Introduction

Buschke-Ollendorf syndrome (BOS) is an uncommon syndrome characterized by osteopoikilosis and other bone abnormalities, accompanied by skin lesions, most frequently connective tissue nevi. BOS is caused by mutations in the \( \text{LEMD3} \) gene, which encodes the inner nuclear membrane protein Man1. We describe a unique case of osteopoikilosis associated with late-onset localized scleroderma and familial \( \text{LEMD3} \) mutations.

Case Report

A 72-year-old woman presented with adult-onset diffuse morphea and bullous skin lesions. Evaluation revealed multiple hyperostotic lesions (osteopoikilosis) suggestive of BOS. DNA sequencing identified a previously undescribed nonsense mutation (Trp621X) in the \( \text{LEMD3} \) gene encoding Man1. Two additional family members were found to have osteopoikilosis and carry the same \( \text{LEMD3} \) mutation.

Conclusions and Relevance

We report a unique familial \( \text{LEMD3} \) mutation in an individual with osteopoikilosis and late-onset morphea. We propose that this constellation represents a novel syndromic variant of BOS.
The etiology of morphea is unknown and its pathogenesis remains poorly understood. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine implicated in fibrosis in multiple organs [13]. The profibrotic responses elicited by TGF-β involve both Smad-dependent canonical, as well as Smad-independent noncanonical intracellular signaling pathways [14, 15]. Alterations in TGF-β expression or function and in its downstream signaling mediators are implicated in the pathogenesis of localized scleroderma and systemic sclerosis [16]. Man1, the protein encoded by LEMD3, is intricately linked to TGF-β biology and has complex effects on modulating TGF-β responses. On one hand, Man1 interacts directly with TGF-β superfamily ligands, including bone morphogenic proteins (BMPs) and activin [17]. On the other hand, Man1 binds, via its C-terminal domain, directly to Smad [17, 18]. Importantly, Man1 negatively regulates Smad-mediated TGF-β signaling in a variety of cell types [2, 17–23]. Despite these recent molecular insights, the full spectrum of LEMD3 mutations and their impact on TGF-β biology and their functional role in the phenotypic expression of BOS remain poorly understood.

Genetic variants of LEMD3 have been associated with distinct clinical phenotypes in addition to BOS. These include isolated osteopoikilosis and melorheostosis [1, 2, 8, 24–30]. We propose that this case represents a novel variant of BOS.

2. Case Report

A previously healthy 72-year-old Caucasian woman presented with six months' progressive skin tightening and discoloration affecting her arms, shoulders, chest, and lower legs. Subsequently, painful erythematous patches appeared on her back, breasts, and belt line. She had no family history of scleroderma or other autoimmune disease. Physical examination demonstrated firmly indurated and hyperpigmented lesions on the arms, shoulders, chest, belt line, and lower legs and scaly erythematous and partially bullous patches over both breasts (Figures 1(a)–1(c)). She had no sclerodactyly, nailfold microvascular abnormalities or other manifestations of systemic sclerosis, and serologic tests for antinuclear, anti-Scl-70, and anti-centromere antibodies were negative. Radiographs of the hands, feet, and knees revealed numerous well-demarcated bone densities (osteopoikilosis) bilaterally (Figure 3). Based on the presence of osteopoikilosis and skin lesions, the diagnosis of BOS was made, and genomic DNA sequencing was undertaken (see below). Further investigation identified three family members (school-aged nieces and nephews on the paternal side) who had asymptomatic osteopoikilosis, but no skin lesions. Treatment of the index case included psoralens and ultraviolet light A, oral calcitriol hydroxychloroquine, and mycophenolate mofetil, as well as topical calcipotriene, betamethasone dipropionate, and...
pimecrolimus. She showed slow partial resolution of skin lesions. Subsequent course was complicated by recurrent episodes of hemorrhagic olecranon bursitis and hemorrhagic bullae over the chest, abdomen, and back.

2.1. Cutaneous Histopathology. A punch biopsy of lesional skin yielded square-shaped tissue with fibrosis and a cellular infiltrate (Figures 1(d)–1(g)). The upper dermis showed bul- lous changes including edema and dilated vessels consistent with lichen sclerosus et atrophicus. Masson’s trichrome and elastin stains revealed dense dermal collagen deposition and increased elastic fiber accumulation (Figure 2).

2.2. DNA Sequencing. Index case DNA was extracted from peripheral blood using a commercial kit (Sigma, St. Louis, MO). Sanger sequencing of the entire LEFD3 gene identified a heterozygous nonsense mutation c.1863G > A which results in a change at amino acid 621 that converts a tryptophan residue to a stop codon (p.Trp621X). This nucleotide change is predicted to truncate Man1 at amino acid 621, resulting in deletion of the second transmembrane helical domain and DNA-binding and Smad-interacting domains [31] (Figure 4). The mutant gene product is predicted to lack the Smad-binding domain of Man1 required for antagonizing TGF-β signaling. This LEFD3 mutation was not present in the exome variant server database (http://evs.gs.washington.edu/EVS/) representing 13,000 control alleles [including 8,600 alleles from individuals of European descent] or in the 1000 Genomes Project database (http://www.1000genomes.org/).
3. Literature Survey and Discussion

First described in 1928, BOS is an uncommon familial syndrome characterized by osteopoikilosis associated with skin manifestations [32, 33]. In children with BOS, osteopoikilosis has been reported to be accompanied by fibrotic skin lesions, including linear scleroderma, part of the morphea spectrum disorders [5, 6, 34–36]. We are unaware of a previous description of late-onset generalized morphea associated with osteopoikilosis.

The present case might represent the coexistence of two distinct disorders affecting the skin and bone. We consider this unlikely however. As osteopoikilosis has an estimated prevalence of 2/100,000 and morphea of 0.02–0.04/100,000 [37], the extreme rarity of these two conditions makes their occurrence in the same individual by chance highly unlikely. A favored alternative explanation is that late-onset generalized morphea associated with osteopoikilosis seen in the present case is in fact syndromic and represents a novel BOS variant that falls within the phenotypic continuum linked with osteopoikilosis.

Previous studies have led to identification of LEMD3 as the gene that is mutated in BOS [2]. In addition, different LEMD3 mutations have also been linked with nonsyndromic familial forms of both osteopoikilosis and melorheostosis [2]. In order to review current knowledge of BOS and its cutaneous manifestations, a PubMed survey using the search terms “BOS”, “Ollendorf Buschke”, “Buschke-Ollendorf”, “osteopoikilosis”, “melorheostosis”, “LEMD3”, and “Man1” was undertaken (Table 1). Over 30 reported cases with LEMD3 loss-of-function mutations linked with these phenotypes were identified [1, 2, 8, 24–28, 30, 38, 39] (Table 1). Cutaneous manifestations include connective tissue nevi, fibrous nodular lesions (collagenomas or elastomas), and linear scleroderma [26].

A review of over 100 published cases of BOS showed that connective tissue nevi (dermatofibrosis lenticularis disseminata) were the most frequent cutaneous manifestation. The diagnosis of BOS was characteristically made before the age of 16. A survey of cases of LEMD3-associated skin and bony lesions revealed 28 cases of melorheostosis associated with linear scleroderma, typically affecting skin adjacent to the bone lesions, with a majority of these individuals developing linear (localized) scleroderma in childhood (Table 2). However, melorheostosis frequently occurs in the absence of LEMD3 mutations [8], and thus far none of the LEMD3 mutation–proven cases of melorheostosis (Table 1) have coincided with linear scleroderma. One report of osteopoikilosis associated with scleroderma described a patient with sclerodactyly and Raynaud phenomenon, suggesting coexistent systemic sclerosis and isolated osteopoikilosis rather than syndromic BOS [6].

LEMD3 mutations show variable penetrance. There is extreme variability in the associated phenotypes, even among individuals harboring identical mutations [2]. Given such a high degree of heterogeneity and incomplete penetrance, the causal role of any particular LEMD3 mutation in a specific phenotype is difficult to discern. Although the TGF-β/Smad signaling pathway plays a pivotal role in both skin and bone homeostasis, it remains unclear how Man1-Smad interactions are affected by the BOS mutations, and whether they contribute to clinical features. While the novel LEMD3 mutation described in this report is predicted to alter the C-terminal domain of Man1 required for R-Smad interactions [23], our functional studies failed to demonstrate consistent alterations in TGF-β/Smad signaling in the BOS skin fibroblasts.

The coexistence of morphea and lichen sclerosus et atrophicus (LSA) changes is also of note. While this combination has been previously reported as a cause of bullous changes [40–43] in morphea, the association is relatively common in adults. A recent retrospective study confirmed the coexistence of these two entities in 26 of 91 (28.5%) of adult morphea patients compared to only 1 of 381 children with morphea [44]. Bullous LSA changes are primarily inflammatory [45] and some have suggested that LSA may represent subepithelial morphea in this context [46]. Therefore, whether the LSA changes are related to the LEMD3
Figure 4: Characterization of novel LEMD3 mutation. (a) 3D predicted conformation of native and mutated p.Trp620X Man1 protein (EsyPred3d modeling software) [31]. Note deletion of the DNA-binding and R-Smad recognition domains. (b) Amino acid sequence of Man1; letters represent amino acids as defined by IUPAC. The Trp620X codon is indicated. (c) List of functional domains and presence of domains in normal and mutated Man1 protein. (d) DNA sequence of LEMD3, highlighting the novel c.1863G > A mutation.
### Table 1: Previously reported LEMD3 mutations.

|                     | Point mutations | Insertions/deletions/duplications/indels |
|---------------------|-----------------|-----------------------------------------|
|                     | 94X             |                                         |
| 457C > T            |                 | Buschke-Ollendorff syndrome [30]         |
| 620X                |                 |                                         |
| 641X                |                 |                                         |
| 1323C > A           |                 |                                         |
| 1609C > T           |                 |                                         |
| 1801G > T           |                 |                                         |
| 1873C > T           |                 |                                         |
| 1913T > A           |                 |                                         |
| 2032C > T           |                 |                                         |
| 2203C > T           |                 |                                         |
| 2564G > A           |                 |                                         |
| (Missense/nonsense) |                 |                                         |
| 332,333 insTC       |                 | Buschke-Ollendorff syndrome [28]         |
| 830 dupA            |                 | Melorheostosis [8]                       |
| 1033–1035 delGGGinsC|                 | Osteopoikilosis [2]                      |
| 1185 dupT           |                 | Osteopoikilosis [2]                      |
| 1914 dupA           |                 | Buschke-Ollendorff syndrome [8]          |
| 1941 +5delG         |                 | Osteopoikilosis [2]                      |
| 2154 dupA           |                 | Osteopoikilosis [2]                      |
| Entire gene deletion|                 | Osteopoikilosis [2]                      |
| None                |                 | Buschke-Ollendorff syndrome [47]         |
| Splicing            |                 |                                         |
| IVS1 ds +1 G-A      |                 | Collagenoma [26]                        |
| IVS12 ds +1 G-A     |                 | Buschke-Ollendorff syndrome [48]         |

### Table 2: Cases of scleroderma-spectrum disease and LEMD3-type bony lesions.

| Study (1st author) | Juvenile-onset linear scleroderma | Adult-onset linear scleroderma | Systemic sclerosis | Generalized morphea | Melorheostosis | Osteopoikilosis |
|--------------------|-----------------------------------|--------------------------------|-------------------|---------------------|----------------|-----------------|
| Thompson [49]      | x                                 | x                              | x                 | x                   | x              |                 |
| Maroteaux [9]      | x                                 | x                              | x                 | x                   | x              |                 |
| Muller [10]        | x                                 | x                              | x                 | x                   | x              |                 |
| Pascaud-Ged [50]   | x                                 | x                              | x                 | x                   | x              |                 |
| Moreno Alvarez [51]| x                                 | x                              | x                 | x                   | x              |                 |
| Saghafi [7]        | x                                 | x                              | x                 | x                   | x              |                 |
| Soffa [52]         | x                                 | x                              | x                 | x                   | x              |                 |
| Takeda [53]        | x                                 | x                              | x                 | x                   | x              |                 |
| Nakajima [54]      | x                                 | x                              | x                 | x                   | x              |                 |
| Miyachi [55]       | x                                 | x                              | x                 | x                   | x              |                 |
| Siegel [56]        | x                                 | x                              | x                 | x                   | x              |                 |
| Birtane [57]       | x                                 | x                              | x                 | x                   | x              |                 |
| Endo [58]          | x                                 | x                              | x                 | x                   | x              |                 |
| Shivanand [12]     | x                                 | x                              | x                 | x                   | x              |                 |
| Weissmann [6]      | x                                 | x                              | x                 | x                   | x              |                 |
| **Present case**   | x                                 | x                              | x                 | x                   | x              |                 |

x: presence of feature in case report.
mutation or are simply part of the morphea phenotype is unclear.

4. Summary

In summary, we describe a case of osteopoikilosis associated with late-onset generalized morphea and associated LSA changes in an elderly individual carrying a previously undescribed familial mutation in LEM3. We propose that in this case morphea and osteopoikilosis are linked, representing an unclear.

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References

[1] S. Baasanjav, A. Jamshir, M. Kolanczyk et al., “Osteopoikilosis and multiple exostoses caused by novelmutations in LEM3 and EXT1 genes respectively—coincidence within one family,” BMC Medical Genetics, vol. 11, no. 1, article 110, 2010.

[2] J. Hellemans, O. Preobrazhenska, A. Willaert et al., “Loss-of-function mutations in LEM3 result in osteopoikilosis, Buschke-Ollendorff syndrome and morphea,” Nature Genetics, vol. 36, no. II, pp. 1213–1218, 2004.

[3] T. G. Wojcikowsky, M. R. Monticelo, B. Keiserman, and O. A. Monticelo, “Osteopoikilosis: what does the rheumatologist must know about it?” Clinical Rheumatology, vol. 31, no. 4, pp. 745–748, 2012.

[4] A. Korekawa, H. Nakano, Y. Toyomaki et al., “Buschke-Ollendorff syndrome associated with hypertrophic scar formation: a possible role for LEM3 mutation,” The British Journal of Dermatology, vol. 166, no. 4, pp. 900–903, 2012.

[5] M. H. Mordant, “Osteopoikilosis with disseminated dermatofibrosis,” Archives Belges de Dermatologie et de Syphiligraphie, vol. 14, no. 1, pp. 83–87, 1958.

[6] G. Weissmann, “Scleroderma associated with osteopoikilosis,” A.M.A. Archives of Internal Medicine, vol. 101, no. 1, pp. 108–113, 1958.

[7] M. Saghafi, M. Sahebari, and L. Goshayeshi, “Linear sclerosis in association with morphea,” Journal of Clinical Rheumatology, vol. 16, no. 2, pp. 99–100, 2010.

[8] J, Hellemans, P. Debeer, M. Wright et al., “Germline LEM3 mutations are rare in sporadic patients with isolated morphea,” Human Mutation, vol. 27, no. 3, p. 290, 2006.

[9] P. Maroteaux and M. Lamy, “Morphea, osteopetra and circumscribed scleroderma,” Annales de Pediatrie, vol. 8, pp. 576–580, 1961.

[10] S. A. Muller and E. D. Henderson, “Morphea, osteopoikilosis and linear scleroderma,” Archives of Dermatology, vol. 88, pp. 142–145, 1963.

[11] E. Pascaud-Ged, J. Rihouet, J. L. Pascaud, and J. Rousseau, “Morphea, osteopoikilosis and linear scleroderma,” La Semaine des Hopitaux : Organe Fonde Par L'Association D'enseignement Medical des Hopitaux de Paris, vol. 58, no. 17, pp. 1056–1059, 1982.

[12] G. Shivanand and D. N. Srivastava, “Morphea, osteopoikilosis and scleroderma,” Clinical Imaging, vol. 28, no. 3, pp. 214–215, 2004.

[13] A. Leask and D. J. Abraham, “TGF-β signaling and the fibrotic response,” The FASEB Journal, vol. 18, no. 7, pp. 816–827, 2004.

[14] A. Moustakas, S. Souchelnytskyi, and C. H. Heldin, “Smad regulation in TGF-β signal transduction,” Journal of Cell Science, vol. 114, no. 24, pp. 4359–4369, 2001.

[15] A. Moustakas and C. H. Heldin, “Non-Smad TGF-β signals,” Journal of Cell Science, vol. 118, no. 6, pp. 1537–1538, 2005.

[16] J. Varga and B. Pasche, “Transforming growth factor beta as a therapeutic target in systemic sclerosis,” Nature Reviews Rheumatology, vol. 5, no. 4, pp. 200–206, 2009.

[17] D. Pan, L. D. Estévez-Salmerón, S. L. Stroschein et al., “The integral inner nuclear membrane protein MAN1 physically interacts with the R-smad proteins to repress signaling by the transforming growth factor-β superfamily of cytokines,” The Journal of Biological Chemistry, vol. 280, no. 16, pp. 15992–16001, 2005.

[18] F. Lin, J. M. Morrison, W. Wu, and H. J. Worman, “MAN1, an integral protein of the inner nuclear membrane, binds Smad2 and Smad3 and antagonizes transforming growth factor-β signaling,” Human Molecular Genetics, vol. 14, no. 3, pp. 437–445, 2005.

[19] F. Lin, D. L. Blake, I. Callebaut et al., “MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin,” The Journal of Biological Chemistry, vol. 275, no. 7, pp. 4840–4847, 2000.

[20] W. Wu, F. Lin, and H. J. Worman, “Intracellular trafficking of MAN1, an integral protein of the nuclear envelope inner membrane,” Journal of Cell Science, vol. 115, no. 7, pp. 1361–1372, 2002.

[21] A. Ishimura, J. K. Ng, M. Taira, S. G. Young, and S.-I. Osada, “MAN1, an inner nuclear membrane protein, regulates vascular remodeling by modulating transforming growth factor β signaling,” Development, vol. 133, no. 19, pp. 3919–3928, 2006.

[22] L. Bengtsson, “What MAN1 does to the Smads: TGF-β superfamily of cytokines,” The FEBS Journal, vol. 274, no. 6, pp. 1374–1382, 2007.

[23] E. Kondé, B. Bourgeois, C. Tellier-Lebegue et al., “Structural analysis of the Smad2-MAN1 interaction that regulates transforming growth factor-β signaling at the inner nuclear membrane,” Biochemistry, vol. 49, no. 37, pp. 8020–8032, 2010.

[24] O. Dereure, “Buschke-Ollendorff syndrome: inactivating mutation of the LEM3 gene,” Annales de Dermatologie et de Vénéréologie, vol. 132, no. 6–7, part 1, p. 593, 2005.
[25] A. R. Couto, J. Bruges-Armas, C. A. Peach et al., “A novel LEMD3 mutation common to patients with osteopoikilosis with and without morphea,” Calciﬁed Tissue International, vol. 81, no. 2, pp. 81–84, 2007.

[26] D. Hershkovitz, D. B. Amitai, and E. Sprecher, “Familial cutaneous collagenomas resulting from a novel mutation in LEMD3,” The British Journal of Dermatology, vol. 156, no. 2, pp. 375–377, 2007.

[27] B. Menten, K. Buyssse, F. Zahir et al., “Osteopoikilosis, short stature and mental retardation as key features of a new micro-deletion syndrome on 12q14,” Journal of Medical Genetics, vol. 44, no. 4, pp. 264–268, 2007.

[28] S. Mumm, D. Wenkert, X. Zhang, W. H. McAlister, R. J. Mier, and M. P. Whyte, “Deactivating germline mutations in LEMD3 cause osteopoikilosis and Buschke-Ollendorff syndrome, but not sporadic morphea,” Journal of Bone and Mineral Research, vol. 22, no. 2, pp. 243–250, 2007.

[29] Y. Zhang, M. Castori, G. Ferranti, M. Paradisi, and B. P. Wordsworth, “Novel and recurrent germline LEMD3 mutations causing Buschke-Ollendorff syndrome and osteopoikilosis but not isolated morphea,” Clinical Genetics, vol. 75, no. 6, pp. 556–561, 2009.

[30] B. Burger, D. Hershkovitz, M. Indelman et al., “Buschke-Ollendorff syndrome in a three-generation family: inﬂuence of a novel LEMD3 mutation to tropoelastin expression,” European Journal of Dermatology, vol. 20, no. 6, pp. 693–697, 2010.

[31] C. Lambert, N. Léonard, X. De Bolle, and E. Depierreux, “ESyPred3D: prediction of proteins 3D structures,” Bioinformatics, vol. 18, no. 9, pp. 1250–1256, 2002.

[32] A. Buschke, “Uber scleroderma,” Wiener Klinische Wochenschrift, vol. 39, pp. 955–957, 1902.

[33] A. Buschke and H. Ollendorf-Curth, “Ein Fall von Dermatofibrosis lenticularis disseminata und Osteopathia condensans disseminata,” Dermatologische Wochenschrift, vol. 86, pp. 257–262, 1928.

[34] D. Loreck, I. Tausch, and H. Albrecht-Nebe, “Buschke-Ollendorff syndrome: combination of dermatofibrosis lenticularis disseminata with osteopoikilosis,” Radiologia Diagnostica, vol. 25, no. 3, pp. 283–291, 1984.

[35] F. Massolo, M. G. Bertazzoni, A. Caroli, S. Sardelli, M. Cellini, and E. Mazzone, “Melorheostosis linear scleroderma with osteopoikilosis. Description of a clinical case,” La Pediatría Médica e Chirúrgica, vol. II, no. 5, pp. 555–557, 1989.

[36] I. Tausch, D. Loreck, H. Albrecht-Nebe, H. Klug, and T. Thormann, “Dermatofibrosis lenticularis disseminata with osteopoikilosis (Buschke-Ollendorff syndrome),” Dermatologische Monatsschrift, vol. 170, no. 5, pp. 322–331, 2005.

[37] L. S. Peterson, A. M. Nelson, W. P. D. Su, T. Mason, W. M. O’Fallon, and S. E. Gabriel, “The epidemiology of morphea (localized scleroderma) in Olmsted County 1960–1993,” The Journal of Rheumatology, vol. 24, no. 1, pp. 73–80, 1997.

[38] E. Ben-Asher, E. Zelzer, and D. Lancet, “LEMD3: the gene responsible for bone density disorders (Osteopoikilosis),” Israel Medical Association Journal, vol. 7, no. 4, pp. 273–274, 2005.

[39] J. K. Gass, J. Hellemans, G. Mortier, M. Griffiths, and N. P. Burrows, “Buschke-Ollendorff syndrome: a manifestation of a heterozygous nonsense mutation in the LEMD3 gene,” Journal of the American Academy of Dermatology, vol. 58, supplement 1, no. 5, pp. S103–S104, 2008.

[40] J. A. K. Patterson and A. B. Ackerman, “Lichen sclerosus et atrophicus is not related to morphea. A clinical and histologic study of 24 patients in whom both conditions were reputed to be present simultaneously,” American Journal of Dermatopathology, vol. 6, no. 4, pp. 323–335, 1984.

[41] S. Shono, M. Imura, M. Ota, A. Osaku, S. Shinomiya, and K. Toda, “Lichen sclerosus et atrophicus, morphea, and coexistence of both diseases: histological studies using lectins,” Archives of Dermatology, vol. 127, no. 9, pp. 1352–1356, 1991.

[42] S. Yasar, C. T. Muncucoglu, Z. A. Serdar, and P. Gunes, “A case of lichen sclerosus et atrophicus accompanying bullous morphea,” Annals of Dermatology, vol. 23, supplement 3, pp. S354–S359, 2011.

[43] M. Taveira, M. Selores, V. Costa, and A. Massa, “Generalized morphea and lichen sclerosus et atrophicus successfully treated with sulphasalazine,” Journal of the European Academy of Dermatology and Venereology, vol. 12, no. 3, pp. 283–284, 1999.

[44] A. Kreuter, J. Wischniewski, S. Terras, P. Altmeier, M. Stücker, and T. Gambichler, “Coexistence of lichen sclerosus and morphea: a retrospective analysis of 472 patients with localized sclerodermatoma from a German tertiary referral center,” Journal of the American Academy of Dermatology, vol. 67, no. 6, pp. 1157–1162, 2012.

[45] A. Rencic, S. Goyal, M. Mofid, F. Wigley, and H. C. Nousari, “Bullous lesions in scleroderma,” International Journal of Dermatology, vol. 41, no. 6, pp. 335–339, 2002.

[46] S. Virdi and A. J. Kanwar, “Generalized morphea, lichen sclerosus et atrophicus associated with oral submucosal ﬁbrosis in an adult male,” Indian Journal of Dermatology, Venereology and Leprology, vol. 75, no. 1, pp. 56–59, 2009.

[47] M. Yadegari, M. P. Whyte, S. Mumm et al., “Buschke-Ollendorff syndrome: absence of LEMD3 mutation in an affected family,” Archives of Dermatology, vol. 146, no. 1, pp. 63–68, 2010.

[48] H. Kobayashi, M. Kasahara, M. Hino et al., “A novel heterozygous splice-site mutation of LEM domain-containing 3 in a Japanese kindred with Buschke-Ollendorff syndrome,” Journal of Endocrinological Investigation, vol. 30, no. 3, pp. 263–265, 2007.

[49] N. M. Thompson, C. E. Allen, G. S. Andrews, and F. N. Gilbwald, “Scleroderma and melorheostosis; report of a case,” The Journal of Bone and Joint Surgery, vol. 33, no. 3, pp. 430–433, 1951.

[50] E. Pascaud-Ged, J. Rihouet, J. L. Pascaud, and J. Rousseau, “Melorheostosis, osteopoikilosis and linear scleroderma,” Annales de Radiologie Medecine Nucleaire, vol. 24, no. 8, pp. 643–646, 1981.

[51] M. J. Moreno Alvarez, M. A. Lázaro, G. Espada, H. A. Barceló, and A. Maldonado Cocco, “Linear scleroderma and melorheostosis: case presentation and literature review,” Clinical Rheumatology, vol. 15, no. 4, pp. 389–393, 1996.

[52] D. J. Soffa, D. J. Sire, and J. H. Dodson, “Melorheostosis with linear sclerodermatous skin changes,” Radiology, vol. 114, no. 3, pp. 577–578, 1975.

[53] T. Takeda, N. Ogura, S. Jodo et al., “A case of melorheostosis with linear sclerodermatous skin changes,” Ryumachi, vol. 35, no. 3, pp. 580–584, 1995.

[54] I. Nakajima, R. Okuyama, H. Tagami, S. Aiba, and Y. Kuramoto, “Linear melorheostotic scleroderma without melorheostosis,” Acta Dermato-Venereologica, vol. 86, no. 2, pp. 163–164, 2006.

[55] Y. Miyachi, T. Horio, A. Yamada, and T. Ueo, “Linear melorheostotic scleroderma with hypertrichosis,” Archives of Dermatology, vol. 115, no. 10, pp. 1233–1234, 1979.

[56] A. Siegel and H. Williams, “Linear scleroderma and melorheostosis,” British Journal of Radiology, vol. 65, no. 771, pp. 266–268, 1992.
[57] M. Birtane, M. Eryavuz, H. Ünal, and F. Tüzün, “Melorheostosis: report of a new case with linear scleroderma,” *Clinical Rheumatology*, vol. 17, no. 6, pp. 543–545, 1998.

[58] H. Endo, A. Katsumi, K. Kuroda, A. Utani, H. Moriya, and H. Shinkai, “Increased procollagen α1(I) mRNA expression by dermal fibroblasts in melorheostosis,” *British Journal of Dermatology*, vol. 148, no. 4, pp. 799–803, 2003.