Response to Letter Regarding Article, “Genetic Architecture of Abdominal Aortic Aneurysm in the Million Veteran Program”

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In Response:

We appreciate the comments from Drs. Zhang and Liu on our two recent publications that aimed to identify the genetic factors associated with abdominal aortic aneurysm (AAA)1,2. In one paper, we performed a genome-wide association study (GWAS) on 180,000 study participants to interrogate common variants, and in the other, we developed the machine learning approach, HEAL, to analyze rare nonsynonymous variants in 401 whole genomes. We acknowledge the direct overlap between these two discoveries is relatively little: among the 24 genes identified from the common variants, only two (ERG, SMYD2) were found in the protein-protein interaction modules (“HEAL modules”) as an extension to the genes identified from the rare variants (“HEAL genes”). However, in a broader search, 26 additional genes in our HEAL modules were also reported in a large collection of AAA genes derived from ~100 studies3. On the other hand, we replicated ten known AAA loci in our GWAS study. Therefore, there are numerous known AAA genes identified in either of our studies. So why was there little overlap?

One possible explanation is the two datasets focused on different aspects of the genome. The input for our rare variant study was deeply-sequenced whole genomes, in which half of the called variants were rare (AF<0.01) in the low P value group (GWAS P < 0.001). This enrichment grew from 6-fold (Fisher’s exact P=0.03) to 17-fold (Fisher’s exact P=0.005) as we lowered the allele frequency cutoff from 0.001 to 0.0001, suggesting the HEAL gene signals were contained in the GWAS results, albeit these signals were relatively weak due to the limited statistical power of GWAS for rare events.

Note that we focused on rare variants with nonsynonymous effects. One known marker gene for AAA is Interleukin-6 (IL6), on which an intron variant was captured by our GWAS but missed entirely in our rare variant analysis. However, when examining regulatory regions

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in the same genomes where the rare variant study was performed, a strong IL6 signal was evident (manuscript in preparation).

Rare variants are often young in origin and exert larger effects on diseases and reproductive fitness, whereas common variants can impact both essential and weakly-associated disease genes. A recent study systematically interrogated rare variants in complex diseases and discovered both known and novel genes, suggesting common and rare variants could converge on the same biological pathways or function distinctly. As for AAA, future studies will better reveal how common and rare variants work in tandem to affect this disease.

Disclosures

Disclosures from our original manuscripts:

J.L., C.P., S.Z., P.S.T., and M.S. are listed as inventors on a pending patent related to the HEAL framework. J.L. is a cofounder and scientific advisory board member of SensOmics. M.S. is a cofounder and scientific advisory board member of Personalis, SensOmics and Qbio, January and Fitricine and is a scientific advisory board member of Genapsys and Epinomics.

Dr Klarin has received consulting fees from Regeneron Pharmaceuticals unrelated to the work in this article. Dr DuVall reports grants and nonfinancial support from the Department of Veterans Affairs during the conduct of the study; and grants from AbbVie Inc, Amgen Inc, Anolinx LLC, Astellas Pharma Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim International GmbH, Celgene Corporation, Eli Lilly and Company, Genentech Inc, Gilead Sciences Inc, GlaxoSmithKline PLC, Innocrin Pharmaceuticals Inc, Janssen Pharmaceuticals Inc, Janssen Pharmaceuticals Inc, Janssen, Myriad Genetics Laboratories Inc, Novartis International AG, and Parexel International Corporation outside the submitted work. Dr Damrauer receives research support to his institution from RenalytixAI and is a paid consultant for Calico Labs. Dr Kathiresan is a founder of Maze Therapeutics, Verve Therapeutics, and San Therapeutics; holds equity in Catabasis and San Therapeutics; is a member of the scientific advisory boards for Regeneron Genetics Center and Corvidia Therapeutics; served as a consultant for Acceleron, Eli Lilly, Novartis, Merck, NovoNordisk, Novo Ventures, Ionis, Alynlam, Aegerion, Huag Partners, Noble Insights, Leerink Partners, Bayer Healthcare, Illumina, Color Genomics, MedGenome, Quest, and Medscape; and reports patents related to a method of identifying and treating a person having a predisposition to or afflicted with cardiometabolic disease (20180010185) and a genetics risk predictor (20190017119).

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