Circulation: Genomic and Precision Medicine

REVIEW

Human Genetics Informing Drug Development in Cardiovascular Disease: Interleukin-6 Signaling as a Case Study

Emil deGoma, MD; John Walsh, MD; Marios K. Georgakis, MD, PhD

ABSTRACT: Cardiovascular disease remains the leading cause of death worldwide, calling for the development of novel therapeutics. Over the past 3 decades, substantial investments in human genetic research have unveiled the genetic architecture of cardiovascular disease, offering promising novel therapeutic targets. These discoveries have been instrumental in the development of several cardiovascular drug development programs, such as those targeting proprotein convertase subtilisin/kexin type 9, lipoprotein (a), apo C_3, and angiopoietin-like 3. Large-scale resources such as population-based biobanks and data repositories, now enable human genetic data to be leveraged at scale and inform not only target selection, but also clinical drug development. This review highlights the transformative potential of human genetics in cardiovascular drug development, focusing on IL (interleukin)-6 signaling as a case study. Specifically, we discuss how IL-6 signaling was pinpointed as a key causal mediator of atherosclerosis by genetic data, shaping the current development landscape for anti–IL-6 therapeutics in cardiovascular disease. Recent genetic studies employing innovative methodologies have provided key insights into prioritizing indications for clinical testing, informing repurposing strategies, optimizing clinical trial design for population selection, and assessing safety signals. Despite this progress, methodological challenges, such as pleiotropic effects of genetic variants, extrapolation of small genetic associations to large interventional effects, and the predominance of European-derived data, highlight the need for careful interpretation. Continued methodological advances, coupled with the emergence of high-throughput omics data and detailed cardiovascular phenotyping, promise unprecedented opportunities to refine drug discovery and development.

Key Words: atherosclerosis ■ cardiovascular diseases ■ cytokines ■ genetics ■ immune system ■ inflammation

Cardiovascular disease (CVD) remains the leading cause of death worldwide and is associated with substantial economic and quality-of-life burdens.[1–3] Despite advances in the management of vascular risk factors, the rates of CVD remain alarmingly high and are projected to further increase in the coming decades, highlighting the need for novel therapeutic and preventive strategies.[1] However, investment in cardiovascular drug development has stagnated, leading to a deceleration in the development of new therapeutics for CVD indications.[4] For example, between 2011 and 2023, only 28 molecular entities were approved for cardiovascular indications, which is in stark contrast to 573 new entities approved between 2000 and 2022 for cancer.[5,6] This is partly attributed to prior cardiovascular drug failures, safety concerns, commercial viability, the high cost of cardiovascular outcome trials, and the uncertainties surrounding regulatory approval of new therapies or indications.[4] Accelerating the discovery and development of novel CVD therapeutics is essential for decreasing CVD burden in the community.

Analyses of human genetic data provide valuable insights into target discovery and drug development.[7,8] Advances such as the sequencing of the human genome and the development of high-throughput genotyping and analytic technologies have facilitated the discovery of

Correspondence to: Marios K. Georgakis, MD, PhD, Institute for Stroke and Dementia Research, University Hospital LMU, Ludwig-Maximilians-University (LMU), Feodor-Lynen-Str. 17, 81377 Munich, Germany. Email marios.georgakis@med.uni-muenchen.de

For Sources of Funding and Disclosures, see page 460.

Circulation: Genomic and Precision Medicine is available at www.ahajournals.org/journal/circgen

Nonstandard abbreviations and acronyms

ANGPTL3	angiopoietin-like 3
CAD	coronary artery disease
CIRT	Cardiovascular Inflammation Reduction Trial
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
CXCL10	C-X-C motif chemokine ligand 10
Fg	fibrinogen
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6
IL6R MR	Interleukin-6 Receptor Mendelian Randomization Analysis
IL6R	interleukin-6 receptor
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
Lp-PLA2	lipoprotein-associated phospholipase A2
mIL-6R	membrane bound interleukin-6 receptor
MR	Mendelian randomization
NLRP3	NOD-, LRR- and pyrin domain-containing protein
OR	odds ratio
PCSK9	proprotein convertase subtilisin/kexin type 9
SAA	serum amyloid A
sIL-6R	soluble interleukin-6 receptor

hundreds of genomic loci associated with CVD.[9] Analyzing genetic variation, especially in genes encoding drug targets, enables in silico predictions of the effects of interfering with these molecules, offering insights analogous to pharmacological interventions. These analyses have been empowered by the increasing availability of large-scale resources including population-based biobanks, genetic, and phenotypic data repositories, and initiatives aimed at deeply sequencing the human genome across diverse populations. Retrospective analyses of drug development programs have shown that drugs targeting molecules with genetic support are 2.6× as likely to gain regulatory approval.[10] In fact, genetic evidence has directly informed the development of CVD therapeutics, contributing to successful development programs targeting PCSK9 (proprotein convertase subtilisin/kexin type 9),[8] Lp(a) (lipoprotein [a]),[11–13] apo C_3,[14] ANGPTL3 (angiopoietin-like 3),[14] factor XI,[15] and IL (interleukin)-6 signaling.[16–18]

Here, we summarize how genetic studies may support cardiovascular drug development using IL-6 signaling as a case study. We discuss opportunities to leverage human genetics for target selection, indication prioritization, repurposing strategies, optimization of clinical trial design, and safety assessment.

IL-6 SIGNALING IN CVD

Atherosclerosis is the main underlying cause of CVD and is largely driven by inflammation. Decades of preclinical, epidemiological, and clinical investigations have identified key molecular pathways driving atheroinflammation,[19–27] with IL-6 signaling emerging as a critical target for atheroprotective immunotherapies.[28] IL-6 is a central regulator of the acute-phase response, driving the production of CRP (C-reactive protein), Fg (fibrinogen), and SAA (serum amyloid A).[29] Within atherosclerotic lesions, IL-6 is primarily produced by macrophages and foam cells in response to IL-1 and exacerbates local inflammation, likely contributing to plaque destabilization and rupture.[30–33] Epidemiological studies have shown consistent associations between circulating levels of hs-CRP (high-sensitivity CRP), a key downstream biomarker of IL-6 pathway activity, and cardiovascular risk.[34,35] Prospective cohort studies have similarly provided evidence that higher levels of IL-6 are associated with a higher risk of major adverse cardiovascular events.[36] Preclinical studies in mouse models of atherosclerosis have shown that genetic or pharmacological inhibition of IL-6 signaling is associated with a lower burden of atherosclerosis.[37]

Notably, findings from cardiovascular outcome trials targeting upstream regulators of IL-6 signaling with colchicine and canakinumab in patients with atherosclerosis have shown significant reductions in major adverse cardiovascular events.[24–26] Subgroup analyses of the Phase 3 CANTOS trial for canakinumab, an anti–IL-1β monoclonal antibody, showed that the reduction in major adverse cardiovascular events was greatest in participants who achieved robust inhibition of the IL-6 pathway,[27,38] reinforcing IL-6 signaling as a central mediator of residual inflammatory risk. The subgroup of participants who achieved IL-6 levels in the lowest tertile on canakinumab had a hazard ratio of 0.65 (95% CI, 0.53–0.81) for major adverse cardiovascular events and a hazard ratio of 0.41 (95% CI, 0.27–0.64) for cardiovascular mortality after adjusting for covariates including baseline level of IL-6. On the contrary, treatment with low-dose methotrexate did not lower vascular risk or hs-CRP levels in the CIRT (Cardiovascular Inflammation Reduction Trial),[39] thus emphasizing the importance of specifically targeting atherosclerosis-specific inflammatory pathways. Although 2 trials showed efficacy for colchicine in lowering major adverse cardiovascular events risk among patients with coronary artery disease (CAD; LoDoCo2 and COLCOT), the largest and most recent trial of patients with acute myocardial infarction (CLEAR SYNERGY [OASIS-9])[40] failed to show any benefit. Colchicine is a long-used drug that inhibits microtubule formation and is believed

to exert its main anti-inflammatory action by inhibiting NLRP3 (NOD-, LRR- and pyrin domain-containing protein) inflammasome, leading to downstream downregulation of IL-1β and IL-6 signaling activity.[41–43] The reason for the lack of benefit in CLEAR SYNERGY remains unclear and may be attributable to inadequate control of inflammation, given the on-treatment least-squares mean hs-CRP levels of 3.0 mg/L (95% CI, 2.6–3.5), in contrast to median hs-CRP levels of 0.94 mg/L and 1.12 mg/L in the positive trials LoDoCo2 and COLCOT, respectively.[44] Effective anti-inflammatory therapies need to carefully balance between efficacy and safety, particularly in mitigating risks associated with immunomodulation. Neither CANTOS[24] nor the colchicine trials reduced mortality,[25,26] and both canakinumab[24] and colchicine[26] were associated with adverse effects including fatal infections. IL6R (IL-6 receptor) inhibitors, such as tocilizumab or sarilumab, in patients with autoimmune disorders have been associated with neutropenia, as well as common bacterial infections, such as skin infections, urinary tract infections, and pneumonia.[24,45,46]

These data have supported the advancement of clinical trials examining the effect of direct inhibitors of the IL-6 signaling pathway for the treatment and prevention of CVD. In the RESCUE phase 2 trial in patients with chronic kidney disease (CKD), ziltivekimab, a monoclonal antibody targeting IL-6, showed dose-dependent reductions in hs-CRP levels of 77%, 88%, and 92% with monthly subcutaneous doses of 7.5, 15, and 30 mg, respectively; 67%, 82%, and 96% of patients achieved hs-CRP levels below 2 mg/L.[47] Similarly, in the POSIBIL$_6$ESKD phase 2b trial in patients on hemodialysis, clazakizumab, another anti–IL-6 monoclonal antibody, displayed reductions in hs-CRP of 86%, 90%, and 92% at monthly intravenous doses of 2.5, 5, and 10 mg, respectively; 79%, 82%, and 79% of patients achieved hs-CRP below 2 mg/L.[48] Both trials showed reductions in additional pharmacodynamic biomarkers downstream of IL-6, including Fg, SAA, and Lp(a), as well as safety profiles allowing for progression to phase 3 cardiovascular outcome studies. Notably, there was no signal regarding adverse changes in lipids or severe sustained thrombocytopenia or neutropenia in either phase 2 study. Currently, several clinical trials assessing anti–IL-6 monoclonal antibodies are underway including one phase 2 trial for pacibekitug (TRANQUILITY [URL: https://www.clinicaltrials.gov; Unique identifier: NCT06362759]), as well as 4 phase 3 trials for ziltivekimab (ZEUS [URL: https://www.clinicaltrials.gov; Unique identifier: NCT05021835], ATHENA [URL: https://www.clinicaltrials.gov; Unique identifier: NCT06200207], HERMES [URL: https://www.clinicaltrials.gov; Unique identifier: NCT05636176], ARTERMIS [URL: https://www.clinicaltrials.gov; Unique identifier: NCT06118281]) and a phase 3 study for clazakizumab (POSIBIL$_6$ESKD [URL: https://www.clinicaltrials.gov; Unique identifier: NCT05485961]).

IDENTIFYING THE CAUSAL DENOMINATOR OF ATHEROINFLAMMATION WITH HUMAN GENETICS

Human genetics has played a pivotal role in pinpointing IL-6 signaling as a causal mediator of atheroinflammation in CVD, triggering drug development in this direction. In the 1990s and 2000s, data from several observational prospective cohort studies showed robust associations between circulating inflammatory biomarker levels such as CRP, Fg, and Lp-PLA2 (lipoprotein-associated phospholipase A_2), and risk of incident CVD.[49–52] These molecules were potential causal mediators of atheroinflammation and could represent potential candidate targets of anti-inflammatory therapies.[53] However, early human genetic studies that applied a method called Mendelian randomization (MR) contradicted this idea (Figure 1). Briefly, MR leverages randomly assorted germline genetic variants associated with specific exposures as proxies to examine potential causal relationships with outcomes.[54] In addition to providing valuable insights into the cause of cardiometabolic diseases, MR studies have also identified promising drug targets.[55] Variants in genes encoding target proteins can serve as proxies for studying drug perturbation.[56]

Two independent studies detected genetic variants in the gene encoding CRP that led to increases in circulating CRP levels. If CRP had a causal role in the pathogenesis of CVD, one would expect these variants to also increase the risk of CAD, in concordance with observational studies linking CRP levels to CAD risk. However, in both studies, there was no evidence of an effect on risk of CAD.[57,58] Similarly, MR studies failed to provide evidence for a causal involvement of Fg and Lp-PLA2 in CVD, despite evidence for strong dose-dependent associations in observational studies. Specifically, neither a genetic variant in the beta-fibrinogen gene promoter that increases Fg levels[59] nor variants within *PLA2G7* linked to higher activity of Lp-PLA2 were associated with CAD risk.[51,60]

In search of the causal inflammatory mediator of atherosclerosis, 2 landmark studies published in 2012 focused on variants in the gene encoding the *IL6R*. These studies reported significant associations of a common variant, rs2228145 (Asp358Ala), estimated to be present in ≈40% of individuals of European descent, with risk of CAD.[61,62] The rs2228145 SNP leads to a change from adenine to cytosine in exon 9 of *IL6R* that encodes for the IL-6R protein. This change leads to an amino acid change from aspartic acid to alanine at position 358 of the IL-6R protein. The study conducted by the IL6R Genetics Consortium and Emerging Risk Factors Collaboration showed that Asp358Ala was associated with a lower risk of CAD (3.4%) per allele.[61] The variant was also associated with decreasing concentrations of CRP (7.5%) and Fg (1%) with every copy of 358Ala and

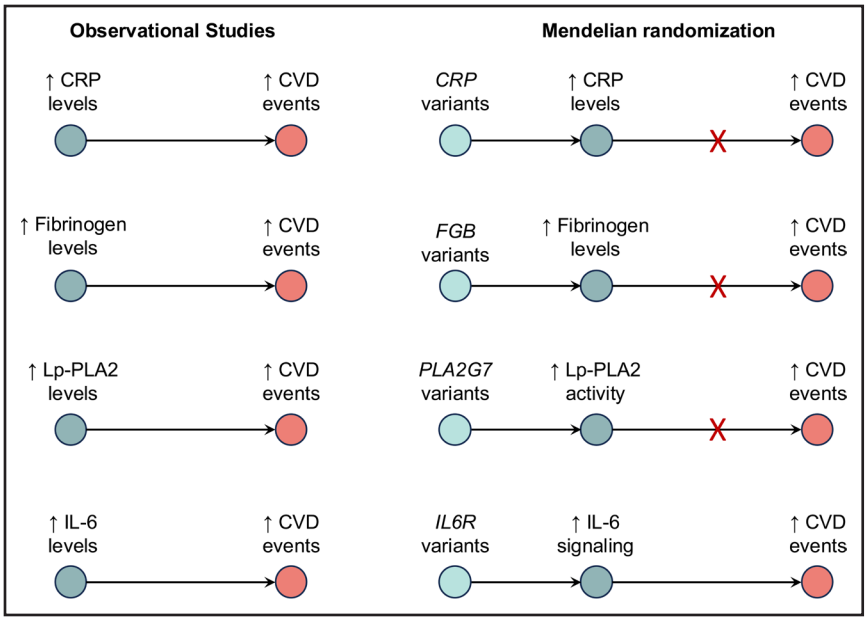

Figure 1. Detecting the causal denominator of atheroinflammation. Comparisons of the results of (1) prospective population-based studies supporting dose-dependent associations of circulating levels of CRP (C-reactive protein), Fg (fibrinogen), Lp-PLA2 (lipoprotein-associated phospholipase A_2), and IL (interleukin)-6 with incident cardiovascular disease (CVD) events (**left**) and (2) those of Mendelian randomization studies studying genetic instruments consisting of variants within the genes coding for key proteins of the respective pathways in association with lifetime risk of CVD events (**right**).

increasing concentrations of IL-6 (14.6%) and sIL-6R (soluble IL-6R; 34.3%).[61] Similarly, the IL6R MR Consortium (Interleukin-6 Receptor Mendelian Randomization Analysis) identified an association between rs7529229, a variant in strong linkage disequilibrium with rs2228145, and a lower risk for CAD-related events (OD, 0.95 per allele [95% CI, 0.93–0.97]).[62] This variant was also associated with decreased CRP levels (8.4% decrease per allele [95% CI, 7.3–9.4]), as well as increased circulating IL-6 levels (9.4% increase per allele [95% CI, 8.3–10.6]) and sIL-6R (14.9% increase per allele [95% CI, 13.1–16.7]).[62] Future studies also showed significant associations of this variant with peripheral artery (odds ratio [OR], 0.95 [95% CI, 0.94–0.97])[63] and abdominal aortic aneurysm (OR, 0.91 [95% CI, 0.90–0.92]).[64]

In an effort to understand the mechanism by which rs2228145 regulates IL-6 signaling, Ferreira et al[65] discovered 358Ala to be associated with increased sIL-6R concentrations (35% increase per copy) and reduced surface expression of IL-6R on both cluster of differentiation 4+T cells and monocytes (≤28% reduction per allele, $P=5.6\times10^{-22}$) likely contributing to reduced clearance of IL-6 by mIL-6R (membrane-bound IL-6R) within the liver. This is hypothesized to explain the apparent paradox of higher circulating levels of IL-6 and lower downstream signaling (ie, lower hs-CRP) as well as lower CAD risk with this genetic variant.[65] The Asp358Ala substitution leads to an increase in the shedding of mIL-6R, producing higher levels of sIL-6R in the blood. This is the result of enhanced proteolytic ectodomain shedding of mIL-6R by the disintegrin and metalloproteinases ADAM10 and ADAM17, leading to a large increase in sIL-6R levels.[66] Indeed, rs2228145 is the main determinant of circulating sIL-6R levels.[65] The higher cleavage of IL-6R to sIL-6R leads to decreases in mIL-6R in hepatocytes, immune cells, and possibly epithelial cells, thus leading to a decrease in the activity of classic IL-6 signaling. While not experimentally validated, according to Rose-John et al[67] the increase in sIL-6R levels could also influence IL-6 trans-signaling. In the circulation, IL-6 binds to sIL-6R, the levels of which can vary less (change up to 10-fold as a response to inflammation) when compared with variations in levels of IL-6, which can increase as much as 1000-fold. The complex of IL-6 and sIL-6R in the circulation binds with very high affinity to sgp130, the levels of which remain rather unaltered during inflammation. The complex can be seen as a buffer for IL-6 activity, as it does not allow bound IL-6 to exert its proinflammatory actions. As such, the levels of sIL-6R may be a key determinant of the buffer capacity of the system and its ability to cushion overstimulation to IL-6 (Figure 2).[66]

GENETICS INFORMING CLINICAL DEVELOPMENT

Selection of Indications

Genetics can inform several aspects of clinical development, particularly as it relates to selection of potential therapeutic indications. The emergence of genome-wide association studies and cohort consortia decoding the genetic architecture of human traits in very large sample sizes offered new opportunities for MR explorations. Using large genomic data sets for circulating CRP levels, it became possible to discover more genetic variants in the *IL6R* locus associated with downregulated IL-6 signaling (Figure 3).

Statistical development in MR methodologies offered the framework for pooling these variants, thus increasing statistical power. With these expanded instruments, it became possible to explore the impact on multiple different outcomes, thus directly expanding the list of potential

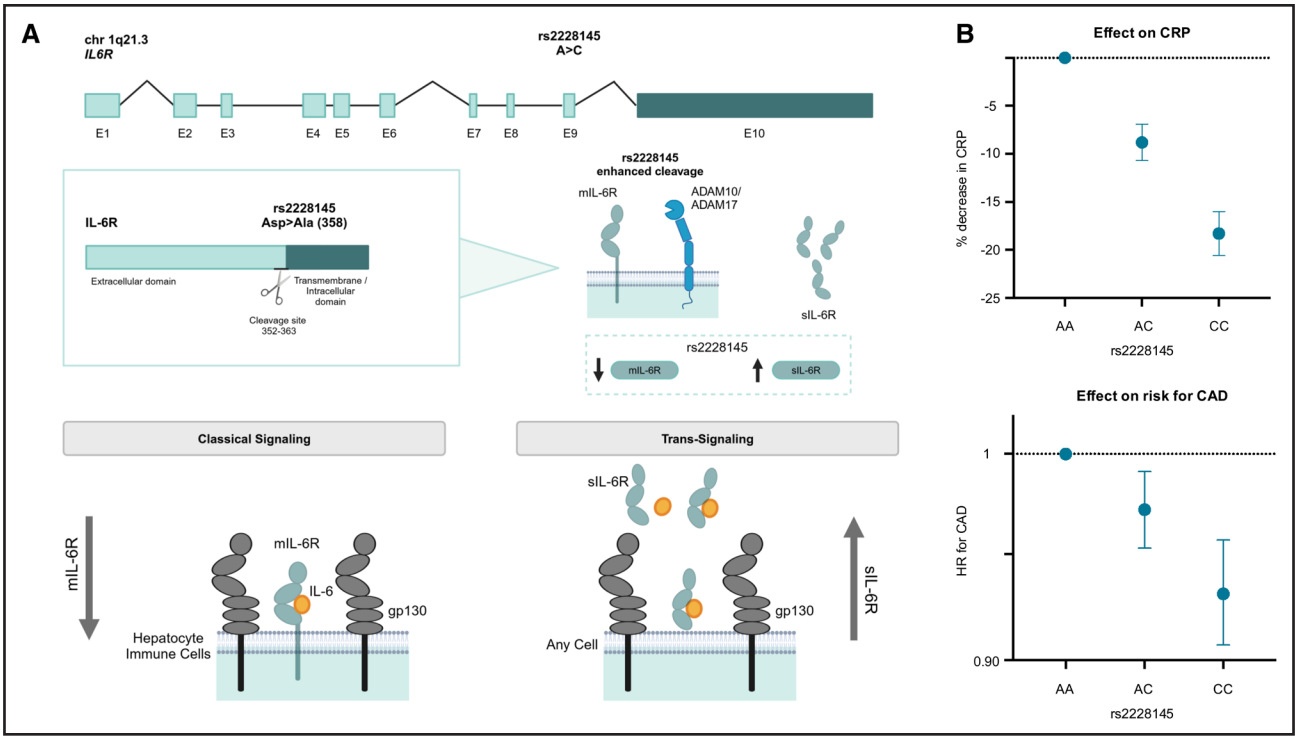

Figure 2. The use of the *IL6R* (interleukin-6 receptor) variant rs2228145 as a genetic proxy of IL (interleukin)-6 signaling downregulation.

A, rs2228145 leads to change from adenine (A) to cytosine (C) in exon 9 of *IL6R* that encodes for the mIL-6R (membrane-bound IL-6R) protein, resulting in an amino acid change from aspartic acid (Asp) to alanine (Ala) at position 358. This variant results in enhanced cleavage of mIL-6R to sIL-6R (soluble IL-6R) by ADAMs, leading to decreased mIL-6R in hepatocytes and immune cells and increased circulating sIL-6R, thus leading to downregulation of the IL-6 signaling cascade. **B**, Associations of rs2228145 genotypes with percentage decrease in CRP (C-reactive protein) and risk for coronary artery disease (CAD). **A** was created in Biorender.com. ADAM indicates A Disintegrin And Metalloproteinase; E, Exon; gp130, glycoprotein 130; and HR, hazard ratio.

indications that could be explored in cardiovascular trials (Figure 4).

For example, a set of 7 conditionally independent variants in the *IL6R* locus (within ±300 kB of *IL6R*) that are significantly ($P<5\times10^{-8}$) associated with decreases in CRP levels, are also associated with higher circulating IL-6 and sIL-6R levels, and lower Fg levels—these effects are consistent with the mechanism of tocilizumab, an IL-6R inhibitor approved for autoimmune disease indications.[18] MR analyses revealed that these *IL6R* proxies of IL-6 signaling downregulation were associated with lower risk of ischemic stroke (OR per 1 SD decrease in CRP levels, 0.89 [95% CI, 0.82–0.97]), CAD (OR, 0.84 [95% CI, 0.77–0.90]), myocardial infarction (OR, 0.88 [95% CI, 0.81–0.96]), aortic aneurysm (OR, 0.51 [95% CI, 0.37–0.68]), and carotid plaque (OR, 0.87 [95% CI, 0.77–0.99]).[18] Employing a different approach, another study selected genetic variants based on their effects on sIL6R levels and came to similar conclusions.[79] Particularly, in the field of ischemic stroke, which is etiologically highly heterogeneous, genetic data have helped prioritize large artery atherosclerotic and cryptogenic stroke as potential targets for IL-6 targeting therapies.[18,72] A thorough analysis of phenotypes related to cerebral small vessel disease suggests no effect of genetically downregulated IL-6 signaling on clinical, imaging, or histopathology traits related to the underlying pathology of arteriolosclerosis.[80] The 7-variant genetic instrument was used to successfully predict the pharmacological effects of tocilizumab in patients with polymyalgia rheumatica,[81,82] as well as in the setting of COVID-19 sepsis.[83–85] A more recent larger genome-wide association study for CRP[86] increased the list of independent proxies of IL-6 signaling within the *IL6R* locus to 26,[68,87] thus further increasing power for detecting promising effects. Although the majority of these studies have included primarily populations of European ancestry, genetic proxies of IL-6R downregulation have been identified in a Japanese population (rs1386821, rs12133641, and rs1588075) and have also been associated with lower risk for CAD (OR, 0.38 per 1 SD decrease in CRP [95% CI, 0.32–0.46]).[88] Figure 4 summarizes the effects of IL-6 signaling downregulation through the use of *IL6R* genetic proxies on cardiovascular outcomes scaled to the natural variation in CRP observed across carriers of the rs2228145 variants (18% decrease in CRP) or a composite score of the 26 variants (30% decrease in CRP), as determined in the population-based UK Biobank study. Thus, genetic studies can largely inform the landscape of clinical indications to be targeted by pharmacological interventions against IL-6 signaling.

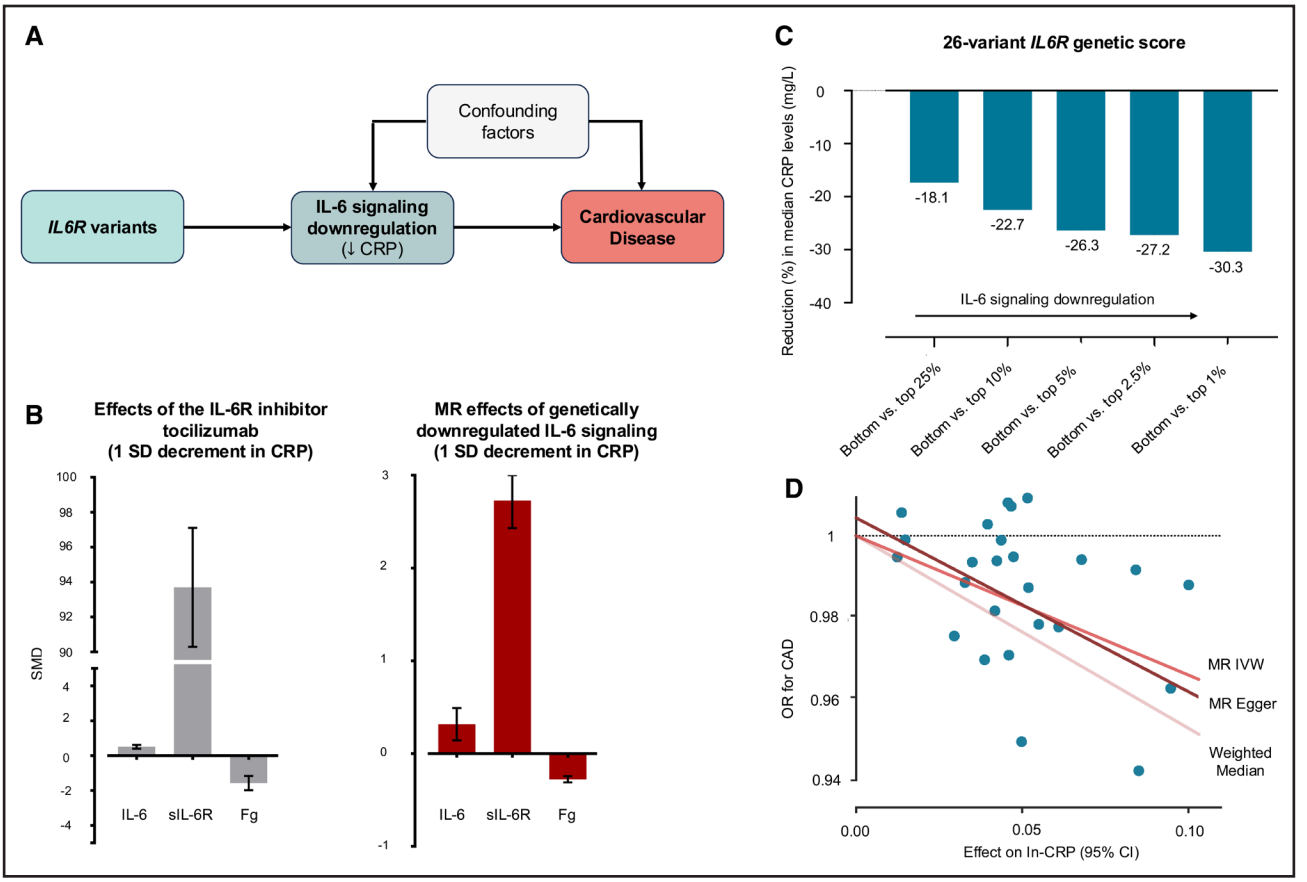

Figure 3. Use of multivariant genetic instruments proxying IL (interleukin)-6 signaling inhibition to predict effects on cardiovascular outcomes.

A, Framework for Mendelian randomization (MR) analyses using CRP (C-reactive protein) levels as a readout of IL-6 signaling activity to detect variants proxying IL-6 signaling downregulation. **B**, Comparable effects observed between pharmacological inhibition of IL-6R (IL-6 receptor) with tocilizumab vs a multivariant genetic instrument of IL-6 signaling downregulation on circulating IL-6, sIL-6R (soluble IL-6R), and Fg (fibrinogen) levels (adapted from Georgakis et al.[18] This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.). **C**, Percentual and absolute reduction in CRP levels across the distribution of an *IL6R* genetic score of the 26-variant instrument in the population-based UK Biobank study. **D**, Genetic downregulation of CRP is associated with lower odds of coronary artery disease (CAD) across different MR methods (reanalyzed from Georgakis et al[68]). IVW indicates inverse-variance weighted; Ln, natural log-transformed; OR, odds ratio; and SDM, standardized mean difference.

REPURPOSING POTENTIAL AND SAFETY

The increasing availability of large-scale biobanks that house genetic and phenotypic data has facilitated systematic cross-phenotype associations, otherwise referred to as phenome-wide association studies.[89] These phenotypes (collectively termed a phenome) have been characterized using data from electronic health records and provide a representative clinical landscape of an individual's health conditions (Figure 5A).[89] Phenome-wide association studies have revealed significant associations between genetically downregulated IL-6 signaling and lower risk for rheumatoid arthritis (OR, per 0.1 SD lower CRP, 0.93 [95% CI, 0.90–0.96]) and type 2 diabetes (OR per 1 SD lower CRP, 0.44 [95% CI, 0.73–0.88]).[17,83] *IL6R* variants have also been associated with lower risk for SARS-CoV-2 infection (OR, 0.92 [95% CI, 0.89–0.95]; OR versus negatively tested individuals, 0.92 [95% CI, 0.89–0.97]) and lower risk of COVID-19 hospitalization (OR versus nonhospitalized COVID-19, 0.88 [95% CI, 0.78–0.99]; OR versus population, 0.91 [95% CI, 0.87–0.96]).[83] Although the findings cannot be directly translated to a setting of very severe COVID-19 infection, tocilizumab was also found to improve outcomes, including survival, in critically ill patients with COVID-19 receiving organ support in intensive care units.[93] Beyond cardiovascular end points, the rs2228145 *IL6R* variant has been associated with several other phenotypes including skin, musculoskeletal, pulmonary, renal, and eye conditions; some of which were replicated in larger cohorts.[16] Although these data can generate repurposing ideas for alternative indications, they also highlight potential safety concerns of downregulation of IL-6 signaling. Genetic downregulation of IL-6 signaling has been associated with neutropenia and increased risk for infections including those

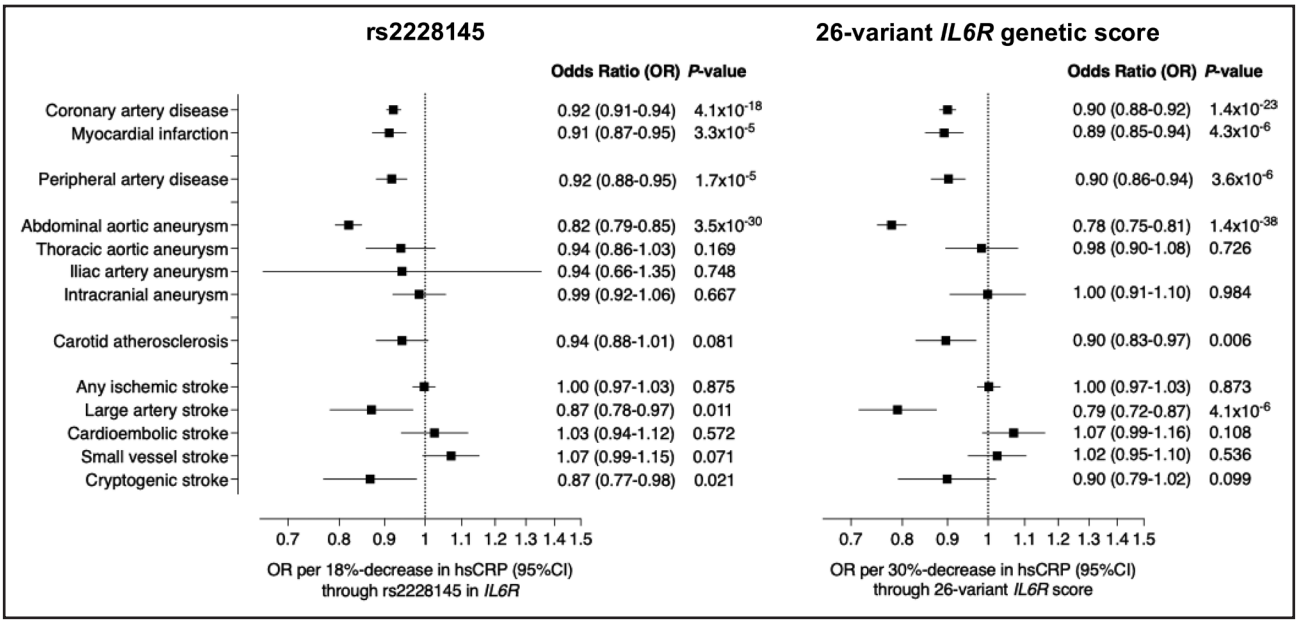

Figure 4. Cardiovascular indications associated with genetically proxied IL (interleukin)-6 signaling downregulation. *IL6R* genetic proxies of cardiovascular risk per 18% decrease in hs-CRP (high-sensitivity C-reactive protein) as determined by rs2228145 (**left**) and per 30% decrease in hs-CRP as determined by a 26-variant *IL6R* genetic instrument (**right**), which is the natural variation observed across these genetic instruments in the population-based UK Biobank study. The odds ratios (ORs) have been calculated with inverse-variance weighted Mendelian randomization analyses using summary statistics from genome-wide association studies case-control studies for these outcomes.[69–78]

of the skin and urinary tract.[17] This aligns with clinical trial data in patients with autoimmune disorders demonstrating that IL-6 inhibition may predispose patients to infectious complications (when compared with placebo).[24] These findings highlight the need for careful patient selection, infection monitoring, and risk-benefit assessment in the clinical deployment of IL-6-targeting therapies for CVD.

TRIAL DESIGN

Beyond identification of indications and assessment of potential side effects, genetic studies may also support the design of phase 2 and 3 trials, thus accelerating clinical development pipelines. Findings from recent analyses of the UK Biobank have provided potential insight into patient populations that may best benefit from IL-6 signaling inhibitors (Figure 5B). For example, the associations between genetically proxied IL-6 signaling and the risk of CVD was a linear function of absolute and not percentual (logarithmically transformed) changes in hs-CRP levels (hazard ratio 0.90 per 1 mg/dL decrement in absolute hs-CRP [95% CI 0.85–0.94]),[68] thus suggesting that larger absolute changes in hs-CRP might lead to larger decreases in CVD risk. This implies that patients with the highest baseline hs-CRP levels, with the opportunity for greater absolute hs-CRP reductions, might benefit the most from IL-6 signaling inhibition for CVD prevention and could be prioritized for selection in clinical trials.[68] In addition, given the increased risk for CAD in patients with CKD, Yu et al[90] also investigated genetic variants mimicking IL-6 signaling inhibition and their effect on cardiovascular events in individuals with and without CKD. Interestingly, there was a significant interaction between the *IL6R* rs2228145 variant and CKD, with rs2228145 being more strongly associated with incidence for CAD among individuals with CKD.[90] In line with this genetic finding, the phase 3 ZEUS trial testing ziltivekimab is enrolling patients with moderate-to-severe CKD and hs-CRP levels ≥2 mg/L. A similar interaction has been observed with clonal hematopoiesis of indeterminate potential, an age-related, proinflammatory, and proatherogenic state characterized by clonal expansion of hematopoietic stem cells due to somatic leukemogenic mutations. The *IL6R* rs2228145 variant was found to be more strongly associated with CVD risk in patients with large clonal hematopoiesis of indeterminate potential clones (hazard ratio, 0.46 [95% CI, 0.29–0.73]; $P<0.001$).[91] Whether cardiovascular outcomes trials testing IL-6 signaling inhibition should be enriched with patients with clonal hematopoiesis of indeterminate potential remains to be determined, but a post hoc analysis of the CANTOS trial also showed a larger cardioprotective effect of canakinumab among patients with evidence of clonal hematopoiesis of indeterminate potential.[94]

An interesting subtype of MR analyses, factorial MR, assesses potential interactions between genetic proxies for different under investigation targets, thus potentially providing evidence for the additive effects of targeting different mechanisms.[95] This can be of special interest in

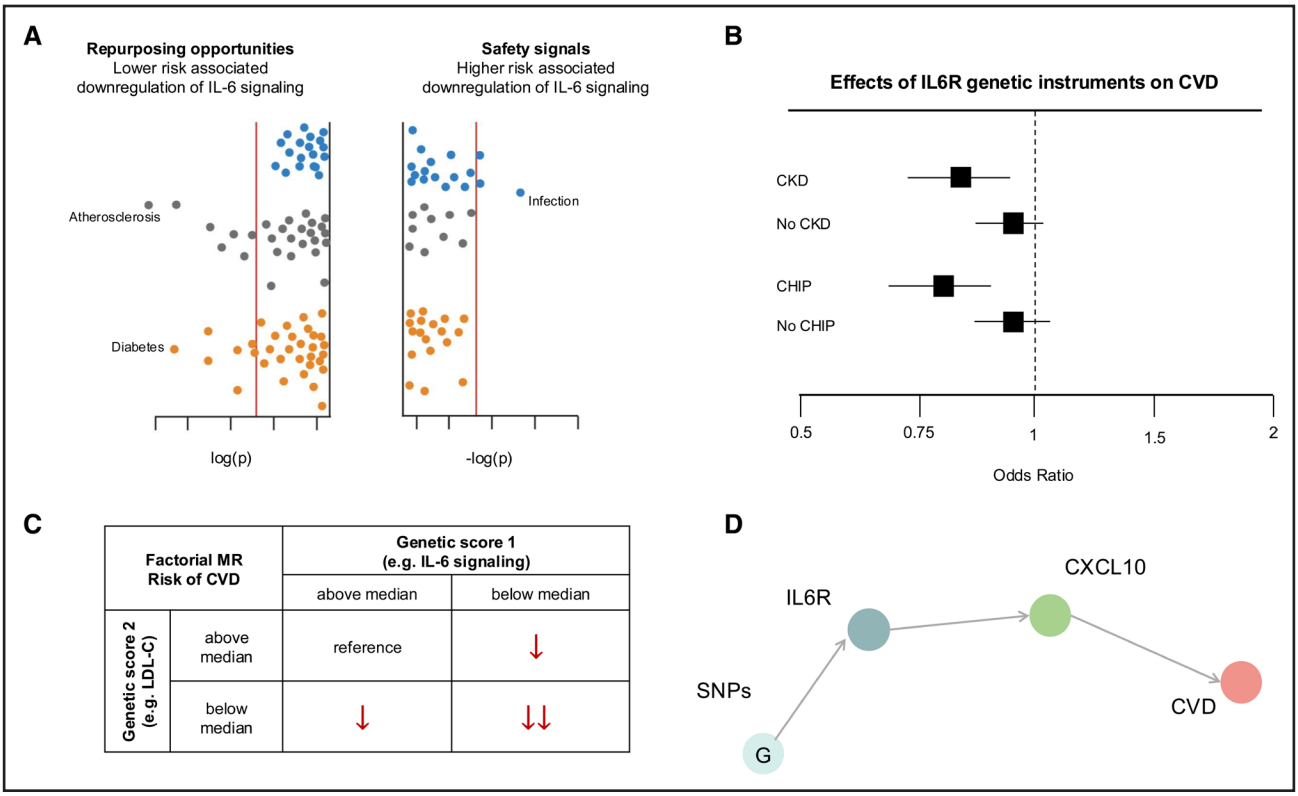

Figure 5. Conceptual schematic highlighting opportunities for human genetics to inform drug development pipelines.
A, Identification of safety implications and potential repurposing opportunities with phenome-wide association studies.[17] **B**, Population selection for maximizing efficacy in clinical trials.[90,91] **C**, Assessment of joint effects through factorial Mendelian randomization (MR) designs.[87] **D**, Identification of alternative drug targets by multiomic data integration.[92] CHIP indicates clonal hematopoiesis of indeterminate potential; CKD, chronic kidney disease; CVD, cardiovascular disease; CXCL10, C-X-C motif chemokine ligand 10; IL-6, interleukin-6; IL6R, interleukin-6 receptor; LDL-C, low-density lipoprotein cholesterol; and SNP, single nucleotide polymorphism.

chronic diseases, like atherosclerotic CVD, where different treatment options are already available. For example, Ference et al[96] previously showed that genetically lowered low-density lipoprotein cholesterol (LDL-C) mediated by variants within *NPC1L1* (coding for the target of ezetimibe) and *HMGCR* (coding for the target of statins) displayed 5.8 mg/dL lower LDL-C and 10.8% additively lower log-linear CAD risk (OR, 0.892 [95% CI, 0.854–0.932]), thus providing support that inhibiting both targets simultaneously could provide additional benefit beyond individual inhibition of each target. In the inflammation space, previous analysis supports that genetically downregulated IL-6 signaling through *IL6R* and genetically lowered LDL-C through genome-wide variation are also associated with additive lower lifetime risk of CVD (for individuals with IL-6 and LDL-C genetic scores below the median OR, 0.92 [95% CI, 0.90–0.95]), suggesting that IL-6 signaling inhibition has the potential to provide reductions in CVD risk beyond LDL-C lowering[87] (Figure 5C).

ADDITIONAL TARGET IDENTIFICATION

By focusing on the *IL6R* locus, most genetic studies have provided evidence for the CVD-lowering potential of inhibiting IL-6 signaling activity by targeting IL-6R. This is mainly related to the availability of genetic variants of higher frequency in this locus, especially in European populations, which offers more opportunities for leveraging to explore downstream effects. It does not, however, prove higher efficacy of any potential pharmacological intervention, when compared with other targets in the same pathway. Some preliminary efforts have focused on the gene encoding IL-6 itself, as well as further upstream on the NLRP3 inflammasome. Using *IL-6* variants associated with *IL-6* expression and lower CRP levels, 1 MR study showed that a genetically proxied 1 mg/L decrease in CRP levels by *IL-6* was associated with lower risk for CAD (OR, 0.86 [95% CI, 0.77–0.96]), an effect comparable to the same genetically proxied CRP reduction caused by variants in *IL6R* (OR, 0.90 [95% CI, 0.86–0.95]).[97] It should be noted although that the selected variants did not meet genome-wide thresholds of significance, thus raising concerns about instrument strength.[97] The NLRP3 inflammasome is an upstream regulator of IL-6 signaling with the selective oral inhibitor dapansutrile, having shown an acceptable safety and tolerability profile in a phase 1b trial of patients with stable systolic heart failure.[98] Carriers of a common intronic variant in the gene coding for NLRP3 (rs10754555) that influences *NLRP3* gene expression and NLRP3

activity in peripheral blood mononuclear cells had higher CRP and SAA levels, as well as higher risk for CAD and cardiovascular mortality.[99] Focusing on potential targets downstream to IL-6 signaling, a recent study integrating genomic and proteomic data applied MR to explore proteomic mediators of genetic proxies of IL-6 signaling on risk for different cardiovascular outcomes.[92] Genetically downregulated IL-6 signaling was associated with lower circulating levels of CXCL10 (C-X-C motif chemokine ligand 10) and, in turn, genetically proxied circulating levels of CXCL10 were associated with risk for CAD, peripheral artery disease, and large artery atherosclerotic stroke.[92] In a mediation framework, 67% of the effects of genetically downregulated IL-6 signaling were mediated by declines in CXCL10 levels, thereby highlighting CXCL10 as a protective protein that may serve as a promising drug target for atherosclerosis downstream to the IL-6/IL-6R complex.[92] However, additional studies will be necessary to further elucidate its potential clinical utility (Figure 5D).

METHODOLOGICAL ASPECTS AND FUTURE OPPORTUNITIES

In cardiovascular medicine, the efficacy of medications is ultimately tested in large-scale Phase 3 cardiovascular outcomes trials. Although biomarkers like CRP are commonly used as primary end points in Phase 2 studies of anti-inflammatory treatments, only LDL-C, glycated hemoglobin, and blood pressure measurements are recognized by the Food and Drug Administration as approved surrogates of efficacy for cardiovascular risk reduction. As a result, most drugs move to costly phase 3 studies, typically recruiting >5000 patients followed for over 3 years, often without robust evidence of efficacy. In this context, human genetic studies offer a cost-effective approach to assess the potential efficacy and safety of new therapeutics, aiding in the prioritization of candidates for investment in large cardiovascular outcome trials. However, genetic studies have inherent limitations that must be carefully considered.[54]

First, MR studies depend on specific assumptions that are often violated. The genetic instruments used must influence outcomes solely through the exposure of interest (ie, perturbation in a specific drug target) and not via alternative pleiotropic pathways.[100] While drug-target MR studies typically use variants within the locus of the target gene (*cis*- versus *trans*-acting variants), high correlations due to linkage disequilibrium between neighboring variants and commonalities in function of neighboring genes can lead to violations of this assumption—specifically, the selected variants might act by either directly influencing the expression or function of neighboring genes or by being in strong linkage disequilibrium with other variants influencing the expression or function of neighboring genes.[101,102] Associations should, therefore, be validated using positive control outcomes or biomarkers influenced by the pharmacological intervention that the instruments are supposed to proxy.

Second, MR studies assess the lifelong impact of small genetic perturbations, which may differ substantially from the pronounced effects of short-term pharmacological interventions. For example, genetic variants influencing LDL-C show consistently larger effects on risk of CAD per unit reduction in LDL-C than LDL-C–lowering treatments.[103] Although LDL-C appears to have a cumulative and largely log-linear association with risk of CVD,[104] there is no clear evidence that IL-6 signaling follows the same pattern. This raises uncertainty about how genetic findings translate to short-term pharmacological interventions. Furthermore, we cannot exclude the possibility of nonlinear relationships between IL-6 signaling and cardiovascular risk, which could further complicate extrapolation from genetic data. Compensatory mechanisms induced by pharmacological IL-6 inhibition may also differ from those occurring in genetic variation, leading to discrepancies between MR-predicted effects and clinical trial outcomes. Prior case studies highlight the importance of translating genetic predictions within the appropriate clinical context. For instance, while genetic variants reducing lower factor XI activity are strongly associated with lower cardioembolic stroke risk,[72,105,106] asundexian, an oral factor XIa inhibitor, was inferior to the standard anticoagulant apixaban in preventing stroke in patients with atrial fibrillation.[107]

Third, the majority of available genetic data are derived from individuals of European ancestry, limiting the generalizability of findings to other populations. This lack of diversity can affect the transferability of genetic associations and reduce the applicability of MR-derived insights to global cardiovascular drug development. Efforts to address this limitation include leveraging biobanks with broader ancestral representation, such as the Million Veteran Program,[108] All of Us,[109] and Biobank Japan,[110] as well as integrating multiancestry genome-wide association studies to enable downstream MR analyses across ancestries. In addition, emerging statistical methodologies for trans-ethnic MR analyses may enable a more diverse representation in future studies.[111] Expanding representation in genetic research remains essential to ensure equitable translation of genetic discoveries into therapeutic applications.

Fourth, due to the low variance explained by genetic variants, MR studies require very large sample sizes to achieve sufficient statistical power. The level of genetic variation within loci varies across the genome, influenced by evolutionary pressures, functional constraints, and genomic context.[112] Consequently, studying certain genes is more feasible than others.

Fifth, the exact biological mechanisms underlying the effects of selected genetic variants are often poorly characterized. Without robust in vitro or in vivo experiments, conclusions rely heavily on associational data, which may lack mechanistic clarity.

Sixth, conventional MR analyses assume a linear relationship between gene perturbation and the outcome of interest, which might not be biologically plausible. Introducing variants with significantly different magnitudes of effects, such as rare loss-of-function or gain-of-function variants in the analyses may contribute to elucidating nonlinear effects. Emerging methods to assess nonlinear relationships could offer deeper insights. Finally, communication of genetic findings to the broader community involved in drug discovery and development remains a challenge.[113] Clear translation of genetic evidence into actionable insights will be critical for integrating these data into the drug discovery pipeline.

Finally, although genetic studies provide valuable insights into potential drug targets, they do not account for key

real-world factors such as cost-effectiveness, accessibility, and regulatory challenges. IL-6 inhibitors, like other biologics, face high production costs and complex pricing dynamics, which could limit their widespread adoption. These factors highlight the importance of integrating economic and policy considerations alongside genetic and clinical trial evidence to facilitate successful translation into clinical practice.

CONCLUSIONS AND FUTURE OPPORTUNITIES

The emergence of IL-6 signaling as a key therapeutic target in atherosclerotic CVD exemplifies the potentially transformative role of human genetic studies in informing different stages of cardiovascular drug development. Beyond prioritization of promising targets, human genetic studies can inform indication selection, exploration of repurposing opportunities, and population selection for clinical trials. Human genetics also enhances the selection of relevant safety end points and enables comparative analyses of emerging drugs on top of established therapies. In addition, although genetic data has largely informed the development of protein-targeted therapeutics, there is growing potential for these data to inform RNA-based therapeutics and other emerging modalities. The integration of additional high-throughput omics technologies—such as whole-genome sequencing, whole-exome sequencing, transcriptomics, metabolomics, and proteomics—with increasingly detailed cardiovascular phenotypes offers unprecedented opportunities to refine drug discovery and development. By leveraging these advances, human genetics can not only accelerate the identification of disease-modifying therapies but also support a more nuanced understanding of patient heterogeneity, fostering the development of precision medicine strategies in CVD.

ARTICLE INFORMATION

Affiliations

Tourmaline Bio, Inc, New York, NY (E.G., J.W.). Institute for Stroke and Dementia Research (ISD), Ludwig Maximilian University Hospital, Ludwig Maximilian University Munich, Germany (M.K.G.). Program in Medical and Population Genetics and Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, MA (M.K.G.). Munich Cluster for Systems Neurology (SyNergy), Germany (M.K.G.).

Acknowledgments

Writing support was provided by Talisa Silzer, PhD, of Sixsense Strategy Group Inc, a Herspiegel company, and was funded by Tourmaline Bio Inc.

Sources of Funding

Dr Georgakis is supported by the German Research Foundation (ID 512461526), the Fritz-Thyssen Foundation (Ref. 10.22.2.024MN), and the Hertie Foundation (ID P1230035).

Disclosures

Drs deGoma and Walsh are employees and shareholders of Tourmaline Bio Inc. Dr Georgakis reports consulting fees by Tourmaline Bio Inc, Pheiron GmbH, and Gerson Lehrman Group Inc.

REFERENCES

1. Joynt Maddox KE, Elkind MSV, Aparicio HJ, Commodore-Mensah Y, de Ferranti SD, Dowd WN, Hernandez AF, Khavjou O, Michos ED, Palaniappan L, et al; American Heart Association. Forecasting the burden of cardiovascular disease and stroke in the United States through 2050—prevalence of risk factors and disease: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e65–e88. doi: 10.1161/CIR.0000000000001256
2. Kazi DS, Elkind MSV, Deutsch A, Dowd WN, Heidenreich P, Khavjou O, Mark D, Mussolino ME, Ovbiagele B, Patel SS, et al; American Heart Association. Forecasting the economic burden of cardiovascular disease and stroke in the United States through 2050: a presidential advisory from the American Heart Association. *Circulation*. 2024;150:e89–e101. doi: 10.1161/CIR.0000000000001258
3. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403:2100–2132. doi: 10.1016/s0140-6736(24)00367-2
4. Fordyce CB, Roe MT, Ahmad T, Libby P, Borer JS, Hiatt WR, Bristow MR, Packer M, Wasserman SM, Braunstein N, et al. Cardiovascular drug development: is it dead or just hibernating? *J Am Coll Cardiol*. 2015;65:1567–1582. doi: 10.1016/j.jacc.2015.03.016
5. Jiang Y, Liu P, Qiu Z, Zhou M, Cheng M, Yang T. The U.S. FDA approved cardiovascular drugs from 2011 to 2023: a medicinal chemistry perspective. *Eur J Med Chem*. 2024;275:116593. doi: 10.1016/j.ejmech.2024.116593
6. Scott EC, Baines AC, Gong Y, Moore R, Pamuk GE, Saber H, Subedee A, Thompson MD, Xiao W, Pazdur R, et al. Trends in the approval of cancer therapies by the FDA in the twenty-first century. *Nat Rev Drug Discovery*. 2023;22:625–640. doi: 10.1038/s41573-023-00723-4
7. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, et al. The support of human genetic evidence for approved drug indications. *Nat Genet*. 2015;47:856–860. doi: 10.1038/ng.3314
8. King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. *PLoS Genet*. 2019;15:e1008489. doi: 10.1371/journal.pgen.1008489
9. Walsh R, Jurgens SJ, Erdmann J, Bezzina CR. Genome-wide association studies of cardiovascular disease. *Physiol Rev*. 2023;103:2039–2055. doi: 10.1152/physrev.00024.2022
10. Minikel EV, Painter JL, Dong CC, Nelson MR. Refining the impact of genetic evidence on clinical success. *Nature*. 2024;629:624–629. doi: 10.1038/s41586-024-07316-0
11. Kronenberg F. Lipoprotein(a): from causality to treatment. *Curr Atheroscler Rep*. 2024;26:75–82. doi: 10.1007/s11883-024-01187-6
12. Nandakumar R, Matveyenko A, Thomas T, Pavlyha M, Ngai C, Holleran S, Ramakrishnan R, Ginsberg HN, Karmally W, Marcovina SM, et al. Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects. *J Lipid Res*. 2018;59:2397–2402. doi: 10.1194/jlr.P082834
13. Nicholls SJ, Nissen SE, Fleming C, Urva S, Suico J, Berg PH, Linnebjerg H, Ruotolo G, Turner PK, Michael LF. Muvalaplin, an oral small molecule inhibitor of lipoprotein(a) formation: a randomized clinical trial. *JAMA*. 2023;330:1042–1053. doi: 10.1001/jama.2023.16503
14. Tomlinson B, Wu QY, Zhong YM, Li YH. Advances in dyslipidaemia treatments: focusing on ApoC3 and ANGPTL3 inhibitors. *J Lipid Atheroscler*. 2024;13:2–20. doi: 10.12997/jla.2024.13.1.2
15. Presume J, Ferreira J, Ribeiras R. Factor XI inhibitors: a new horizon in anticoagulation therapy. *Cardiol Ther*. 2024;13:1–16. doi: 10.1007/s40119-024-00352-x
16. Cai T, Zhang Y, Ho YL, Link N, Sun J, Huang J, Cai TA, Damrauer S, Ahuja Y, Honerlaw J, et al; VA Million Veteran Program. Association of interleukin 6 receptor variant with cardiovascular disease effects of interleukin 6 receptor blocking therapy: a phenome-wide association study. *JAMA Cardiol*. 2018;3:849–857. doi: 10.1001/jamacardio.2018.2287
17. Georgakis MK, Malik R, Li X, Gill D, Levin MG, Vy HMT, Judy R, Ritchie M, Verma SS, Nadkarni GN, et al; Regeneron Genetics Center. Genetically downregulated interleukin-6 signaling is associated with a favorable cardiometabolic profile. *Circulation*. 2021;143:1177–1180. doi: 10.1161/CIRCULATIONAHA.120.052604
18. Georgakis MK, Malik R, Gill D, Franceschini N, Sudlow CLM, Dichgans M; INVENT Consortium; CHARGE Inflammation Working Group. Interleukin-6 signaling effects on ischemic stroke and other cardiovascular outcomes: a Mendelian randomization study. *Circ Genom Precis Med*. 2020;13:e002872. doi: 10.1161/CIRCGEN.119.002872

19. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. *Nat Rev Drug Discov.* 2021;20:589–610. doi: 10.1038/s41573-021-00198-1
20. Engelen SE, Robinson AJB, Zurke YX, Monaco C. Therapeutic strategies targeting inflammation and immunity in atherosclerosis: how to proceed? *Nat Rev Cardiol.* 2022;19:522–542. doi: 10.1038/s41569-021-00668-4
21. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet.* 2010;375:132–140. doi: 10.1016/S0140-6736(09)61717-7
22. Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, Borglykke A, Di Angelantonio E, Gudnason V, Rumley A, Lowe GD, et al. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J.* 2014;35:578–589. doi: 10.1093/eurheartj/eht367
23. Papadopoulos A, Palaiopanos K, Bjorkbacka H, Peters A, de Lemos JA, Seshadri S, Dichgans M, Georgakis MK. Circulating interleukin-6 levels and incident ischemic stroke: a systematic review and meta-analysis of prospective studies. *Neurology.* 2022;98:e1002–e1012. doi: 10.1212/WNL.0000000000013274
24. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al; CANTOS Trial Group. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
25. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med.* 2020;383:1838–1847. doi: 10.1056/NEJMoa2021372
26. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med.* 2019;381:2497–2505. doi: 10.1056/NEJMoa1912388
27. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet.* 2018;391:319–328. doi: 10.1016/S0140-6736(17)32814-3
28. Zhang H, Dhalla NS. The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. *Int J Mol Sci.* 2024;25:1082. doi: 10.3390/ijms25021082
29. Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. *Nat Rev Drug Discov.* 2018;17:395–412. doi: 10.1038/nrd.2018.45
30. Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, Jones SR, Toth PP. Inflammation and cardiovascular disease: from mechanisms to therapeutics. *Am J Prev Cardiol.* 2020;4:100130. doi: 10.1016/j.ajpc.2020.100130
31. Didion SP. Cellular and oxidative mechanisms associated with interleukin-6 signaling in the vasculature. *Int J Mol Sci.* 2017;18:2563. doi: 10.3390/ijms18122563
32. Katkenov N, Mukhatayev Z, Kozhakhmetov S, Sailybayeva A, Bekbossynova M, Kushugulova A. Systematic review on the role of IL-6 and IL-1β in cardiovascular diseases. *J Cardiovasc Dev Dis.* 2024;11:206. doi: 10.3390/jcdd11070206
33. Ridker PM. Inhibiting interleukin-6 to reduce cardiovascular event rates. *J Am Coll Cardiol.* 2021;77:1856–1858. doi: 10.1016/j.jacc.2021.02.060
34. Ridker PM, Moorthy MV, Cook NR, Rifai N, Lee IM, Buring JE. Inflammation, cholesterol, lipoprotein(a), and 30-year cardiovascular outcomes in women. *N Engl J Med.* 2024;391:2087–2097. doi: 10.1056/NEJMoa2405182
35. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE; PROMINENT, REDUCE-IT, and STRENGTH Investigators. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet.* 2023;401:1293–1301. doi: 10.1016/S0140-6736(23)00215-5
36. Mehta NN, deGoma E, Shapiro MD. IL-6 and cardiovascular risk: a narrative review. *Curr Atheroscler Rep.* 2024;27:12. doi: 10.1007/s11883-024-01259-7
37. Akita K, Isoda K, Sato-Okabayashi Y, Kadoguchi T, Kitamura K, Ohtomo F, Shimada K, Daida H. An interleukin-6 receptor antibody suppresses atherosclerosis in atherogenic mice. *Front Cardiovasc Med.* 2017;4:84. doi: 10.3389/fcvm.2017.00084
38. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J.* 2018;39:3499–3507. doi: 10.1093/eurheartj/ehy310
39. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, et al; CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med.* 2019;380:752–762. doi: 10.1056/NEJMoa1809798
40. Jolly SS, d'Entremont MA, Lee SF, Mian R, Tyrwhitt J, Kedev S, Montalescot G, Cornel JH, Stankovic G, Moreno R, et al. Colchicine in acute myocardial infarction. *N Engl J Med.* 2024;392:633–642. doi: 10.1056/nejmoa2405922
41. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. *Clin Ther.* 2014;36:1465–1479. doi: 10.1016/j.clinthera.2014.07.017
42. Leung YY, Yao Hui LL, Kraus VB. Colchicine--update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum.* 2015;45:341–350. doi: 10.1016/j.semarthrit.2015.06.013
43. Opstal TSJ, Hoogeveen RM, Fiolet ATL, Silvis MJM, The SHK, Bax WA, de Kleijn DPV, Mosterd A, Stroes ESG, Cornel JH. Colchicine attenuates inflammation beyond the inflammasome in chronic coronary artery disease: a LoDoCo2 proteomic substudy. *Circulation.* 2020;142:1996–1998. doi: 10.1161/CIRCULATIONAHA.120.050560
44. Tardif JC, Kouz S. Efficacy and safety of colchicine and spironolactone after myocardial infarction: the CLEAR-SYNERGY trial in perspective. *Eur Heart J Acute Cardiovasc Care.* 2024;13:843–844. doi: 10.1093/ehjacc/zuae135
45. Broca F, Souchaud-Debouverie O, Liuu E, Roblot P, Martin M. Severe infections in patients treated with tocilizumab for systemic diseases other than rheumatoid arthritis: a retrospective multicenter observational study. *Eur J Rheumatol.* 2023;10:18–22. doi: 10.5152/eurjrheum.2022.22028
46. Fleischmann R, Genovese MC, Lin Y, St John G, van der Heijde D, Wang S, Gomez-Reino JJ, Maldonado-Cocco JA, Stanislav M, Kivitz AJ, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. *Rheumatology (Oxford).* 2020;59:292–302. doi: 10.1093/rheumatology/kez265
47. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, Lo L, Kling D, Pergola P, Raj D, et al; RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet.* 2021;397:2060–2069. doi: 10.1016/S0140-6736(21)00520-1
48. Chertow GM, Chang AM, Felker GM, Heise M, Velkoska E, Fellström B, Charytan DM, Clementi R, Gibson CM, Goodman SG, et al. IL-6 inhibition with clazakizumab in patients receiving maintenance dialysis: a randomized phase 2b trial. *Nat Med.* 2024;30:2328–2336. doi: 10.1038/s41591-024-03043-1
49. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.* 2004;350:1387–1397. doi: 10.1056/NEJMoa032804
50. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, Smeeth L, Deanfield JE, Lowe GD, Rumley A, et al. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. *Int J Epidemiol.* 2009;38:217–231. doi: 10.1093/ije/dyn217
51. Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, et al; Lp-PLA(2) Studies Collaboration. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet.* 2010;375:1536–1544. doi: 10.1016/S0140-6736(10)60319-4
52. Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, Kostis JB, Wilson AC, Folsom AR, Wu K, Benderly M, et al; Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA.* 2005;294:1799–1809. doi: 10.1001/jama.294.14.1799
53. Lowe GD, Pepys MB. C-reactive protein and cardiovascular disease: weighing the evidence. *Curr Atheroscler Rep.* 2006;8:421–428. doi: 10.1007/s11883-006-0040-x
54. Gill D, Dib MJ, Cronjé HT, Karhunen V, Woolf B, Gagnon E, Daghlas I, Nyberg M, Drakeman D, Burgess S. Common pitfalls in drug target Mendelian randomization and how to avoid them. *BMC Med.* 2024;22:473. doi: 10.1186/s12916-024-03700-9
55. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. *Nat Rev Cardiol.* 2017;14:577–590. doi: 10.1038/nrcardio.2017.78

56. Gill D, Georgakis MK, Walker VM, Schmidt AF, Gkatzionis A, Freitag DF, Finan C, Hingorani AD, Howson JMM, Burgess S, et al. Mendelian randomization for studying the effects of perturbing drug targets. *Wellcome Open Res*. 2021;6:16. doi: 10.12688/wellcomeopenres.16544.2
57. Elliott P, Chambers JC, Zhang W, Clarke R, Hopewell JC, Peden JF, Erdmann J, Braund P, Engert JC, Bennett D, et al. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. *JAMA*. 2009;302:37–48. doi: 10.1001/jama.2009.954
58. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med*. 2008;359:1897–1908. doi: 10.1056/NEJMoa0707402
59. Keavney B, Danesh J, Parish S, Palmer A, Clark S, Youngman L, Delépine M, Lathrop M, Peto R, Collins R. Fibrinogen and coronary heart disease: test of causality by "Mendelian randomization". *Int J Epidemiol*. 2006;35:935–943. doi: 10.1093/ije/dyl114
60. Casas JP, Ninio E, Panayiotou A, Palmen J, Cooper JA, Ricketts SL, Sofat R, Nicolaides AN, Corsetti JP, Fowkes FGR, et al. PLA2G7 genotype, lipoprotein-associated phospholipase A2 activity, and coronary heart disease risk in 10 494 cases and 15 624 controls of European ancestry. *Circulation*. 2010;121:2284–2293. doi: 10.1161/CIRCULATIONAHA.109.923383
61. Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, Gao P, Saleheen D, Rendon A, Nelson CP, et al; IL6R Genetics Consortium Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet*. 2012;379:1205–1213. doi: 10.1016/S0140-6736(11)61931-4
62. Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, Guo Y, Chung C, Peasey A, Pfister R, et al; Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. *Lancet*. 2012;379:1214–1224. doi: 10.1016/S0140-6736(12)60110-X
63. Levin MG, Klarin D, Georgakis MK, Lynch J, Liao KP, Voight BF, O'Donnell CJ, Chang KM, Assimes TL, Tsao PS, et al; VA Million Veteran Program. A missense variant in the IL-6 receptor and protection from peripheral artery disease. *Circ Res*. 2021;129:968–970. doi: 10.1161/CIRCRESAHA.121.319589
64. Burgess S, Cronjé HT, deGoma E, Chyung Y, Gill D. Human genetic evidence to inform clinical development of IL-6 signaling inhibition for abdominal aortic aneurysm. *Arterioscler Thromb Vasc Biol*. 2025;45:323–331. doi: 10.1161/atvbaha.124.321988
65. Ferreira RC, Freitag DF, Cutler AJ, Howson JM, Rainbow DB, Smyth DJ, Kaptoge S, Clarke P, Boreham C, Coulson RM, et al. Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. *PLoS Genet*. 2013;9:e1003444. doi: 10.1371/journal.pgen.1003444
66. Garbers C, Monhasery N, Aparicio-Siegmund S, Lokau J, Baran P, Nowell MA, Jones SA, Rose-John S, Scheller J. The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases. *Biochim Biophys Acta*. 2014;1842:1485–1494. doi: 10.1016/j.bbadis.2014.05.018
67. Rose-John S, Jenkins BJ, Garbers C, Moll JM, Scheller J. Targeting IL-6 trans-signalling: past, present and future prospects. *Nat Rev Immunol*. 2023;23:666–681. doi: 10.1038/s41577-023-00856-y
68. Georgakis MK, Malik R, Richardson TG, Howson JMM, Anderson CD, Burgess S, Hovingh GK, Dichgans M, Gill D. Associations of genetically predicted IL-6 signaling with cardiovascular disease risk across population subgroups. *BMC Med*. 2022;20:245. doi: 10.1186/s12916-022-02446-6
69. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, Weeks EM, Wang M, Hindy G, Zhou W, et al; Biobank Japan. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nat Genet*. 2022;54:1803–1815. doi: 10.1038/s41588-022-01233-6
70. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, et al. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130. doi: 10.1038/ng.3396
71. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, et al; COMPASS Consortium. Stroke genetics informs drug discovery and risk prediction across ancestries. *Nature*. 2022;611:115–123. doi: 10.1038/s41586-022-05165-3
72. Georgakis MK, Parodi L, Frerich S, Mayerhofer E, Tsivgoulis G, Pirruccello JP, Slowik A, Rundek T, Malik R, Dichgans M, et al; NINDS Stroke Genetics Network (SiGN). Genetic architecture of stroke of undetermined source: overlap with known stroke etiologies and associations with modifiable risk factors. *Ann Neurol*. 2022;91:640–651. doi: 10.1002/ana.26332
73. Klarin D, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, Lee KM, Shao Q, Huffman JE, Natarajan P, et al; VA Million Veteran Program. Genome-wide association study of peripheral artery disease in the Million Veteran Program. *Nat Med*. 2019;25:1274–1279. doi: 10.1038/s41591-019-0492-5
74. Roychowdhury T, Klarin D, Levin MG, Spin JM, Rhee YH, Deng A, Headley CA, Tsao NL, Gellatly C, Zuber V, et al; DiscovEHR. Genome-wide association meta-analysis identifies risk loci for abdominal aortic aneurysm and highlights PCSK9 as a therapeutic target. *Nat Genet*. 2023;55:1831–1842. doi: 10.1038/s41588-023-01510-y
75. Klarin D, Devineni P, Sendamarai AK, Angueira AR, Graham SE, Shen YH, Levin MG, Pirruccello JP, Surakka I, Karnam PR, et al; VA Million Veteran Program. Genome-wide association study of thoracic aortic aneurysm and dissection in the Million Veteran Program. *Nat Genet*. 2023;55:1106–1115. doi: 10.1038/s41588-023-01420-z
76. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, Reeve MP, Laivuori H, Aavikko M, Kaunisto MA, et al; FinnGen. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613:508–518. doi: 10.1038/s41586-022-05473-8
77. Bakker MK, van der Spek RAA, van Rheenen W, Morel S, Bourcier R, Hostettler IC, Alg VS, van Eijk KR, Koido M, Akiyama M, et al; HUNT All-In Stroke. Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. *Nat Genet*. 2020;52:1303–1313. doi: 10.1038/s41588-020-00725-7
78. Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP, Lovering RC, Tajuddin SM, Winkler TW, Graff M, et al; MEGASTROKE Consortium. GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nat Commun*. 2018;9:5141. doi: 10.1038/s41467-018-07340-5
79. Rosa M, Chignon A, Li Z, Boulanger MC, Arsenault BJ, Bosse Y, Theriault S, Mathieu P. A Mendelian randomization study of IL6 signaling in cardiovascular diseases, immune-related disorders and longevity. *NPJ Genom Med*. 2019;4:23. doi: 10.1038/s41525-019-0097-4
80. Tchuisseu-Kwangoua LA, Omarov M, Shatunov A, Markus HS, Kamtchum-Tatuene J, Georgakis MK. Genetic downregulation of interleukin-6 signaling and arteriolosclerotic cerebral small vessel disease: a drug target Mendelian randomization analysis. *medRxiv*. Preprint posted online December 14, 2024. doi: 10.1101/2024.12.13.24318994
81. Zhao SS, Gill D. Genetically proxied IL-6 receptor inhibition and risk of polymyalgia rheumatica. *Ann Rheum Dis*. 2022;81:1480–1482. doi: 10.1136/annrheumdis-2022-222578
82. Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, Richez C, Truchetet ME, Wendling D, Toussirot E, Perdriger A, Gottenberg JE, Felten R, et al. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: a randomized clinical trial. *JAMA*. 2022;328:1053–1062. doi: 10.1001/jama.2022.15459
83. Bovijn J, Lindgren CM, Holmes MV. Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19. *Lancet Rheumatol*. 2020;2:e658–e659. doi: 10.1016/S2665-9913(20)30345-3
84. Larsson SC, Burgess S, Gill D. Genetically proxied interleukin-6 receptor inhibition: opposing associations with COVID-19 and pneumonia. *Eur Respir J*. 2021;57:2003545. doi: 10.1183/13993003.03545-2020
85. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, Abbott A, Abdallah N, Abdelaziz A, Abdelfattah M, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet*. 2021;397:1637–1645. doi: 10.1016/s0140-6736(21)00676-0
86. Said S, Pazoki R, Karhunen V, Võsa U, Ligthart S, Bodinier B, Koskeridis F, Welsh P, Alizadeh BZ, Chasman DI, et al. Genetic analysis of over half a million people characterises C-reactive protein loci. *Nat Commun*. 2022;13:2198. doi: 10.1038/s41467-022-29650-5
87. Georgakis MK, Malik R, Burgess S, Dichgans M. Additive effects of genetic interleukin-6 signaling downregulation and low-density lipoprotein cholesterol lowering on cardiovascular disease: a 2×2 factorial Mendelian randomization analysis. *J Am Heart Assoc*. 2022;11:e023277. doi: 10.1161/JAHA.121.023277
88. Zhao SS, Gill D. Genetically proxied IL-6 receptor inhibition and coronary artery disease risk in a Japanese population. *Clin Ther*. 2024;46:657–658. doi: 10.1016/j.clinthera.2024.04.015
89. Bush WS, Oetjens MT, Crawford DC. Unravelling the human genome–phenome relationship using phenome-wide association studies. *Nat Rev Genet*. 2016;17:129–145. doi: 10.1038/nrg.2015.36
90. Yu Z, Zekavat SM, Honigberg MC, Natarajan P. Genetic IL-6 signaling modifies incident coronary artery disease risk in chronic kidney disease. *J Am Coll Cardiol*. 2022;79:415–416. doi: 10.1016/j.jacc.2021.11.020

91. Bick AG, Pirruccello JP, Griffin GK, Gupta N, Gabriel S, Saleheen D, Libby P, Kathiresan S, Natarajan P. Genetic interleukin 6 signaling deficiency attenuates cardiovascular risk in clonal hematopoiesis. *Circulation*. 2020;141:124–131. doi: 10.1161/CIRCULATIONAHA.119.044362
92. Prapiadou S, Živković L, Thorand B, George MJ, van der Laan SW, Malik R, Herder C, Koenig W, Ueland T, Kleveland O, et al. Proteogenomic data integration reveals CXCL10 as a potentially downstream causal mediator for IL-6 signaling on atherosclerosis. *Circulation*. 2024;149:669–683. doi: 10.1161/CIRCULATIONAHA.123.064974
93. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, et al; REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384:1491–1502. doi: 10.1056/NEJMoa2100433
94. Svensson EC, Madar A, Campbell CD, He Y, Sultan M, Healey ML, Xu H, D'Aco K, Fernandez A, Wache-Mainier C, et al. TET2-driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial. *JAMA Cardiol*. 2022;7:521–528. doi: 10.1001/jamacardio.2022.0386
95. Rees JMB, Foley CN, Burgess S. Factorial Mendelian randomization: using genetic variants to assess interactions. *Int J Epidemiol*. 2019;49:1147–1158. doi: 10.1093/ije/dyz161
96. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2×2 factorial Mendelian randomization study. *J Am Coll Cardiol*. 2015;65:1552–1561. doi: 10.1016/j.jacc.2015.02.020
97. Cupido AJ, Asselbergs FW, Natarajan P, Ridker PM, Hovingh GK, Schmidt AF; CHARGE Inflammation Working Group. Dissecting the IL-6 pathway in cardiometabolic disease: a Mendelian randomization study on both IL6 and IL6R. *Br J Clin Pharmacol*. 2022;88:2875–2884. doi: 10.1111/bcp.15191
98. Wohlford GF, Van Tassell BW, Billingsley HE, Kadariya D, Canada JM, Carbone S, Mihalick VL, Bonaventura A, Vecchie A, Chiabrando JG, et al. Phase 1B, randomized, double-blinded, dose escalation, single-center, repeat dose safety and pharmacodynamics study of the oral NLRP3 inhibitor dapansutrile in subjects with NYHA II-III systolic heart failure. *J Cardiovasc Pharmacol*. 2020;77:49–60. doi: 10.1097/FJC.0000000000000931
99. Schunk SJ, Kleber ME, März W, Pang S, Zewinger S, Triem S, Ege P, Reichert MC, Krawczyk M, Weber SN, et al; eQTLGen consortium. Genetically determined NLRP3 inflammasome activation associates with systemic inflammation and cardiovascular mortality. *Eur Heart J*. 2021;42:1742–1756. doi: 10.1093/eurheartj/ehab107
100. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*. 2014;23:R89–R98. doi: 10.1093/hmg/ddu328
101. Tambets R, Kolde A, Kolberg P, Love MI, Alasoo K. Extensive co-regulation of neighboring genes complicates the use of eQTLs in target gene prioritization. *HGG Adv*. 2024;5:100348. doi: 10.1016/j.xhgg.2024.100348
102. Turco G, Chang C, Wang RY, Kim G, Stoops EH, Richardson B, Sochat V, Rust J, Oughtred R, Thayer N, et al. Global analysis of the yeast knockout phenome. *Sci Adv*. 2023;9:eadg5702. doi: 10.1126/sciadv.adg5702
103. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472. doi: 10.1093/eurheartj/ehx144
104. Ference BA, Braunwald E, Catapano AL. The LDL cumulative exposure hypothesis: evidence and practical applications. *Nat Rev Cardiol*. 2024;21:701–716. doi: 10.1038/s41569-024-01039-5
105. Georgi B, Mielke J, Chaffin M, Khera AV, Gelis L, Mundl H, van Giezen JJJ, Ellinor P, Kathiresan S, Ziegelbauer K, et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. *Stroke*. 2019;50:3004–3012. doi: 10.1161/STROKEAHA.119.026545
106. Gill D, Georgakis MK, Laffan M, Sabater-Lleal M, Malik R, Tzoulaki I, Veltkamp R, Dehghan A. Genetically determined FXI (factor XI) levels and risk of stroke. *Stroke*. 2018;49:2761–2763. doi: 10.1161/STROKEAHA.118.022792
107. Piccini JP, Patel MR, Steffel J, Ferdinand K, Van Gelder IC, Russo AM, Ma CS, Goodman SG, Oldgren J, Hammett C, et al; OCEANIC-AF Steering Committee and Investigators. Asundexian versus apixaban in patients with atrial fibrillation. *N Engl J Med*. 2025;392:23–32. doi: 10.1056/NEJMoa2407105
108. Verma A, Huffman JE, Rodriguez A, Conery M, Liu M, Ho YL, Kim Y, Heise DA, Guare L, Panickan VA, et al. Diversity and scale: genetic architecture of 2068 traits in the VA Million Veteran Program. *Science*. 2024;385:eadj1182. doi: 10.1126/science.adj1182
109. All of Us Research Program Genomics Investigators. Genomic data in the All of Us Research Program. *Nature*. 2024;627:340–346. doi: 10.1038/s41586-023-06957-x
110. Nagai A, Hirata M, Kamatani Y, Muto K, Matsuda K, Kiyohara Y, Ninomiya T, Tamakoshi A, Yamagata Z, Mushiroda T, et al; BioBank Japan Cooperative Hospital Group. Overview of the BioBank Japan Project: study design and profile. *J Epidemiol*. 2017;27:S2–S8. doi: 10.1016/j.je.2016.12.005
111. Hou L, Wu S, Yuan Z, Xue F, Li H. TEMR: trans-ethnic mendelian randomization method using large-scale GWAS summary datasets. *Am J Hum Genet*. 2025;112:28–43. doi: 10.1016/j.ajhg.2024.11.006
112. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR; 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature*. 2015;526:68–74. doi: 10.1038/nature15393
113. We need a genomics-savvy healthcare workforce. *Nat Med*. 2023;29:1877–1878. doi: 10.1038/s41591-023-02522-1