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BACK TO THE DRAWING BOARD Reply to the Editor:

Neonates and infants with complex congenital heart disease are at increased risk for adverse neurodevelopmental outcomes relative to children without heart disease. If risk factors for such adverse outcomes could be identified, alternative treatment approaches tailored to different phenotypes might be developed. Further, insights about the mechanistic explanation for adverse outcomes associated with certain risk factors may suggest strategies to mitigate the potential deleterious impact of the risk factor. In this context, a recent report describing worse neurodevelopmental outcomes after congenital heart surgery in patients with mannose-binding lectin (MBL) deficiency was particularly intriguing.¹ Interestingly, there was also a suggestion in the report that this association may be age related, in that the association was greatest in younger patients. As with any novel observation, the findings must be validated and confirmed; unfortunately, however, the same investigators were unable to do so when they studied mannose-binding lectin deficiency in 2 similar populations.² Indeed, mannose-binding lectin deficiency actually appeared to be neuroprotective in certain subpopulations.

Although the original observation was not confirmed in the validation study, we believe that the follow-up report by Kim and colleagues² is nonetheless very valuable. Most fundamentally, investigators interested in neurodevelopment can be confident that they have the most current information available. Perhaps even more importantly, the community must acknowledge the intellectual rigor of Kim and colleagues² in “correcting” the record. All too often, a promising initial report appears in the literature, but no confirmatory (or contradictory) sequel is available. Is this because no validation study was done? Or is it because the attempt at replication was unsuccessful, and a negative study was less attractive to both investigators and editors? In an era in which trust in the scientific community can no longer be taken for granted (if it ever was), Kim and colleagues² have provided both first-class science and an example of how to “do it right.” They are to be applauded for providing what the noted sage Paul Harvey might have called “the rest of the story.”

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GENETIC ASSOCIATION STUDIES: IS NON-REPLICATION FAILURE OR PROGRESS?

Reply to the Editor:

Early last year, Kim and colleagues¹ presented a study entitled, “Autosomal Dominant Mannose-Binding Lectin Deficiency Is Associated With Worse Neurodevelopmental Outcomes After Cardiac Surgery in Infants.” The article was published soon after, statistically robust and supported by biologically plausible literature. In brief, the article reported that a common genetic variant in human *MBL2* (rs1800450) was associated with increased developmental problems after cardiac surgery. In this issue of the *Journal*, the same authors examine multiple cohorts for associations of rs1800450 with psychomotor developmental index, mental developmental index, and functional status. For mental developmental index, they found no association ($P = .52$). For both psychomotor developmental index and functional status, they found a marginally significant association, but the direction of the effect was now the opposite of their previous finding: it was protective, not damaging. Is it a surprise that the same group has now failed to validate their earlier findings? The authors correctly report that “most initial reports of genotype-phenotype associations are not subsequently validated.” In fact, nonreplication is exceedingly common. If true, why bother? Or is there something else to learn?

Kim and colleagues report, “These results could reflect underlying differences between cohorts.... As well, these results may reflect differential effects of mannose-binding lectin deficiency at varying stages of neurodevelopment. Alternatively, this *MBL2* variant may reflect the effects of another, closely correlated, causal variant in this region.”¹ As always, more could be done to validate findings, such as measuring *MBL2* protein level, analyzing additional *MBL2* genotype data beyond the single nucleotide polymorphism, or resequencing of samples to ensure correct genotypes. These additional studies might address the possibilities that other variants that interact with *MBL2* itself, of the highly polymorphic promoter that might prominently affect proteins levels, or other steps in the signaling pathway.²

Another consideration is the “winner’s curse,” first described with respect to conflict resolution but can be argued might be at play in some single locus genetic studies. The example is of an auction where the average bidder accurately estimates value; some bidders will underestimate, and others will overestimate. However, the bidder who most greatly overestimates value will typically win the auction; the amount they overestimate will often be greater than the difference between the winning bid and his bid. Thus, the winner of an auction should expect to find that what they bought is worth substantially less than their prior estimate.³ Although different factors are at play, a group focused on a certain gene could fall prey to a similar fate more common than not.

Replication of positive findings from genetic association studies has long served as the gold standard for establishing validity of observed genotype–phenotype associations. In addition to adequate statistical power and sound epidemiologic design aimed at minimizing biases, suggested criteria for successful replication studies include (1) same genetic variant, (2) same direction of association, (3) same definition of the phenotype, and (4) same ethnic group as reported in the discovery study.⁴ An important factor contributing to single-digit replication rates is the low ratio of false-positive to false-negative findings inherent to genome-wide and other large-scale genetic studies.⁵ Some warn that with more frequent high-resolution genotyping, the number of potentially relevant genetic markers will increase exponentially, making the same genetic-variant component of the replication requirement not only unfeasible but also meaningless. Complementary or alternative approaches such as simulations, combined analysis of multiple populations, or ultimately a true gold standard of functional validation could together provide a more and rigorous validation of genetic association findings.⁶

In essence, Kim and colleagues’ studies¹ are not wrong, they just were not replicated. And that may not be bad news. Ioannidis⁷ described 2 extremes of gene association