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Desmosterolosis presenting with multiple congenital anomalies

Mersedeh Rohanizadegan[a,b], Stephanie Sacharow[a,b,*]

[a] Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, USA
[b] Harvard Medical School, Boston, MA, USA

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ABSTRACT

Desmosterolosis is a rare multiple congenital anomaly syndrome caused by a defect in the enzyme 3-beta-hydroxysterol delta-24-reductase (DHCR24) in the cholesterol biosynthesis pathway. Defects in this enzyme cause increased level of the cholesterol precursor desmosterol while disrupting development of cholesterol, impacting embryogenesis. A total of 9 cases of desmosterolosis have been reported to date. We report a 20-month-old male from consanguineous parents with multiple congenital anomalies including corpus callosum hypoplasia, facial dysmorphism, cleft palate, pectus deformity, short and wide neck and distal contractures. On analysis of the regions of homozygosity found by microarray, we identified *DHCR24* as a candidate gene. Sterol quantitation showed a desmosterol level of 162 μg/mL (nl: 0.82 ± 0.48). Genetic testing confirmed the diagnosis with a homozygous likely pathogenic mutation (p.Glu191Lys) in the *DHCR24* gene. Our case expands the known diagnostic spectrum for Desmosterolosis. We suggest considering Desmosterolosis in the differential diagnosis of patients who present with concurrent agenesis of the corpus callosum with white matter atrophy and ventriculomegaly, retromicrognathia with or without cleft palate, hand contractures, and delay of growth and development. Children of consanguineous mattings may be at higher risk for rare recessive disorders and testing for cholesterol synthesis defect should be a consideration for affected children. Initial evaluation can be performed using sterol quantitation, followed by genetic testing.

1. Introduction

Desmosterolosis (OMIM 602398) is an autosomal recessive disorder that is caused by defects in the *DHCR24* gene coding for the enzyme 3-beta-hydroxysterol-delta-24-reductase in the cholesterol biosynthesis pathway (Waterham et al., 2001). This enzyme metabolizes desmosterol to cholesterol as the last step of conversion of lanosterol to cholesterol (Clayton, 1998; FitzPatrick et al., 1998; Kelley and Herman, 2001). Increased levels of desmosterol in plasma, tissue and cultured cells have been reported in desmosterolosis (Waterham et al., 2001).

Cholesterol is vitally important in the body for manufacturing membranes, hormones, cell signaling, and for the induction of SHH-related pathways (Simons and Ehehalt, 2002; Riobo, 2012; Stottmann et al., 2011). Desmosterol and 7-dehydrocholesterol are each the penultimate product in parallel pathways for cholesterol biosynthesis. Smith-Lemli-Opitz syndrome (Opitz, 1999; Irons et al., 1994) results from a block in sterol delta-7-reductase causing accumulation of 7-dehydrocholesterol, and has highly variable expression with well described diagnostic findings including the nearly omnipresent 2–3 toe syndactyly. Desmosterolosis is a lesser-known disorder and is still being characterized (Porter and Herman, 2010).

In 1998, Fitzpatrick et al. reported the first case of desmosterolosis, a female born at 34 weeks gestation who died shortly after birth. Features described included macrocephaly with MRI findings of ventricular dilatation and corpus callosum agenesis, hypoplastic nasal bridge, thick alveolar ridges, gingival nodules, cleft palate, total anomalous pulmonary venous drainage, ambiguous genitalia, short limbs and generalized osteosclerosis. Post-mortem gas chromatography-mass spectrometry in kidney, liver and brain revealed elevated level of desmosterol (FitzPatrick et al., 1998). In 2002, Andersson et al. reported the first living case of desmosterolosis in an infant who presented with severe microcephaly, agenesis of corpus callosum, facial dysmorphic features, clubfoot and persistent patent ductus arteriosus, and a 100-fold increase in the level of desmosterol both in plasma and cultured lymphoblasts (Andersson et al., 2002). Zolotushko et al. (2011) described a consanguineous Israeli Bedouin family with six affected family members of which four were living. All affected individuals described had microcephaly, microretrognathia, psychomotor and growth retardation, hand contractures, underdeveloped corpus callosum and ventriculomegaly (Zolotushko et al., 2011).

Since then, a total of 9 patients with diagnosis of desmosterolosis have been reported in the literature. Dias et al. described an affected

* Corresponding author. Division of Genetics and Genomics, Boston Children's Hospital, Hunnewell 5 (HU 537), 300 Longwood Ave, Boston, MA 02115, USA.
E-mail address: stephanie.sacharow@childrens.harvard.edu (S. Sacharow).

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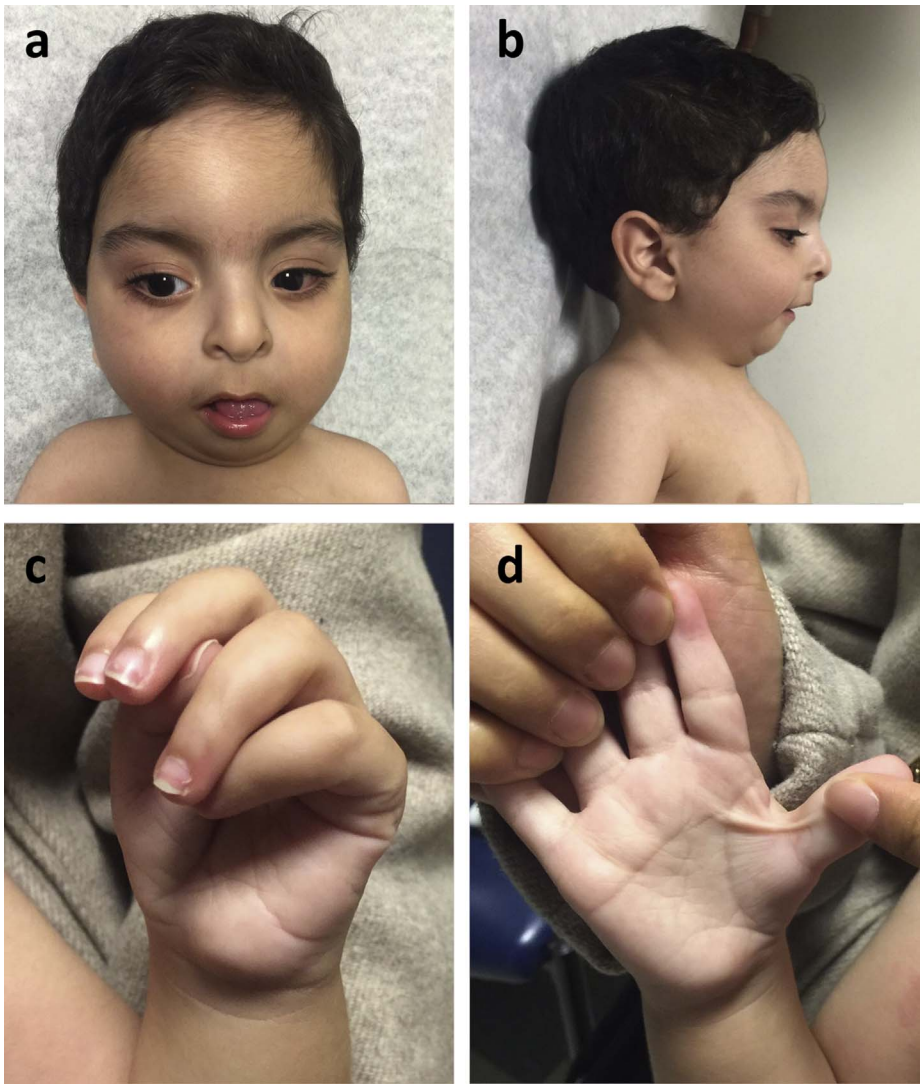

Fig. 1. Pictures of the patient at initial presentation i.e. 20 months of age, showing (a) facial dysmorphism, (b) low set and posteriorly rotated ears, retro-micrognathia, (c–d) transverse palmar crease and contractures of the inter-phalangeal joints.

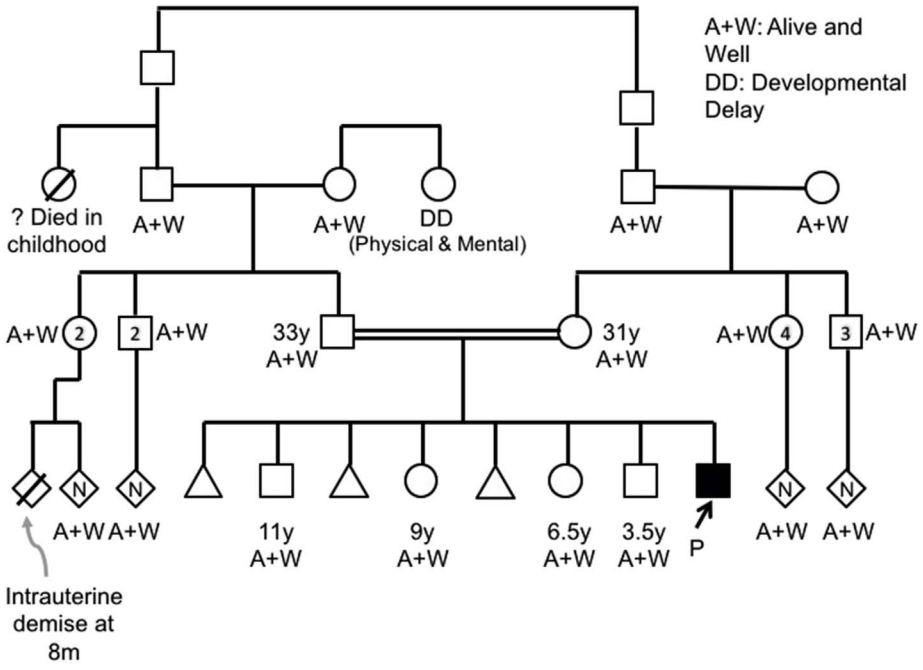

Fig. 2. Pedigree of the patient and his family.