HHS Public Access

Author manuscript

Genet Med. Author manuscript; available in PMC 2018 September 21.

Published in final edited form as:

Genet Med. 2018 August ; 20(8): 800–801. doi:10.1038/gim.2017.213.

Mosaic Disorders and the Taxonomy of Human Disease

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In this issue of the Journal, Rodriguez-Laguna et al[1] identify somatic mosaic variants in *PIK3CA* in patients who had been assigned the diagnosis of CLAPO syndrome (*C*apillary malformation of the lower lip, *L*ymphatic malformation predominant on the face and neck, *A*symmetry, and *P*artial/generalized *O*vergrowth, MIM 613089). The findings in this paper raise interesting and important questions, which begins with the question of whether CLAPO syndrome was a legitimate diagnostic entity to begin with.

The designation of "CLAPO syndrome" was coined in a 2008 publication by the research group who also wrote the accompanying paper in this issue of the journal. They described six patients with what they proposed to be a distinct clinical diagnostic entity[2]. This entity was discussed in several review articles[3–5], which included several of the original report authors but also others who are authoritative in this field, and were subject to peer and/or editorial evaluation. None of the papers that followed the original report suggested CLAPO was not a valid diagnostic entity. As well, CLAPO is a phenotype entry in OMIM. I conclude that prior to the findings published in this issue, CLAPO *was* a valid clinical diagnostic entity, to the extent that that phenotypic classification alone is a valid approach to disease taxonomy (which is a critical caveat).

Based on the findings in this issue of the Journal, we now know that CLAPO is associated with mosaic activating variants in *PIK3CA,* raising anew question of the validity of this diagnostic entity. Mosaic *PIK3CA* variants were first described in a series of four papers in 2012 in patients with a range of phenotypes that included overgrowth, vascular malformation, CNS anomalies, and pigmentary findings. Prior descriptors of some of these phenotypes included CLOVES syndrome, Megalencephaly-Capillary Malformation (MCAP or M-CM), Klippel-Trenaunay syndrome, and isolated anomalies such as single digit macrodactyly. This litany of associations with mosaic *PIK3CA* variants was surprising and confusing. The CLAPO findings add to that conundrum and the situation begs for rationalization and clarity. In 2014 we gathered a group of experts at the NIH to wrestle with this challenge and moved toward a unification of the distinct entities under the umbrella term

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CONFLICT OF INTEREST PAGE

LGB receives royalties from Genentech Corp, is an advisor to the Illumina Corp, and receives honoraria from Wiley-Blackwell. LGB, received support from the Intramural Research Program of the National Human Genome Research Institute grants HG200328 11 and HG200388 03.

of *PIK3CA*-Related Overgrowth Spectrum or PROS[6]. The designation of this as a spectrum acknowledged a critical fact – no rational, objective, and clear clinical delineation can be made amongst these entities. Subsequent to our designation of the CLOVE syndrome eponym (Congenital, Lipomatous Overgrowth, with Vascular anomalies and Epidermal nevi, later amended to CLOVES for Skeletal findings[7]) in 2009, we have come to recognize that this 'syndrome' was an artifact of the clinical pattern recognition approach to disease delineation. It was correct that the patients we diagnosed with CLOVES were distinct from those with Proteus syndrome (as subsequently confirmed by molecular data[8]), but it was incorrect that those five findings represented a distinct clinico-pathologic entity. Indeed, we have come to recognize just as many or more patients with four, three, two, or just one of those findings, all of which are due to the same or similar variants in *PIK3CA*. These variant phenotypes blend continuously with one another. This recognition led us to conclude that there is no rational, objective, definable way to distinguish, for example, a patient with CLOVES syndrome from many other patients with *PIK3CA*-related overgrowth, and therefore, CLOVES syndrome does not exist as a valid, unitary clinical diagnostic entity. The same is likely true for Klippel-Trenaunay syndrome, Hemihyperplasia-multiple lipomatosis, CLAPO, and all other mosaic overgrowth disorders associated with *PIK3CA* activating variants. While the designation of CLAPO as a distinct clinical entity was reasonable in 2008, with the availability of precise molecular data this designation is not supportable today. The use of CLAPO as a clinical diagnostic entity should be discontinued and patients with that diagnosis should instead be re-diagnosed as having PROS.

These considerations of PROS spectrum have implications far beyond patients with somatic variants in *PIK3CA*. The question is whether diseases should be taxonomically organized based on their molecular or their phenotypic attributes. Our current diagnostic thinking is overwhelmingly phenotypic. But, as molecular insights accrue, a tidal wave of evidence in favor of molecular taxonomy is building. In somatic cancer genetics, it is already here. Oncologists are beginning to treat tumors based on their molecular profile, irrespective of their clinical or histologic attributes. But cancer provides important evidence against a unitary molecular taxonomy of *PIK3CA*-related phenotypes. Many tumors have somatic *PIK3CA* variants – many of which are exactly the same somatic variants found in patients with PROS. Such a *PIK3CA* variant in a malignancy is in a context of dozens or hundreds of other somatic variants. Even if a clinician is willing to accept PROS as a single spectrum disorder, they would be very unlikely to say that a patient with lung cancer and *PIK3CA* variant has the same taxonomic disease entity as does a patient with isolated macrodactyly. This was the indeed the rationale for a multiaxis diagnostic system for disease[9], which conceptualized a disease entity as having three primary attributes; phenotype, genotype, and environment. A unitary clinico-pathologic disease entity was one that had commonality of each of these three attributes. Clearly, this was not an idea that caught fire, but it has influenced thinking along these lines. Dr. Bonnie Pagon, editor of GeneReviews, has adopted a variation of this concept by describing disorders as phenotype-gene dyads. For example, one can describe a patient's diagnosis as being "*KRAS*-related Noonan Syndrome". This is simpler than the multiaxis concept but captures the same fundamental concept. In this framework, *KRAS*-related Noonan syndrome is distinct from *SOS1*-related Noonan syndrome, just as it is distinct from *KRAS*-related Schimmelpenning-Feuerstein-

Mims syndrome, but distinct in a very different way – in one case phenotypic and another molecular.

It is unjustifiable at this stage to suggest that either the multi-axis or GeneReviews dyad approach to designating disorders addresses all of the challenges. One challenge is modifiers and complex genetic disorders – these don't fit well into frameworks that are designed for single gene disorders. Another is again illuminated by mosaicism. There is no rational lower boundary that can be established for the mosaicism level. Patients with recognizable PROS phenotypes have variant allele frequencies between a few percent and 50% in the affected parts of the body, but the cells with the variants may be a very small fraction of their total body cell number. What is the lower limit of this? What is the tissue or cell type that harbors that variant, which must play a key role in determining the presence and nature of the phenotype. Undoubtedly, a person with one cell with a *PIK3CA* activating variant does not have PROS. *Reductio ad absurdum*. Addressing this threshold problem will be a challenge.

These limitations aside, what CLAPO and PROS tells us is that we have to being thinking about disease entities and diagnoses as having more than one attribute re taxonomic classification. The wrong question is whether we should be using phenotype or genotype, because the answer is that we have to use both, simultaneously, in all patients. Precisely how we do that is an opportunity for further theoretical work as well as clinical and molecular research. But there is no doubt that genomic characterization challenges our unimodal approach to disease taxonomy and we have to develop an effective way to think about our patients on multiple levels, based on multiple attributes, concurrently.

Acknowledgments

The author is supported by the Intramural Research Program of the National Human Genome Research Institute. The author is grateful to Teri Manolio M.D., Ph.D for helpful comments on a previous draft of this commentary.

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