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COMMENTARY

Mosaicism and the taxonomy of human disease

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Abstract Two papers in this special issue of Cold Spring Harbor *Molecular Case Studies* on Mosaicism throw light on an interesting conundrum in mosaic disorders. This conundrum centers on thresholds for the definition of mosaic disorders and how to reconcile the incredible inter- and intrapatient variability of mosaic disorders with the clinical imperative to have clear and distinct categorical diagnoses.

The first is a paper on "Bockenheimer disease" by Sudduth et al. (2021), which provides one interesting example. A clinical entity described by Bockenheimer in 1907 is said to comprise "… a venous malformation (VM) involving most of the length of an extremity with all tissue planes affected (i.e., skin, subcutis, muscle, bone)." Sudduth et al. studied nine individuals that fit this clinical description and found the *TEK* (formerly known as *TIE2*) c.2740C > T p.(Leu914Phe) variant in the mosaic state in all nine individuals. This discovery demonstrates that Bockenheimer disease, which is mosaic, is allelic to multiple cutaneous and mucosal venous malformations MCMVM, MIM 600195, which is the constitutional disorder caused by variants in *TEK*.

The second is a paper on an entity called cerebrofacial vascular metameric syndrome (CVMS; but which also has the eponyms of Bonnet–Dechaume–Blanc and Wyburn–Mason) by Sheppard et al. (2021). In that work, CVMS is defined as vascular malformations in at least two of three adjacent zones: brain, orbit, and face. Sheppard et al. studied three individuals with this presentation and found that all of them had one of three well-known somatic gain-of-function variants in *PIK3CA*. This makes CVMS allelic to a range of disorders associated with *PIK3CA*-activating variants, both constitutional and mosaic.

Although the etiologies of these two phenotypes are solved, the studies from Sudduth and Sheppard raise yet other questions—what exactly is "Bockenheimer disease," and how is it distinct from MCMVM? What exactly is CVMS and how is it distinct from CLAPO syndrome (613089), CLOVE syndrome (612918), cerebral cavernous malformations 4 (155,500), and megalencephaly-capillary malformation-polymicrogyria syndrome (602,501)? Interestingly, the authors of these two publications came to different conclusions on this question.

Sudduth et al. (2021) in their manuscript define "Bockenheimer disease" as a venous malformation that "(1) affects most of the length of an extremity and (2) extends from the skin to the bone." It is not further defined what "most of the length" means. The descriptor of "extends from the skin to the bone" is a bit challenging for this reader to interpret. Elsewhere in the paper they use the phrase "involves all tissue planes," which seems to be a bit more specific, although it is not clear how the clinician is to make this determination. Their definition does not exclude much greater involvement than a limb, as would be seen in MCMVM, so if this definition were used literally, many individuals with MCMVM would also meet the

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criteria for "Bockenheimer disease," which I suspect was not intended. The minor point would be that this definition might warrant more specificity. But the larger issue is that "Bockenheimer disease" appears to be an anatomically limited, mosaic form of MCMVM, much the same as segmental neurofibromatosis is an anatomically limited, mosaic form of neurofibromatosis. The question is whether the claim that Bockenheimer disease is a distinct entity can survive scrutiny—does that term describe a "unitary and distinct diagnostic entity"?

In contrast, Sheppard et al. take the opposite approach with CVMS. In their discussion, the finding of mosaic *PIK3CA* variants in these individuals leads them to "… propose that CVMS be recognized as part of the *PIK3CA*-related overgrowth spectrum." This proposal is readily justifiable and consistent with an established body of evidence that the phenotypic range associated with mosaic gain-of-function variants of *PIK3CA* is broad and continuous, with little to suggest boundaries to distinguish entities that were historically delineated by clinical attributes (CLOVES, Klippel–Trenaunay, fibroadipose overgrowth, hemihyperplasia with multiple lipomatosis, isolated lymphatic malformation, CLAPO, macrodactyly, and orofacial overgrowth with peripheral nerve enlargement and perineuriomatous pseudo-onion bulb proliferations, etc.) (Lindhurst et al. 2012; Rios et al. 2013; Keppler-Noreuil et al. 2014; Vahidnezhad et al. 2016; Rodriguez-Laguna et al. 2018; Koutlas et al. 2020).

It is necessary to reconcile continuously variable biologic phenomena with the clinical imperative to have diagnostic categories. It is also essential to reconcile phenotypic diagnostic taxonomy with molecular taxonomy—the latter being a critical motivation for the creation of this journal and the topic of a National Research Council report entitled "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" (Institute of Medicine 2011). The challenge is that it is essential to rationally organize and describe diseases—the question is how. A recent proposal has been made to integrate the molecular etiology of a disorder with a phenotypic descriptor—the dyadic approach (Biesecker et al. 2021), which has been slightly but importantly modified for mosaic disorders (Sapp et al. 2019). In this approach, the germline disorder of venous anomalies associated with TEK variants would be described as "*TEK*-related multiple cutaneous and mucosal venous malformations."

In this scheme there are two components to the description of an entity—etiology and phenotype—and it is proposed that a unitary and distinct diagnostic entity is described by these two attributes. This seems simple, but it is significant because it is saying that that is a single diagnostic entity and that any other dyadic descriptor is a distinct diagnostic entity. The gene half of this scheme is the easy part; the phenotype is much harder. Then, there is mosaicism, which makes categorical diagnoses more challenging. As noted above, the biologic variation represented by mosaicism is continuous and practically infinite; every affected individual likely has a unique distribution of the variant within their tissues. First, it is critical to recognize that if it exists at all, the attributes of "Bockenheimer disease" specified by Sudduth et al. are not a disease at all, but rather a phenotype. The interesting question is whether there is a phenotypic continuum that encompasses "multiple cutaneous and mucosal venous malformations" and "Bockenheimer disease" or are they discontinuous? The assumption must be that it is continuous—I cannot conceive of a mechanism that would produce discontinuity for a mosaic disorder. If the variation is continuous, how can Bockenheimer be distinct? The answer is paradoxical—which is that of course, it cannot, but it does not matter in the end because in fact all such descriptors are heuristics and diagnostic categories are always, to a degree, arbitrarily defined. But defined they must be because if one defines a category, it must have boundaries. Sudduth et al. may want to consider a more precise definition of this phenotypic entity such that we can use a descriptor like *TEK*-related Bockenheimer disease.

We did this recently for Proteus syndrome (Sapp et al. 2019), a disorder associated with *AKT1* mosaic variants that suffers from the same challenges as do mosaic phenotypes

associated with *TEK*. In this scheme, we created a semiquantitative scoring metric for the manifestations of Proteus syndrome and then set boundaries for the diagnosis of *AKT1*-related Proteus syndrome and of AKT1-related mosaic overgrowth (the category for the less significantly affected individuals) and for the phenotypic designation of Proteus syndrome (the descriptor for individuals without a DNA diagnostic result). In this way, we have parameterized what the Proteus syndrome is phenotypically and coupled that to the molecular etiologic descriptor.

Diagnostic labels, descriptors, and schema are as complex and frustrating as they are essential. It will take a good deal of work to sort out all of these issues and get to a point where all individuals can have a diagnostic descriptor that is rational, reflects biologic reality, and serves the needs of both patients and clinicians to practice precision health. The fundamental problem is that diagnoses are categorical and all biologic variation is continuous. Nowhere is this more obvious than in mosaic disorders. An individual with one cell harboring a variant, an individual with all but one cell harboring that variant, and every degree in between those two hypothetical extremes are all mosaic for the same variant. Yet, it is doubtful a clinician would conclude that they all have the same condition. Our diagnostic approach must reconcile the continuous variation that Mother Nature presents to us with the pragmatic realities of clinical diagnosis. This is what is so exciting and challenging about mosaic disorders—they cause us to reexamine some of our simplistic assumptions to create a more robust taxonomy of human disease.

Competing Interest Statement

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REFERENCES

Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, Bennett JT, Bird LM, Carey JC, Chung B, et al. 2021. A dyadic approach to the delineation of diagnostic entities in clinical genomics. *Am J Hum Genet* **108:** 8–15. doi:10.1016/j.ajhg.2020.11.013

Institute of Medicine. 2011. *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. National Academies Press, Washington, DC.

Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, Parker VE, Blumhorst C, Darling T, Tosi LL, Huson SM, Whitehouse RW, Jakkula E, et al. 2014. Clinical delineation and natural history of the *PIK3CA*-related overgrowth spectrum. *Am J Med Genet A* **164A:** 1713–1733. doi:10.1002/ajmg.a.36552

Koutlas IG, Anbinder A-L, Alshagroud R, Cavalcante ASR, Kindi MA, Crenshaw MM, Sapp JC, Kondolf H, Lindhurst MJ, Dudley JN, et al. 2020. Orofacial overgrowth with peripheral nerve enlargement and perineuriomatous pseudo-onion bulb proliferations is part of the *PIK3CA*-related overgrowth spectrum. *Hum Genet Genomic Adv* **1:** 1000009. doi:10.1016/j.xhgg.2020.100009

Lindhurst MJ, Parker VE, Payne F, Sapp JC, Rudge S, Harris J, Witkowski AM, Zhang Q, Groeneveld MP, Scott CE, et al. 2012. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in *PIK3CA*. *Nat Genet* **44:** 928–933. doi:10.1038/ng.2332

Rios JJ, Paria N, Burns DK, Israel BA, Cornelia R, Wise CA, Ezaki M. 2013. Somatic gain-of-function mutations in *PIK3CA* in patients with macrodactyly. *Hum Mol Genet* **22:** 444–451. doi:10.1093/hmg/dds440

Rodriguez-Laguna L, Ibañez K, Gordo G, Garcia-Minaur S, Santos-Simarro F, Agra N, Vallespín E, Fernández-Montaño VE, Martín-Arenas R, Del Pozo A, et al. 2018. CLAPO syndrome: identification of somatic activating *PIK3CA* mutations and delineation of the natural history and phenotype. *Genet Med* **20:** 882–889. doi:10.1038/gim.2017.200

Sapp JC, Buser A, Burton-Akright J, Keppler-Noreuil KM, Biesecker LG. 2019. A dyadic genotype–phenotype approach to diagnostic criteria for Proteus syndrome. *Am J Med Genet C Semin Med Genet* **181:** 565–570. doi:10.1002/ajmg.c.31744

Sheppard S, Sanders V, Srinavasan A, Finn L, Adams D, Elton A, Amlie-Lefond C, Nelson Z, Dmyterko V, Jensen B, et al. 2021. Cerebrofacial vascular metameric syndrome is caused by somatic pathogenic variants in *PIK3CA*. *Cold Spring Harb Mol Case Stud* **7:** a006147. doi:10.1101/mcs.a006147

Sudduth C, Konczyk D, Smits P, Eng W, Al-Ibraheemi A, Upton J, Greene A. 2021. Bockenheimer disease is associated with a TEK variant. *Cold Spring Harb Mol Case Stud* **7:** a006119. doi:10.1101/mcs.a006119

Vahidnezhad H, Youssefian L, Uitto J. 2016. Klippel-Trenaunay syndrome belongs to the *PIK3CA*-related overgrowth spectrum (PROS). *Exp Dermatol* **25:** 17–19. doi:10.1111/exd.12826