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CASE REPORT

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Expanding the phenotype of anauxetic dysplasia caused by biallelic *NEPRO* mutations: A case report

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Abstract

The cartilage hair hypoplasia and anauxetic dysplasia (CHH-AD) spectrum encompasses a group of rare skeletal disorders, with anauxetic dysplasia (ANXD) at the most severe end of the spectrum. Biallelic variants in *RMRP*, *POP1*, and *NEPRO* (*C3orf17*) have previously been associated with the three currently recognized ANXD types. Generally, all types are characterized by severe short stature, brachydactyly, skin laxity, joint hypermobility and dislocations, and extensive skeletal abnormalities visible on radiological evaluation. Thus far, only five patients with type 3 anauxetic dysplasia (ANXD3) have been reported. Here, we describe one additional ANXD3 patient. We provide a detailed physical and radiological evaluation of this patient, in whom we identified a homozygous variant, c.280C > T, p.(Arg94Cys), in *NEPRO*. Our patient presented with clinically relevant features not previously described in ANXD3: atlantoaxial subluxation, extensive dental anomalies, and a sagittal suture craniosynostosis resulting in scaphocephaly. We provide an overview of the literature on ANXD3 and discuss our patient's characteristics in the context of previously described patients. This study expands the phenotypic spectrum of ANXD, particularly ANXD3. Greater awareness of the possibility of atlantoaxial subluxation, dental anomalies, and craniosynostosis may lead to more timely diagnosis and treatment.

KEYWORDS
anauxetic dysplasia, cartilage hair hypoplasia, NEPRO, POP1, RMRP

1 | INTRODUCTION

The cartilage hair hypoplasia and anauxetic dysplasia (CHH-AD) spectrum comprises a group of rare autosomal recessive skeletal disorders with variable phenotypes. Recently, a revision was proposed by Unger et al. (2023), classifying CHH-AD into nosology group 11 (NOS 11). NOS 11-0020 comprises metaphyseal dysplasia without hypotrichosis (MDWH, MIM #250460), cartilage hair hypoplasia (CHH, MIM #250250) and anauxetic dysplasia (ANXD) type 1 (ANXD1, MIM #607095), all of which have been associated with variants in the *RMRP* gene (Ridanpää et al., 2001; Thiel et al., 2005). NOS 11-0030 comprises the CHH-like ANXD2 (MIM #617396) and NOS 11-0040 comprises the CHH-like ANXD3 (MIM #618853), which have been associated with variants in the *POP1* and *NEPRO* genes, respectively (Glazov et al., 2011; Maddirevula et al., 2018). Both the RNA encoded by *RMRP* and the protein encoded by *POP1* are components of the nuclear and mitochondrial RNA-processing endoribonucleases (RNAse MRPs) (Glazov et al., 2011; Thiel et al., 2005), and the protein product

of the *NEPRO* gene is known to interact with various subunits of RNAse MRPs (Wang et al., 2015). Together with ANXD1 and ANXD2, ANXD3 is on the severe skeletal end of the CHH-AD spectrum and is clinically characterized by severe short stature, brachydactyly, skin laxity, and joint hypermobility and dislocations. Radiographic findings tend to be variable in all ANXD types, but common findings are ovoid-shaped vertebrae with platyspondyly, hypoplastic or squared ilia, hypoplastic acetabulae, small femoral epiphyses with narrow femoral necks, irregular metaphyses and short and broad metacarpals and phalanges (Barraza-García et al., 2017; Narayanan et al., 2019). In ANXD, in contrast to MDWH and CHH, there are no extraskeletal features such as immunodeficiency, anemia, and intestinal manifestations and no predisposition to malignancies. To date, only five ANXD3 patients have been described, from three different families (Maddirevula et al., 2018; Narayanan et al., 2019; Shaheen et al., 2016). Here, we report a new patient with biallelic *NEPRO* variants and additional features that broaden the phenotypic features of ANXD3.

2 | MATERIALS AND METHODS

Trio-based whole-exome sequencing was performed using SureSelect Human All exon V7 (Agilent) target enrichment, and subsequent sequencing on an Illumina NextSeq500 machine. The homozygous or compound heterozygous autosomal recessive, de novo autosomal dominant, and X-linked variants were classified according to standard guidelines in-house based on the AMCG criteria (Richards et al., 2015).

3 | RESULTS

3.1 | Clinical phenotype description

A 7-year-old girl born in an Arabic-speaking community in Eastern Africa was referred to our clinical genetics department for evaluation of short stature and ichthyosis. She was the firstborn of consanguineous parents (Figure S1), who further reported that their shared ancestor was of Arabic descent. The girl was born prematurely after prolonged labor, but no further perinatal details of her birth were available. According to the parents, her growth had stagnated at approximately 1 year of age. Before migrating to the Netherlands, the patient had undergone surgery on her right hip for congenital hip dysplasia. She had experienced recurrent lower respiratory tract infections. Psychological evaluation demonstrated global developmental delay with an average IQ of 55. Shortly before the first scheduled appointment, she was hospitalized after suffering an out-of-hospital cardiac arrest (OHCA) for which no definite cause was identified. Physical examination revealed several facial dysmorphisms (see Table S1), scaphocephaly, oligodontia, and impaired active and passive rotation of the neck (Figure 1). She had disproportionate short stature with a relatively short trunk, genua valga, and a flexion contracture of the left knee. Both hands were short with brachydactyly of all fingers. She also had pedes plani with brachydactyly and clinodactyly of all toes. Digits 2–3 of the left foot showed partial cutaneous syndactyly. Her skin was dry with generalized fine white scaling, but there was also small lamellar scaling on the abdomen, ankles and dorsal feet. The

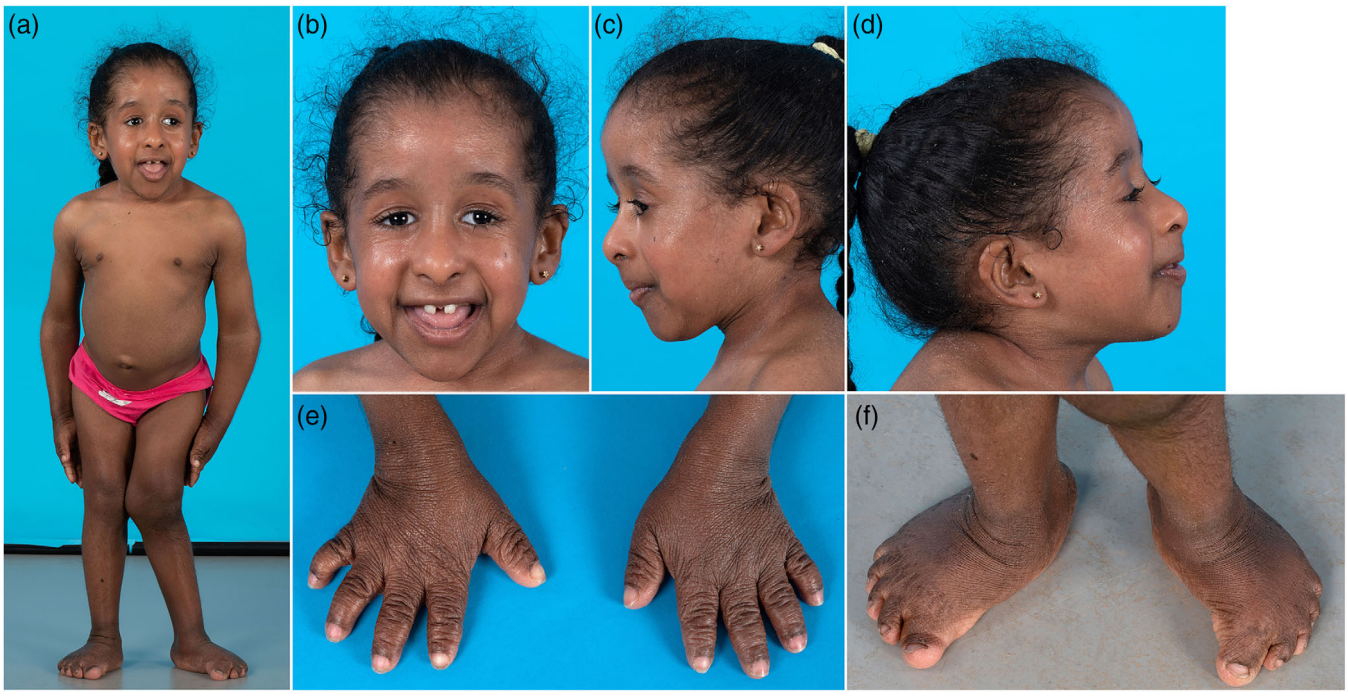

FIGURE 1 Photographs of the patient taken at the age of 8 years and 1 month. We noted severe short stature, genua valga, flexion contracture of the left knee, and pedes plani with pedes adducti metatarsi vari (a). Facial features include mild down slant of the palpebral fissures, strabismus divergens, a short and flat philtrum and oligodontia (b), mild frontal bossing, and overfolded helices (c), (d). Both hands were short with brachydactyly and tapering of the fingers (e). All toes showed brachydactyly and clinodactyly (f).

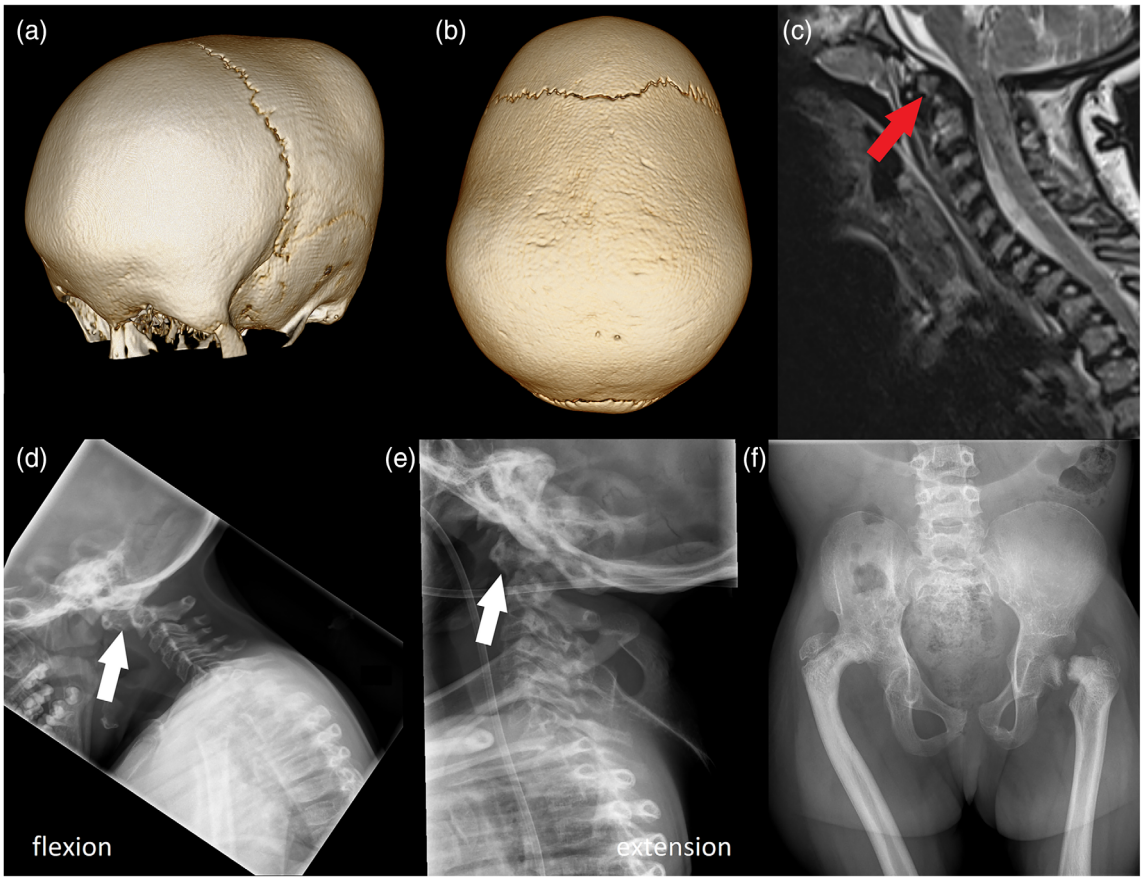

FIGURE 2 Scaphocephaly resulting from sagittal suture craniosynostosis (a, b; 3D computed tomography reconstructions). Os odontoideum (c; sagittal T2 weighted magnetic resonance sequence; red arrow). Increased atlantoaxial distance on the flexion compared to the extension cervical spine radiograph (d,e; white arrow). Right-sided hip-joint ankylosis and left-sided coxa vara with suggestion of long-standing slipped capital femoral epiphysis with secondary changes (f). See Figures S2–S9 for images in higher resolution and additional images.

skin of her face was mostly unaffected. At the last examination (at the age of 8 years and 8 months), she had reached a height of only 84 cm (standard deviation (SD) −8.5 [WHO 2006/2007, height for age]) and a weight of 10.8 kg (SD −0.2 [WHO 2006/2007, weight for length]), with an arm span of 87 cm (SD −6.6 (Gerver & de Bruin, 2001)) and a head circumference of 48.0 cm (SD −2.0 [WHO 2006/2007]).

3.2 | Radiological evaluation

A cranial computed tomography demonstrated scaphocephaly resulting from sagittal suture craniosynostosis (Figures 2a,b, S2) and an os odontoideum, a non-fused part of the dens of vertebra C2 (Figure 2c). Furthermore, magnetic resonance imaging (MRI) of the cranial and cervical spine demonstrated a morphologically narrow subarachnoid channel at the level of the foramen magnum (smallest diameter 8 mm) without apparent myelopathy of the craniocervical myelum and a small pituitary gland. MRI also confirmed the os odontoideum but showed no other abnormalities (Figures 2c, S3).

A skeletal survey performed at 7 years and 5 months of age found severe generalized shortening of all long bones. The bone age based on Greulich and Pyle (1999) and corrected for gender was 6 years and 10 months. Flexion and extension cervical spine radiographs demonstrated an atlantoaxial distance of up to 9 mm in flexion, suggestive of atlantoaxial instability (Figures 2d, e, S4). The spine consisted of 7 cervical vertebrae, 11 thoracic vertebrae, and 5 lumbar vertebrae, of which L1 had a prominent transverse process on the left side (Figure S5). The costochondral junctions showed cupping and the lower ribs were broad and oar-shaped. Thoracic and lumbar vertebral bodies had an ovoid appearance with decreased height in dorsal portions but with mild to moderate thoracic hyperkyphosis. The iliac wings appeared mildly hypoplastic in conjunction with a narrow sacrum and shallow and steep dysplastic acetabuli. On the right side, there was an ankylosis between a luxated femoral head and the iliac wing (Figures 2f, S6). On the left side, the femoral head was hypoplastic and misaligned, with a sclerotic narrow femoral neck, suggestive of longstanding slipped capital femoral epiphysis (SCFE) with secondary degenerative changes. Coxa vara was noted bilaterally (Figure S7). Metaphyseal irregularity was seen in the proximal humerus, distal radius, distal femur, proximal and distal tibia, and the proximal fibula. Hand radiographs showed diffuse shortening, metaphyseal irregularity, and bullet-shaped midphalanges of the second to fifth digits

(Figure S8). The left side showed a Madelung deformity and ivory epiphyses of the second, third, and fourth digits. The respective length proportion of the right femur to tibia/fibula was normal, but there was a significant discrepancy in leg length, with marked bowing of the femur on the left side. An inspection of the dentition showed tooth agenesis, microdontia, short root anomaly, and enamel hypoplasia (Figure S9). The morphology of all elements was abnormal, with bulbous crowns, and the upper frontal teeth showed radiological dens invaginatus. Additionally, the patient had agenesis of two lower second premolars and taurodontia of all first permanent molars. The primary dentition had extensive caries and plaque formation on all elements.

3.3 | Diagnostic testing

Diagnostic whole-exome sequencing revealed a homozygous pathogenic variant, c.280C > T, p.(Arg94Cys) in *NEPRO* (NM_015412.4), leading to a diagnosis of ANXD3. In addition, we identified a homozygous pathogenic variant, c.1156C > T p.(Arg386Cys) in *ALOX12B* (NM_001139.3), which explains the congenital ichthyosis. Both parents were heterozygous carriers of the *NEPRO* and *ALOX12B* variants. Laboratory testing, electrocardiography, and radiographic imaging showed no cardiac, endocrinological, or metabolic abnormalities that could explain the patient's OHCA or short stature.

4 | DISCUSSION

Extensive phenotyping of this female patient revealed several clinically relevant features not previously reported in ANXD3: atlantoaxial subluxation, extensive dental anomalies, and a sagittal suture craniosynostosis resulting in scaphocephaly. As these features were not consistently assessed in previously reported patients with ANXD3 and other ANXD types, their true prevalence in ANXD is unknown.

Prior to our patient, five ANXD3 patients from three different families had been reported (Table S1). Shaheen et al. (2016) and Maddirevula et al. (2018) both reported two siblings, who carry the same homozygous c.280C > T, p.(Arg94Cys) variant in *NEPRO* found in our patient. These four patients were born of consanguineous parents of Arabic descent, as was our patient, further suggesting that this variant is an Arabic founder mutation. In the fifth patient, Narayanan et al. (2019) found a different homozygous *NEPRO* variant, c.435G > C, p.(Leu145Phe), and provided *in silicio* evidence for decreased stability of both mutant proteins.

We critically re-evaluated the radiographs of all the patients reported so far and reviewed the skeletal characteristics of ANXD3 (Table S1). In addition to our patient, only one other patient had congenital hip dysplasia (Shaheen et al., 2016). Since ankylosis of the hip has not been reported before, we speculate that it might be the result of a failed correction acetabular osteotomy.

Atlantoaxial subluxation was previously reported in three patients with ANXD1 and two with ANXD2, but it had not been described in ANXD3. Horn et al. (2001) reported spontaneous developing respiratory insufficiency and tetraplegia in a 4-year-old ANXD1 patient and attributed them to cervical cord compression. Likewise, Thiel et al. (2005) reported an ANXD1 patient with spasticity due to compression. In our patient, radiological imaging demonstrated an os odontoideum, that can contribute to atlantoaxial instability (Smoker, 1994). This prompted us to take additional flexion and extension x-rays, which supported atlantoaxial instability. We could not correlate our patient's OHCA to cervical myelopathy, as she did not show other signs of cervical myelopathy in the weeks before the OHCA or after recovery. Atlantoaxial subluxation poses a risk of severe cervical myelopathy, for which preventive measures can be taken, including external immobilization, internal fixation, and precautions during anesthetic procedures. Greater awareness of the possibility of atlantoaxial subluxation in these patients can inform clinical management, including performing flexion-extension spine radiographs in newly identified ANXD cases and timely referral to a pediatric neurosurgeon.

Tooth agenesis has only been reported in one ANXD1 and three ANXD2 patients (Barraza-García et al., 2017; Horn et al., 2001; Menger et al., 1996). Other dental anomalies have only been reported in one patient by Horn et al. (2001), specifically microdontia, short root anomaly, and taurodontism. Our patient showed these same anomalies, as well as enamel hypoplasia and abnormal morphology of all elements. We consider dental anomalies as a variable feature among ANXD patients, and all require an individualized treatment plan.

Sagittal suture craniosynostosis resulting in scaphocephaly, Madelung deformity, and SCFE have not previously been reported in any CHH-AD spectrum disorders. SCFE has been reported only once in other diseases caused by defects in the ribosome biogenesis pathway: in Shwachman-Diamond syndrome, a rare multi-system disease that also affects the skeleton (Ginzberg et al., 1999). It is likely that the left-sided SCFE we observe is secondary to the right-sided hip-joint ankylosis, resulting from abnormal mechanical stress. Future studies should provide insight into whether craniosynostosis and Madelung deformity are part of the skeletal phenotype of ANXD3.

All ANXD types may also exhibit an extraskeletal phenotype that includes motor and cognitive developmental delays and frequent airway infections, as seen in our patient (Akgün-Doğan et al., 2018; Barraza-García et al., 2017; Narayanan et al., 2019). In contrast to most previously reported patients, our patient did not exhibit skin laxity, but this may simply be masked by the ichthyotic epidermal hyperproliferation. It is believed that the main pathogenic basis for the features of all CHH-AD spectrum disorders are defects in the ribosomal biogenesis pathway, although the specific mechanisms remain unknown (Thiel & Rauch, 2011; Trainor & Merrill, 2014). However, this has been questioned by Abdulhadi-Atwan et al. (2020), so further research is needed to elucidate the molecular pathways involved.

In conclusion, we present an extensive phenotypical and radiological evaluation of a newly identified ANXD3 patient. Novel findings include atlantoaxial subluxation, dental anomalies, and craniosynostosis, and we urge greater awareness of the full clinical spectrum in ANXD3 patients to enable timely diagnosis and optimal treatment.

AUTHOR CONTRIBUTIONS

P. Christian Remmelzwaal, Hermine E. Veenstra-Knol, and Marrit M. Hitzert phenotyped the patient clinically. Martijn V. Verhagen performed radiographic phenotyping. P. Christian Remmelzwaal and Marrit M. Hitzert conceived and conceptualized the content of the manuscript. Jan D.H. Jongbloed provided exome sequence analysis. P. Christian Remmelzwaal and Martijn V. Verhagen wrote the manuscript. Jan D.H. Jongbloed, Peter C. van den Akker, Hermine E. Veenstra-Knol, and Marrit M. Hitzert contributed to review-editing of the manuscript. MMH supervised the project.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

PATIENT CONSENT STATEMENT

Diagnostic genetic testing was performed after written informed consent from the parents, in accordance with local regulations. Written informed consent was obtained from both parents for the publication of clinical information and patient photographs.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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