

CLINICAL REPORT

A new case of Greenberg dysplasia and literature review suggest that Greenberg dysplasia, dappled diaphyseal dysplasia, and Astley–Kendall dysplasia are allelic disorders

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Abstract

Background: Greenberg dysplasia is a rare, autosomal recessive, prenatal lethal bone dysplasia caused by biallelic pathogenic variants in the lamin B receptor (*LBR*) gene. Pathogenic variants in *LBR* are also associated with Pelger–Huët anomaly, an autosomal dominant benign abnormality of the nuclear shape and chromatin organization of blood granulocytes, and Pelger–Huët anomaly with variable skeletal anomalies, a mild, regressing to moderate–severe autosomal recessive condition. Conditions with abnormal sterol metabolism and different genetic basis have clinical and radiographic features similar to Greenberg dysplasia, for example X-linked dominant chondrodysplasia punctata, Conradi–Hünemann type, and CHILD syndrome, and other conditions with unknown genetic etiology display very similar features, for example, dappled diaphyseal dysplasia and Astley–Kendall dysplasia.

Methods: We present a fetus with typical clinical and radiographic features of Greenberg dysplasia, and review the literature.

Results: Genetic testing confirmed the diagnosis Greenberg dysplasia: homozygosity for a pathogenic variant in *LBR*.

Conclusion: Comparing the clinical and radiographic phenotypes of Greenberg dysplasia, dappled diaphyseal dysplasia, and Astley–Kendall dysplasia, we suggest that these are allelic disorders.

KEYWORDS

abnormal sterol metabolism, Greenberg dysplasia, *LBR*, Skeletal dysplasia

1 | INTRODUCTION

Greenberg dysplasia (OMIM #215140) is a very rare, prenatally lethal, autosomal recessive bone dysplasia (Greenberg et al., 1988). It is also referred to as HEM skeletal dysplasia

due to the characteristic clinical features of hydrops, ectopic calcification, and the moth-eaten appearance of long bones and the pelvis (Chitayat et al., 1993).

Greenberg dysplasia is caused by biallelic pathogenic variants in the lamin B receptor (*LBR*) gene located on

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chromosome 1q42.1. *LBR* encodes an important inner nuclear membrane protein (LBR) that binds to the chromatin and lamin B proteins (LMNB1 and LMNB2) (Clayton et al., 2010; Herrmann & Zwerger, 2010). *LBR* seems to have two functions: (a) a structural function in the organization of chromatin and nuclear shape and (b) an enzymatic sterol reductase function in the metabolic pathway of cholesterol synthesis (Clayton et al., 2010).

Variants in *LBR* are associated with several other, significantly milder conditions than Greenberg dysplasia. Heterozygous pathogenic *LBR* variants cause benign abnormalities of the nuclear shape and chromatin organization of the granulocytes. This finding is known as Pelger–Huët anomaly (PHA, OMIM #169400) and in isolation seems to have no medical implications (Hoffmann et al., 2002). Homozygosity and compound heterozygosity for *LBR* variants cause Pelger–Huët anomaly with mild skeletal anomalies (PHASK, OMIM #618019), a mild and self-regressing condition (Borovik, Modaff, Waterham, Krentz, & Pauli, 2013; Hoffmann et al., 2002; Sobreira et al., 2015). Another phenotype with moderately severe skeletal dysplasia was also recently described, broadening the spectrum of *LBR*-related disorders (Thompson et al., 2019).

In all, 11 fetuses with Greenberg dysplasia (or HEM dysplasia) have previously been described; in seven of these biallelic pathogenic variants in *LBR* was identified. Other conditions caused by defects in sterol metabolism have clinical features similar to Greenberg dysplasia. An example is X-linked dominant chondrodysplasia punctata, Conradi–Hünemann type (CDPX2, OMIM #302960) caused by pathogenic variants in *EBP* (Braverman et al., 1999). Although there may be overlapping clinical features between CDPX2 and Greenberg dysplasia, most patients can be differentiated on clinical, radiographic, and molecular grounds (Offiah et al., 2003). Other strikingly similar bone dysplasia are described as separate clinical entities to Greenberg dysplasia: dappled diaphyseal dysplasia (Carty, Kozlowski, & Sillence, 1989), Astley–Kendall dysplasia (Astley & Kendall, 1980), and a similar lethal, short-limbed bone dysplasia (Nairn & Chapman, 1989). Molecular data have not been provided for any of the latter cases.

We present a fetus with typical clinical features of Greenberg dysplasia and homozygosity for a pathogenic variant in *LBR*. On critical review of the phenotypes of Greenberg dysplasia, dappled diaphyseal dysplasia, and Astley–Kendall dysplasia, we suggest that these are allelic disorders.

2 | MATERIALS AND METHODS

The pregnant mother of the fetus was identified and investigated clinically in the Fetal Medicine Unit/Genetics Department of a tertiary maternity hospital. Fetal images

were reviewed by GM and RS following referral for a diagnostic opinion. The mother and her husband gave written informed consent for publication of their baby's findings according to local ethics committee requirements.

2.1 | Genetic analyses

High-resolution SNParray was performed on DNA from chorionic villous sampling (CVS) as part of clinical care of the pregnant mother and the fetus.

Following a limited clinical postmortem examination including a skeletal survey, bidirectional fluorescent direct sequencing (Sanger) of all coding regions and intron–exon boundaries of *LBR* was performed on PCR-amplified DNA from the deceased fetus.

2.2 | Literature search

We used the following terms searching PubMed for relevant literature: Greenberg dysplasia, *LBR*, dappled diaphyseal dysplasia, and Astley–Kendall dysplasia (February 20, 2019).

3 | RESULTS

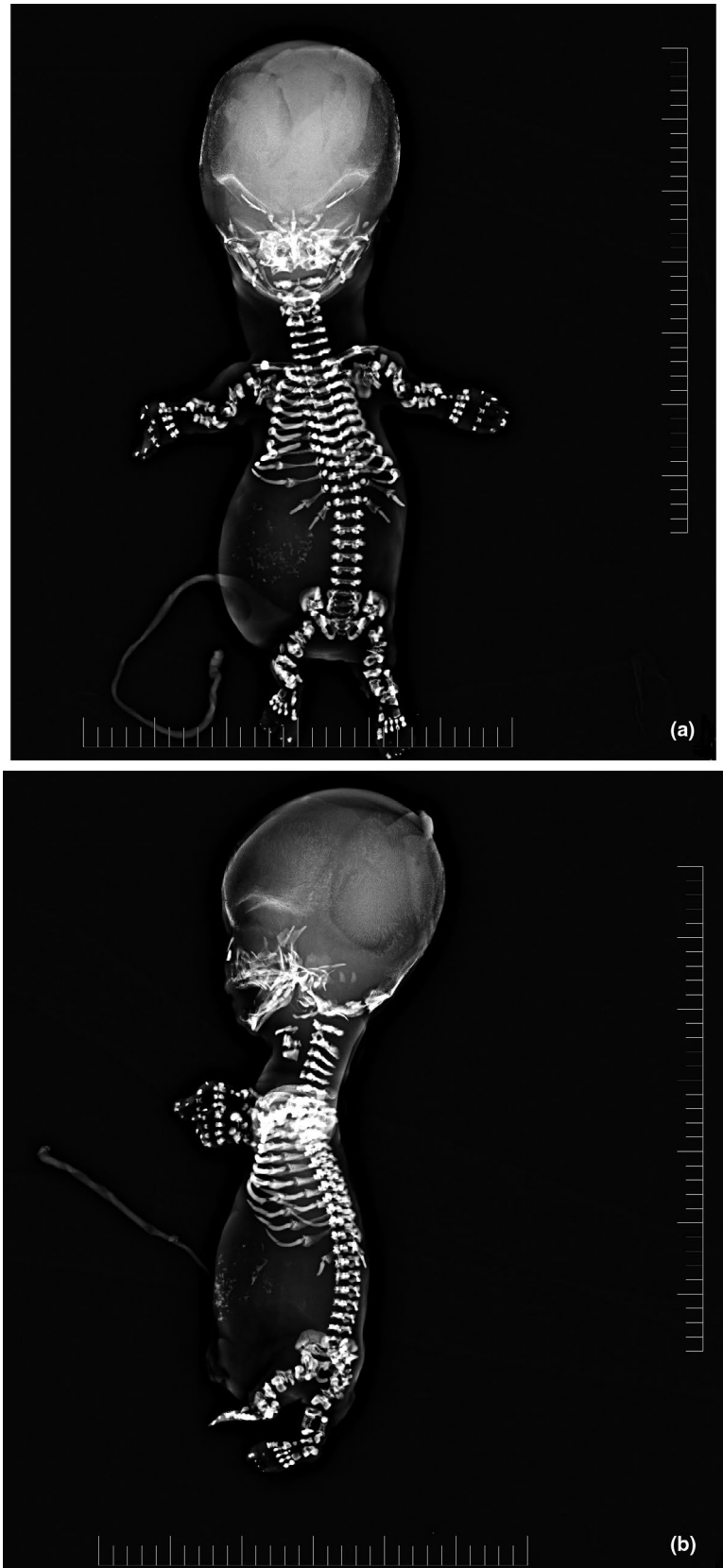
3.1 | Clinical report

This fetus was the second pregnancy of a healthy, consanguineous couple. A routine 12-week ultrasound revealed short long bones, a small chest, and generalized hydrops. Nuchal translucency was 8.4 mm, CRL 75.2 mm. Initially, a diagnosis of Jeune asphyxiating thoracic dystrophy was considered given the narrow thorax. At 15 weeks + 5 days of gestation, ultrasound showed marked fetal edema, a chest circumference under the 5th centile, flat diaphragm, and polydactyly of both feet. Absence of the fetal heartbeat confirmed intra-uterine death.

The parents consented to a postmortem external examination, radiology, and skin sampling for fibroblast culture. Fetal examination showed growth parameters below the 5th centile for gestational age, large eyes with blue sclerae, hypertelorism, low set ears, hypoplastic midface, bilateral post-axial polydactyly of the feet and a small chest with protuberant abdomen. Hydrops was clinically evident along with remnants of a cystic hygroma (loose skin in the neck). Relevant negative findings were an intact palate, no additional external non-skeletal malformations, and no evidence of cataracts.

The postmortem skeletal survey (Figure 1) demonstrated relative lack of ossification of the skull for gestational age, marked platyspondyly and stippled spine, small thorax, transverse rib defects (“cut-glass” appearance), rhizo-mesomelic shortening

FIGURE 1 (a, b) Relative lack of ossification of the skull, platyspondyly, and stippling of the spine, small thorax, transverse rib defects (“cut-glass” appearance), rhizo-mesomelic shortening and deformity of all four limbs, punctate epiphysis, stippled tarsal and carpal bones, and widespread ectopic ossification (ossification islands). Speckled ossification in the abdominal region, punctate calcification in the articular skeleton, and a “moth-eaten” appearance of the pelvic bones



and deformity of all four limbs, punctate epiphyses, stippled tarsal and carpal bones, and widespread ectopic ossification (ossification islands). Speckled ossification was present in the abdominal region, possibly in the region overlying the liver and thought to represent evidence of extra-medullary hematopoiesis. Areas of punctate calcification were present throughout the articular skeleton. The pelvic bones had an unusual appearance and contour, suggestive of a “moth-eaten” appearance.

3.2 | Genetic studies

By 15 weeks of gestation, SNParray on DNA from chorionic villous sampling (CVS) showed multiple regions of homozygosity (5.2% of the genome) consistent with the known consanguinity; no genomic imbalance was detected.

Postmortem, Sanger sequencing of DNA from the deceased fetus showed homozygosity for an *LBR* variant (c.1748G > A, p. Arg583Gln; NM_002296.4).

The detected *LBR* variant changes a highly conserved residue in the sterol reductase domain (Clayton et al., 2010). The variant was previously found in compound heterozygosity with a 4-base pair deletion in another fetus with Greenberg dysplasia (Clayton et al., 2010).

4 | LITERATURE SEARCH

In all, 11 fetuses with Greenberg dysplasia have previously been described in the literature; in seven of these biallelic pathogenic variants in *LBR* was identified (Chitayat et al., 1993; Clayton et al., 2010; Giorgio et al., 2019; Greenberg et al., 1988; Horn, Faber, Meiner, Piskazeck, & Spranger, 2000; Konstantinidou et al., 2008; Waterham et al., 2003). Two fetuses with dappled diaphyseal dysplasia (Carty et al., 1989), two fetuses with Astley–Kendall dysplasia (Astley & Kendall, 1980), and three fetuses with an intermediate phenotype were reported (Elcioglu & Hall, 1998); In these seven latter fetuses, genetic testing of *LBR* was not performed.

5 | DISCUSSION

Greenberg et al. first described this lethal chondrodysplasia with congenital hydrops in two siblings born to consanguineous parents (Greenberg et al., 1988). The cardinal features were severe bone dysplasia, hydrops, very short long bones with a moth-eaten appearance, disordered ectopic ossification centers, and platyspondyly. Two fetuses were subsequently reported with post-axial polydactyly of the hands (Chitayat et al., 1993; Waterham et al., 2003), and one further fetus reported with additional non-skeletal malformations including an omphalocele (Horn et al., 2000). Astley and Kendall

previously described a similar bone dysplasia in a stillborn fetus (Astley–Kendall dysplasia) (Astley & Kendall, 1980). In 1989, Carty et al. and Nairn and Chapman separately described a lethal bone dysplasia with similar features to Greenberg dysplasia: Carty et al. reported their condition as dappled diaphyseal dysplasia (DDD) (Carty et al., 1989); Nairn and Chapman variously described three siblings from a consanguineous relationship as having features consistent with either DDD or Astley–Kendall dysplasia (Nairn & Chapman, 1989). Later, Elçioglu and Hall presented a fetus with features of both chondrodysplasia punctata (CDP) and osteogenesis imperfecta (OI), describing this fetus as a further example of Astley–Kendall dysplasia (Elcioglu & Hall, 1998). Elçioglu and Hall disagreed with previous suggestions that DDD and Greenberg dysplasia may represent the same condition with different severity of clinical features, and suggest that these disorders can be differentiated on radiological grounds.

Functional studies of cultured fibroblasts from a fetus with Greenberg dysplasia confirmed that causative variants in *LBR* lead to a 3β -hydroxysterol Δ^{14} -reductase deficiency (Waterham et al., 2003). As mentioned earlier, homozygosity, compound heterozygosity, and heterozygosity for *LBR* variants are reported in patients with Pelger–Huët anomaly with or without variable skeletal abnormalities (PHASK and PHA) (Hoffmann et al., 2002). These studies support that Pelger–Huët anomaly with and without skeletal abnormalities of varying degree and Greenberg dysplasia are allelic disorders representing a disease spectrum ranging from very mild to extremely severe (lethality). Further confirmation is provided by the evidence that the healthy mother of the fetus with Greenberg dysplasia reported by Waterham et al. showed hypolobulated nuclei in 60% of her granulocytes, a classic feature of Pelger–Huët anomaly and representing the heterozygous state of 3β -hydroxysterol Δ^{14} -reductase deficiency (Waterham et al., 2003). Further studies on sterol metabolism support the association (Borovik et al., 2013; Sobreira et al., 2015; Thompson et al., 2019; Tsai, Zhao, Turner, & Schlieker, 2016), and Giorgio et al. recently described in detail how variants in different functional domains, and different types of mutations lead to a continuum of *LBR*-associated phenotypes (*LBR* genotype–phenotype correlation) (Giorgio et al., 2019).

The demonstration of the underlying defects in the cholesterol biosynthesis pathway in Greenberg dysplasia has shed light on the clinical features overlapping with other disorders in the same pathway, for example CDPX2 caused by variants in *EBP*. Females with CDPX2 are often born with an erythematous rash following the Blaschko's lines, which fades over time to leave a phenotype including variable ichthyosis (Herman, 2000). This overlaps with the clinical phenotype seen in patients with CHILD syndrome: Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects, caused by variants in both *EBP*

TABLE 1 Most consistent features in reported fetuses with clinical and radiographic similarities to Greenberg dysplasia (includes the fetus we present)

Clinical and radiographic features	Astley–Kendall (N = 2)	Nairn & Chapman (N = 3)	Greenberg/HEM (N = 12)	DDD (N = 2)
Relative lack of ossification of skull vault	+	+	+	+
Stippling of spine	+	+	+	+
Platyspondyly	+	+	+	+
Small thorax	+	+	+	+
Transverse translucent rib defects	+	+	+	+
Short deformed limbs	+	+	+	+
Stippled carpal and tarsal bones	+	+	+	+
Punctate epiphyses	+	+	+	+
Hydrops	–	–	+	+

and *NSDHL*. The phenotypic overlap is not surprising perhaps, given that *NSDHL* encodes a sterol dehydrogenase or decarboxylase that is part of the C-4 sterol demethylase protein complex and precedes the sterol- Δ^8 - Δ^7 -isomerase step, encoded by *EBP*, in the cholesterol biosynthetic pathway (Herman, 2003). Other disorders caused by variants more distally in the cholesterol biosynthesis pathway can also present with rhizomelia and post-axial polydactyly, including Smith–Lemli–Opitz syndrome and desmosterolosis (Herman, 2003). There is also therefore evidence of overlapping clinical phenotypes in disorders caused by variants in genes involved in the synthesis of cholesterol.

With recent advances in genomic medicine, it is apparent that the phenotypes of conditions are much wider than previously thought. It is therefore likely that, given current knowledge of sterol metabolism, the disorders described as Astley–Kendall dysplasia and DDD, along with the fetuses described by Nairn and Chapman, all form part of a spectrum of disorders due to defects in the post-squalene cholesterol biosynthesis pathway (Herman, 2003). Neither Astley–Kendall dysplasia nor DDD appear on OMIM as the molecular basis has not been elucidated; however, phenotypic overlap and common association to *LBR* have previously been suggested (Bonafe et al., 2015; Spranger, Brill, Nishimura, Superti-Furga, & Unger, 2012).

All the fetuses discussed by Elçioglu and Hall have some clinical differences from Greenberg dysplasia, which is the focus of their paper (Elçioglu & Hall, 1998). However, there are significant similar clinical and radiographic features seen

in all the reported fetuses (Table 1), which could form the basis of a consistent clinical phenotype for this spectrum of disorders. All features are also seen in the fetus we present, and perhaps hydrops is only seen in the most severe cases and is not a prerequisite for bone dysplasia caused by defects in the cholesterol biosynthesis pathway. This case illustrates the difficulty in diagnosing a specific skeletal dysplasia prenatally (Savarirayan et al., 2018), and the importance for post-mortem radiographic evaluation to maximize the chances of diagnosis of a rare skeletal dysplasia such as Greenberg dysplasia.

Further studies would help elucidate whether any or all of these previously described rare bone dysplasia are allelic to Greenberg dysplasia and caused by biallelic variants in *LBR*.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Pernille Axél Gregersen, Victoria McKay, and Ravi Savarirayan wrote the manuscript. Maie Walsh, Erica Brown, and George McGillivray contributed with important input to and work on relevant parts of the manuscript. All authors reviewed and came with input to the entire final manuscript.

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