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# Cutaneous skeletal hypophosphatemia syndrome (CSHS) is a multilineage somatic mosaic *RAS*opathy



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**Background:** We recently demonstrated multilineage somatic mosaicism in cutaneous skeletal hypophosphatemia syndrome (CSHS), which features epidermal or melanocytic nevi, elevated fibroblast growth factor (FGF)-23, and hypophosphatemia, finding identical *RAS* mutations in affected skin and bone.

**Objective:** We sought to: (1) provide an updated overview of CSHS; (2) review its pathobiology; (3) present a new patient with CSHS; and (4) discuss treatment modalities.

**Methods:** We searched PubMed for “nevus AND rickets,” and “nevus AND hypophosphatemia,” identifying cases of nevi with hypophosphatemic rickets or elevated serum FGF-23. For our additional patient with CSHS, we performed histopathologic and radiographic surveys of skin and skeletal lesions, respectively. Sequencing was performed for *HRAS*, *KRAS*, and *NRAS* to determine causative mutations.

**Results:** Our new case harbored somatic activating *HRAS* p.G13 R mutation in affected tissue, consistent with previous findings. Although the mechanism of FGF-23 dysregulation is unknown in CSHS, interaction between FGF and MAPK pathways may provide insight into pathobiology. Anti-FGF-23 antibody KRN-23 may be useful in managing CSHS.

**Limitations:** Multilineage *RAS* mutation in CSHS was recently identified; further studies on mechanism are unavailable.

**Conclusion:** Patients with nevi in association with skeletal disease should be evaluated for serum phosphate and FGF-23. Further studies investigating the role of *RAS* in FGF-23 regulation are needed. (J Am Acad Dermatol 2016;75:420-7.)

**Key words:** congenital melanocytic nevus; cutaneous skeletal hypophosphatemia syndrome; epidermal nevus; fibroblast growth factor-23; mosaicism; nevus syndrome; rickets.

## GENETIC MOSAICISM

Mosaic organisms harbor 2 or more genetically distinct cell types. The generation of a mosaic requires a nonlethal somatic mutation in 1 cell of a developing embryo; this mutant cell divides and gives rise to mutant daughters that populate 1

### Abbreviations used:

CSHS: cutaneous skeletal hypophosphatemia syndrome  
FGF: fibroblast growth factor  
FGFR: fibroblast growth factor receptor

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or more parts of the organism.<sup>1</sup> Germline mosaicism occurs when a mutation affects germ cell progenitors, allowing the mutation to be inherited by subsequent generations, whereas pure somatic mosaicism spares germ cells and is thus noninheritable. Genetic mosaicism of the skin can often be appreciated as lesions appearing along the lines of Blaschko, which follow the dorsal-ventral migration pattern of mutant ectodermal progenitors. Other patterns have been observed in somatic mosaicism of the skin, including phylloid patterns and large coatlike patches crossing the midline.<sup>1</sup>

### NEVUS SYNDROMES: A SPECTRUM OF GENETIC MOSAICISM

Congenital melanocytic nevi and epidermal nevi that include both keratinocytic and sebaceous subtypes are examples of somatic mosaicism arising via postzygotic activating *RAS* mutations.<sup>2-4</sup> Laser capture microdissection and whole exome sequencing found causative *RAS* mutations in epidermal keratinocytes and sebocytes of the lesions, whereas the underlying dermis, blood leukocytes, and adjacent, unaffected skin were wild type. In phacomatosis pigmentokeratocytica, *RAS* mutations are found in both keratinocytes and melanocytes, giving rise to both organoid nevi and speckled lentiginous nevi.<sup>5</sup>

Although most cases of epidermal or melanocytic nevi are nonsyndromic, some occur with abnormalities in other organs, including the eye, brain, muscle, and vasculature.<sup>6-10</sup> Nevi with systemic findings (nevus syndromes) highlight the spectrum of potential end organ effects of *RAS* mosaicism, which depend on mutation timing during development. Schimmelpenning-Feuerstein-Mims syndrome, which features sebaceous nevi variably associated with neurologic abnormalities such as intellectual disability and epileptic seizures, along with ocular and skeletal deformities, is likely a result of an early mutation affecting a multipotent progenitor.<sup>2,11</sup> Nearly all cases of syndromic nevi, especially those with abnormalities in nonectoderm-derived tissues, demonstrate extensive skin surface involvement, consistent with early embryonic somatic mutation.<sup>12</sup>

### CUTANEOUS SKELETAL HYPOPHOSPHATEMIA SYNDROME

Cutaneous skeletal hypophosphatemia syndrome (CSHS) features epidermal or melanocytic nevi and

hypophosphatemic rickets with elevated levels of a serum phosphatonin, fibroblast growth factor (FGF)-23.<sup>13</sup> Patients often require phosphate and calcitriol supplementation to maintain mineral homeostasis.

In 1977, Aschinberg et al<sup>14</sup> reported the first case of CSHS in a 5-year-old boy with linear verrucous

nevi and severe rickets. Serum phosphate and tubular resorption of phosphate were low, indicating renal phosphate wasting (2.0 mg/dL, normal: 3.0-4.5 mg/dL), whereas serum alkaline phosphatase was high. Serum parathormone and calcium levels were within normal limits. At that time, FGF-23 had not been identified. Interestingly, surgical excision of fibroangiomas from the face and left lower limb resulted in reduction

of musculoskeletal pain and normalization of phosphate levels within 4 weeks. The authors postulated a secretory mechanism originating from the skin for pathobiology. They tested this hypothesis by homogenizing excised lesions and injecting them into a dog, and within 1 hour postprocedure found increased renal wasting of phosphate secondary to decreased reabsorption, although without changes in serum phosphate.<sup>14</sup> The authors did not find similar amelioration of phosphate excretion after excision of an epidermal nevus in the same patient, although subsequent reports did. Ivker et al<sup>15</sup> reported a female infant with CSHS who, despite medical therapy, exhibited a low serum phosphate of 0.87 to 0.97 mmol/L (normal <1 year of age: 1.56-2.29 mmol/L), along with an extensive linear epidermal nevus involving various parts of the body. At 21 months of age, areas of the nevus were excised, with histopathologic confirmation of verrucous epidermal nevus. Shortly after the operation, serum phosphate values transiently climbed to 1.51 mmol/L, but later dropped, prompting subsequent nevus excisions at 27 months and stabilization of serum phosphate at 1.29 to 1.61 mmol/L.<sup>15,16</sup> It was unclear whether oral medication was continued during this period. Lastly, in a 2003 report by Saraswat et al<sup>17</sup> of a 22-year-old man with phacomatosis pigmentokeratocytica and hypophosphatemic rickets, normalization of serum phosphate and reduction in phosphaturia was observed after carbon-dioxide laser ablation of the skin lesions. It is unknown whether this normalization was

### CAPSULE SUMMARY

- Cutaneous skeletal hypophosphatemia syndrome results from multilineage activating *RAS* mutations in skin and bone.
- The presence of *RAS* mutation in bone suggests that this drives abnormal fibroblast growth factor-23 regulation.
- Excision or laser ablation of nevi is not recommended in patients with hypophosphatemia.

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