Mission Impossible or Mission Futile?

Estimating Penetrance for Malignant Hyperthermia

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In this issue of Anesthesiology, Ibarra Moreno *et al.*[1] report a multicenter evaluation of previous anesthetic history of patients who have a history of malignant hyperthermia (MH) under anesthesia and their family members. This work will have involved considerable effort to collate the data and evaluate the clinical histories. The major and vital clinical message is to reinforce that MH can occur in patients who have previously experienced uneventful anesthesia with MH-triggering anesthetics. The implication is that a negative personal anesthesia history does not obviate the need to take a family history of adverse anesthesia events, nor should it lower the anesthesiologist's index of suspicion concerning the potential for the patient to develop MH.There are several other interesting observations contained within the data generated by Ibarra Moreno *et al.*,[1] one being that the well-known male predominance of MH probands cannot be explained by different levels of exposure to MH triggering anesthesia, but it is one of their key aims—the estimate of penetrance of variants in the *RYR1* gene (the gene encoding the skeletal muscle isoform of the ryanodine receptor, which is the gene principally implicated in MH)—that requires comment.

"In [malignant hyperthermia] there are several strands of genetic evidence that [malignant hyperthermia] susceptibility, at least in some families, is associated with two or more genetic abnormalities."

The concept of penetrance was introduced in the literature almost 100 yr ago as an explanation for patterns of heredity that diverged from the expected patterns of Mendelian inheritance, all of which assumed single-gene traits,[2] and by the 1950s, the term itself was in use.[3] Indeed, the first report of an MH family described incomplete penetrance of the condition because an obligate genetic carrier had received general anesthesia but had not developed MH.[4] For genetic conditions typically presenting at birth, we can readily estimate penetrance on the basis of its current standard definition as the proportion of individuals who have a disease-causing genotype who express the phenotype. But can such estimates be usefully derived for the penetrance of *RYR1* variants in MH?

Reduced penetrance is often associated with autosomal dominant disorders and is likely due to modifying genetic or environmental factors, or both. It would have been no surprise, therefore, that the inheritance pattern of the first MH family was described as autosomal dominant with incomplete penetrance.[4] However, in a landmark review 20 yr ago, Scriver and Waters[5] illustrated how inheritance patterns that are presumed to represent reduced penetrance in Mendelian heredity could be better explained by non-Mendelian genetic models. Indeed, in MH there are several strands of genetic evidence that MH susceptibility, at least in some families, is associated with two or more genetic abnormalities.[6–8] Furthermore, studies of human MH muscle[9] and *in vivo* and *in vitro* experiments in transgenic *RYR1* knock-in mouse models of MH[10–12] show marked differences in the severity of the MH phenotype caused by different variants in the *RYR1* gene. Collectively, these genetic and functional observations suggest a threshold (non-Mendelian) genetic model for MH susceptibility in which "weaker" *RYR1* variants require coinheritance of other genetic abnormalities in order for their combined effects to be severe enough for a patient to be clinically susceptible.

Even if we assume that at least some *RYR1* variants do operate in an autosomal dominant manner, there are a

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number of problems in estimating the penetrance of such rare pharmacogenetic disorders, which require an environmental trigger. The penetrance of MH could be handled similarly to a late-onset disorder such as Huntington disease where the average age by which the condition presents is used to estimate penetrance,[13] but this would not account for the variable number of general anesthetics received by individuals at any specified age. Alternatively, the penetrance of MH could be defined by the presence or absence of a reaction after a certain number of anesthetics, but this ignores observations that not all anesthetic events are equally likely to trigger a reaction in any one susceptible individual.[14,15] With either a time-based or exposure-based cutoff for determining penetrance, identification of the first individual within a family presenting with a clinical reaction, the proband, is a signal to avoid subsequently exposing potentially susceptible family members to triggering anesthesia. Inclusion of these relatives is likely to underestimate penetrance. The rarity of clinical MH reactions means that studies relying on clinical reactions to identify those with a high-risk genotype are likely to lack power, especially when penetrance should relate to individual variants rather than all variants associated with a phenotype. A multicenter approach as used by Ibarra Moreno *et al.*[1] pools resources to increase power, but inevitably increases the variability of genetic background, which will impact the estimates of penetrance of Mendelian disorders and confound attempts to unravel the genetic bases of complex traits.

Estimation of the likelihood of developing a reaction in probands compared to relatives is also difficult. The MH reaction of the proband is the route to ascertaining such families, yet it is not possible to remove this reaction from the study to correct for ascertainment (sampling) bias, which is standard practice in population genetic studies. Nor is it possible, after diagnosis in the proband, to reliably control for the number of subsequent anesthetic events per individual, resulting in a reaction or otherwise. Furthermore, we do not know if we are selecting for individuals carrying pathogenic variants that lead to a reaction with the first or second exposure to anesthetic triggers, as opposed to those variants that are likely to trigger only after many exposures; again, this fuels ascertainment bias.

The ascertainment bias associated with the selection of families only on the basis of a known MH reaction might artificially inflate any estimate of penetrance. Alternatively, we could approach an estimate of penetrance by comparing the observed incidence of MH reactions to that predicted based on an estimate of the population prevalence of *RYR1* variants predisposing to MH. Based on genomic data from large low-risk (for MH at least) cohorts, an estimate of individuals carrying currently defined pathogenic *RYR1* variants in the general population is approximately 1:1,500. From these data, for a country the size of the United Kingdom with a population of ~60 million, we can project that there are ~40,000 people who carry pathogenic *RYR1* variants. Contrast this to the fewer than 2,500 MH-susceptible individuals whom we (the United Kingdom national MH referral center in Leeds) have definitively diagnosed during the last 48 yr. Similarly, we would anticipate that 2,000 to 4,000 of those carrying pathogenic *RYR1* variants in the United Kingdom would receive general anesthesia each year, whereas we identify only around 20 new cases of MH per annum. The estimate of penetrance obtained from these data (5 to 10%) is considerably lower than that of Ibarra Moreno *et al.*,[1] but perhaps more interestingly, seems incompatible with the idea that all of the currently defined pathogenic *RYR1* variants play a major role in determining MH susceptibility.

Our final illustration of the futility of trying to estimate the penetrance of *RYR1* variants in MH goes back to the definition of penetrance. This requires the genotype in any one individual to be described as penetrant or not penetrant, whereas MH-susceptible individuals may express the phenotype during one exposure but not another. There is still much to learn about the genetic factors predisposing to MH. *RYR1* is a large gene, and the 48 variants currently regarded as pathogenic will not be a complete list. Many more rare variants remain to be characterized, and those found to date cause changes in coding sequence only (noncoding sequence has not been studied). If the phenotypic consequences of a pathogenic *RYR1* variant are significantly influenced by other variants, leading to stratification of the combined data, we would be unaware. In the meantime, the work of Ibarra Moreno *et al.*[1] highlights important clinical messages that need to be understood by every anesthesiologist.

Competing Interests

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References

1. Ibarra Moreno CA, Hu S, Kraeva N, Schuster F, Johannsen S, Rueffert H, Klingler W, Heytens L, Riazi S: An assessment of penetrance and clinical expression of malignant hyperthermia in individuals carrying diagnostic ryanodine receptor 1 gene mutations. Anesthesiology 2019; 131:983–91
2. Danforth CH: The heredity of unilateral variations in man. Genetics 1924; 9:199–211
3. Allen G: The meaning of concordance and discordance in estimation of penetrance and gene frequency. Am J Hum Genet 1952; 4:155–72

4. Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD: Anaesthetic deaths in a family. Br J Anaesth 1962; 34:395–6
5. Scriver CR, Waters PJ: Monogenic traits are not simple: Lessons from phenylketonuria. Trends Genet 1999; 15:267–72
6. Robinson RL, Curran JL, Ellis FR, Halsall PJ, Hall WJ, Hopkins PM, Iles DE, West SP, Shaw MA: Multiple interacting gene products may influence susceptibility to malignant hyperthermia. Ann Hum Genet 2000; 64(pt 4):307–20
7. Robinson R, Hopkins P, Carsana A, Gilly H, Halsall J, Heytens L, Islander G, Jurkat-Rott K, Müller C, Shaw MA: Several interacting genes influence the malignant hyperthermia phenotype. Hum Genet 2003; 112:217–8
8. Miller DM, Daly C, Aboelsaod EM, Gardner L, Hobson SJ, Riasat K, Shepherd S, Robinson RL, Bilmen JG, Gupta PK, Shaw MA, Hopkins PM: Genetic epidemiology of malignant hyperthermia in the UK. Br J Anaesth 2018; 121:944–52
9. Carpenter D, Robinson RL, Quinnell RJ, Ringrose C, Hogg M, Casson F, Booms P, Iles DE, Halsall PJ, Steele DS, Shaw MA, Hopkins PM: Genetic variation in RYR1 and malignant hyperthermia phenotypes. Br J Anaesth 2009; 103:538–48
10. Yang T, Riehl J, Esteve E, Matthaei KI, Goth S, Allen PD, Pessah IN, Lopez JR: Pharmacologic and functional characterization of malignant hyperthermia in the R163C RyR1 knock-in mouse. Anesthesiology 2006; 105:1164–75
11. Yuen B, Boncompagni S, Feng W, Yang T, Lopez JR, Matthaei KI, Goth SR, Protasi F, Franzini-Armstrong C, Allen PD, Pessah IN: Mice expressing T4826I-RYR1 are viable but exhibit sex- and genotype-dependent susceptibility to malignant hyperthermia and muscle damage. FASEB J 2012; 26:1311–22
12. Lopez JR, Kaura V, Diggle CP, Hopkins PM, Allen PD: Malignant hyperthermia, environmental heat stress, and intracellular calcium dysregulation in a mouse model expressing the p.G2435R variant of RYR1. Br J Anaesth 2018; 121:953–61
13. Brinkman RR, Mezei MM, Theilmann J, Almqvist E, Hayden MR: The likelihood of being affected with Huntington disease by a particular age, for a specific CAG size. Am J Hum Genet 1997; 60:1202–10
14. Ramirez JA, Cheetham ED, Laurence AS, Hopkins PM: Suxamethonium, masseter spasm and later malignant hyperthermia. Anaesthesia 1998; 53:1111–6
15. Hopkins PM: Malignant hyperthermia: Pharmacology of triggering. Br J Anaesth 2011; 107:48–56