New Syndrome
A Previously Undescribed Syndrome Combining Fibular Agenesis/Hypoplasia, Oligodactylous Clubfeet, Anonychia/Ungual Hypoplasia, and Other Defects

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We describe an apparently new genetic syndrome in six members of a family living in a remote area in Northeastern Brazil. This syndrome comprises: short stature due to a marked decrease in the length of the lower limbs (predominantly mesomelic with fibular agenesis/marked hypoplasia), grossly malformed/deformed clubfeet with severe oligodactyly, upper limbs with acromial dimples and variable motion limitation of the forearms and/or hands, severe nail hypoplasia/anonychia sometimes associated with mild brachydactyly and occasionally with pre-axial polydactyly. This syndrome is apparently distinct from the syndrome of brachydactyly-ectrodactyly with fibular aplasia or hypoplasia (OMIM 113310), the syndrome of fibular aplasia or hypoplasia, femoral bowing and poly-, syn-, and oligodactyly (OMIM 228930), and from other previously described conditions exhibiting fibular agenesis/hypoplasia.

Key words: new genetic syndrome; fibular agenesis/hypoplasia; nail hypoplasia/anonychia; oligodactylous clubfeet


INTRODUCTION

Here we describe six individuals with an apparently new genetic syndrome. They belong to a family living in Riacho de Santana, a small town in the westernmost part of the Northeastern Brazilian state of Rio Grande do Norte (roughly 6°30′S 38°W, Fig. 1). All affected individuals are of predominantly Caucasian Mediterranean origin, descendants of the Portuguese who settled in the region some hundreds of years ago. The pedigree of the family is depicted in Figure 2.

The family was ascertained during a multidisciplinary study currently undertaken in the remote areas of rural Northeastern Brazil to detect families affected with genetic conditions. It is known that the populations living in this region have high inbreeding rates as a result of small population sizes and geographic isolation.
CLINICAL REPORTS

After obtaining informed consent for participation and publication of results, as well as institutional review board approval, all affected individuals of this family and all other relatives suspected of having any limb defect or malformation were evaluated clinically by at least two medical geneticists (F.K. and P.A.O.) and their collaborators.

Almost all living persons shown in the pedigree of Figure 2 were seen personally, especially the unaffected first-degree relatives of the affected individuals here reported; every effort has been made to ask family members about the clinical status of the few persons not examined personally.

All affected individuals were photographed and studied radiographically. Blood samples for DNA extraction were collected for future genetic studies. We evaluated six affected individuals (Figs. 3–10).

GAC (IV-31), the propositus, was 47 years old. His height was approximately 1.35 m, crown–pubis distance (cpd) approximately 90 cm, pubis–ground distance (pgd) approximately 45 cm. Upper limbs: very hypoplastic distal phalanx of right index finger with impaired flexion; onychia and nail hypoplasia of digits I, II, III bilaterally; third finger with swan...

![Fig. 1. Map of NE Brazil locating study site of the present family.](image1)

![Fig. 2. Pedigree of present family.](image2)
neck defect bilaterally; acromial dimples bilaterally, limited supination bilaterally. Lower limbs: severe postural deformity of both lower limbs which are grossly asymmetric due to traumatic lesion plus severe hypoplasia of the right femur (<20 cm long), length of left femur ~35 cm, thin legs with bilateral fibular agenesis (confirmed by X-ray examination), grossly malformed/deformed clubfeet with talipes equinovarus and severe oligodactyly.

MAS (IV-16), 66 years old, sister of the propositus, height 1.33 m, cpd 75 cm, pgd 60 cm. Upper limbs: anonychia and ungual hypoplasia of digits I, II, III bilaterally; third finger with a swan neck defect bilaterally; acromial dimples bilaterally; limited extension and supination movements bilaterally; muscular strength of upper limbs moderately decreased. Lower limbs slightly asymmetric (L>R), thin legs with fibular agenesis (confirmed by X-ray examination), grossly malformed/deformed clubfeet with talipes equinovarus, oligodactyly with most toes absent—only a hallux at left, hallux plus another toe (second? fifth?) at right.

FAC (IV-20), 59 years old, brother of the propositus, height 1.50 m, cpd 90 cm, pgd 60 cm. Upper limbs: pre-axial polydactyly, anonychia, and ungual hypoplasia of the first three digits at right, including the supernumerary finger which may be the second one, since the first one is evidently a thumb; third finger with a swan neck defect bilaterally; acromial dimples bilaterally; large encapsulated lipoma in the right deltoid region; forearm supination and pronation deficit bilaterally; limb muscular strength conserved. He has also large inguinal-scrotal herniae. Lower limbs: asymmetric (R>L) and similar to those of the three affected sibs described; genua valga; thin legs with bilateral fibular agenesis (confirmed by X-ray examination), grossly malformed/deformed clubfeet with talipes equinovarus (left) and varus (right), severe oligodactyly with just one complete bone axially (first, with most toes absent).

JA (V-12), 10 years old, son of the propositus, height 1.58 m. Upper limbs: complex pre- and post-axial polydactyly/syndactyly at left associated with homolateral limited extension, flexion and supination of the forearm. No defect of right upper limb (including the hand, that showed no defect at X-ray examination) or of both lower limbs.

MLG (IV-1), 45 years old, first cousin once removed of the propositus, height 1.53 cm; cpd 91 cm, pgd 62 cm. Upper limbs: anonychia and ungual hypoplasia of digit II in both hands; third finger with a swan neck defect bilaterally; acromial dimples but with no limitations in supination, extension, and pronation of the forearm. Lower limbs: slight asymmetry (L>R); genua valga; markedly thin legs, X-ray images showing hypoplastic fibulae and femora, deformed talipes equinovarus bilaterally without oligodactyly or any other conspicuous defect (Figs. 4–10).

Taking into account the phenotype of all affected members in the nuclear family described here, we can characterize this apparently new syndrome by...
the following signs: short stature (<25th centile of the normal length for age and sex) especially striking in those cases with a marked decrease in the length of the lower limbs, which is in all cases predominantly mesomelic (but with the involvement of all long bones of thighs and legs) with fibular agenesis/marked hypoplasia, grossly malformed/deformed clubfeet (commonly talipes equinovarus) with severe oligodactyly (in several instances with absence of various bone rays of the feet), upper limbs showing variable motion limitation of the forearm and/or hand (supination, pronation, flexion, extension), severe nail hypoplasia (sometimes true anonychia) associated with mild brachydactyly and (simple or complex) pre-axial polydactyly. Another interesting finding in this family was the acromial dimples or congenital supraspinous lossae (McKusick MIM %102350), skin depressions that occur symmetrically on the back of the shoulders overlying the acromial process of the scapulae; they are a virtually constant anomaly in the 16q deletion syndrome, but in non-aneuploid individuals they are considered a normal, benign familial trait transmitted in an autosomal dominant mode.

DISCUSSION

The structure of the pedigree suggests the possibility of autosomal dominant inheritance with incomplete penetrance. Under this hypothesis, the maximum-likelihood estimate of the rate of penetrance is \( K = 0.324 \) (95% confidence limits = 0.139–0.585), using a method that took into account all of the information contained in the genealogy, including the information given by the so-called “normal trees” of individuals descending from obligate carriers of the gene [Rogatko et al., 1986]. Since the rate of consanguineous marriages in the region to which the family belongs is strikingly high (~20–30%), we cannot discard the possibility of autosomal recessive inheritance, in spite of the apparent lack of consanguinity between the parents of all affected individuals here reported. It is even possible that individual V-12 has a condition unrelated to the main abnormalities (fibular, foot, and nail defects) exhibited by almost all other affected family members, but his affected uncle IV-20 presents also with pre-axial polydactyly and the elbow joint problems presented by the boy are found to some extent in almost all affected members of his family. It seems clear that nothing about the details discussed in this paragraph can be proven at this point but they will certainly be sorted out by the comprehensive molecular studies currently undertaken in our center.

So far, only two conditions presenting fibular agenesis associated with one or more of the other defects/deformities found in the family reported here have been described previously:

1. Brachydactyly-ectrodactyly with fibular “aplasia” or hypoplasia, OMIM 113310 [Lewin and Opitz, 1986; Genuardi et al., 1990; Evans et al., 2002].
2. Fibular “aplasia” or hypoplasia, femoral bowing and poly-, syn-, and oligodactyly, OMIM 228930 [Fuhrmann et al., 1980, 1982; Pleiffer et al., 1988;
Lipson et al., 1991; Kumar et al., 1997; Aynaci et al., 2001; Huber et al., 2003; Woods et al., 2006.

Evans et al. [2002] listed all published cases of familial fibular “aplasia”/hypoplasia with ectrodactyly; the phenotype described here does not fit any of them. Fuhrmann syndrome has some defects in common with the condition presented here, such as the occurrence of nail aplasia/hypoplasia and polydactyly, but the latter is post-axial, the bone...
defects seem to be more conspicuous and complex, and some affected individuals show extraskeletal manifestations.

None of the limb anomalies reported above violate the fibular field postulated by Lewin and Opitz [1986].

Clinical similarities (however, superficial) to some aspects of the patients reported here and split hand foot malformation (SHFM3), especially the nail dysplasia, "camptodactyly" (actually swan neck deformity) of the fingers, and hand anomalies, would suggest that this syndrome may be a variant of SHFM3, mapped to 10q24 [Elliott and Evans, 2006]. Microsatellites mapped near the critical region were genotyped (D10S1686, D10S185, D10S192, D10S597, and D10S1696). The analyses showed no evidence of linkage. As stated above, other linkage studies are under way in our center at the University of São Paulo.

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REFERENCES