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A Danish family with dominant deafness-onychodystrophy syndrome

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Abstract

Background: The rare hereditary disorder "dominant deafness and onychodystrophy (DDOD) syndrome" (OMIM 124480) has been described in a few case reports. No putative DDOD gene or locus has been mapped and the cause of the disorder remains unknown.

Main observations: We present here three male family members in three generations with sensori-neural deafness, onychodystrophy and brachydactyly inherited via autosomal dominant transmission. The family members presented with absent fingernails on the first and fifth digits. As to the feet, there were absent nails on second to fifth toes in two family members, whereas the third family member only had absent nails on the fifth toe. The proband had late dentition and his father a history of late dentition, but otherwise the teeth appeared normal. Comparative genomic hybridization array analysis (Agilent 400k oligoarray) of the proband did not detect any copy number variation.

Conclusion: This Danish family fits within the spectrum of dominant deafness and onychodystrophy syndrome and further characterises this rare disorder. (*J Dermatol Case Rep*. 2013; 7(4): 125-128)

Introduction

Inherited malformations of the nails and digits can be isolated findings, or they can be associated with genetic syndromes. When hearing loss and nail abnormalities coexist as developmental features, a possible connection between these conditions should be suspected because the skin and nails, together with the membranous labyrinth of the inner ear, are derived from the embryonic ectoderm. The congenital disease "deafness and onychodystrophy" (DOD) is described with either autosomal dominant or recessive inheritance. Few families with "dominant deafness and onychodystrophy (DDOD) syndrome" (OMIM 124480) have been reported in the literature, the latest publication being in 2011.[1] No putative DDOD gene or locus has been mapped and the cause of the disorder remains unknown. The recessive form of DOD is more severe — DOOR (OMIM 220500) — with deafness, onychodystrophy, osteodystrophy and mental retardation.

We report here a family with three male members in three generations presenting with congenital onychodystrophy, brachydactyly and sensorineural deafness inherited via autosomal dominant transmission. Our family fits within the spectrum of "dominant deafness and onychodystrophy syndrome" and further describes and characterises this rare disorder.

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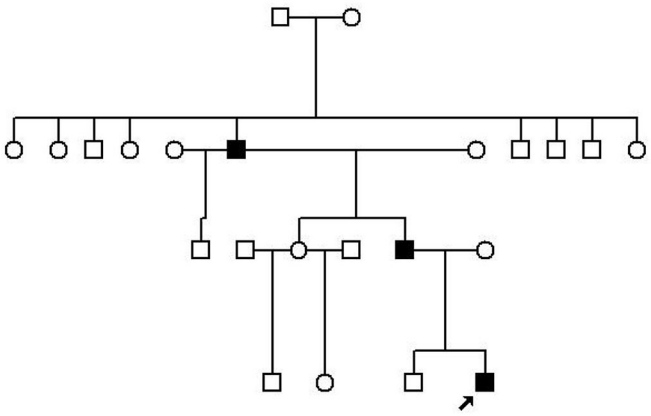
The pedigree of the family is shown in Figure 1. The genetic details of this family were not possible to clarify further as the cases had congenital deafness.

The proband was a seven-month-old boy with hearing loss and hypoplastic nails on fingers and toes. Both parents were deaf, but otherwise healthy. The father was ethnically Danish. The mother was an adopted Asian child, whose etiology of deafness was unknown. The proband's elder brother, who was 4 years old, had normal hearing and normal physical appearence. The proband was born vaginally at term (38 weeks and 3 days) after an uneventful pregnancy. His birth weight was 2630g. Shortly after birth, he developed



Family pedigree. Square – males, circles – females. *Arrow* shows the proband.

■ Black: Family members with deafness, onychodystrophy and brachydactyly.

Figure 1

Family pedigree. Arrow marks the proband. Black: Family members with DDOD syndrome.

jaundice and lethargy, but recovered quickly with phototherapy. The boy has showed a slightly retarded motor development. He was evaluated by a neuro-paediatrician at 9 month, 18 month and 21 month of age and his evaluation is on-going because of delayed motor and language development. At 16 month of age he had late dentition, as he only had three teeth, the first one presenting at about 13 month of age. All three teeth were of normal appearance. Audiograms showed hearing loss (sensorineural deafness), and the boy had a cochlear implant at one year of age. An MRI scan of the cerebrum was normal. On physical examination, the boy presented with a broad nose and epicanthal folds, which were considered to be normal findings given his Asian background. It was noted that he had aplastic nails on the first and fifth digits. The other nails were small and rudimentary, and his fingers were short. His toenails were completely absent (Fig. 2A). A comparative genomic hybridization array (Agilent 400k oligoarray) performed in 2010 detected no genomic copy number variation.

The proband's 29-year-old father, whose deafness was diagnosed in infancy, similarly presented with onychodystrophy and brachydactyly. His sister and half-brother were both normally developed with normal hearing. On clinical examination, hypoplastic fingernails on second to fourth digits and absence of fingernails on the first and fifth digits were noted. Bulbous fingertips were observed on second to fourth digits. His nails were absent on second to fifth toe. The nail on the first toe was very small and rudimentary. More fingers and toes were shorter than normal (Fig. 2B), especially the fifth finger. The thumbs were finger-like, but not triphalangeal. Skeletal defects were shown on roentgenograms of his hands, showing bilaterally absent phalanges intermedia on the fifth fingers. Moreover, shortened lumpy distal phalanges of the second, third and fourth fingers were observed. Roentgenograms of his feet showed symmetrical skeletal anomalies with absence of a phalanx in the lateral four toes, and with only one phalanx on the left little toe (Fig. 2C,D). His facial appearance was considered normal. No skin or hair anomalies were observed. He had a history of late dentition, although a full number of teeth with normal appearance were observed. Otherwise he was healthy.

The proband's grandfather, a 58-year-old man, had eight siblings with normal hearing and normal physical appearance. He was the only child presenting with onychodystrophy and an otologic history of deafness diagnosed at the age of two. His parents were also reported with normal hearing and normal nails on hands and feet.

Examination of his hands revealed absence of nails on the thumbs and hypoplastic nails on the remaining fingers, which were shorter than normal. The thumbs were finger-like, but not triphalangeal. On the feet, symmetrical absence of nails on the fifth toes was noted (Fig. 2E). Otherwise he was healthy except for a diagnosis of hypertension. On general examination, his facial appearance was normal. No dental anomalies were observed.

Discussion

We report here a family with three males in three generations with a vertical and direct transmission of onychodystrophy, brachydactyly and congenital hearing loss, suggesting the diagnosis of deafness and onychodystrophy with autosomal dominant inheritance. Since the proband's grandfather's eight siblings and parents were reported with normal hearing and normal nails, we suspect a *de novo* mutation occurring with him, but reduced penetrance could also be a possibility.

A few reports describe the syndrome of hereditary deafness and onychodystrophy (Table 1). In 1961 the first case report of familial deafness, onychodystrophy and strabismus was published.[2] It reported two affected sisters with consanguineous parents, suggesting autosomal recessive inheritance, but without mental retardation, excluding DOOR.

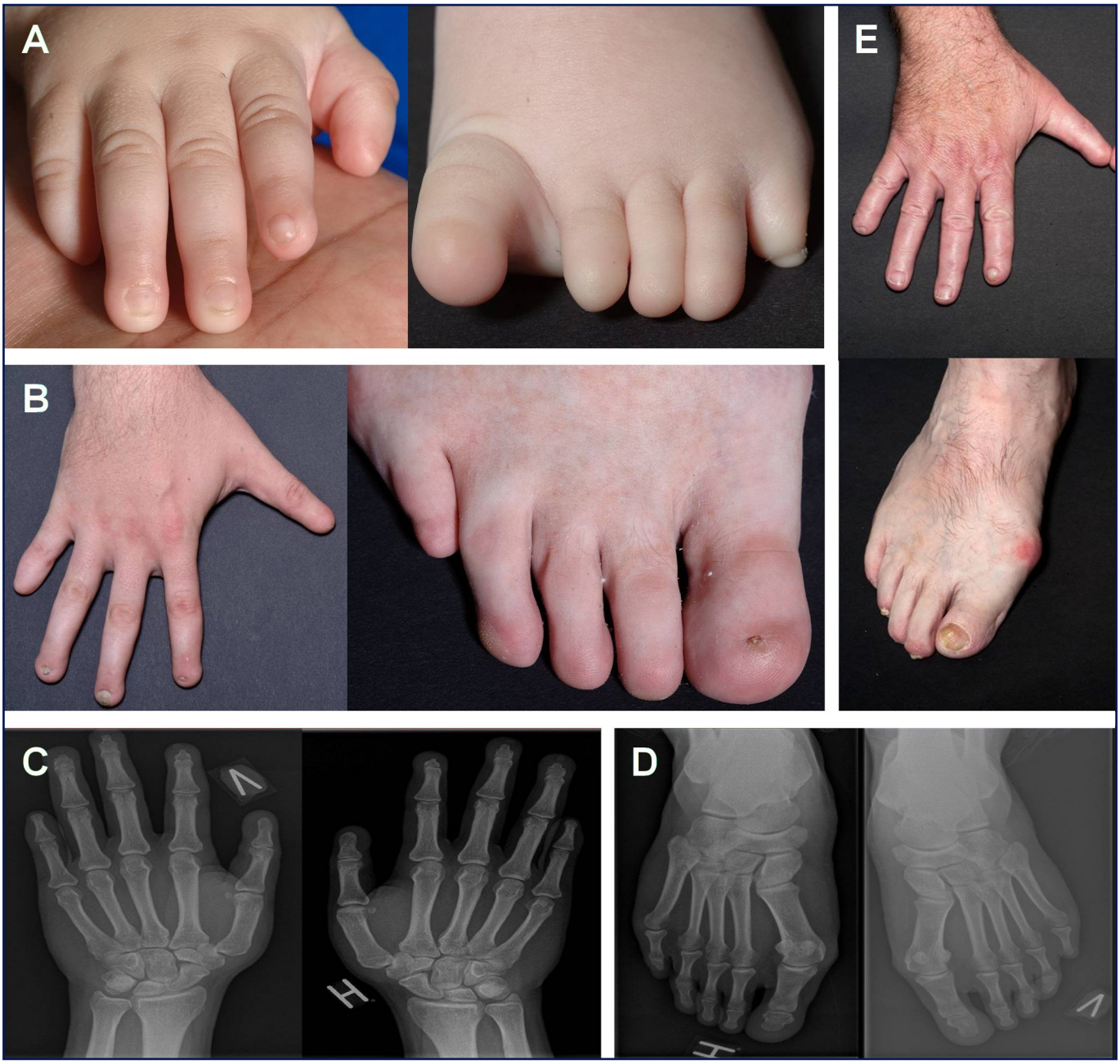


Figure 2

A) Photographs of the proband´s right hand and left foot at 7 month of age. B) Photographs of the right hand and foot of the proband´s father showing onychodystrophy and brachydactyly. C) Roentgenograms of the proband´s father´s hands. D) Roentgenograms of the proband´s father´s feet. E) Photographs of the right hand and foot of the proband´s grandfather showing onychodystrophy and brachydactyly.

The following year, Robinson *et al.* described a kindred (five (four described) cases in three generations) with an autosomal dominant inheritance pattern of onychodystrophy, syndactyly, polydactyly, dental malformations and deafness.[3] Later, two additional publications reported onychodystrophy and deafness associated with skeletal abnormalities involving the fingers and toes such as triphalangeal thumbs and hypoplastic or absent distal phalanges shown on roentgenograms. The described anomalies were, in both families, considered to be inherited via a autosomaldominant transmission.[4,5] In 1999, Kondoh *et al.* described the DDOD syndrome with manifestation of short thumbs and 5th fingers in addition to deafness and onychodystrophy.[6] These findings are similar to our family's disorder, noting that the brachydactyly is more pronounced in our kindred. Moreover, our family also presents with dental anomalies as other DDOD reports.[3,6] This family is also similar to a DDOD kindred described in 2011 by White and Fahey presenting with deafness, brachydactyly, onychodystrophy and bulbous fingertips,[1] but differs somewhat from the dysmorphic facial features, aplasia cutis and epilepsy which they presented with.

No putative DDOD gene or locus has been mapped and the cause of the disorder remains unknown. Thus, the present kindred, together with at least one of the other families,

represent a possibility of mapping the putative DDOD gene.

When hearing loss and nail abnormalities coexist, in three family members, a common cause is to be suspected, as the skin and the nails, together with the membranous labyrinth of the inner ear, are derived from the embryonic ectoderm. This really only leaves two differential diagnoses in this case; DDOD and the more severe DOOR — with deafness, onychodystrophy, osteodystrophy and mental retardation — with recessive inheritance. The inheritance pattern and the phenotypic features of our family both fit the DDOD syndrome.

In summary, this family has "dominant deafness and onychodystrophy syndrome", similar to other published cases, and further describes and characterises this rare disorder. Our family and the previously published cases underline that deafness, brachydactyly and onychodystrophy are the hallmarks of this rare disorder, with autosomal dominant transmission. Features like late dentition, conical teeth, oligodontia, bulbous swelling of terminal phalanges, triphalangeal thumb and brachydactyly are also a part of the DDOD syndrome, but presents with greater variability. The phenotypes described in this family all fits within the previously described DDOD phenotype.

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Table 1. Comparison of our family with previously published cases with deafness and onychodystrophy.

	Our family	White and Fahey, 2011	Kondoh *et al*, 1999	Moghadam and Statten, 1972	Goodman *et al*, 1969	Robinson *et al*, 1962	Feinmesser and Zelig, 1961
No. of affected individuals	3	3	3	2	2	4	2
Absent/hypoplastic nails	3/3	3/3	3/3	2/2	2/2	+	2/2
Deafness	3/3	3/3	3/3	2/2	2/2	2/4	2/2
Brachydactyly	3/3	1/2	—	Short distal phalanges	Short distal phalanges	—	—
Bulbous swelling of terminal phalanges	+	+	—	+	+	—	—
Thumbs	Finger-like	Finger-like	Short thumb	Triphalangeal thumb	Triphalangeal thumb	—	—
Cutis aplasia	—	1/3	—	—	—	—	—
Polydactyly	—	—	—	—	—	1/4	—
Syndactyly	—	—	—	—	—	1/4	—
Dental anomalies	Late dentition	—	Late dentition, small or conical teeth, oligodontia	—	—	Late dentition, oligodentia, coniform teeth	—
Copy number variation	None	None	—	—	—	—	—
Inheritance pattern	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Two sisters with consanguineous parents. No mental retard.

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