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Brief report

Identification of a Ninein (*NIN*) mutation in a family with spondyloepimetaphyseal dysplasia with joint laxity (leptodactylic type)-like phenotype

Melanie Grosch [a], Barbara Grüner [a], Stephanie Spranger [b], Adrian M. Stütz [c], Tobias Rausch [c], Jan O. Korbel [c], Dominik Seelow [d], Peter Nürnberg [e], Heinrich Sticht [f], Ekkehart Lausch [g], Bernhard Zabel [g], Andreas Winterpacht [a,*], Andreas Tagariello [a]

[a] Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany
[b] Praxis für Humangenetik, Bremen, Germany
[c] European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
[d] Department of Neuropaediatrics, Charité-Universitätsmedizin Berlin, Berlin, Germany
[e] Cologne Center for Genomics (CCG), University of Cologne, Cologne, Germany
[f] Division of Bioinformatics, Institute of Biochemistry, University of Erlangen-Nuremberg, Erlangen, Germany
[g] Centre for Pediatrics and Adolescent Medicine, Freiburg University Hospital, Freiburg, Germany

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ABSTRACT

Spondyloepimetaphyseal dysplasia with joint laxity-leptodactylic type (SEMDJL2) is an autosomal dominant skeletal dysplasia which is characterized by midface hypoplasia, short stature, joint laxity with dislocations, genua valga, progressive scoliosis, and slender fingers. Recently, heterozygous missense mutations in *KIF22*, a gene which encodes a member of the kinesin-like protein family, have been identified in sporadic as well as familial cases of SEMDJL2. In the present study homozygosity mapping and whole-exome sequencing were combined to analyze a consanguineous family with a phenotype resembling SEMDJL2. We identified homozygous missense mutations in the two nearby genes *NIN* (Ninein) and *POLE2* (DNA polymerase epsilon subunit B) which segregate with the disease in the family and were not present in 500 healthy control individuals and in the 1094 control individuals contained within the 1000-genomes database. We present several lines of evidence that mutant Ninein is most likely causative for the SEMDJL2-like phenotype. The centrosomal protein NIN shows a functional relationship with KIF22 and other proteins associated with chromosome congression/movement, centrosomal function, and ciliogenesis, which have been associated with skeletal dysplasias. Moreover, compound heterozygous missense mutations at more N-terminal positions of Ninein have very recently been identified in a family with microcephalic primordial dwarfism. Together with the present report this strongly supports a fundamental role of Ninein in skeletal development.

1. Introduction

Lepto-SEMDJL, leptodactylic- or Hall-type SEMD-JL (SEMDJL2, MIM 603546) is an autosomal dominant skeletal dysplasia (Hall et al., 1998), which is characterized by short stature; midface hypoplasia; joint laxity leading to dislocations particularly of the hip and knee joints; genua valga; progressive scoliosis and long, slender, distally tapering fingers (Hall et al., 2002). Recently, heterozygous missense mutations in *KIF22*, a gene which encodes a member of the kinesin-like protein family, have been identified in sporadic as well as familial cases of SEMDJL2 (Boyden et al., 2011; Min et al., 2011). Although the exact biological function of KIF22 is unknown, it has been suggested that KIF22 is involved in chromosome congression and segregation during mitosis, chromosome stability, and the control of primary cilium formation (see Boyden et al., 2011; Min et al., 2011).

Here, we report a consanguineous family of Turkish origin that presented with clinical and radiological features similar to SEMDJL2. Using genome-wide homozygosity mapping and whole-exome sequencing, we identified two homozygous missense mutations in the genes *NIN* (Ninein) and *POLE2* (DNA polymerase epsilon subunit B), which are located in close proximity to each other, and present several lines of evidence that mutant Ninein is causative for the SEMDJL2-like phenotype. Recently, the first compound heterozygous missense mutation in the *NIN* gene has been identified in a family with microcephalic primordial dwarfism. Together with the present report, the two mutations strongly support a fundamental role of Ninein in skeletal development.

* Corresponding author at: Institute of Human Genetics, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Schwabachanlage 10, D-91054 Erlangen, Germany. Tel.: +49 9131 852 2019; fax: +49 9131 852 3232.
E-mail address: Andreas.Winterpacht@uk-erlangen.de (A. Winterpacht).

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2. Subjects and methods

2.1. A family with SEMDJL2-like phenotype

We investigated a consanguineous family of Turkish origin, with 4 affected individuals born to first-cousin parents. The pedigree (Fig. 1a) strongly suggests an autosomal recessive mode of inheritance.

Proposita (IV.1): Pregnancy was uneventful but delivery at term was complicated by breech presentation. The newborn female was small for gestational age, length was about 45 cm (−3 SD), weight and head circumference, however, have not been recorded. Bilateral hip dysplasia was treated conservatively and as late as at 7 years for the first time by surgical means followed by several further operations.

Early motor development was markedly delayed but no exact data could be recalled by her parents. Speech and intellectual development were normal and the girl was able to attend regular school. During childhood, the girl's main complaints were painful hip- and knee joints but also general laxity of her small and large joints. Menarche occurred at 13 years.

Physical examination at age 35 years revealed disproportionate short stature with a height of 129 cm (−5.2 SD, based on Turkish growth data), arm span of only 109 cm (however, restricted extension of elbow joints has to be considered) and a weight of 34 kg (BMI = 20.1). Head circumference (OFC) was 52 cm (3rd centile for female adults, but considering height corresponding to a girl of age 9 years, 52 cm is about the 50th centile). The patient's face is somewhat flat, her nose is short

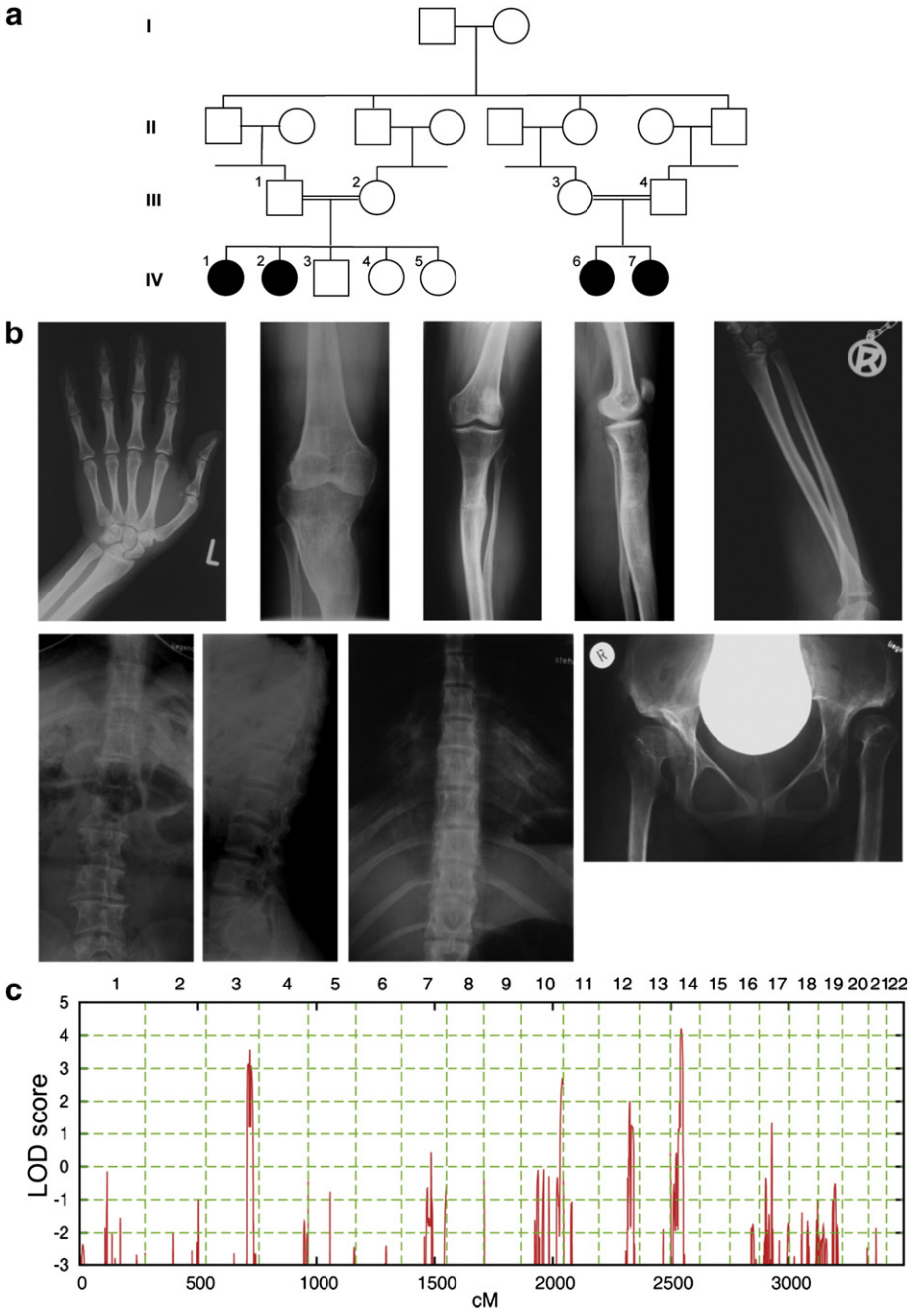

Fig. 1. (a) Pedigree of the SEMD-JL family. DNA was available for individuals marked with an Arabic numeral. (b) Radiographs from the index patient taken at an age of 35 years. (c) Parametric multipoint LOD score profile across the human genome of consanguineous kindred. Human chromosomes (numbered on top) are depicted from pter (left) to qter (right) on the x-axis. Genetic distance is presented in cM. Note the presence of significant LOD scores within chromosome 3 (LOD score, 3.5) and chromosome 14 (LOD score, 4.2).