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Waiting in Anticipation

The Genetics of Pulmonary Arterial Hypertension

Genetic anticipation is a phenomenon in which the age of onset of an autosomal dominant disease becomes earlier with each successive generation. Inherited diseases that show anticipation are most often caused by triplet repeat expansions, tandemly repeated sequences of three bases, for example (CAG)_n. Such sequences typically show a variable number of repeats in the general population but become pathogenic when they expand beyond a certain threshold. Perhaps the most striking example of this is myotonic dystrophy, caused by a CTG repeat sequence in the 3'-untranslated region of the *DMPK* gene. In the space of three generations, this sequence can evolve from a mildly pathogenic mutation associated with late-onset disease to a massive expansion of the repeat element that causes a very severe congenital form (1). The propensity for repeat expansion is also dependent on the sex of the transmitting parent, the congenital form being mainly associated with maternal transmission (2).

The familial form of pulmonary arterial hypertension (PAH) is inherited as an autosomal dominant condition with reduced penetrance, meaning that not everyone who inherits the causative gene will actually develop the disease and it may completely skip one or more generations. A further complexity is that the penetrance is higher in females than males. Despite this, PAH may appear to show anticipation, with childhood-onset cases suddenly

occurring in families that previously showed the more typical onset in the middle decades of life (3). This led to the suggestion that PAH might be caused by a triplet repeat mutation (4). However, when the bone morphogenetic protein receptor II (*BMP2*) gene was identified as the major cause of familial PAH (5, 6), it became clear that the mutation spectrum was the regular mix of missense, nonsense, and frameshift mutations seen in the majority of genetic diseases. With no molecular explanation, the cause of anticipation in PAH has remained an enigma.

In this issue of the *Journal*, Larkin and colleagues (pp. 892–896) present a reanalysis of 53 PAH families from the registry at Vanderbilt University (7). They hypothesized that the perceived anticipation could in fact be an ascertainment bias because in the most recent generations, only the early-onset cases would be apparent. An extended period of observation would be required to ascertain other individuals who might still develop PAH later in life. They therefore focused on families with *BMP2* mutations and considered only individuals who were born before 1955. Evidence from the registry suggests that 90% of cases are diagnosed by age 55, so in this way they could obtain almost full ascertainment of individuals who were ever likely to develop PAH. Without this correction, the average age of diagnosis clearly decreased across the generations, whereas the age-truncated data eliminated this difference. One limitation of this approach based on age of diagnosis is that, by definition, only affected individuals are included in the analysis; unaffected individuals who carried the mutant gene but never developed the disease were not

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considered. To address this, Kaplan-Meier survival analysis was performed including unaffected mutation carriers. This analysis also eliminated statistical evidence for anticipation. Additionally, the study provides updated estimates of the penetrance of *BMPR2* mutations, which averaged 27% overall: 42% in females and 14% in males. However, the true penetrance can only be determined when all members of a family are genotyped and followed up for six or more decades, a nearly impossible task.

Even though genetic anticipation now seems unlikely, the genetics of PAH remains complex. One of the major questions still outstanding is why PAH may present in childhood and yet many individuals with the mutation live to an advanced age without ever developing symptoms of the disease. It has been proposed that PAH arises as a multistep cancer-like process with the accumulation of somatic mutations in the cells of the pulmonary circulation (8–10). Although there is no evidence for loss of the wild-type *BMPR2* allele in the vascular lesions of familial PAH (11), there is a growing body of evidence to support the existence of additional genetic damage, involving chromosome breaks and other mutations that might contribute to disease manifestation (12, 13). This could explain much of the variability in age of onset, as these additional mutations are presumably random events, yet the inheritance pattern of PAH is distinct from familial cancers, in which acquisition of somatic mutation is well recognized, and where the penetrance is usually much higher and age of onset less variable. Aside from somatic mutation, inherited sequence variation in other genes may modify disease expression. In addition, environmental factors are also likely to play an important role in concert with genetic susceptibility, for example *BMPR2* mutations associated with anorexigen-associated PAH (14). One emerging concept is that the level of *BMPR-II* expression may be critical to disease penetrance, with disease occurring when *BMPR-II* falls below a threshold (15). Relevant to this, the level of *BMPR-II* expression is reduced by estrogen, microRNAs, inflammation, and hypoxia, all of which have been implicated in the pathobiology of PAH. Lastly, a proportion of unaffected carriers of *BMPR2* mutations may actually have some degree of subclinical disease but have not lost sufficient lung vasculature to become symptomatic. Ultimately, the challenge for genetic research remains to elucidate the molecular triggers of PAH, so that we may predict who is most likely to become affected and work toward preventing this potentially fatal disease. The authors have generated a valuable resource for this rare but important disease to address these questions, but further insights are likely to require larger national and international collaborative registries of families with PAH.

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