We report here 4 patients with restrictive dermopathy (RD) who presented in the paediatric and dermatology department of the University of Heidelberg from 1996 until 2017. All of the patients were premature infants displaying the pathognomonic clinical picture of RD: tense, vulnerable and translucent skin, superficial erosions, joint contractures, reduced motoricity and a typical facies with a small pinched nose, mouth fixed in an o-position, low-set ears and micrognathia (Fig. 1). Skin biopsies for light and electron microscopy showed collagen bundles parallel to the skin surface and a hypoplasia of appendages as common pathological findings. In 2 biopsies, the collagen fibres were small and in 3 of the 4 patients the rete ridges were flattened and elastic fibres were reduced or arranged in tiny clumps (Fig. 2b). All 4 babies developed respiratory insufficiency and died between days 6 and 32 after birth. (For more detailed information on each case see Table S1). RD has a pathognomonic phenotype; however, the underlying structural skin changes remain to be defined.
One possible explanatory approach may be a developmental arrest of extracellular matrix components, e.g. elastic fibres. As this hypothesis has not yet been addressed, immunohistochemical analysis of elastic fibres was performed in healthy newborns and those with RD.

RESULTS AND DISCUSSION

RD is a rare, lethal, autosomal recessive genodermatosis, first described as a distinct entity in 1986 by Witt et al. (1), whereas the first clinical reports by Antoine (2) allegedly date back to 1929. Navarro et al. identified the disease as a laminopathy in 2004 (3). Laminopathies include different diseases, such as Hutchinson-Gilford progeria syndrome, mandibulocral dysplasia, and dilatative cardiomypathy. They are based on defects of the nuclear membrane protein lamin A. The main cause of RD is an autosomal recessive gene defect of the ZMPSTE24 gene. There are different mutations observed in patients with RD, but the most common one is c.1085_1086 in exon 9 (4). The mutations identified to date lead to a loss of function of the zinc-metalloproteinase ZMPSTE24. As a result, the nuclear-membrane precursor protein prelamin A cannot be completely processed to lamin A (5, 6), leading to a loss of mature lamin A and an increase in the intermediate stage farnesylated prelamin A. This intermediate stage of lamin A accumulates at the nuclear rim, causes misshapen nuclei (7–9) and has an intrinsic toxic effect on cells (7, 10–12).

RD has a characteristic clinical picture, as seen in our 4 patients. Additional findings are skeletal abnormalities, including clavicular hypoplasia and abnormalities in the long bones. The mean gestational age is 31 weeks, and foetal dyskinesia is present in all reported cases (13). Affected patients have lung hypoplasia and inspiratory dysfunction due to thoracic stiffness. Respiratory insufficiency is the most common cause of death in patients with RD. Some patients are stillborn, and most patients die within the first days of birth. The longest reported survival is 120 days (14). Currently, there is no curative therapy for RD. Therefore, prenatal diagnosis by chorionic villus biopsy or amniocentesis and providing genetic advice to affected families play an important role. Histological findings of the skin are a disordered distribution pattern may be one explanation for the tightened skin in patients with RD.

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