. PPS has some features in common with Van der Woude syndrome (VWS), also inherited as an autosomal dominant condition, with cleft lip/palate and, more distinctively, lower lip pits. Although the gene for VWS has not yet been identified, it has been localised to within 1.6 cM in the region 1q32-41. To determine whether PPS and VWS represent allelic forms of the same gene, three families were genotyped for markers flanking and within the critical region. A multipoint lod score of 2.7 was obtained, with no evidence of recombination, supporting the hypothesis that these two disorders are allelic.

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Keywords: pterygium; van der Woude syndrome; cleft lip; cleft palate

Popliteal pterygium syndrome (PPS) is a rare autosomal dominant disorder, thought to occur with an incidence of approximately 1 in 300 000 live births.[1] It was first described by Trelat[2] in 1869. The main clinical manifestations are popliteal webbing (58%), cleft lip (58%), cleft palate (93%), lower lip pits (46%), syndactyly (50%), genital anomalies (37%), and nail anomalies (33%). Other reported clinical features include syngnathia, ankyloblepharon, talipes, and digital reduction defects.[3] There is no growth disturbance and intelligence is usually normal. It is an autosomal dominant condition which shows both inter- and intrafamilial variation.[3–6]

This syndrome has some features in common with the Van der Woude syndrome (VWS), also inherited as an autosomal dominant condition.[7] VWS is the most frequent form of syndromic orofacial clefting, accounting for up to 2% of all cleft cases, and is one of the rare monogenic syndromes where clefts of both the primary and secondary palate are seen within the same family.[8] Lower lip pits or eminences are present in approximately 80% of gene carriers and around 50% are thought to have a cleft (one third cleft of the palate alone and two thirds cleft of the lip with or without cleft palate). These pits, which may resemble a depression or furrow, represent the opening of a tract leading from a mucous gland embedded in the lip.[7] Although the gene for VWS has not yet been identified, it has been localised to within 1.6 cM in the region 1q32-41, between the markers D1S205 and D1S491.[9] The maximum size of the critical region is approximately 850 kb. There is no evidence of genetic heterogeneity for VWS. Owing to the phenotypic overlap between these two syndromes, the gene for VWS can be considered a suitable candidate for PPS.

We report the clinical findings in previously unreported families (table 1) and present the linkage analysis data, consistent with linkage to 1q32.

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Table 1 The phenotypes of the individual family members

Family number	*1*	*1*	*1*	*1*	*1*	*2*	*2*	*2*	*3*	*4*	*4*	*4*
Subject number	*II.1*	*II.3*	*III.1*	*III.2*	*III.4*	*II.2*	*III.1*	*III.2*	*II.3*	*I.1*	*II.1*	*II.2*
Sex	M	M	F	F	F	M	M	M	F	M	M	F
Orofacial												
Cleft lip	−	−	−	−	++	++	++	−	−	++	+++	+++
Cleft palate	−	−	++	+	++	++	++	++	++	++	++	++
Lower lip pits	−	−	−	−	−	+	++	+++	+	++	+++	++
Oral synechiae	−	−	+	−	−	+	+++	+++	++	++	+++	++
Thin upper lip	+	+	+	+	+	+	+	+	+	+	+	+
Ankyloblepharon	−	−	−	+	+	−	+	+	−	−	+	−
Cutaneous/musculoskeletal												
Hand syndactyly	−	−	−	−	+	+	−	−	+	−	−	−
Toe syndactyly	+	+++	+	+++	++	+++	−	−	++	++	++	++
Popliteal web	++	++	−	+++	++	++	−	−	+	++	++	+++
Triangular overgrowth over big toe	?	+	−	+		+	−	−	−	+	++	+
Bifid toenail	−	−	−	−	−	−	−	−	+	−	−	−
Genitalia												
Hypoplastic labia majora/scrotum	?	+	−	++	++	++	−	++	++	−	+++	++
Abnormal pubic hair	?	+	+	++	++	++			++	+	+	+

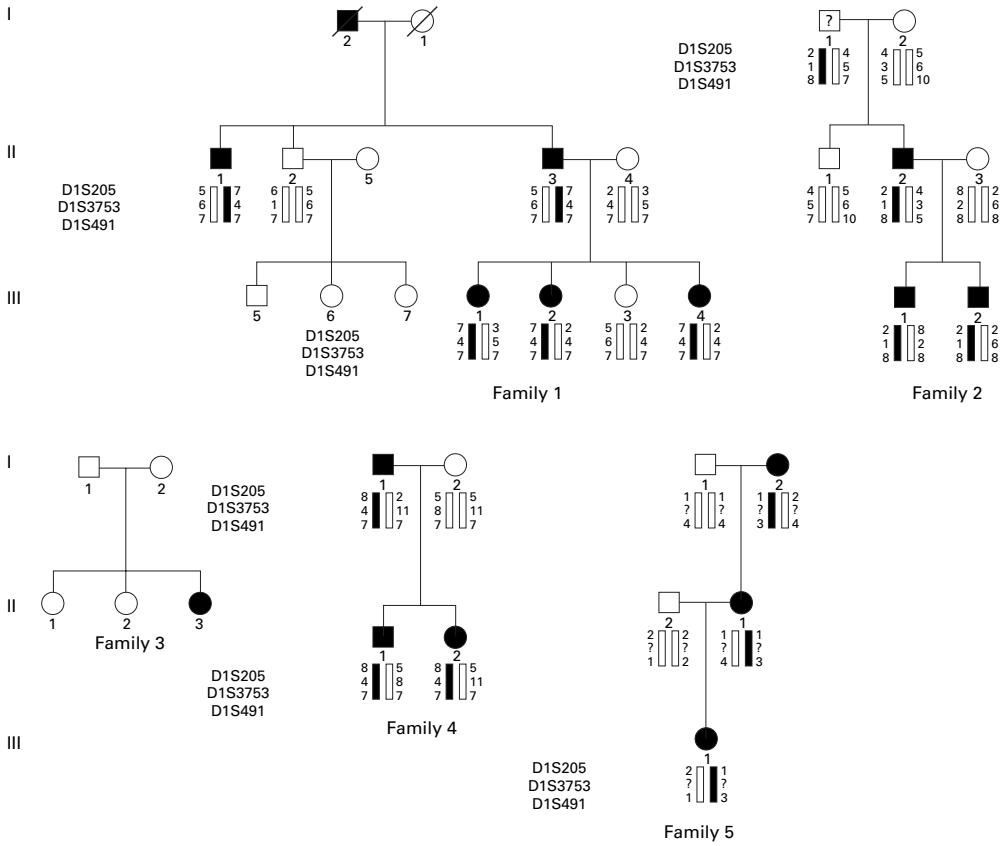

Figure 1 Pedigrees of families 1-5, showing the haplotypes for pedigrees 1, 2, 4, and 5. Filled symbols represent affected subjects.

Case reports

FAMILY 1

The proband initially presented to the genetics clinic at the age of 28 years, requesting preconceptional counselling (fig 1, family 1, III.2). A diagnosis of popliteal pterygium syndrome (PPS) had previously been made. There was a family history of PPS, with her father, paternal uncle, and two of her three sisters also affected. On examination she was found to be quite severely affected, with extensive popliteal webs bilaterally, extending from the ischial tuberosities to the Achilles tendons (fig 2A, B). These had been managed conservatively with regular physiotherapy, as vascular and nervous tissue within the pterygium was considered to be at risk if divided surgically. The webbing prevented extension at the knees, which were held in fixed flexion at an angle of approximately 90°. Despite this she was mobile. A fibrous cord was palpable in the web. A pyramidal wedge of soft tissue was seen overlying the first toenails bilaterally, with syndactyly of toes 2-4. The genitalia were involved with absence of the labia majora and abnormal distribution of pubic hair extending down the inner aspect of the upper thigh. Her mouth was small with a thin upper lip and unusual inward slanting of the lower teeth. No lower lip pits were noted. A submucous cleft palate was present which had not resulted in significant speech problems. There were no abnormalities of the upper limbs.

Her father, II.3, was the third child of unrelated parents. II.3 was born with a right sided popliteal web, with a characteristic pyramidal folding of tissue over the first toenail (fig 2C). The web had been corrected surgically, although this had resulted in some peroneal nerve damage, with abnormal sensation and sweating in the foot. His oldest brother, II.1, was born with a popliteal web on his right leg, which was treated surgically. This did not prevent him from having a very active life. There was no cleft lip or palate in either of these men. Although neither of their parents was known to have clefts or popliteal webbing, their father was thought to have slightly unusual speech and his brother was said to have toe syndactyly. No further information is available on these subjects, but this suggests that I.2 may have been a gene carrier.

Two out of three sisters of the proband were also affected. III.1 has mild 2/3 toe syndactyly and a repaired cleft of the soft palate. The youngest sister, III.4, was born with a unilateral cleft lip and palate (UCLP), syndactyly of fingers 2/3/4/5 on both hands (fig 2D), and minimal popliteal webbing bilaterally.

FAMILY 2

The proband (II.2, fig 1, family 2) was born at term to healthy, unrelated parents, following a pregnancy complicated by hyperemesis treated with an anti-emetic (name unknown). Birth weight was 2950 g. At birth a number of anomalies were identified, including multiple oral synechiae, unilateral cleft lip and palate, popliteal web extending from the heels to the genitalia, bifid scrotum, bilateral talipes equinovarus, and syndactyly of toes 2/3/4/5 on the right

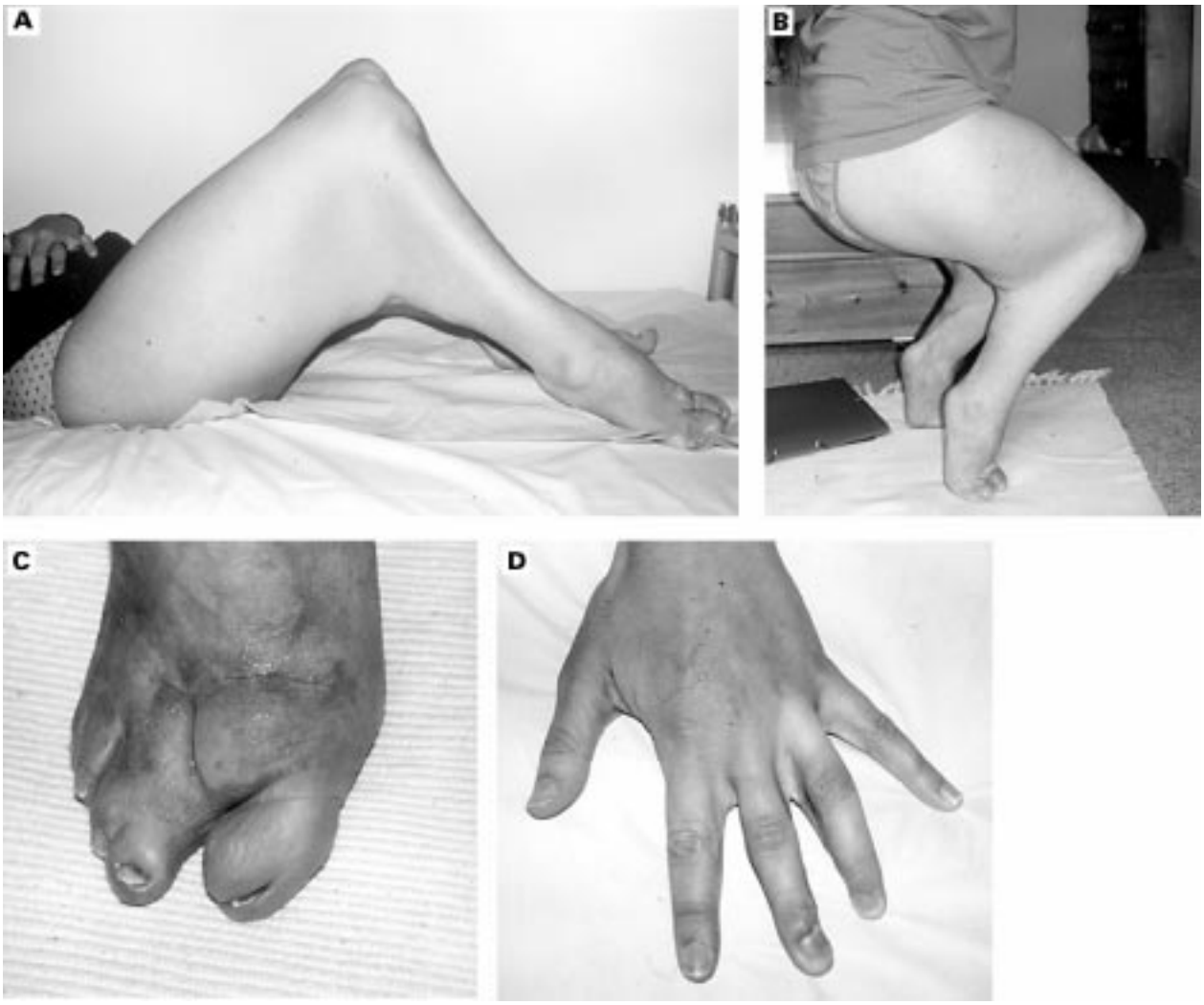

Figure 2 Family 1. (A, B) Extensive popliteal web in III.2. (C) Pyramidal overfold of tissue over the big toenail and 2/3 toe syndactyly in II.3. (D) Skin syndactyly in the hands in family 1, III.4. (All photographs reproduced with permission.)

foot (fig 3A, B). He underwent multiple operations over the first 12 years of life. There were no other medical problems and his developmental progress was normal. Although he does have some physical limitations he now walks well and is fully mobile. His first child (III.1) was found to have a unilateral cleft lip and palate at the time of detailed anomaly scan at 19 weeks' gestation, which was confirmed postnatally. Multiple oral synechiae were also present, which restricted jaw movement and required surgical release. Ankyloblepharon was noted (fig 3C). No other physical abnormalities, in particular of the lower limbs and genitalia, were identified. He developed bilateral cysts of the lower lip over the first year of life, which resulted in excess drooling and have been surgically excised on several occasions (fig 3D). Developmental progress has been normal, other than speech difficulties related to the cleft.

The second child (III.2) was born following an unremarkable pregnancy. Serial antenatal ultrasound scanning had shown no abnormality. A cleft palate, oral synechiae, and hypoplastic scrotum were seen on postnatal examination. Other than release of the oral frenulae and repair of the cleft palate, the child has had no subsequent medical problems and continues to make good developmental progress.

Although there was no clinical evidence that either parent of II.2 was a gene carrier, several more distant relatives of I.1 were thought to have had feeding problems and possibly a cleft palate.

FAMILY 3

II.3 (fig 1, family 3) was referred to the genetics clinic at the age of 21 for genetic counselling. She had a history of cleft palate and microform cleft lip. The diagnosis of Van der Woude syndrome had been considered because of the presence of bilateral lower lip pits (fig 4). There was no relevant family history. Her parents are healthy and unrelated. She was born at 33 weeks' gestation with a birth weight of 1400 g following a pregnancy initially complicated by first trimester hyperemesis (treated with Debendox) and then Rhesus incompatibility requiring several in utero blood transfusions and an exchange transfusion at 24 hours of age. At this time it was noted that she had tight tendons extending down in the popliteal region bilaterally and was unable to extend her legs fully. Her Achilles

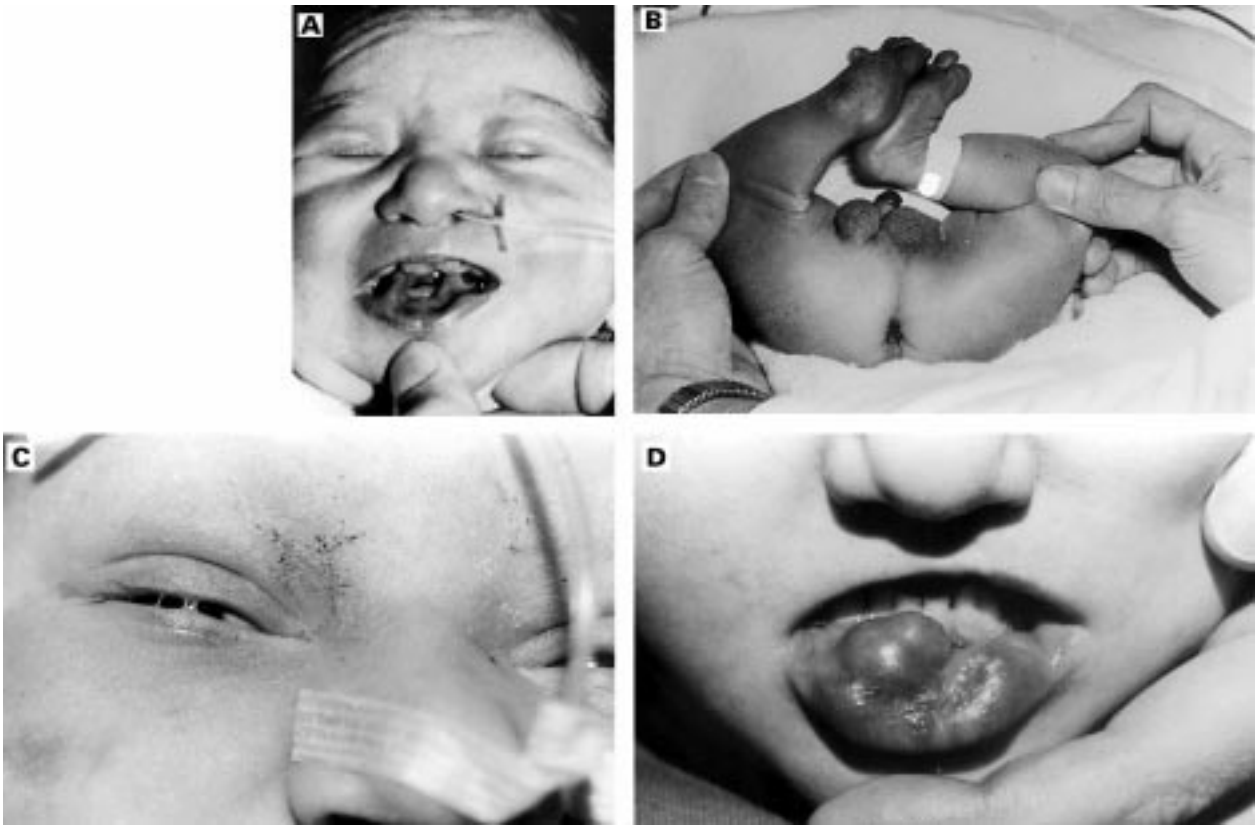

Figure 3 Family 2. (A) Oral syngnathia seen in II.2. (B) Bifid scrotum and bilateral popliteal webbing in II.2. (C) Ankyloblepharon in III.1. (D) Cysts of the lower lip in III.1.

tendons were also noted to be tight. Surgical release of the tendons was performed at the age of 18 months.

When seen in the clinic the repaired cleft palate was noted and lower lip pits seen bilaterally. There were no other dysmorphic features. Minimal skin syndactyly of digits 2/3/4 on the left hand was present. Linear thickening of the tissues extending from the upper leg to the foot was seen dorsally, more extensive on the left side. She was able to extend both knees fully. The left big toenail was smaller than the right. She had a double left second toenail. The labia majora were absent. Pubic hair was noted to extend onto the inner upper thighs, particularly on the left side. The diagnosis of popliteal pterygium syndrome was made. No features of the syndrome were noted in either parent on examination.

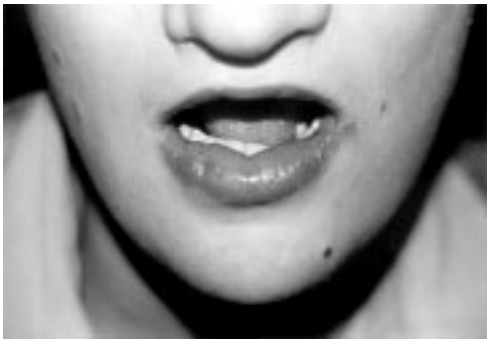

Figure 4 Family 3. Symmetrical eminences of the lower lip in II.3.

FAMILY 4

In this family, I.1 had oral synechiae at birth, a unilateral cleft lip and palate with lower lip pits, popliteal pterygia, and cryptorchidism. Minimal syndactyly of toes 2/3/4 was present. II.1 was born with a bilateral cleft of the lip and palate, lower lip pits, oral synechiae, and ankyloblepharon. Popliteal pterygia were present. The scrotum was absent, although the testes were palpable. Syndactyly of toes 2/3 and partial syndactyly of toes 3/4 was noted. The sister of II.1, II.2, was also born with a bilateral cleft of the lip and palate, lower lip pits, popliteal pterygia, hypoplasia of the labia majora, and syndactyly of toes 2/3/4.

FAMILY 5

The clinical details of this family have previously been published.[6]

Linkage studies

To test whether PPS and VWS represent allelic forms of the same gene, evidence of linkage was sought between markers at the VWS locus on 1q32 and families with PPS.

Methods

The critical VWS region lies in the region flanked by the polymorphic markers D1S205 and D1S491.[9] The marker D1S3753 lies between these markers. PCR reactions were performed using fluorescently labelled primers in a 5 µl volume (0.5 µl dNTPs, 0.5 µl PCR buffer (containing 10 mmol/l Tris-HCl, 50 mmol/l KCl, pH 8.3), 0.5 µl $MgCl_2$ buffer (2.5 mmol/l $MgCl_2$) , 0.125 µl each of both forward

and reverse primers for markers D1S205, D1S491, and D1S3753 respectively, 2.5 µl DNA (12.5 ng DNA), 0.7 µl H_2O, and 0.05 µl of Ampli*Taq* Gold. Initial denaturing at 94°C was carried out for 10 minutes, followed by 20 cycles of 92°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds, with a final extension step for 10 minutes at 72°C.

The PCR products for each DNA sample were pooled, then 1.2 µl of this pooled product was added to 1.2 µl of a loading buffer mix, containing deionised formamide with blue dye and a ROX size standard. The mixture was denatured for three minutes before loading onto a polyacrylamide gel and electrophoresed on an ABI 377 analyser, using Genescan and Genotyper software. Linkage analysis was carried out using the parametric function of Genehunter.[10]

Results

The genotypes of the subjects for the markers D1S205, D1S491, and D1S3753 are shown on the pedigrees in fig 1. No recombinants are seen. Using the lod score function of Genehunter, with a fully penetrant dominant model, the maximum lod score obtained was 2.7, where the status of I.1, family 2, is given as unknown. If the status of this subject is given as affected, then the maximum lod score obtained is 3.0. These results are consistent with linkage between PPS and 1q32 (VWS locus).

Discussion

The families described show both the intra- and interfamilial variation in the clinical phenotype of the popliteal pterygium syndrome. In family 1, the popliteal webbing varied from severe webbing leading to a flexion deformity of approximately 90° at both knees in one subject to the presence of a fibrous cord, not affecting function, in another. The clefting anomaly also varied from a submucous cleft to bilateral cleft lip and palate, although no gene carrier in this family had lower lip pits. The severity of the clefting did not correlate with the severity of the popliteal anomaly. In family 2, ankyloblepharon, oral synechiae, and lower lip pits were prominent features.

Counselling issues are important. PPS is inherited as an autosomal dominant condition with variable expression, although most cases are sporadic. It is important that this syndrome is recognised and included in the differential diagnosis of both orofacial clefting with lower lip pits and syndromes with pterygia. Differentiating between VWS and PPS can sometimes be difficult owing to the overlapping phenotype. Cases with VWS should be examined carefully to exclude abnormality of the lower limbs. The diagnosis of PPS is often made only when a severe case with many of the phenotypic features presents. Diagnosis is important in terms of genetic counselling. Before starting a family, II.3 (family 1) and his wife had requested a genetic consultation. They were told that the condition had most likely been inherited as an autosomal recessive trait and the offspring risk was therefore small. The cleft palate and mild 2/3 toe syndactyly in their first child were not thought to be related. The diagnosis of PPS was made after the birth of the second, more severely affected child.

Appropriate therapy includes surgical management of the popliteal web, cleft lip and palate surgery, and electrolysis therapy for unwanted pubic hair. Surgical correction should be approached with caution as vessels and nerves run in the free edge of the web and may thus be compromised during such a procedure. Unwanted extension of pubic hair onto the inner thigh was mentioned by several affected females. Antenatal USS may identify some of the associated anomalies.

Various hypotheses have been put forward to try and explain the underlying pathogenesis. These have included a primary microvascular abnormality with associated oedema leading to disturbance of epithelial tissues, resulting in adhesion formation,[11] excessive epithelial growth leading to fusion and secondary mesenchymal involvement,[12] a primary collagen defect,[13] or a loss of programmed cell death.[5] Both genetic and histopathological studies will help to elucidate the underlying nature of the syndrome.

Although we present preliminary linkage studies consistent with linkage to the Van der Woude locus on chromosome 1q32, further families need to be studied to establish linkage. However the study supports the theory that these disorders are allelic. Once the gene has been identified and mutations detected, the pathological and molecular basis for PPS and VWS will become evident.

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