2024 ASHG presidential address: Incomplete penetrance and variable expressivity: Old concepts, new urgency

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Summary

This article is based on the address given by the author at the 2024 meeting of The American Society of Human Genetics (ASHG) in Denver, CO. A video of the original address can be found at the ASHG website.

If one reviews the types of addresses that past ASHG Presidents have delivered, there is a fascinating range. Adopting the approach of the first ASHG President, Herman Muller,[1] which has since been used by many of my predecessors, I decided to speak about a specific topic in human genetics. As per my talk title, I will be discussing the related concepts of incomplete penetrance and variable expressivity. I hope to explain why I believe that these old genetic ideas have taken on new urgency and provide a vision of the important opportunities in human genetics and precision medicine deriving from current challenges.

For Mendelian disorders—so-called single gene traits—penetrance is the probability that an individual with a pathogenic variant develops the related disease. If it is 100%, we label that as complete penetrance; if it is less than 100%, penetrance is deemed incomplete (Figure 1). Expressivity is defined as the degree to which trait expression differs among affected individuals. If it differs, we call that variable expressivity. And, of course, traits can exhibit both incomplete penetrance and variable expressivity.

The concepts of penetrance and expressivity are about 100 years old.[3] So, what factors are driving the urgency now? I believe that the combination of the falling price of genome sequencing—an amazing and enabling force in human genetics—and the sometimes misapplication of penetrance and expressivity is putting us on a collision course: as we seek to leverage the former, the latter is creating challenges for the robust enactment of precision medicine.

Let me illustrate the potential problem with a thought experiment. An experienced group intends to advance precision medicine through genetic screening of the population. They assemble a list of the genes to be screened and the relevant information. Of course, this group has important decisions to make about age of onset and actionability for their list. However, they are likely to insist that the genes on the screening list have relatively high penetrance. This, in turn, raises the question: How do we know what the penetrance is for a given gene:trait pair? The usual answer has been: from careful review of the literature about that gene:trait pair.

In nearly all instances, estimates of penetrance for gene-trait pairs are derived as follows: A cohort with the trait is assembled, probands are genotyped, and cascade testing is performed to find additional genotype+ relatives, who are then phenotyped (Figure 2). This allows penetrance to be calculated. I want to propose that we call such estimates $\text{Penetrance}_{\text{Familial}}$. But, of course, what the precision medicine team will do is *not* analogous to that. Rather, the analog is to genotype-first studies using biobanks, for which investigators genotype participants, identify those carrying pathogenic alleles, and then extract phenotypes from the available records. (A quick pause to acknowledge that the ways in which individuals in biobanks are ascertained, the criteria used to curate alleles as pathogenic, and the limitations of available phenotypic information are very important factors. Permit me to assume that all of that has been done perfectly.) The resulting estimate of penetrance I will call $\text{Penetrance}_{\text{Population}}$. The crucial question for precision medicine is: are $\text{Penetrance}_{\text{Familial}}$ and $\text{Penetrance}_{\text{Population}}$ the same?

A related issue pertains to the important improvement in human genetic research, normalizing return of secondary findings to participants electing to receive them. This, of course, has relied on the efforts of an ACMG working group, which has been evolving their list of gene:trait pairs since 2013.[4] They anticipated the likelihood that $\text{Penetrance}_{\text{Population}}$, which is the relevant one, would be less than $\text{Penetrance}_{\text{Familial}}$. However, penetrance was not

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https://doi.org/10.1016/j.ajhg.2025.01.010.

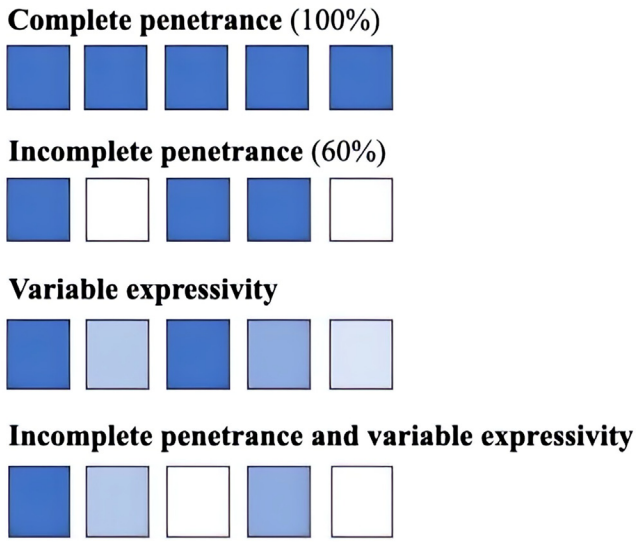

Figure 1. Conceptual reference of penetrance and expressivity
Squares represent individuals with the same genotype, with shaded squares indicating that the individual displays the related phenotype and non-shaded squares indicating the individual does not display the related disease phenotype. Line one shows complete penetrance, where all individuals display the related phenotype. Line two shows incomplete penetrance, where 60% of the individuals display the related phenotype. Line three shows that all individuals display the related phenotype, from severe manifestations to milder presentations. Line four shows incomplete penetrance and variable expressivity, where the genotype varies both in the severity of presentation and in penetrance across the population. Figure is adapted from Kingdom and Wright,[2] with permission from Carolyn Wright, and the figure legend is nearly identical to that of Figure 1 of that paper.

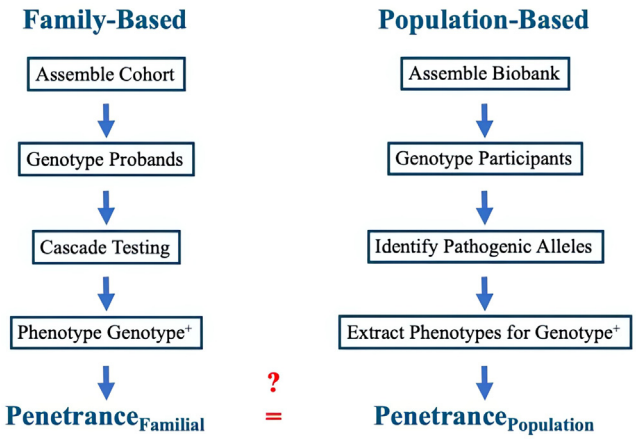

Figure 2. Schematic showing the family-based (left) and population-based (right) approaches to determining penetrance for a gene:trait pair
The family-based approach results in $Penetrance_{Familial}$, while the population-based method results in $Penetrance_{Population}$.

included in their methodology for version 1. In version 2, penetrance was added to the methodology, but the gene list relies on $Penetrance_{Familial}$.[5] The authors wrote "Among the challenges inherent in developing and curating this list, we recognize the presumption of high penetrance for these genes and disease based on potentially biased case ascertainment," showing that they understood that assumptions about $Penetrance_{Population}$ based on $Penetrance_{Familial}$ were potentially problematic. This past summer, the group issued a position paper about penetrance, alerting the human genetics community to this issue and thoughtfully discussing the equities.[6]

Several Mendelian traits have been studied using genotype-first methodology, attempting to address the previously posed question: are $Penetrance_{Familial}$ and $Penetrance_{Population}$ the same? The answer for the traits studied to date is that, in most cases, $Penetrance_{Population}$ is significantly less than $Penetrance_{Familial}$.[2] And, if the study is performed using a cohort skewed toward healthy persons such as the UK Biobank, penetrance is even lower. For example, maturity-onset diabetes in the young was studied in biobanks by groups at Geisinger and the University of Exeter in the UK.[7] For probands and genotype+ family members, penetrance of diabetes among *HFN4A* pathogenic allele carriers was 90% or more, while the estimates for $Penetrance_{Population}$ were only 20%–30%. In contrast, $Penetrance_{Familial}$ and $Penetrance_{Population}$ were equal for the trait hyperglycemia among carriers of *GCK* pathogenic variants.[7] This appears to be the exception, not the rule.

I have been discussing the importance of ascertainment *vis á vis* penetrance, but comparable differences are found for expressivity. As an example, Brittany Wenger in my group examined heights among carriers of pathogenic alleles for Noonan syndrome, a trait for which short stature is a feature.[8] Her results from the health care-based biobank at Mount Sinai called Bio*Me* and for UK Biobank participants revealed that only 2 of 21 carriers, or just under 10%, were below the 3rd percentile as adults. In contrast, 40% of individuals diagnosed with Noonan syndrome have final adult heights below the 3rd percentile.[9]

To understand how we arrived at our current definitions and understanding of penetrance and expressivity, I decided to trace their intellectual history. This turned out to be quite challenging—I didn't know and neither did anyone else whom I approached. Former ASHG President Aravinda Chakravarti helpfully pointed me to a paper by Edgar Altenburg and ASHG first President Muller about a *Drosophila* wing trait called truncate.[10] Their paper, published in 1920, is a *tour de force*. They realized that "the inheritance of truncate…seemed from the first to be irreconcilable with Mendelian principles." Remarkably, Altenburg and Muller used linkage analysis to map the gene for truncate to chromosome 2 but also showed that there was at least one genetic modifier each on chromosomes 1 and 3. Reading this, one realizes that such genetic complexity must have been present with some frequency in the Columbia fly room, but that the group selectively studied Mendelian traits that behaved simply. There were, after all, plenty of those, and the complex ones were just too challenging. With respect to the history of penetrance and expressivity, this paper turned out to be a dead end.

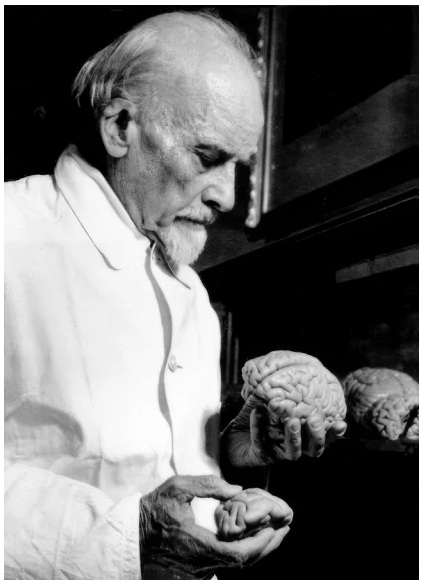

Figure 3. Oskar Vogt, 1943. Image via Ross Wolfe, *The Charnel-House.*

Altenburg and Muller never discussed the concepts *per se*, and there wasn't any follow up from them on truncate.

A few years later, the interaction of two men—Vladimir Lenin, the founder of the Soviet Union, and Oskar Vogt, a German neuroscientist (Figure 3)—led to the coining of the terms penetrance and expressivity.[3] Vogt pursued a structure-function paradigm, believing that the minutiae of brain anatomy would explain various neurological disorders. He was one of the best neuroanatomists in the world in the 1920s. During this interwar period, the Germans and Russians were collaborating extensively scientifically. So, in 1924, when Lenin died, the Soviet authorities summoned Vogt to Moscow to dissect Lenin's brain with the question: why was Lenin so brilliant? If that sounds laughable, recall that something similar was done with Einstein's brain thirty years later.

When Vogt arrived in Moscow in 1925 to start his study of Lenin's brain, he was introduced to leading young scientists, notably those pursuing *Drosophila* genetics, a Russian strength in the pre-Lysenko era.[3] Among them were the Timofeev-Ressovskys, a husband-and-wife team who were studying a *Drosophila* wing vein trait called *Radius incompletus*. This trait was notable for its incomplete penetrance. The Timofeev-Ressovskys outcrossed the trait's allele onto different fly strains, showing that penetrance levels varied among the derived lines. Another young scientist whom Vogt met was Romaschoff, who was studying a trait of variable coloration patterns of the fly abdomen called *Abdomen abnormalis*. Romaschoff showed that the degree of expressivity depended upon the wetness of the fly food but was heritable.

When Vogt got back to Berlin, he did two things. He recruited the Timofeev-Ressovskys to his institute, which had dire consequences for them after World War II. Vogt also got both groups to publish papers in 1925 and, in 1926, wrote a piece, in which he coined the terms penetrance and expressivity.[11–13] Importantly, Vogt made mistakes as he set forth the concepts of penetrance and expressivity. He conflated gene and allele but, more critically, he seems to have missed the fact that the penetrance of *radius incompletus* was dependent on genetic background and varied from one genetic background to another. Put another way, penetrance was not a fixed parameter.

The concepts of penetrance and expressivity were picked up in England through Waddington about a decade later.[3] Interestingly, the concepts did not make it into American genetics textbooks until the mid-1950s, and that was driven by Dobzhansky, who had emigrated from the Soviet Union where he had known the Timofeev-Ressowskys and Romaschoff.

The errors committed by Vogt with respect to penetrance and expressivity have echoed down to us today. To demonstrate that, let us look at the Wikipedia entry for penetrance (https://en.wikipedia.org/wiki/Penetrance): "Penetrance in genetics is the proportion of individuals carrying a particular variant of a gene (genotype) and also express an associated trait (phenotype)." I have underlined the word "the" for emphasis. The implication of this definition is that penetrance is a fixed parameter. The Wikipedia entry for penetrance also contains the 2nd error descended from Vogt, stating that, "*BRCA1* is an example of a genotype with reduced penetrance. By age 70, the mutation is estimated to have a breast cancer penetrance of around 65% in women." Here, gene and allele are being conflated, implying that penetrance is equal across all alleles. I will discuss below that this is incorrect.

If penetrance and expressivity are variable, what are the factors driving that variability? The current best understanding divides the driving factors into three broad buckets: genetic factors, environmental exposures including epigenetic factors, and stochasticity, also known as randomness.[2] The relative contributions of those buckets to the variability in penetrance and expressivity are generally not clear for human genetic traits. I will briefly discuss two of these buckets: genetic factors and environmental exposures.

For a study from Carolyn Wright's group, fluid intelligence as measured in UK Biobank participants was examined.[14] As one would expect, fluid intelligence in participants found to harbor *no* pathogenic variant for a Mendelian developmental disorder was better than in those who harbored one DD variant (Figure 4). Then, a polygenic risk score for educational attainment was applied. The impact of that PRS is quite similar for both groups, meaning that the expressivity of those harboring a DD variant depended on genetic interactions with the complex trait represented by this PRS. In fact, the impact of the DD variant on fluid intelligence is equivalent to 20 percentile points on that PRS. Put another way, knowledge of only the allele status for the Mendelian DD trait is insufficient to accurately predict outcomes, which actually

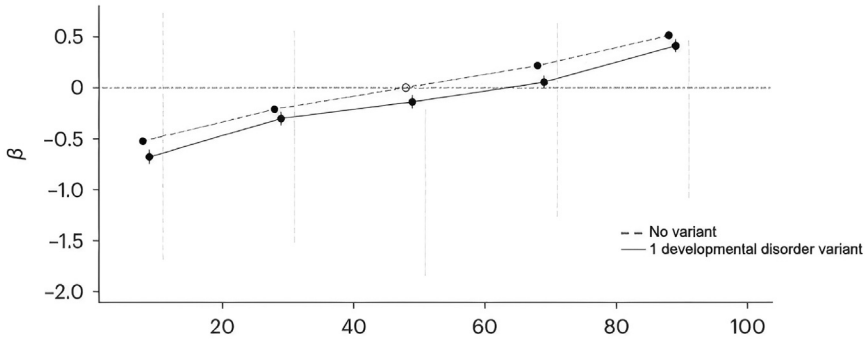

Figure 4. Additive effect of rare developmental disorder variant burden and educational attainment-polygenic score on fluid intelligence
Modified version of Figure 3 from Kingdom et al.[14] with permission from Carolyn Wright.

depend on the more holistic sense of genotype. For common and less common genetic variants affecting penetrance and expressivity, we have deep insights into plausible biological mechanisms through they might interact with the large-effect Mendelian alleles (Figure 5). Needless to say, working out the specifics is far from trivial.

James Ware's group in London studied penetrance of the Mendelian trait familial hypertrophic cardiomyopathy at the allele level using UK Biobank data.[15] Their penetrance estimates for pathogenic and likely pathogenic alleles of the two commonest genes causing this cardiac trait varied widely, from one for which the confidence interval includes complete penetrance to one with penetrance of only 10% (Figure 6). One pathogenic splice site variant in *MYBP3* (not shown) had a penetrance of 1%. The need to understand penetrance at the allele, not gene, level is apparent if the promise of precision medicine is to be fulfilled.

Next, I turn to a brief consideration of the impact of environmental exposures. While we have rare spectacular examples—neurodevelopmental outcomes in individuals with phenylketonuria depending on diet being probably the best known one—gene by environment studies for Mendelian traits have been difficult to power adequately and, thus, few such interactions are well established. In one such study, Garry Cutting's group examined the impact of climate temperature on lung function among individuals with cystic fibrosis.[16] Three independent cohorts were studied, all yielding similar estimates of the negative impact of increased temperature. How many environmental factors are affecting penetrance and expressivity and their aggregate effect sizes on Mendelian traits remains obscure.

Before summarizing, I want to recount another piece of genetics history to make a point about the interactiveness of genetic and environmental factors with respect to penetrance and expressivity. As recounted in the ASHG publication *Facing Our History*, there was a shameful period in the 1970s when incorrect assertions about the heritability of intelligence and scientifically nonsensical, but socially harmful, claims of genetic inferiority among Black people were promulgated by Jensen, Shockley, and others.[17] While the ASHG regrettably refrained from rebutting those genetic falsehoods, some scientists did step forward. One of them, the renowned evolutionary geneticist Richard Lewontin, made seminal points about how we need to think about the interactions between genetic factors and environmental ones with respect to heritability.[18,19] He pointed out that interactions between genotypes and environment can take rather different and complex shapes, forming what Woltereck first termed in the early 1900s as *Reaktionsnorm*, based on observations of the crustacean *Daphnia*.[20] Today, these are called norms of reaction. Lewontin knew well about norms of reaction because his PhD advisor at Columbia in the mid 1950s was Dobzhansky, who was writing about them then. Interestingly, norms of reaction continue to be studied by ecologists but have been basically lost to human geneticists.

In Figure 7, I am showing three potential norms of reaction from Lewontin's papers. Focusing on the one on the left, one can appreciate that the impact of two different genotypes (G1 and G2) on phenotype flips depending on the state of the environment. If environments are randomly distributed around E′, then the net impact of environment is zero. However, if either genotype predominates, there is a strong average environmental effect. For the norm of reaction depicted in the middle figure, genotype barely affects phenotype at the environment on the extreme right

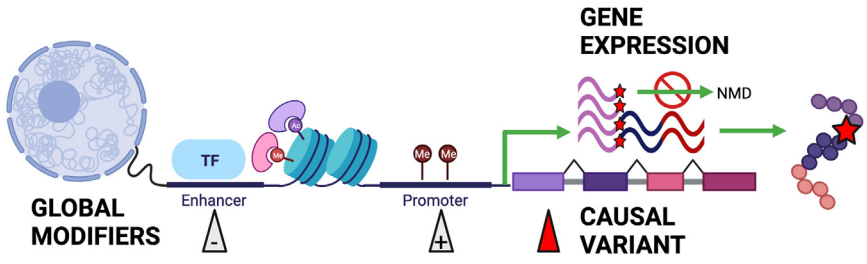

Figure 5. Biological mechanisms that can affect penetrance and expressivity of monogenic disease-causing genetic variants
Figure and figure legend from Figure 2 in Kingdom and Wright.[2]

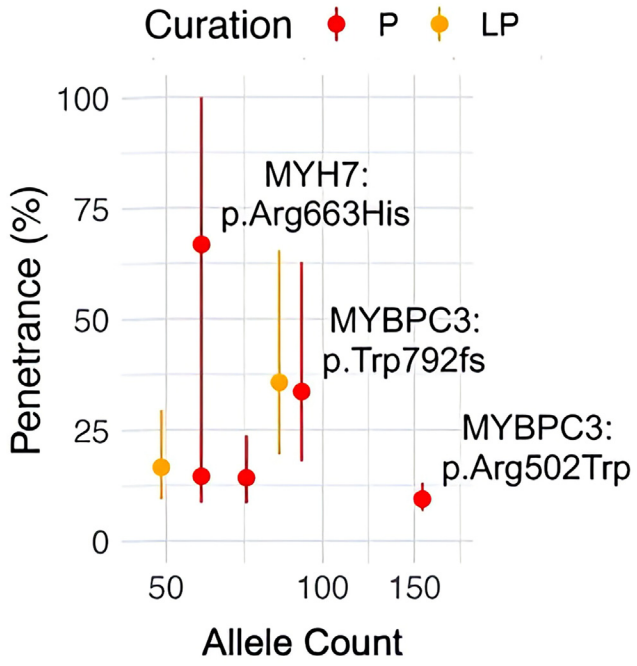

Figure 6. Variant-specific estimates of penetrance for recurrently observed variants in *MYH7* and *MYBPC3* associated with hypertrophic cardiomyopathy

The variants shown were identified multiple times in affected individuals and population reference datasets, so penetrance could be estimated. Present is the estimated penetrance with 95% confidence interval. Allele count is indicated on the x axis. P, pathogenic; LP, likely pathogenic. Figure and figure legend are adapted from Figure 4 of McGurk et al.[15]

but impacts it dramatically for environmental states on the left. Finally, there is the special norm of reaction shown on the right. Here, both genotype and environment matter across the spectrum consistently. Lewontin's point was that only when this norm of reaction is present can one accurately use the analysis of variance as per Fisher that leads to our usual formulation of heritability and environmental variance contributing to complex traits.

I recount this because norms of reaction are equally applicable as we come to grips with the complexity underlying penetrance and expressivity for Mendelian traits. Depending on the relevant norm of reaction for a given trait, the penetrance of its disease alleles need not be stable in different environments.

To summarize, I hope that I have convinced you that the promise of precision medicine requires that we correct errors in our understanding of penetrance and expressivity made nearly a 100 years ago that continue to reverberate among us today. Penetrance varies depending on how carriers of Mendelian disease variants are ascertained, such that $\text{Penetrance}_{\text{Population}}$ generally does not equate with $\text{Penetrance}_{\text{Familial}}$. Moreover, genotype needs to be thought of in a holistic sense, not focused entirely on the causal Mendelian variant. Penetrance and expressivity will often be allele specific, not stable across the entire gene-trait pair. Penetrance and expressivity can also be dependent on environmental factors. Norms of reaction can be relevant in understanding how genetic and environmental factors interact, rendering penetrance and expressivity as potentially variable in a context-specific manner.

As scientists in the field of human genetics and genomics, we have both challenges and opportunities to enable the full potential of precision medicine. We need to elaborate $\text{Penetrance}_{\text{Population}}$ for Mendelian traits for which we feel population screening or return of results are worthwhile. As reflected at sessions during ASHG meetings, we have enormous scientific expertise in methods for studying Mendelian disorders and complex traits, but they tend to be siloed. We need to marry these approaches. We need to parse the relative contributions of genetic and environmental factors to penetrance and expressivity. I am arguing that we need to bring back the concept of norms of reaction to our field and grapple with their importance for understanding Mendelian traits. Figuring out how to accomplish much of this in a robust way in the face of the rarity of Mendelian traits is a tremendous challenge. It will require ingenuity, collaboration, and perseverance.

Acknowledgments

I wish to acknowledge the following persons listed here, all of whom provided concepts that I have presented in my address: Aravinda Chakravarti, Adam Gordon, Greg Radick, Sahotra Sarkar, and Caroline Wright. Largely, I relied on their ideas, just repackaging them for this address. I also thank Mafalda Barbosa and Andy Sharp who provided helpful feedback on my presentation.

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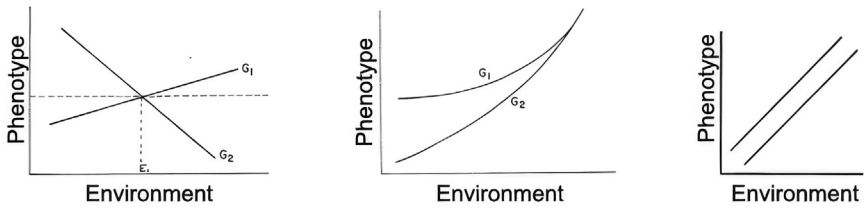

Figure 7. Norms of reaction

Phenotypes (y axis) are plotted against environment (x axis) for two genotypes (G_1 and G_2). Left and middle panels are Figures 1 and 2, respectively, from Feldman and Lewontin[19] (reproduced with permission); the right panel is Figure 1 h from Lewontin.[18]

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