

Progressive Osseous Heteroplasia is not an Autosomal Dominant Trait but Reflects Superimposed Mosaicism in Different *GNAS* Inactivation Disorders

Abstract

Progressive osseous heteroplasia (POH) is a rarely occurring genetic condition characterized by severe segmental ossification involving the skin and deep connective tissues including the muscles. So far, the disorder is generally described as an autosomal dominant trait. By contrast, the following arguments are in favor of the alternative concept that POH should rather be taken as a non-specific segmental manifestation of different *GNAS* inactivation disorders such as Albright hereditary osteodystrophy (AHO) with hormone resistance, AHO without hormone resistance, and osteomatosis cutis. Presently, POH has got its own OMIM number 166350 but this is obviously wrong because the disorder does not reflect heterozygosity for a *GNAS* mutation. Conversely, the disorder is most likely due to an early event of postzygotic loss of heterozygosity with loss of the corresponding wild-type allele. This alternative concept, as proposed in 2016, offers a plausible explanation for the following features of POH. Familial occurrence is usually absent. POH is usually observed in families with one of the three *GNAS* inactivation disorders as mentioned above. Mosaicism is suggested by the pronounced segmental manifestation of POH and by its lateralization. Some patients have, in addition to POH, bilaterally disseminated features of osteomatosis cutis or AHO, and other patients have family members with one of these nonsegmental disorders. Remarkably, POH tends to appear much earlier than the nonsegmental *GNAS* inactivation disorders. – Molecular support of the concept was documented in a superficial variant of POH called ‘plate-like osteoma cutis’. In several other autosomal dominant skin disorders, molecular corroboration of the theory of superimposed mosaicism has been provided. – For all of these reasons, it is unlikely that POH can further be taken as a distinct autosomal dominant trait. Generation of more molecular data in multiple cases of POH occurring in *GNAS* inactivation disorders will be crucial to corroborate the proposed concept.

Keywords: *GNAS* inactivation disorders, loss of heterozygosity, mosaic skin disorder, superimposed mosaicism

I read with great interest the well-documented report of Drs. Sahu and coworkers on unilateral “progressive osseous heteroplasia (POH)” in a 3-year-old boy.^[1] Initial cutaneous calcifications were noted at the age of 2 months. Subsequently, the boy developed pronounced ossifications in the dermis and subcutis corresponding to the area of segmental cutaneous involvement. The authors correctly describe the view, as presently promulgated worldwide, that POH is a distinct autosomal dominant disorder caused by *GNAS* inactivating mutations in a heterozygous state.^[2-5]

As opposed to this and apart from the beaten path, I’m arguing that POH is

not a Mendelian trait.^[6] Most likely, it represents a superimposed mosaic manifestation of at least three different autosomal dominant *GNAS* inactivation disorders in the form of Albright hereditary osteodystrophy (AHO) with hormone resistance (OMIM 103580), AHO without hormone resistance (OMIM 612463), and osteoma cutis (OMIM 166350).^[5]

Historical note on the naming of superimposed mosaicism

The concept of superimposed mosaicism was first proposed as a hypothesis in 1996.^[7] Initially, it was called “type 2 segmental manifestation”,^[8] and later “type 2 segmental

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mosaicism”.[9] Recently, the idea was renamed as “superimposed mosaicism”.[10] The word ‘segmental’ seems dispensable because all manifestations of superimposed mosaicism occur in a segmental form.

Description of the genetic concept

In autosomal dominant skin disorders, a well-known form of mosaic involvement is simple segmental mosaicism caused by a very early postzygotic new mutation in an otherwise healthy embryo [Figure 1]. By contrast, in an embryo being heterozygous for such a disorder there may occur, at a very early developmental stage, a postzygotic event of loss of heterozygosity (LOH) resulting in loss of the corresponding wild-type allele, which gives rise to a homozygous or hemizygous cell. The segmental outgrowth of the arising mutant clone results in a pronounced mosaic involvement being superimposed on the nonsegmental heterozygous phenotype of the same disorder [Figure 1].^[8]

Molecular data supporting the concept of superimposed mosaicism

Molecular findings in support of this theory have already been documented in a superficial variant of POH called “plate-like osteoma cutis”^[11] and in a mouse model.^[12,13] Moreover, molecular proof of principle was provided in several other autosomal dominant skin disorders [Table 1].

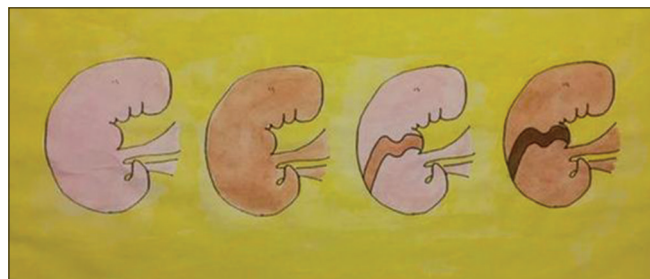


Figure 1: Two different types of segmental mosaicism as noted in autosomal dominant skin disorders. From left to right: Healthy embryo; heterozygous embryo, showing diffuse involvement; simple segmental mosaicism, reflecting heterozygosity; superimposed mosaicism, reflecting loss of heterozygosity

Table 1: Autosomal dominant skin disorders with superimposed mosaic manifestation confirmed at the molecular level

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| Darier disease ^[14] |
| Hailey-Hailey disease ^[15] |
| Glomangiomas ^[16] |
| Gorlin syndrome ^[17] |
| Legius syndrome ^[18] |
| Neurofibromatosis 1 ^[19] |
| Osteomas cutis ^[11] |
| Porokeratosis (DSAP and plaque type) ^[20] |
| PTEN hamartoma syndrome ^[21,22] |

The concept of superimposed mosaicism applied to the report of Drs. Sahu and coworkers

The statement of Drs. Sahu *et al.*^[1] that “POH is caused by heterozygous inactivating mutations of *GNAS*” is in line with the majority of the presently available literature,^[2-5, 23-25] but it is most likely wrong. Conversely, POH appears to be caused by an early postzygotic event of loss of heterozygosity at the *GNAS* locus, resulting in superimposed segmental biallelic mosaicism.^[6] Moreover, the diagnostic criterion of “evidence for paternal inheritance” is questionable because maternal inheritance of POH has also been documented.^[26,27]

The authors report that there was no history of “similar lesions” in the family members. It should be borne in mind that the patient’s relatives should not be examined for similar lesions but for the presence of mild, inconspicuous disseminated features of AHO or osteoma cutis.^[28] In my view, this little boy will most likely develop, in his later life, the disseminated skin lesions of osteoma cutis,^[29-31] but AHO cannot be excluded as yet.

Besides, the proposed concept would offer a plausible explanation for some diagnostic criteria of POH mentioned by the authors, such as the lateralized involvement and “age at onset younger than 1 year”.^[1]

Conclusive Remarks

Since 2016 when the concept of superimposed mosaicism of POH was proposed,^[6] no additional supporting molecular findings were published. Hence, in view of the limited human data^[11] the concept cannot be taken as proven, which is why the following alternate hypotheses should also be taken into account. An as yet unknown modifier gene may explain why several patients have POH in addition to pseudohypoparathyroidism type 1A.^[32] Moreover, epigenetic conditioning may affect one or several segments of the body, resulting in POH.^[27,33] On the other hand, an etiological relationship with genomic imprinting, which plays a major role in the severity of pseudohypoparathyroidism type 1A, is rather unlikely because POH has been described in all of the three types of *GNAS* inactivation disorders as known so far.^[6]

Generation of more molecular data in multiple cases of POH occurring in *GNAS* inactivation disorders will be crucial to proving the present hypothesis. For the time being, however, POH should not simply be regarded as an autosomal dominant trait reflecting heterozygosity, but the alternative theory of superimposed mosaicism should also be considered.

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Conflicts of interest

There are no conflicts of interest.

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