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INTRODUCTION

Unsolved recognizable patterns of human malformation: Challenges and opportunities

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Due to the efforts of the clinical and scientific communities and boosted by recent advances in genetic technologies, we now understand the molecular mechanisms underlying most of the frequent and recognizable human malformation syndromes. However, some well-established human malformation syndromes remain without a molecular diagnosis despite intensive investigation. This issue of *Seminars* mines the phenotypic entries in OMIM and estimates that of the documented 2,034 unsolved entries likely to represent a rare genetic disease, only 160 are well-established and possibly amenable to investigation. This issue also reviews well-characterized and extensively investigated human malformation syndromes and associations that remain unsolved, including the following: Dubowitz syndrome (MIM 223370%), Hallermann–Streiff syndrome (MIM 234100%), PHACE syndrome (MIM 606519), Oculocerebrocutaneous syndrome (MIM 164180), Aicardi syndrome (MIM 304050%), Gomez–Lopez–Hernandez syndrome and Rhombencephalosynapsis (MIM 601853%), VACTERL (MIM 192350%), and Nablus syndrome (MIM #608156). Possible explanations for their intractability to molecular diagnosis are explored, including genetic and phenotypic heterogeneity, mosaicism, epigenetics, gene–environment interactions, and other non-Mendelian contributions. Finally, this issue of *Seminars* presents a path forward for these unsolved rare conditions and suggests a renewed focus on solving amendable OMIM disorders. It is clear that the way forward will require new technologies, global cooperation, and data sharing; these will also be necessary to help reach the vision of the International Rare Diseases Research Consortium (IRDiRC), that is to enable all people living with a rare disease to receive an accurate diagnosis, care and available therapy within 1 year of coming to medical attention.

KEYWORDS

malformations, associations, syndromes, unsolved rare diseases, molecular mechanisms, IRDiRC

1 | BACKGROUND

One of the main goals of the clinical geneticist and dysmorphologist is to arrive at an underlying explanation of the clinical presentation for the patient under their care, yet it has long been recognized this can be an imperfect science. Historical studies have shown that even after a detailed history, physical examination, and laboratory workup, a diagnosis is reached for fewer than 50% of patients presenting to a genetics clinic (Shashi et al., 2014). It is important to note that, historically, these diagnoses were "clinical only" for the majority of patients. In 2018 it can be argued that a patient is not completely diagnosed until the underlying causal variant or disease mechanism has been identified; progress has been remarkable in this regard. Beginning in the 1970s and 1980s, the genetic basis for recognizable conditions began to be uncovered. These advances were accelerated by, among others, the human genome project, positional cloning, molecular cytogenetics, SNP homozygosity mapping, and candidate gene sequencing. The most remarkable progress came with the development and wide spread use of next generation sequencing (NGS) technologies, most notably exome sequencing (Boycott, Vanstone, Bulman, & MacKenzie, 2013). Exome sequencing has not only become an invaluable research tool for rare disease discovery, but increasingly a

widely-adopted clinical tool as well. Indeed, studies have demonstrated that exome sequencing can provide a diagnosis for 25–60% of patients, depending on the population studied and timing of sequencing in the diagnostic pathway (Stark et al., 2016; Yang et al., 2014). Importantly, this transformative technology has resulted in the identification of more than 1,000 novel human disease genes, and has even brought to light new disease mechanistic paradigms including the high frequency of de novo mutation as a cause of severe developmental disorders (de Ligt et al., 2012).

Approximately 50 years ago, the first Conference on the Clinical Delineation of Birth Defects was held at the Johns Hopkins Hospital in May of 1968. As an appendix to the published proceedings of that conference, the visionary dysmorphologist, David W Smith, published the article 'Recognizable Patterns of Malformations in Childhood' (Smith, 1969); this 15 page article, consisting primarily of tables, was a clear precursor to his classical textbook: first published in 1970 and now in its 7th edition (Jones, Jones, & del Campo, 2013). In his original article he enumerated 130 recognizable disorders as a means to guide a pediatrician towards a diagnosis that could inform patient care and genetic counseling. Perhaps not surprisingly, the underlying molecular or biochemical defect for the majority of these conditions was unknown at the time, with the exception of two teratogens, a small number of then-detectable cytogenetic disorders (mostly aneuploidies and large deletion syndromes), and a handful of biochemical disorders (the mucopolysaccharidoses).

2 | THEMES OF THE ISSUE

Fifty years later, the majority of disorders published in the original Smith article have now been solved (i.e., their molecular mechanism has been identified) but there remain a few recognizable syndromes in the current edition for which the underlying molecular mechanism remains unknown despite extensive investigations by multiple research groups using exome sequencing and, in some cases, genome sequencing. The reasons for which these recognizable syndromes remain intractable to discovery efforts are numerous, but likely include mechanisms such as extreme genetic heterogeneity, undetected genomic alterations, abnormal gene regulation, mosaicism, and complex inheritance (e.g., digenic inheritance or gene–environment interaction). In this issue of *Seminars* we highlight recognizable syndromes and associations that remain unsolved following exome sequencing, hypothesize possible disease mechanisms, and discuss next steps to uncover their causes. Herein we have invited expert authors to review eight such classic and recognizable disorders, selected based on their relative frequency in the literature and representing several different presumed disease mechanisms (Table 1). Six of the eight recognizable syndromes reviewed in this issue of *Seminars* are represented in Smith's current textbook, while seven have been reported in more than 100 patients and described in the literature for more than 30 years (Table 1).

This issue of *Seminars* leads off with Dubowitz syndrome (MIM 223370), a condition first reported in 1965 and now reported more than 200 times (Dubowitz, 1965). In their research article, Innes, McInnes, and Dyment review the literature and provide evidence that both clinical and molecular/causal heterogeneity is likely the primary explanation why a major gene has yet to be identified for this disorder (Innes, McInnes, & Dyment, 2018). The same phenomenon is likely underlying the complexity of other recognizable conditions not included in this issue, including Toriello-Carey syndrome (Toriello, Colley, & Bamshad, 2016), Fryns syndrome (Bone et al., 2017; Thompson & Cole, 2016), PEHO syndrome (Chitre et al., 2018), and 3C syndrome (Elliott et al., 2013; Kolanczyk et al., 2015). Ideally, an underlying and possibly novel gene will be identified for some of the patients that were initially reported with Dubowitz syndrome (or most closely resemble such patients) to provide clarity on the spectrum of clinical features of this and similar syndromes and ultimately identify common biological pathways that might explain the phenotypic overlap among the reported patients.

Hallermann–Streiff syndrome (MIM 234100) is a highly-recognizable condition that was first reported over 100 years ago, with more than 100 published cases (Aubry, 1893). This condition is the most common condition represented in the original Smith's article that remains unsolved. In their review, Schmidt and Wollnik make note of the heterogeneity in presentation of some clinical cases, yet there are many published patients with a highly recognizable or "classic" phenotype. The majority of the cases in the literature are sporadic, typically suggesting a de novo germline or mosaic cause for the disorder (Schmidt & Wollnick, 2018). Rarely, classically-affected females have had children, and there has yet to be a convincing familial recurrence. Taken together, and given that conventional exome sequencing has been unrevealing, other mechanisms, both genetic and nongenetic, merit further exploration.

Siegel reviews PHACE syndrome (MIM 606519) and the highly-related phenotype, LUMBAR syndrome, that combine infantile hemangiomas with multiple recurrent congenital anomalies (Siegel, 2018). While the etiology for these entities is not yet known, Siegel makes the argument that tissue-specific low level mosaicism for known cancer genes is a compelling hypothesis that requires further study. Such investigations clearly require access to deep sequencing, but also to the involved tissues. The classic paper by Happle (1987) outlined the features of recognizable malformation syndromes that suggest that they are caused by underlying somatic mosaicism; over the intervening 30 years all of these disorders have subsequently been proven to be mosaic except Oculocerebrocutaneous (Delleman-Oorthuys) syndrome (OCCS; MIM 164180). In this issue, Moog and Dobyns review efforts to solve this condition, which is characterized by a triad of congenital eye, brain, and skin malformations (Moog & Dobyns, 2018). OCCS is more frequently reported in males, and likely represents another disorder due to unidentified mosaicism. A disorder with appreciable clinical overlap but observed almost exclusively in females is Aicardi syndrome (MIM 304050), which is characterized by a triad of callosal agenesis, infantile spasms, and chorioretinal lacunae. Herein, Wong and Sutton review the literature and evidence of a genetic mechanism for Aicardi syndrome, including the prevailing theory of mosaicism for an X-linked gene that is lethal in males (Wong & Sutton, 2018).

Gomez–Lopez–Hernandez (GLH; MIM 610853) syndrome is characterized by syndromic features (Gomez, 1979) in addition to the rare and striking CNS malformation: rhombencephalosynapsis. Some

TABLE 1 Recognizable syndromes and associations currently without a molecular cause

Disorder (MIM identifier)	First reported[a]	Published cases	Described in Smith's[b]	Possible mechanism
Dubowitz syndrome (%223370)	1965	100s	Yes	Clinical and genetic heterogeneity
Hallermann–Streiff syndrome (%234100)	1893, 1948, 1950	100s	Yes, including 1st edition	Genetic heterogeneity or novel genomic mechanism
PHACE syndrome (606519)	1978, 1985	100s	Yes	Tissue-specific mosaicism
Oculocerebrocutaneous (Delleman-Oorthuys) syndrome (OCCS) (164180)	1981	100s	No	Tissue-specific mosaicism
Aicardi syndrome (%304050)	1965	100s	No	Tissue-specific mosaicism in X-linked gene associated with male lethality
Rhombencephalosynapsis (RES)/Gomez–Lopez–Hernandez syndrome (GLH) (%601853)	1979, 1982	100s	Yes	Non-Mendelian
VACTERL association (%192350)	1973	100s	Yes	Non-Mendelian
Nablus syndrome (#608156)	2000	10s	Yes	Coding or noncoding variant in either cis or trans as second 'hit'

MIM = Mendelian Inheritance in Man.

[a] We recognize that many, if not all, disorders may have been reported in part or in whole in older literature; dates acknowledge earliest "modern" description of recognizable pattern.

[b] Jones, K. L., Jones, M. C., & del Campo, M. (2013). Smith's recognizable patterns of human malformation (Seventh). Philadelphia, PA: Elsevier Saunders.

patients with this malformation also have features of VACTERL association (MIM 192350), a commonly reported and nonrandom co-occurrence of multiple congenital malformations (Quan & Smith, 1973). In their contributions, Aldinger and Doherty and Solomon, respectively, enumerate the large number of approaches attempted to date, as well as plausible mechanisms and strategies going forward to resolve these disorders (Aldinger et al., 2018; Solomon, 2018). Both papers have cited recent and interesting work (Shi et al., 2017; Sparrow et al., 2012) suggesting the contribution of gene–environment interactions in patients with multiple congenital anomalies, including vertebral and cardiac defects. Further concerted studies will undoubtedly be necessary to further explore gene–environment interaction, which likely underlie other recognizable malformation syndromes such as femoral facial syndrome (MIM 134780) (Lacarrubba-Flores et al., 2018).

To round out the eight recognizable syndromes and associations is Nablus syndrome, this review highlights the question of when is a disorder fully solved at the molecular level? First described in 2001 and now reported in more than 10 individuals (Allanson, 2001; Jamuar et al., 2015), Nablus syndrome (MIM #608156) has been given a '#' designation in OMIM because all patients with this rare and highly recognizable phenotype have an overlapping 8q21.3 deletion. However, as reviewed by Allanson, Smith, Forzano, Lin, Raas-Rothschild, Howley, and Boycott, this deletion is necessary but not sufficient to cause the Nablus phenotype as several individuals with overlapping deletions do not have the characteristic facial features of Nablus (Allanson et al., 2018). In their article they review possible explanations for this phenomenon, including one locus and two locus (digenic) models, and the types of studies that would be necessary to confirm the various theories. In the one locus model, a rare variant or even more likely a common SNP on the other copy of chromosome 8 would be necessary for the expression of the typical facial features of Nablus syndrome; this would be analogous to the discovery of the molecular mechanism underlying TAR syndrome (Albers et al., 2012), which interestingly was one of the original 130 recognizable syndromes first recorded by Smith (1969).

Finally, this issue of *Seminars* addresses the scope of the unsolved genetic conditions that currently exist; there are many more recurrently-published and clinically-established syndromes where the molecular mechanism is unknown than what is presented in Smith's textbook. In their commentary, Hartley, Balci, Rojas, Eaton, Dyment, and Boycott mine the invaluable OMIM resource of approximately 7,000 catalogued Mendelian rare diseases. They estimate that 160 of these diseases are "well established" phenotypes that remain unsolved (Hartley et al., 2018). The global rare disease community would be well-served by the study of these disorders, including, whenever possible, their originally-described families.

3 | GOING FORWARD

In preparing this volume, several themes have become evident. The first is that the international community of clinical geneticists, dysmorphologists and pediatricians has done a remarkable job of recognizing hundreds of discrete malformation syndromes, for which the overwhelming majority have now been solved. While many new syndromes are now being resolved by a genotype-first approach to discovery, many key recognizable syndromes remain 'unsolved', including 160 well-established phenotypes in OMIM. The reasons that such discovery efforts fail are myriad and most likely include both technical limitations and complex biology; approaches that overcome these barriers to discovery are currently few in number. Going forward, the use of new technologies ('omic approaches,

animal models) and even further concerted efforts in collaboration and data sharing will be needed. It goes without saying that identifying the bases of these syndromes will further the understanding of these specific syndromes (allowing for enhanced patient care and counseling of families), but will likely also inform the study of many other unsolved rare diseases. This issue of *Seminars* will have served its purpose if it has encourage the reader to consider other unsolved disorders and the possible approaches to resolve them. This progress will be necessary to help reach the vision of the International Rare Diseases Research Consortium: to enable all people living with a rare disease to receive an accurate diagnosis, care and available therapy within 1 year of coming to medical attention (Austin et al., 2018).

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CONFLICT OF INTEREST

None.

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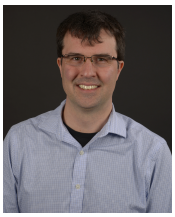

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