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Population-enriched innate immune variants may identify candidate gene targets at the intersection of cancer and cardio-metabolic disease

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Both cancer and cardio-metabolic disease disparities exist among specific populations in the US. For example, African Americans experience the highest rates of breast and prostate cancer mortality and the highest incidence of obesity. Native and Hispanic Americans experience the highest rates of liver cancer mortality. At the same time, Pacific Islanders have the highest death rate attributed to type 2 diabetes (T2D), and Asian Americans experience the highest incidence of non-alcoholic fatty liver disease (NAFLD) and cancers induced by infectious agents. Notably, the pathologic progression of both cancer and cardio-metabolic diseases involves innate immunity and mechanisms of inflammation. Innate immunity in individuals is established through genetic inheritance and external stimuli to respond to environmental threats and stresses such as pathogen exposure. Further, individual genomes contain characteristic genetic markers associated with one or more geographic ancestries (ethnic groups), including protective innate immune genetic programming optimized for survival in their corresponding ancestral environment(s). This perspective explores evidence related to our working hypothesis that genetic variations in innate immune genes, particularly those that are commonly found but unevenly distributed between populations, are associated with disparities between populations in both cancer and cardio-metabolic diseases. Identifying conventional and unconventional innate immune genes that fit this profile may provide critical insights into the underlying mechanisms that connect these two families of complex diseases and offer novel targets for precision-based treatment of cancer and/or cardio-metabolic disease.

KEYWORDS

innate immune variants, pleiotropic actions, cancer disparities, cardio-metabolic disparities, population-enriched variants, candidate protein targets

1 Introduction

1.1 Double-edged swords: important factors connecting metabolic disorders and cancer development

The following perspective was written in response to an invited *Frontiers* research topic to explore methods, mechanisms, and hypotheses that may ultimately identify and exploit biological processes contributing to complex disease progression and molecular interactions enabling cross-talk between cancer and cardio-metabolic disease. Based on our hypothesis that innate immunity differences contribute to observed population disease disparities in cancer and metabolic disorders, we apply a functional genomics approach to identify specific innate immune genes as potential therapeutic targets at the intersection of these two complex disease families.

1.2 Framing precision drug target discovery in the context of health disparities

1.2.1 Defining health disparities

The US National Institute on Minority Health and Health Disparities (NIMHD) defines health disparities as "a health difference (compared with the general population), based on one or more health outcomes (such as the overall rate of disease incidence, prevalence, morbidity, mortality or survival) that adversely affect disadvantaged populations." In the US, such populations include Blacks/African Americans, Hispanics/Latinos, Asians, American Indians/Alaska Natives, and Native Hawaiians/other Pacific Islanders) (1). Diverse sources, from sponsored websites (such as 2 and associated links) to peer-reviewed articles summarizing disparities in one or more diseases between two or more populations, provide ample evidence for differences in cancer (3), cardio-metabolic disease (4) and overall health risks and outcomes (5) based on ethnic background/geographic ancestry. By way of illustration, Tables 1, 2 summarize disparities in cancer incidence and mortality among US ethnic populations (adapted from 6) and population differences in overall mortality rates of cancer and cardio-metabolic diseases (adapted from 7), respectively.

Assessing health differences between populations is complicated because results may vary depending on the size and granular composition of the populations being compared. On the one hand, evaluating larger, more heterogeneous populations improves statistical reliability, but this approach may mask disparities among subpopulations. For example, among Asians in the US (8) and Asia (9), the incidence of liver cancer varies widely based on geography and/or geographic ancestry. Further, trends in incidence and/or mortality may change due to cohort variations in age, exposure to risk, and geographic location, as is the case for liver (10) and breast cancer incidence (11) in the US and for global cancer mortality rates (e.g., 12).

Defining/distinguishing populations is a critical aspect of evaluating health disparities. Many analyses have been based on self-identified ethnicity; it stands to reason that this approach is likely to align more closely with social determinants of health. In contrast, a relatively precise biological assessment of geographic ancestry can be obtained using genetic markers to identify ethnic origins. In this approach, selected ancestry informative markers (AIMs) were initially used to evaluate genetic admixture and geographic ancestry and provide valuable background information when comparing individuals representing different populations (13). Improved methods and more extensive and complete reference datasets have further refined admixture mapping (14).

For the purposes of this perspective, we will refer to populations as they are defined by individual authors; populations in Section 3 are defined according to Karczewski (15). The interested reader is referred to a recent book chapter entitled "Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field" written by the National

TABLE 1 Ethnic Disparities in US Cancer Incidence and Mortality.

	EA	AA	ASN/PI	NA/AN	HISP
Cancer Incidence	breast	prostate	*stomach*	colon kidney liver lung stomach uterine	*uterine*
Cancer Mortality	lung	breast colon prostate uterine	*stomach*	kidney liver stomach	*liver*

adapted from "Table 9. Incidence and Mortality Rates for Selected Cancer by Race and Ethnicity, US" (6).
standard font indicates most frequently occuring cancer among aggregate populations; italics indicate most frequently occuring cancer for a specific ethnic group (not aggregate).
EA, European American, non-Hispanic White; AA, African American, non-Hispanic Black; ASN/PI, Asian American/Pacific Islander; NA/AN, Native American/Alaskan Native; HISP, Hispanic/Latino.

TABLE 2 Deaths from Cancer, Cardio-Metabolic, and Infectious Diseases in the US as of 2018.

Cause of Death	Aggregate	EA	AA	NA/AN	ASN	PI	HISP
heart disease	23.1%	23.4%	**23.6%**	*18.0%*	21.3%	23.5%	19.8%
cancer	21.1%	21.2%	20.4%	*16.8%*	**25.1%**	21.9%	20.5%
stroke	5.2%	5.1%	5.7%	*3.6%*	**7.6%**	6.2%	5.5%
diabetes	3.0%	*2.5%*	4.5%	5.6%	4.1%	**7.3%**	4.6%
infection (flu, pneumonia)	2.1%	2.1%	*1.8%*	2.3%	**3.3%**	2.2%	2.1%
kidney disease	1.8%	*1.6%*	**2.8%**	1.8%	2.1%	2.2%	2.1%
liver disease	*	1.4%	1.0%	**6.2%**	*0.9%*	1.3%	3.2%
hypertension	*	*1.1%*	1.9%	*1.1%*	**2.1%**	1.4%	1.4%

adapted from Tables C & D in "Deaths: Leading Causes for 2018." Heron, M. National Vital Statistics Reports 70(4) (7).
bold indicates highest mortality rate for given cause of death.
italics indicates lowest mortality rate for given cause of death.
*aggregate data were only available for top ten causes of death.

Academies of Sciences' Committee on the Use of Race, Ethnicity, and Ancestry as Population Descriptors in Genomics Research (16) for a thorough treatment of this subject.

1.2.2 Past and present challenges to advancing research in the biology of health disparities

Cancer and cardio-metabolic disease disparities have multifactorial etiologies, including biological, behavioral, environmental, and social components. There is ample evidence that these disparate etiological factors are not adequately understood in isolation from one another. The interested reader is referred to reviews on the impact of physical, social, and chemical environments on the biology of health disparities (17–19) and on the biological impacts of stress (20), including racism-induced stress and increased allostatic load (21–23), all of which are beyond the scope of this perspective.

The relative contribution of biology to cancer and cardio-metabolic disparities continues to be a matter of debate among scientists in various disciplines and even among biologists themselves (24). The hesitation to consider geographic ancestral differences in biology among some mainstream biomedical scientists is just one of several obstacles that have hindered a rigorous study of the biology of health disparities.

Social forces continue to hinder the participation of minority populations in medical research and to limit their access to medical care. For example, an entrenched and well-founded mistrust of the medical establishment in the US exists among minority populations due to a long history of abuses (25). Limited access to healthcare and subpar healthcare quality further exacerbate health disparities in minority populations, leading to lower life expectancy in American Hispanic and Black populations (26).

Traditional research approaches and the most widely available resources in the biomedical sciences have also unintentionally hindered a rigorous characterization of the biological differences that underlie health disparities. *In vitro* studies employ samples and cell lines obtained most often from individuals of European descent (27, 28) and the majority of clinical trials disproportionately enroll individuals from this same population (29, 30). Thus, at multiple stages in the drug research and development cycle, biases exist towards agents optimized for those of European ancestry. Fortunately, the need to increase the diversity of human samples and cell lines and to engage diverse study populations in biomedical research and clinical trials has recently gained the attention and enthusiastic support of pre-eminent scientists (29, 31–33) and the NIH (34).

1.2.3 Considering geographic ancestry in the development of effective treatments

The human genome possesses a high degree of variation. According to a 2016 meta-analysis of 60,706 individuals of diverse ancestries, an average of 1 in 8 bases of the coding sequence were variants, and 72% of these had not been previously identified and/or characterized (35). Wide genetic variations within populations are at least as diverse as genetic variations between populations (36). This finding implies that not all genetic variations contribute to putative biological differences between populations.

Genetic differences associated with geographic ancestry, such as AIMs, may result in the uneven among populations distribution of gene variants. In many cases, these variants are uncommon, and/or their impact on protein expression, function, or disease is either insignificant or unknown. However, an intriguing study by Ahsan et al. (37) identified 65 "minor" drug response alleles that were present in more than 50% of individuals in at least one population; in other words, in some populations, the variant was more common than the wild type/canonical protein. Consistent with this is a body of clinical evidence that specific drug responses vary according to geographic ancestry, with outcomes that range from lack of efficacy to drug-related pathology and death in one or more minority populations (38–40). Therefore, we sought to identify population-specific potential therapeutic targets at the intersection of cancer and cardio-metabolic disease, in part by hand-curating gene variants with "minor" alleles that were common in at least one major population (as defined by 15) but that were significantly less common in at least one other major population.

1.3 Innate immunity as a biological driver of health disparities

Gene variants that confer protective immunity are retained in each population to optimize survival. For example, in the case of those with African ancestry, gene variants retained in the pan-African genome have been identified that provide defense against indigenous pathogens such as malaria and trypanosomiasis (African sleeping sickness/Chagas disease). The selective pressure imposed by pathogens on gene variation is impressive; in the case of malaria, variants of at least 40 different genes are thought to protect against one or more species of *Plasmodium* (41, 42).

Unfortunately, immune protection frequently involves a trade-off where protective innate immune variants may introduce new pathologies. For example, among the gene variants that protect against malaria, *HbS* also promotes sickle cell anemia, *HbE* promotes thalassemia, *G6PD* variants promote hemolytic anemia, and Duffy antigen receptor (*DARC*) variants are associated with increased breast cancer metastasis and mortality (43, 44). Similarly, the same *APOL1* variants shown to protect against severe trypanosomiasis are also associated with nephropathy (45, 46).

Several lines of evidence affirm that innate immune genes are highly adaptable and optimized to respond to local pathogens. First, within the human genome, genes associated with immunity are under the strongest selective pressure (47, 48). Second, selective pressure on immune genes is pathogen-driven (49, 50). Third, the geographic distribution of populations bearing the highest frequency of *HbS* (51) and *DARC* (52) gene variants closely resemble the geographic distribution of the malarial strains they protect against. Finally, according to their geographical ancestry, populations differ in their susceptibility to infectious disease (53), in their immune response to pathogens (54) and even in their macrophage function and circulating cytokine levels (55–57). All of these findings indicate that protective innate immune variants are distributed among individuals based on their geographic ancestry.

It is important to note that genes associated with innate immunity are structurally and functionally diverse. Some are well-characterized participants in inflammation, including but not limited to cytokines, chemokines, and pattern recognition receptors (lectins, Toll-like receptor (TLR) family members, and NLRs) and their related pathways. However, as illustrated by the variety of genes that protect against malaria (summarized in Table 3), others are pleiotropic, expressed in non-immune tissues and/or frequently better known for their "day jobs". Most of the protective variants listed in Table 3 can be tied directly to immunity. Still, a few (such as *APOE*, *G6PD*, glycophorin (*GYP*), hemoglobin (*HB*), and haptoglobulin (*HP*)) would be considered unconventional innate immune genes.

TABLE 3 Innate immune genes that provide protection against malaria (adapted from **41**, **42**).

Gene	Name/Function	Expression	Association with Disease (based on titles available in Google Scholar)
ABO	ABO blood group	secreted	cancer, cardiovascular disease, diabetes, obesity, NAFLD
APOE	apolipoprotein E	secreted	cardiovascular disease, obesity, diabetes, NAFLD, cancer
CD36, thrombospondin receptor, scavenger receptor B3	broad specificity receptor for proteins and lipids	adipose, liver, others	cardiometabolic disease, cancer
CR1, CD35, C3b/C4b complement receptor, Knops blood group antigen		erythrocytes, leukocytes, glomerular podocytes, splenic DCs	gallbladder and liver cancer, diabetes, kidney disease
*DARC, FY, ACKR1, CD234, CCBP*1	Duffy atypical chemokine receptor	erythrocytes, endothelia	breast cancer, prostate cancer, cardiometabolic disease
FCGRA2, CD32	low affinity Fc receptor	phagocytes	breast cancer, cardiovascular events
G6PD	glucose-6-phosphatase dehydrogenase rate-limiting step to pentose-phosphate, NADPH	lymphoblasts, granulocytes	cancer, diabetes, cardiovascular disease
GYPA,B,C, CD235a,b,c	glycophorin A,B,C sialoglycoproteins	A broad expression	
		B,C erythrocytes	C leukemia, oral cancer
HBA, HBB	hemoglobin, O2/CO2 transport	erythrocytes	thalassemia, sickle cell anemia
HLA-B	component of MHC class I	broad expression	elimination of infected or transformed cells

(Continued)

TABLE 3 Continued

Gene	Name/Function	Expression	Association with Disease (based on titles available in Google Scholar)
HLA-DR series (A,B1,3,4,5)	components of MHC class II	antigen presenting cells	elimination of infected or transformed cells
HP	haptoglobulin, plasma protein that binds Hb	liver, others	diabetic nephropathy and coronary artery disease
ICAM1, CD54	intercellular adhesion molecule 1, receptor for CD11a or b/CD18 integrins and rhinovrius	immune and endothelial cells	cancer, diabetes, obesity
IFNAR1,2	interferon alpha (and beta) receptor, subunits 1 and 2	broad expression	1 gastric, colorectal, breast cancer; 2 lung cancer, diabetes
IFNG	interferon gamma	circulating	cancer, diabetes
IFNGR1,2	IFN gamma receptor 1 (CD119), 2	broad expression	1,2 cancer
IL1A/IL1B	interleukin 1A, 1B	circulating	A, B cancer, obesity; B diabetes
IL1RN	IL1 receptor antagonist	secreted	cardiovascular disease, cancer, obesity, diabetes
IL10	interleukin 10	circulating	cancer, obesity, diabetes, atherosclerosis
IL10RB	IL10 receptor, subunit beta	broad expression	obesity
IL12B	interleukin 12, beta subunit	circulating	diabetes, cancer
IL4	interleukin 4	circulating	cancer, diabetes
IRF1	interferon regulatory factor 1	broad expression	cancer
MBL2	mannose binding lectin 2, collectin 1	circulating	cancer, diabetes, atherosclerosis
MST1, HGFL	macrophage stimulating 1, hepatocyte growth factor like	secreted	cancer, diabetes, NAFLD, cardiovascular disease
NCR3, CD337	natural cytotoxicity triggering receptor 3	NK cells	cancer
NOS2A	nitric oxide synthase 2	liver, retina, bone, lung, cartilage, fat	cancer, diabetes
PECAM1, CD31	platelet-endothelial cell-adhesion molelcule 1	immune and endothelial cells	cancer, cardiovascular disease, diabetes
PSMB9	proteosome 20S subunit beta 9	MHC II expressing tissues	cancer, diabetes
SCL4A1, CD233, erythrocyte band 3 prot.	chloride/bicarbonate exchanger, Diego blood group	erythrocytes, kidney, bone, others	
	CO2 transport from tissues to lungs, structural protein		cardiovascular disease, colorectal cancer
SELE, CD62E	selectin E	endothelia	cancer
TCRB	T-cell receptor, beta subunit	T-cells	diabetes, cancer
TIRAP, MAL, Myd88-2	TIR domain containing adapter protein	broad expression	cancer, diabetes, NAFLD
TL4	Toll-like receptor 4	broad expression	cancer, obesity, diabetes, NAFLD, cardiovascular
TAP1, ABCB2	transporter 1, ATP binding cassette, subfamily B	broad expression	cancer, diabetes
TNF	tumor necrosis factor	circulating	cancer, obesity, diabetes, NAFLD, cardiovascular disease
TNFSF5	CD40 ligand, CD154, TNF superfamily member 5	circulating	diabetes, cancer, cardiovascular disease, obseity

1.4 Inflammation is a component of cancer and cardio-metabolic diseases

1.4.1 Cancer and inflammation

Hanahan and Weinberg, in their seminal review, describe six hallmarks of cancer, many of which are enabled by mechanisms of immunity, including inflammation (58). Their observations are particularly relevant to this perspective since further research in the field has established that reprogrammed energy metabolism and immune evasion are additional hallmarks (58, 59).

In a previously published perspective, we presented evidence for an association between breast and prostate cancer disparities in African Americans (AAs) and classic innate immune gene variants (interleukins, Toll-like receptors, monocyte activity) more commonly found in AAs (60). Since 2019, Google Scholar (accessed 4/18/23) has listed more than 18,000 publications with titles that include "cancer" and "inflammation," "infection", "immune," "immunity," or "innate"; these publications address a wide range of topics, including immune escape by cancer cells, the contribution of chronic inflammation to tumor progression, and immune-based cancer therapies, that are beyond the scope of this perspective. Notably, less than 40 of these publications (< 0.2%) include the terms "disparity" or "disparities" in their titles. Among this small set of publications are descriptions of population differences in tumor microenvironment and immune signatures in breast (61, 62), head and neck (63–65), lung (66, 67), and colorectal (68, 69) cancers, as well as cancer generally (70). Of particular interest is a recent exploration of the link between racial differences in mitochondrial metabolism and the tumor immune microenvironment (71).

1.4.2 Cardio-metabolic disease and inflammation

The constellation of inter-related cardio-metabolic diseases has been collectively referred to as metabolic syndrome (MetS), and their cumulative effect on global health is massive (reviewed in 72–74). Clinical definitions of MetS vary depending on which disease(s) are of primary interest (reviewed in 75–77). The National Heart Lung and Blood Institute (NHLBI) lists the following MetS risk factors as abdominal obesity and/or insulin resistance, elevated triglycerides and LDL-cholesterol, reduced HDL-cholesterol, hypertension, elevated glucose and pro-thrombotic or pro-inflammatory states (78). Several metabolic diseases have been associated with these risk factors, including hypertension, obesity, atherosclerotic cardiovascular disease, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), and stroke.

Genetic and environmental factors impact cardio-metabolic diseases, and their risk, morbidity, and mortality vary with age, gender, and race/ethnicity (4, 76). Unfortunately, the effects of MetS are not confined to cardio-metabolic co-morbidities, given that MetS is also associated with increases in the incidence and/or mortality of arthritis, chronic kidney disease, schizophrenia, depression and cancer, as noted in references (79, 80).

Inflammation is a key contributor to MetS and associated co-morbidities (81–83), just as MetS pathologies impact inflammation (c.f. 84). In general, low-grade chronic inflammation evoked during metabolic disease stimulates the production of pro-inflammatory cytokines, immuno-modulatory proteins, lipids, and other mediators of inflammation that impact systemic and/or localized tissue inflammation (82, 85). Unfortunately, the treatment of metabolic diseases is complicated by the cross-talk between pro- and anti-inflammatory mechanisms at work among MetS co-morbidities (c.f. 77, 86–88). Further, inflammation from one metabolic disease can also exacerbate other MetS co-morbidities.

As with almost all tissues, organs that regulate systemic metabolism possess innate immune response capabilities. Notably, some organs that regulate overall metabolic homeostasis also impact systemic inflammation. In the case of both adipose tissue (89–91) and liver (92–94), these organs harbor and partner with resident macrophages (ATMs and Kupffer cells, respectively) in inflammation. Further, adipose tissue and liver produce unique immunologically active biomolecules, such as adipokines (86, 95) and bile acids (96–99). Perhaps less appreciated are two additional organs associated with metabolic homeostasis that control systemic levels of immunologically active biomolecules: the gallbladder regulates bile acid levels and the pancreas controls insulin, which levels of insulin, with its known anti-inflammatory effects (100).

Just as mediators of metabolism can impact inflammation, mediators of immunity can impact metabolism. For example, innate immune receptors have demonstrated roles in metabolic disease progression (101), and pro-inflammatory cytokines produced in the adipose tissue of obese individuals contribute to the development of T2D (102). Significantly, biomolecules such as adipokines, insulin, and bile acids mediate metabolism and inflammation. Further, besides their widely recognized role in lipid transport and cellular metabolic homeostasis, serum lipids and lipoproteins also provide innate immune protection (103, 104).

2 A functional genomics approach to novel target discovery

Using functional genomics, we and others have observed associations between specific innate immune gene variants and cancer or metabolic disease risk or outcome that differ according to geographic ancestry (57, 60, 105). Given that immunity including inflammation contributes to the progression of both complex disease families, we have hypothesized that population differences in genetic (and epigenetic) innate immune programs contribute to complex disease disparities between populations. Based on this conceptual framework, this perspective seeks to identify innate immune gene candidates associated with both cancer and cardio-metabolic disease that differ between populations.

Genome wide association studies (GWAS) in general (106) and the Genome Aggregation Database (gnomAD) in particular (107) provide researchers with the capacity to compare thousands of complete genomes from individuals among all largely-grouped populations. These resources catalog gene variations called single nucleotide polymorphisms (SNPs) across the entire genome of each

individual. SNPs are located not only in protein coding genes (including coding exons as well as non-coding introns and remote, up-, down-, and mid-stream regulatory sites), but also across regions associated with short and long non-coding RNAs, chromosomal architecture, and other essential functions that have been previously underappreciated and mislabeled as "junk DNA" (108). The number of genes and the percentage of the human genome they occupy varies depending on their definition (109). Notably, most SNPs associated with disease states or changes in phenotype (95%) are located outside coding exons (110).

Nevertheless, in this perspective, we will focus on widely occurring gene variants that code for changes in the canonical amino acid (aa) sequence, also referred to as missense variants or nonsynonymous SNPs, as a first step towards accelerating the development of optimally safe and active drugs that target understudied protein variants widely found in patients with diverse geographical ancestries. Importantly, nonsynonymous SNPs have the potential to impact protein conformation, activity and/or protein-protein interactions, potentially altering disease states and phenotypes. For simplicity, we have also excluded synonymous SNPs (exonic point mutations that do not alter aa sequence), in spite of mounting evidence that suggests they can function in isoform selection (protein size and sequence), transcript expression levels and stability, translational folding rate, overall conformation, and posttranslational modifications, all of which possess potential functional consequences on cell behavior and disease risk (111–113).

This perspective identifies conventional and unconventional innate immune genes (summarized in Section 3) that meet the following criteria. First, there is evidence that each gene participates in, is a target of, or is associated with innate immunity including inflammation. Second, there is evidence that each gene is associated with at least one form of cancer and at least one cardio-metabolic disease. Finally, each gene occurs among the global population as at least one population-enriched variant, which we define as a widely occurring missense variant distributed unevenly among populations.

We have employed a hand-curated discovery process to identify population-specific innate immune genes at the intersection of cancer and metabolic disease. From the primary and secondary literature, gene lists associated with innate immunity (49, 114, 115), cancer (116, 117), or cardio-metabolic disease (118, 119) were vetted for the following characteristics:

1) Evidence in the primary or secondary literature (accessed through Google Scholar) indicated that the candidate gene was involved in all three disease categories: innate immunity/inflammation, cancer, and cardio-metabolic disease.
2) Indication in gnomAD that the candidate gene occurs as at least one nonsynonymous SNP/missense variant with
    a. a high minor allele frequency (MAF ≥ 0.2 in at least one of the six major populations defined by 15): African/African American (AFR/AA), East Asian (E ASN), non-Finnish European (EUR), Latino/Latina (LAT), Middle Eastern (MID E), and South Asian (S ASN),
    b. a difference in MAF among significant populations of ≥ 0.2 from the highest to lowest frequency.

Note that among genes with missense variants, we chose only those with common variants that occur widely among individuals in one or more populations, i.e., missense variants that occurred in at least 20% of individuals in one or more populations (by definition, having a minor allele frequency (MAF) ≥ 0.20 and varying widely in the frequency of their occurrence among populations. This approach was based on our rationale that variants selected and retained in the human genome provide a survival benefit for the population(s) in which they occur, even as they may also paradoxically contribute to complex disease as discussed above for *HbS* and *APOL1* variants (see Section 1.3).

3 Candidate innate immune genes at the intersection of cancer and cardio-metabolic disease disparities

Among the candidate innate immune genes that we identified at the intersection of cancer and cardio-metabolic disease, we found both "conventional" innate immune genes, such as cytokines and cytokine receptors, pattern recognition receptors, and other genes that have widely acknowledged roles in immune cell function, and "unconventional genes" with pleiotropic functions that include innate immunity, such apolipoproteins, biomolecule transporters, and transcription regulators. Using the approach described in Section 2, three lists of innate immune genes implicated in cancer and cardio-metabolic disease were generated. Each gene listed in the three tables below possesses at least one population-enriched variant with an amino acid replacement that differs in its distribution among populations, suggesting its potential role in both cancer and cardio-metabolic disparities. The 52 genes identified provide a representative but not exhaustive list of candidate genes, thus serving as preliminary data for further investigation.

Section 3.1 summarizes conventional innate immune genes and their corresponding population-enriched variants previously shown to impact disease or biological function. Similarly, Section 3.2 summarizes unconventional innate immune genes (better known for their non-immune functions) and their corresponding population-enriched variants that have been previously shown to impact disease or biological function. Finally, Section 3.3 summarizes genes associated with innate immunity, cancer, and cardio-metabolic diseases and their corresponding population-enriched variants whose impact on disease or biological function has not yet been established.

3.1 Conventional innate immune genes with previously characterized population-enriched variants

Table 4 includes 14 genes best known for their roles in immunity, including inflammation, that are present as at least one population-enriched variant shown to impact biological

function. Among these are cytokines and cytokine receptors, including macrophage inhibitory cytokine 1 (*MIC-1/GDF15*), interleukin 3 and the alpha subunit of its receptor (*IL3* and *IL3RA*), along with subunits for interleukin 4, 6 and 7 receptors (*IL4R, IL6R*, and *IL7R*), and the leptin adipokine receptor (*LEPR*). Additional immune receptors include the soluble receptor for MHC I antigens I (leukocyte Ig-like receptor A3, *LILRA3/CD85E*) and two pattern recognition receptors, the intracellular pattern recognition receptor nucleotide-binding oligomerization domain containing 2 (*NOD2*) and the five transmembrane stimulator of interferon response CGAMP interactor 1 (*STING1/TMEM173*). Also included were the catalytic enzyme in the rate-limiting step of the kynurenine pathway during inflammation indoleamine 2,3-dioxygenase 2 (*IDO2*), the temperature-sensitive cation channel *TRPM8*, and two adhesion molecules, one expressed in lymphocytes (integrin alpha L, *ITGAL/LFA-1/CD11A*) and the other expressed in leukocytes (junctional adhesion molecule-like, *JAML/AMICA*).

3.1.1 Interleukin 3 and interleukin 3 receptor alpha chain

IL-3 is a growth factor produced by activated T-cells (129) that regulates the growth of hematopoietic progenitor cells and activates mature neutrophils and macrophages (208). IL-3 is also implicated in priming (131) and activating (130) basophils. Intriguingly, increased serum levels of IL-3 have recently been associated with the onset of type 2 diabetes in African American women as determined by serum levels of glucose and HbA1c (133). Genetic variations in *IL3* have been noted in colon and rectal cancers (132). The Pro27Ser variant (5-132060785-C-T) has been associated with protection against malaria (134) but also with an increase in miscarriages following *in vitro* fertilization (IVF) in women of various populations (209).

The interleukin 3 receptor is a heterodimer comprised of an interleukin 3-specific alpha chain (IL-3RA, CD123) and the common cytokine beta chain CSF2RB, another candidate listed below in Section 3.3, that also forms dimers with the alpha chains of both GM-CSF and IL-5 receptors. High-affinity IL-3 binding induces hetero-dimerization of IL-3RA and CSF2RB, and subsequent disulfide linkage of these receptor chains is required for receptor activation and CSF2RB phosphorylation (210). IL-3RA expression varies among CD34+ hematopoietic cell types, with negative/low expression in primitive hematopoietic cells and little or no surface expression in early erythroid progenitors, but high expression in B-lymphoid and myeloid progenitors (135). The X-chromosome-linked *IL3RA* Val323Leu variant (X-1378751-G-C) was associated with non-complete response to neoadjuvant chemotherapy against locally advanced rectal cancer in Hong Kong patients (138).

3.1.2 Interleukin 4 receptor alpha chain

The IL-4R alpha chain (IL4R, CD124) forms heterodimers with at least two partners. Type 1 IL-4 receptors are composed of IL-4R complexed with the common cytokine receptor gamma chain (IL2RG, CD132), which may alternatively dimerize with IL-2, IL-7 and IL-21 cytokine receptors, so that IL-2, IL-7, and IL-21 receptors compete with IL-4R for binding to IL2RG. Type 2 IL-4 receptors are composed of IL-4R complexed with IL-13RA1 (IL13Rα1, CD213A1). Thus, IL-4 activates both Type 1 and Type 2 IL-4 receptors, while IL-13 activates Type 2 IL-4 receptors. Both IL-4 and IL-13 signaling through the IL-4R mediate type 2 (humoral, as opposed to type 1 cellular) immunity against helminths, toxins and tropical parasites such as plasmodium (malaria) and trypanosomes (African sleeping sickness/Chagas disease) (139–141, 211). Both IL-4Rα and IL13-Rα1 have also been implicated in cancer progression and were recently identified as prognostic indicators in soft-tissue sarcoma patients when present in the nucleus. IL-4 regulates lipid metabolism (143), and (142) recent findings highlight an intriguing relationship between non-hematopoietic IL-4Rα activation of a non-canonical signaling pathway that regulates a high-fat, high-carbohydrate diet-driven induction of obesity and impacts the severity of obesity-associated sequelae in mice (212). Numerous genetic epidemiological studies have also shown that *IL4* and *IL4R* and their gene polymorphisms play important roles in asthma in various populations. Notably, individuals carrying one or two copies of the *IL4R* Glu400Ala (16-27362551-A-C) minor allele were at higher risk to suffer from allergy (145) and asthma (144, 213).

3.1.3 Interleukin 7 receptor alpha chain

The integral membrane interleukin 7 receptor (IL-7R) transmits pro-inflammatory signals initiated by IL-7 at the cell surface. The functional IL-7 receptor is a heterodimer comprised of the IL-7 receptor alpha chain (IL7R, IL7Rα, CD127) and the same common cytokine receptor gamma chain (IL2RG, CD132) that dimerizes with the IL-4R alpha chain. The assembled IL-7R recognizes not only IL-7 but also thymic stromal lymphopoietin (TSLP), both cytokines with 4 α-helical strands (214). Multiple transcriptional and post-transcriptional mechanisms exist to regulate expression of the IL-7R protein (215). Some of these mechanisms are homeostatic, molecular and cytokine-mediated, where *IL7Rα* transcription decreases in $CD4^+$ and $CD8^+$ cells once naïve T cells become activated. Notably, IL-7 binding to IL-7R activates the Janus kinase (JAK/STAT) pathway, which plays an essential role in lipid metabolism (216). However, peripheral blood mononuclear cells (PBMCs) in breast cancer patients show defects in STAT5 phosphorylation and altered expression of IL-7Rα that ultimately impacts memory T cell development (156).

Notably, compared to the canonical gene, the *IL7R* variants 5-35874473-C-T (rs6897932), 5-35860966-T-C (rs1494558) and 5-35871088-G-A (rs1494555) alter the pathology of autoimmune and infectious diseases due to their impact on IL7R expression and alternative splicing (155). Further, all three population-enriched missense variants of *IL7R* identified in Table 4 show an association with cardio-metabolic disease: Ile66Thr (5-35860966-T-C, rs1494558) with post-transplantation diabetes (158); Val138Ile (5-35871088-G-A, rs1494555) with body mass index (BMI) in lymphoma patients (161), and Ile356Val (5-35876172-A-G, rs3194051) with severe liver disease (162). However, to date only Val138Ile has been associated with increased cancer risk, both in lung (160) and stomach (159).

TABLE 4 Candidate Conventional Innate Immune Genes at the Intersection of Cancer and Cardio-Metabolic Disease.

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
GDF15		growth differentiation factor 15, macrophage inhibitory cytokine 1		induced by HCV	120	regulates hepatocellular carcinoma genes	120	stress, metabolic and cardiovascular disease	121
		MIC-1		mediates tissue tolerance	122	pro- and anti-tumor activity	121	deficiency protects against atherosclerosis	123
19-18386331-T-A (rs1059369)	2 (2)	Ser48Thr	0.38 E ASN to 0.14 MID E	systemic lupus erythematosus (SLE) risk in Chinese population	124				
IDO2		indoleamine 2,3-dioxygenase 2		immunomodulator	125	multiple cancers	126	NAFLD	118
8-39982715-A-G (rs4736794)	3 (2)	Ile140Val (2 of 4 transcripts)	E ASN 0.34 to 0.03 AFR/AA	major depressive disorder symptoms	127				
8-40005362-C-T (rs10109853)	3 (2)	Arg248Trp (2 of 4 transcripts)	S ASN 0.54 to 0.25 E ASN			multiple myeloma risk in a small Japanese cohort	128		
IL3		interleukin 3		hematopoietic growth factor, mast-cell growth factor, multipotential colony stimulating factor	129 130 131	colon cancer risk	132	T2D in obese AA women	133
5-132060785-C-T (rs40401)	1 (1)	Pro27Ser	AFR/AA 0.53 to 0.22 EUR	protection against malaria	134				
IL3RA		interleukin 3 receptor, CD123		production and differentiation of hematopoietic progenitor cells	135	leukemia	136, 137	ligand IL3 implicated in T2D in obese AA women	133
X-1378751-G-C (rs17883366)	2 (2)	Val323Leu	MID E 0.26 to 0.06 AFR/AA			colorectal cancer treatment response	138		
IL4R		interleukin 4 receptor, CD124, IL4RA, IL13 receptor		ligand IL4 provides protection against malaria, schistosomiasis and helminths	139–141	IL4R overexpressed on the surface of multiple cancer types (breast, lung, etc.)	reviewed in 142	IL-4 dysregulation caused decreased lipid metabolism, decreased lipolysis and increased adipogenesis leading to diseases such as obesity and Type 2 Diabetes	143

(Continued)

10.3389/fendo.2023.1286979

TABLE 4 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
16-27362551-A-C (rs1805011)	5 (3)	Glu400Ala	0.53 AFR/AA to 0.06 S ASN	allergy, asthma	144, 145	lung cancer response to radiation	146	type I diabetes?	yes: 147 no: 148, 149
IL6R		IL6 receptor, CD126, Gp80		receptor for pleiotropic cytokine IL6	150	lung and other cancers	151, 152	cardiometabolic disease	153
1-154454494-A-C (rs2228145)	3 (2)	Asp358Ala	0.49 LAT to 0.14 AFR/AA			liver cancer	154		
IL7R		interleukin 7 receptor, CD127, IL7RA		variants involved in autoimmunity and infectious disease	155	reduced in breast cancer	156	type I diabetes	157
5-35860966-T-C (rs1494558)	5 (4)	Ile66Thr	0.75 AFR/AA to 0.42 E ASN					post-transplantation diabetes	158
5-35871088-G-A (rs1494555)	3 (3)	Val138Ile	0.87 AFR/AA to 0.48 E ASN			gastic cancer in EUR, increase lung cancer	159, 160	BMI in lymphoma patients	161
5-35876172-A-G (rs3194051)	3 (1)	Ile356Val	0.34 AFR/AA to 0.07 E ASN					severe liver disease	162
ITGAL		integrin alpha L, LFA-1, CD11A		lymphocyte function associated antigen		renal cancer, gastric cancer prognostic marker	163, 164	bioinformatic assn w aortic valve calcification in metabolic syndrome	165
16-30506720-G-C (rs2230433)	6 (3)	Arg791Thr	0.66 S ASN to 0.14 E ASN			protection against renal cell carcinoma	166		
						risk of IDC breast carcinoma in Han women	167		
JAML		junctional adhesion molecule-like, AMICA		regulates inflammatory cell migration	168, 169	lung cancer	151, 170	diabetic nephropathy	171, 172

(Continued)

10.3389/fendo.2023.1286979

TABLE 4 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
11-118198037-T-C (rs2298831)	8 (5)	Ile322Met	0.36 AFR/AA to 0.07 S ASN	steroid interaction with Duchenne muscular dystrophy in a multi-center European cohort (n=301 cases)	173				
LEPR		leptin receptor, CD295, OBR		required for lymphopoiesis				regulation of fat metabolism, obesity	174, 175
				leptin (ligand) produced by lymphocytes, NK cells, monocytes	176	susceptibility to HBV induced hepatocellular carcinoma	177	NAFLD	86
1-65570758-A-G (rs1137100)	7 (6)	Lys109Arg	0.81 E ASN to 0.10 MID E			colorectal cancer risk	178	early atherosclerosis	179
1-65592830-A-G (rs1137101)	7 (6)	Gln223Arg	0.88 E ASN to 0.34 MID E					obesity in Pacific Islanders	180
LILRA3		leukocyte Ig-like receptor A3, CD85E		soluble receptor for MHC I antigens	181	benign prostatic risk hyperplasia	182	elevated plasma HDL	183
					184	lymphomagenesis risk	185	downregulated in obesity, metabolic syndrome	186
19-54803504-A-C (rs6509862)*	3 (3)	Leu107Arg	0.79 AFR/AA to 0.12 EUR	statin intolerance	187				
NOD2		nucleotide binding oligomerization domain containing 2, CARD15, NLRC2, BLAU, IBD1		immune response, inflammation	188	triple negative breast cancer, therapeutic target	114, 189	deficiency promotes diabetes and NAFLD in mice	190, 191
16-50710713-C-T (rs2066842)	7 (4)	Pro241Ser	0.28 MID E to 0.01 E ASN			assn with follicular lymphoma survival	192		
TMEM173		STING1, stimulator of interferon genes, MPYS		activates IFN innate immune response genes	193, 194	multiple cancers	193, 195	cardiovascular and metabolic disease	196

(Continued)

10.3389/fendo.2023.1286979

TABLE 4 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
5-139477397-C-T (rs7380824)	17 (4)	Arg293Gln	0.41 E ASN to 0.14 EUR	LOF, decreased response to bacterial ligands, poxviruses	197–199				
5-139478340-C-G (rs78233829)	18 (4)	Gly230Ala	0.41 E ASN to 0.14 EUR	altered c-di-GMP lid conformation	198				
5-139481493-C-T (rs11554776)	16 (5)	Arg71His	0.41 E ASN to 0.03 AFR/AA	large effect on loss of function	197, 198				
TRPM8		transient receptor potential cation channel		immune response, inflammation, temperature regulation	200, 201	multiple cancers	202, 203	obesity, blood pressure	204, 205
2-233955144-G-A (rs7593557)	4 (2)	Ser419Asn	0.55 AFR/AA to 0.05 EUR	cold-induced hyperresponsiveness in bronchial asthma	206			blood lipid profile, BMI in Russian population	207

Genes listed have been associated with innate immunity/inflammation, cancer, and cardio-metabolic disease and have at least one variant in the human genome that occurs in at least 20% (Minor Allele Frequency (MAF) ≥ 0.2) of one or more populations. Missense variants are described by their location in the GRCh38 reference genome (accessed from gnomAD v3.1.2), rs number (reference SNP cluster ID), and amino acid location numbers and identities of the original and coded replacement. Populations are defined by Karczewski 2020 (15): African/African American (AFR/AA), East Asian (E ASN), non-Finnish European (EUR), Latino/Latina (LAT), Middle Eastern (MID E), and South Asian (S ASN). The number of affected transcripts listed include total transcripts (first number) and transcripts with missense mutations (in parentheses) that contain the gene variant, but do not include transcripts of any overlapping genes.

10.3389/fendo.2023.1286979

3.2 Unconventional innate immune genes with previously characterized population-enriched variants

Table 5 includes 18 genes representing several classes of proteins primarily associated with non-immune functions that occur as population-enriched variants shown to impact biological function. These genes include transport membrane proteins, consisting of the multidrug resistance pump (*ABCB1*), the Niemann-Pick cholesterol transporter 1 (*NPC1, SLC65A1*), and the Na+-dependent multivitamin transporter (*SLC5A6*). Among the class of regulatory metabolic enzymes are alcohol dehydrogenase (*ADH1C*), mitochondrial dihydroorotate dehydrogenase (*DHODH*), hydroxysteroid (17-beta) dehydrogenase 4 (*HSD17B4*) involved in peroxisomal fatty acid beta-oxidation, and glycogen phosphorylase B (*PYGB*) involved in regulating glycogen mobilization. Among the genes that participate in signal transduction are the membrane glycoprotein signaling co-receptor neuregulin (*NRG1*), phosphodiesterase 10A (*PDE10A*, which regulates cAMP concentrations), along with the small bioactive neuropeptide neuromedin B (*NMB*). Transcription factors and/or nucleic acid binding protein genes coded as population-enriched variants include hypoxia-inducible factor 2A (*EPAS1, HIF2A*), Iroquois homeobox 2 (*IRX2*), mismatch repair MutL homolog 3 (*MLH3*), the novel intracellular and extracellular ribonuclease T2 (*RNASET2*) and the SURP and G-Patch domain containing 1 (*SUGP1*) splicing factor. Also included are the lipid transport protein apolipoprotein B (*APOB*), the triacylglycerol lipase patatin-like phospholipase domain containing 3 (*PNPLA3*), and the adhesion cadherin family member desmoglein 2 (*DSG2*).

3.2.1 Multidrug resistance gene

The ATP binding cassette subfamily B member 1 (*ABCB1*) gene is commonly known as the first of two multidrug resistance (*MDR1*) genes in humans and is one of 48 ABC family members (217). ABCB1 functions at the plasma membrane as a 170 kDa monomer with 12 transmembrane domains (TMs), is glycosylated on the first extracellular loop (between TM1 and TM2), and has two intracellular ATP binding sites (one located between TMs 6 and 7, and the other in the carboxy terminus downstream of TM12). ABCB1 is expressed in a wide range of tissues (such as intestine, colon, placenta, liver, and blood-brain barrier) to protect against the intracellular build-up of xenobiotic molecules in vulnerable cells and organs by expelling toxins, including chemotherapeutics, from the cell interior. Thus, ABCB1 has become a widely-known source of and marker for chemoresistance (c.f. 219). ABCB1 also functions as a broad specificity lipid translocase (326). In a Chinese cohort, a variant in the ABCB1 promoter showed pleiotropic effects related to T2D and lipid metabolism (221). Notably, the *ABCB1* Ser893Ala variant (7-87531302-A-C, rs2032582) has been correlated with obesity in a Japanese population (220) and with increased susceptibility to lung cancer in a Spanish cohort (223). This *ABCB1* variant occurs in 91% of Africans/African Americans, but in only 35-62% of other populations (gnomAD) and was shown to impact drug (etanercept) efficacy in the treatment of Chinese Han patients with ankylosing spondylitis (222).

3.2.2 Mismatch repair protein MutL homolog 3

MLH3 is a homolog of the mismatch repair protein MutL. DNA mismatch repair (MMR) proteins play a vital role in maintaining genome integrity and in antibody maturation during class switch DNA recombination and somatic hypermutation (276). In cases of microsatellite instability, tumors often display somatic mutations in MLH3, while hereditary nonpolyposis colorectal cancer type 7 (HNPCC7) has been associated with germline mutations in the same gene (276, 327). Further, reduced MLH3 expression was observed in individuals diagnosed with grade II and III breast cancer, suggesting MLH3 may serve as a reliable susceptibility marker (278, 328). There was no correlation between the *MLH3* Pro844Leu variant (14-75047125-G-A, rs175080, predominantly found in the Middle East) and susceptibility to colorectal cancer in a predominantly white cohort (279). However, in Chinese patients this variant was associated with both cervical cancer (280) and hepatocellular carcinoma (281).

3.2.3 Apolipoprotein B

Lipoproteins enclose otherwise insoluble lipid particles (made up of a central core of cholesterol esters and triglycerides and an outer layer of phospholipids, free cholesterol, and apolipoproteins) for transport through the blood to various tissues (329). Apolipoprotein B (APOB) serves as the primary carrier for several classes of serum lipid particles, including chylomicrons, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate-density lipoprotein, and lipoprotein. In LDL particles, APOB interacts with the apoB/E (LDL) receptor, facilitating the removal of LDL cholesterol from the circulation via cellular uptake followed by intracellular LDL breakdown. In a small Japanese study correlating variants of genes related to lipid regulation (including apolipoproteins), the population-enriched missense *APOB* variant 2-21002409-C-T (rs1042034) correlated with HCV infection (235) variant has an allele frequency of 0.85 in African American populations but only 0.26 in East Asian populations (gnomAD). Another population-enriched missense *APOB* variant, 2-21008652-G-A (rs676210) (present in 73% of East Asians vs. 15% of Africans/African Americans (gnomAD)) correlated with the occurrence of initial non-cardioembolic ischemic stroke in a small European cohort (239). A third population-enriched missense *APOB* variant, 2-21028042-G-A (rs679899) (present in 85% of East Asians vs. 17% of Africans/African Americans (gnomAD)) and was protective against acute coronary syndrome in a Mexican population (238). This was associated with both hypertension and chronic kidney disease in a cohort of 3696 Japanese individuals (240).

Functional effects of additional *APOB* missense variants have also been reported. The Arg3638Gln variant (2-21005955-C-T, rs1801701), which is present in no more than 10% of any population, was associated with survival outcomes in non-small cell lung cancer (NSCLC) patients (236). Additionally, two

TABLE 5 Candidate Unconventional Innate Immune Genes at the Intersection of Cancer and Cardio-Metabolic Disease.

Gene (SNP)	Affected Transcripts	Name/Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
ABCB1		MDR1, P-glycoprotein 1, ATP binding cassette B1		multidrug resistance, xenobiotic protection	217	gallbladder carcinoma, drug resistance	218, 219	Japanese obesity, diabetes and serum lipids in Chinese	220, 221
7-87531302-A-C (rs2032582)	5 (3)	Ser893Ala	0.91 AFR/AA to 0.35 S ASN	drug efficacy	222	increased lung cancer risk	223		
ADH1C		alcohol dehydrogenase 1C (class I), gamma		downregulated during inflammation in ulcerative colitis,	224	liver cancer	225, 226	endogenous substrate bile acids involved in lipid, glucose and energy metabolism and impact metabolic syndrome	227, 228
				increased expression reduces IL-6 and IL-8 secretion	224	colorectal cancer	229		
				substrates (estrogen, bile acids) impact innate immunity	96, 230	lung cancer	231, 232		
4-99339632-T-C (rs698)	1 (1)	Ile350Val	0.52 EUR to 0.08 E ASN			increased cancer risk in Africans and Asians	233		
4-99342808-C-T (rs1693482)		Arg272Gln	0.52 EUR to 0.08 E ASN			Japanese upper aerodigestive tract cancer	234		
APOB		apolipoprotein B		HCV infection	235	variants associated with NSCLC survival	236	variants in Asian population associated with metabolic syndrome	237
2-21002409-C-T (rs1042034)	1 (1)	Ser4338Asn	0.85 AFR/AA to 0.26 E ASN	HCV infection	235			protective against acute coronary syndrome in Mexican population	238
2-21008652-G-A (rs676210)	1 (1)	Pro2739Leu	0.73 E ASN to 0.15 AFR/AA					stroke	239
2-21028042-G-A (rs679899)	3 (2)	Ala618Val	0.85 E ASN to 0.17 AFR/AA					chronic kidney disease risk among Japanese with hyptertension	240
DHODH		dihydroorotate dehydrogenase		defense against bacteria, viruses and protozoa	241–243	multiple cancers, pro-inflammatory ferroptosis	244, 245	glucose metabolism, insulin resistance	246, 247
16-72008783-A-C (rs3213422)	4 (4)	Lys7Gln	0.75 E ASN to 0.34 MID E	rheumatoid arthritis drug response	248–250				

(Continued)

10.3389/fendo.2023.1286979

TABLE 5 Continued

Gene (SNP)	Affected Transcripts	Name/Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
DSG2		desmoglein 2		receptor for selected adenovirus serotypes	251	multiple cancers	252	pancreatic islet function, insulin resistance	253, 254
18-31542836-G-A (rs2278792)	1 (1)	Arg773Lys	0.48 E ASN to 0.08 AFR/AA					cardiomyopathy in Yi population	255
EPAS1		endothelial PAS domain protein 1, HIF2A, hypoxia-inducible factor 2A		IL31 induction in CD4+ T cells	256	non-small cell lung cancer, colorectal, others	257, 258	dyslipidemia and NAFLD	259
2-46382433-A-C (rs59901247)	2 (1)	Thr766Pro	0.41 AFR/AA to 0.01 S ASN	N-acetylaspartate levels in elite athletes	260				
HSD17B4		hydroxysteroid (17-beta) dehydrogenase 4, DBP, MFE-2, MPF-2, SDR8C1		peroxisomal multifunctional protein (detox)	261	overexpressed in prostate cancer	262	peroxisomal fatty acid oxidation	263
						downregulated in non-small cell lung cancer	264	lipid and bile acid metabolism	265
5-119475838-G-A (rs25640)	18 (7)	Arg131His, Arg106Pro or His	LAT 0.56 to AFR/AA 0.17	homozygous D-bifunctional peroxisomal protein disease	266				
5-119525243-T-C (rs11539471)	20 (7)	Trp536Arg	AFR/AA 0.3 to 0.00 E ASN			protective against endometrial cancer	267		
5-119526018-A-G (rs11205)	21 (7)	Ile584Val	LAT 0.53 to 0.29 S ASN			testicular germ cell tumor risk	268		
IRX2		Iroquois Homeobox 2		mediates expression of immune regulators MMP9 and VEGF	269, 270	sarcomas, breast, leukemia	271, reviewed in 272	VEGF altered in ischemic stroke and atherosclerosis	reviewed in 273
						nasopharyngeal cancer marker	274		
5-2748943-C-A (rs76906087)	2 (1)	Glu255Asp	0.28 S ASN to 0.03 AFR/AA					present in 5/10 Indian congenital heart defects	275
MLH3		mutL homolog protein 3, mismatch repair, HNPCC7		Ig class switch	276	colorectal cancer microsatellite instability	277	mutations only found in breast cancer patients with metabolic disease	278

(Continued)

10.3389/fendo.2023.1286979

TABLE 5 Continued

Gene (SNP)	Affected Transcripts	Name/Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
14-75047125-G-A (rs175080)	4 (3)	Pro844Leu	0.52 MID E to 0.15 E ASN			no assn w CRC in white population	279		
						susceptibility to cervical cancer in Chinese	280		
						hepatocellular carcinoma in Han	281		
NMB		neuromedin B		innate immune response to influenza A virus	282	cervical and other cancers	283	highly expressed in adipose, variants related to obesity	284
15-84657289-G-T (rs1051168)	2 (2)	Pro73Ala	0.37 MID E to 0.05 AFR/AA					obesity	284
NPC1		Niemann Pick cholesterol transporter, SLC65A1		NKT cell development	285	breast cancer	286	obesity	287, 288
				endosomal entry receptor for ebolavirus	289			type 2 diabetes	290
18-23540480-T-C (rs1805082)	3 (2)	Ile858Val	0.63 E ASN to 0.30 MID E					obesity	291
18-23560468-T-C (rs1805081)	2 (1)	His215Arg	0.41 EUR to 0.08 AFR/AA					cardiovascular disease (Iranian)	292
NRG1		neuregulin		macrophage response to yeast	293	NRG1 gene fusions drive multiple solid tumors	294	regulates insulin sensitivity	295
8-32595840-G-A (rs3924999)	21 (17)	Arg30Gln	0.77 E ASN to 0.11 AFR/AA	susceptibility to schizophrenia in Chinese Han	296				
				Fin susceptilibity to reward dependence in major depression	297				
PDE10A		phosphodiesterase 10A		mediator of lung and vascular inflammation	298, 299	ovarian cancer target	300	diabetes, diet-induced obesity, insulin sensitivity	301
6-165654841-C-G (rs880121)	10 (2)	Glu15Asp	0.63 MID E to 0.04 E ASN	sporadic Parkinson's in Chinese Han	302				

(Continued)

10.3389/fendo.2023.1286979

TABLE 5 Continued

Gene (SNP)	Affected Transcripts	Name/Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
PNPLA3		Patatin Like Phospholipase Domain Containing 3, adipnutrin		platelet and monocyte levels	303	hepatic cancer (Europeans, Han Chinese)	304, 305	NAFLD	118, 303
22-43928847-C-G (rs738409)	4 (2)	Ile148Met (2 of 4 transcripts)	0.42 LAT to 0.14 AFR/AA			hepatic cancer	304, 305	NAFLD	303
PYGB		glycogen phosphorylase B		TCR activation stimulates PYGB-dependent glycogenolysis	306	prostate, gastric, non-small cell lung cancers	307–309	carbohydrate metabolism	310
20-25278370-G-T (rs2228976)	1 (1)	Ala303Ser (1 transcript)	0.34 E ASN to 0.08 AFR/AA			present in European desmoid tumors in familiall adenomatous polyposis (FAP)	311		
RNASET2		ribonuclease T2, RNASE6PL		degrades microbial RNAs for recognition by TRL8	312, 313	tumor suppressor in lung and ovarian cancers	151, 313	myocardial lipotoxicity in obesity	314
6-166938616-C-A (rs3777722)	14 (1)	Arg226Met	0.4 E ASN to 0.04 AFR/AA	putative association with preterm birth	315				
SLC5A6		Na+ dependent multivitamin transporter		anti-inflammatory in murine gut	316	gastric cancer	317	lymphocyte metabolic programming	318
				B lymphocyte maturation	318				
2-27201768-G-A (rs1395)	7 (2)	Ser481Phe	0.86 E ASN to 0.24 AFR/AA					serum levels of glucose (during fasting) and pantothenate	319, 320
SUGP1		SURP And G-Patch Domain Containing 1, Splicing Factor 4		altered splicing in innate immunity	321	pan-cancer	322	NAFLD	118
19-19302283-C-T (rs17751061)	8 (1)	Arg290His (1 of 8 transcripts)	0.26 MID E to 0.00 E ASN	serum IgE levels	323			waist-hip ratio fasting insulin and glucose	324 325

Genes listed have been associated with innate immunity/inflammation, cancer, and cardio-metabolic disease and have at least one variant in the human genome that occurs in at least 20% (Minor Allele Frequency (MAF) ≥ 0.2) of one or more populations. Missense variants are described by their location in the GRCh38 reference genome (accessed from gnomAD v3.1.2), rs number (reference SNP cluster ID), and amino acid location numbers and identities of the original and coded replacement. Populations are defined by Karczewski 2020 (15): African/African American (AFR/AA), East Asian (E ASN), non-Finnish European (EUR), Latino/Latina (LAT), Middle Eastern (MID E), and South Asian (S ASN). The number of affected transcripts listed include total transcripts (first number) and transcripts with missense mutations (in parentheses) that contain the gene variant, but do not include transcripts of any overlapping genes.

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nonsynonymous variants unique to the Asian population, namely 2-21006289-G-A (rs144467873, MAF = 0.001253 and 0.0003594 in East and South Asians, respectively, but < 0.00008 for all other populations (gnomAD v2.1.1) and 2-21029662-G-A (rs13306194, MAF = 0.1343 in East Asians, MAF < 0.007 in all other populations) were evaluated for their association with lipid profiles, metabolic syndrome and risk of diabetes in a large Taiwan Biobank study (237). Both variants were independently associated with total, LDL, and non-HDL cholesterol levels, whereas rs144467873 (Arg3527Trp) was associated with elevated lipid levels and metabolic syndrome, while rs13306194 (Arg532Trp) was linked with serum triglyceride levels.

3.2.4 Dihydroorotate dehydrogenase

Dihydroorotate dehydrogenase (DHODH), which catalyzes the initial and rate-limiting step of the *de novo* pyrimidine pathway, is positioned on the inner mitochondrial membrane (330). DHODH has been a therapeutic target for the treatment of rheumatoid arthritis, psoriasis, autoimmune disorders, and Plasmodium, bacterial and fungal infections (241). For over five decades, elevated DHODH expression has been known to promote tumor progression. *De novo* pyrimidine synthesis becomes essential during increased demands for nucleic acid precursors in rapidly dividing cells making cancer cells highly dependent on DHODH and suggesting that this enzyme is a strategic target for cancer therapy (245). Recently, DHODH was also shown to protect against mitochondrial ferroptosis by preventing the lipid peroxidation that triggers this phenomenon (244). Notably, cancer cells exhibit low levels of glutathione peroxidase 4 (GPX4) and inhibition of DHODH hinders respiration, boosts glycolysis and enhances GLUT4 translocation to the plasma membrane (246). This is further supported by the activation of the tumor suppressor p53, which elevates the levels of GDF15/MIC1 (another candidate listed in Table 4), a cytokine known for its appetite-reducing effects and ability to extend lifespan. DHODH inhibition that depletes pyrimidine ribonucleotides is also thought to be responsible for reduced RNA virus replication and decelerated growth in rapidly dividing cells, such as activated T cells and, as just mentioned, cancer cells (243). Interestingly, uridine, a pyrimidine nucleoside present in RNA, has been shown to modulate insulin activity and glycogen synthesis through its interaction with uridine diphosphate (UDP)-glucose (247). The base sequence of the *DHODH* gene is remarkably conserved, with one exception being a prevalent Lys7Gln missense polymorphism (16-72008783-A-C, rs3213422) found in its first exon (248). This variant is found in 75% of individuals in East Asia vs. 34% of individuals in the Middle East (gnomAD) and has been linked with drug (leflunomide) response to rheumatoid arthritis (248–250).

3.3 Population-enriched variants with unknown/uncharacterized function

No known effect on gross phenotype or evidence of association with disease has yet been reported among the population-enriched variants identified with the 20 genes listed in Table 6. However, a newly released resource, GWAS Central (457), was accessed to provide phenotype associations with a subset of variants in Table 6. Further, disease disparities related to the parent gene and/or other variants of the gene were identified and/or the predicted impact of a population-enriched variant on the coded change in protein function were evaluated and listed in Table 6.

3.3.1 Understudied genes SIPA1L2 and TVP23C

Among the 20 genes in Table 6, six of these remain understudied, including the exosomal CCDC105/TEKTL1, the putative protein disulfide isomerase CRELD2, the FAM131C protein with unknown function, the putative immune checkpoint ITPRIPL1 membrane protein, the presumptive neural GTPase activator SIPA1L2, and the putative vesicular protein transporter TVP23C. Notably, evidence of an impact on function does exist for one of two population-enriched variants of *SIPA1L2* and one of three population-enriched variants of *TVP23C*. In the case of *SIPA1L2*, both characterized and uncharacterized variants occur at the same high frequency (MAF = 0.48) in East Asians, but Gly1639Ser increases the number of potential phosphorylation sites, whereas Thr1322Ala reduces them, which may result in different functional outcomes (e.g. changes in activation status and/or protein-protein interactions). In both *SIPA1L2* variants, eight of nine possible transcripts code for missense mutations, whereas with *TVP23C*, only in the canonical transcript does the variant result in a missense mutation among five (Ser256Arg) or twelve (Trp202Arg and Ser199Thr) possible isoforms, some of which are read-through fusions with CDRT4 (CMT1A Duplicated Region Transcript 4). It is likely that the *TVP23C* Trp202Arg and Ser199Thr variants commonly co-occur, given their proximity to one another on the gene and their matching frequency distribution, as both have MAFs that range from 0.54 in East Asians to 0.28 in South Asians. Thus, one might speculate that the unknown functional impact of Ser199Thr matches that of Trp202Arg, which was found in a choriocarcinoma patient (458). Notably, choriocarcinoma shows a geographical disparity as it occurs at a ten-fold greater frequency in Southeast Asia than in the West (reviewed in 439). The third *TVP23C* variant Ser256Arg is most common among Africans/African Americans (MAF = 0.24) and involves the loss of a potential phosphorylation site about 50 amino acid residues downstream of the other two *TVP23C* variants.

3.3.2 Additional representative genes of interest

The remaining 14 genes in Table 6 are better characterized; notably, many have pleiotropic functions beyond the functions initially attributed to them. ATPase Phospholipid Transporting 10D (*ATP10D*) codes for the catalytic subunit of a glycoslyceramide flippase complex at the endoplasmic reticulum (ER), nucleoplasm, and plasma membrane. DnaJ Heat Shock Protein Family (Hsp40) Member B11 (*DNAJB11*) codes for an ER-resident and secreted co-chaperone of BiP/GRP78/HSPA5. Desmocollin 1 (*DSC1*) codes for an adhesive glycoprotein cadherin family member. The Immunoglobulin Like Domain Containing Receptor 1 protein (ILDR1) maintains structural

TABLE 6 Geographic Ancestral Variants with Unknown/Uncharacterized Function.

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
ATP10D		ATPase, class V, type 10D		sphingolipids assoc w/ innate immune response	331	lung cancer	332	controls circulating sphingolipids responsible for atherosclerosis, T2D	333
		transports glucosylceramide, a sphingolipid		downregulated by TGFb in eosinophils	334	colorectal cancer	335		
4-47514685-C-T (rs33995001)	3 (2)	Thr43Ile	0.44 LAT to 0.16 E ASN						
4-47582029-G-A (rs1058793)	4 (1)	Val1240Ile	0.58 E ASN to 0.16 EUR	found in Bulgarian centenarians	336				
4-47591266-G-C (rs4145944)	3 (1)	Ser1389Thr	0.62 AFR/AA to 0.12 E ASN					serum cholesterol	323
		Disease Disparity: Sphingolipid levels are elevated in lupus [337] and hepatocellular carcinoma [338], two diseases with known disparities based on geographic ancestry [339 and 340, respectively]							
CCDC105		coiled-coil domain containing 105, tektin like 1, TEKTL1		HBV infection	341	colon, lung cancer	342, 343	interacts with MESD [344], part of WNT pathway in cancer and cardiovascular disease	345, 346
19-15020518-G-A (rs35352238)	1 (1)	Val245Met	0.54 E ASN to 0.11 AFR/AA						
19-15023114-C-A (rs8112667)	1 (1)	Pro499Thr	0.53 E ASN to 0.18 MID E	serum fibrinogen	323				
		Disease Disparity: interacts with MAGEA11 [347], a biomarker for stomach cancer [348], which shows racial and geographic disparities [reviewed in 349]							
CRELD2		cysteine rich with EGF like domains 2		marker in joint infection	350	multiple cancers	350	cardiometabolic disease	350
22-49921715-C-A (rs8139422)	10 (5)	Asp182Glu	0.51 AFR/AA to 0.03 EUR	age-related macular degeneration	351				
		Disease Disparity: breast [352] and prostate [353] cancers, reviewed in [60]							
CSF2RB		IL3RB, CD131, IL5RB		colony stimulating factor 2 receptor beta surfactant homeostasis	354	variant assoc w leukemia variant assoc w breast cancer	355 356	peptide agonists of EPOR/CD131 heteroreceptor are anti-atherosclerotic	357
22-36930401-G-C (rs16845)	4 (4)	Glu249Gln	0.21 AFR/AA to 0.00 E ASN						
		Disease Disparity: breast cancer [60, 352]							

(Continued)

TABLE 6 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
DNAJB11		ER-associated DnaJ Hsp40 member B11		immune infiltration in thyroid	358	liver, breast, pancreatic cancer	358	diabetes	119
3-186583914-A-G (rs8147)	3 (2)	Ile264Val	0.47 AFR/AA to 0.15 E ASN	rheumatoid arthritis	359				
		Disease Disparity: context-dependent breast cancer [60, 352]							
DSC1		desmocollin 1		reduced in pediatric pneumomia	360	head and neck, ovarian, anal	361–363	prevents HDL biogenesis	360
18-31140184-C-T (rs17800159)	2 (2)	ValIle460Ile	0.48 E ASN to 0.03 AFR/AA						
		Disease Disparity: ovarian cancer [364]							
FAM131C		family with sequence similarity 131 member C		autoimmune target in ApoE KO mice	365	associated with cancer survival	366	upregulated in high fat diet	367
				upregulated in M1 macrophage-rich adipose	368				
1-16058636-C-A (rs1832151)	2 (1)	Ser215Ile	0.33 AFR/AA to 0.0013 E ASN						
1-16060000-C-T (rs71510977)	2 (1)	Arg107Gln	0.78 E ASN to 0.10 AFR/AA						
1-16062531-T-C (rs2863458)	2 (1)	Lys48Glu	0.38 AFR/AA to 0.01 E ASN					waist-hip ratio	324
		Diseaese Disparity: interacts with VSNL1 [369], which is associated with colon cancer [370, 371] and gastric cancer [372], both cancers that show ethnic disparities [373]							
ILDR1		Ig-like domain containing receptor 1		flu virus replication	374	gastric cancer marker	375	diet-induced obesity and hyperglycemia	376
3-121993958-G-C (rs3915061)	5 (3)	Pro264Arg	0.49 S ASN to 0.22 E ASN						
		Disease Disparity: gastric cancer [reviewed in 349, 373]							
ITPRIPL1		inositol triphosphate interacting protein like 1, KIAA1754L		immune checkpoint inhibition of T-cell activation	377	gene methylation assoc w breast cancer	378	diabetic nephropathy	379
2-96328019-C-T (rs2279105)	4 (4)	Thr463Met	0.69 S ASN to 0.21 E ASN	HbA1c	323				
		Disease Disparity: breast cancer [60, 352]							
PDIA6		protein disulfide isomerase A6, ERP5		lymphoid and myeloid development	380 381	NSCLC, breast, bladder, gastic, oral,	382–387	diabetes	119

(Continued)

TABLE 6 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
		TXNDC7 thioredoxin domain containing 7		platelet aggregation and activation		pancreatic cancers			
2-10790777-T-C (rs4807)	6 (6)	Lys214Arg	0.39 E ASN to 0.125 AFR/AA	serum IgE, HbA1c, rheumatoid arthritis	323, 359			age-related macular degeneration	351
		Disease Disparity: breast [60, 352] and gastric cancer [reviewed in 349, 373]							
RB1		retinoblastoma 1 transcriptional co-repressor		associated with Treg infiltration in bladder cancer	388	tumor suppressor in multiple cancers	389	negative association with BMI and insulin resistance	390
13-48599402-T-C (rs1887154)	1 (1, non-cannonical)	Leu99Ser (1 transcript)	0.79 AFR/AA to 0.28 MID E						
		Predicted Impact: potential phosphorylation site introduced (+Ser): RB1 phosphorylation inactivates this tumor suppessor and promotes tumor progression [389], impacts several regulatory pathways and protein-protein interactions [391]							
RPAIN		RPA interacting protein, nuclear transporter, HRIP		variants assoc w/ influenza A virus (RNA) pathogenesis	392 393	alternate splice variants in colon cancer, glioblastoma	394 395	gene expression is associated with BMI	396
17-5422825-C-G (rs12761)	16 (11)	Asn103Lys	0.82 E ASN to 0.22 AFR/AA					BMI	397
		Disease Disparity: colon cancer [398]							
SEMA6D		sematophorin D6		regulates late phase CD4+ T cells response, anti-inflammatory macrophage polarization	399 400, 401	lung cancer, chemoresponse in breast cancer	151, 402	cardiomyocyte development, immune cell metabolism	401 403
15-47764022-A-G (rs3743279)	9 (9)	Asn307Ser	0.24 AFR/AA to 0.00 EUR	skin pigmentation	404				
15-47765874-G-A (rs532598)	9 (8)	Ser478Asn	0.59 E ASN to 0.34 MID E	partial epilepsies, asthma	405, 406				
		Disease Disparity: SEMA6D expression is associated with survival in triple negative breast cancer [407], which occurs disproportionately among women of African descent [352]							
		Predicted Impact: both variants may alter phosphorylation status (+/- Ser) with the potential to alter activity, stability and/or protein-protein interactions							
SIPA1L2		signal induced prolif assoc 1 like 2, SPAR2, SPAL2, KIAA1389		assoc w/ H2O2 release from healthy Caucasian lymphoblastoids	408	metastatic clear cell kidney carcinoma (EUR)	409	identified by bioinformatics in type 2 diabetes	410
				inactivates RAP1 (involved in inflammatory response)	410	varying correlation with 23 cancers	411	gene expression assoc with NAFLD	412

(Continued)

TABLE 6 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
1-232403473-C-T (rs2275303)	9 (8)	Gly1639Ser	0.48 E ASN to 0.00 AFR/AA	Alzheimer's in Asian population	413				
1-232439175-T-C (rs2275307)	9 (8)	Thr1322Ala	0.48 E ASN to 0.22 EUR						
		Disease Disparity: gene shows highest correlation with cancers with known ethnic disparities [411], including bladder [414], esophageal [415], hepatocellular carcinoma [416], and ovarian [364]							
		Predicted Impact: both variants may alter phosphorylation status (+Ser and -Thr) with the potential to alter activity, stability and/or protein-protein interactions							
TBC1D4		AS160 Akt substrate of 160 kD		delivery to chlamydial inclusions	417	breast cancer, multiple myeloma	418, 419	nonsense variant confers insulin resistance and T2D in Greenlandic population	420
13-75286865-A-G (rs557337)	4 (4)	Val1275Ala	0.49 AFR/AA to 0.00 E ASN	fibrinogen	323				
13-75481466-G-A (rs77685055)	3 (3)	Ala101Val	0.29 E ASN to 0.02 AFR/AA	RBC count mean corp. Hb, hematocrit	421–423				
		Disease Disparity: gene associated with cancers that show ethnic disparities, including breast [60, 352] and multiple myeloma [424]							
TESPA1		HSPC257, thymocyte expressed, positive selection associated 1		development and maturation of T cells TCR regulation	425	pan-cancer prognostic	426	mito-assoc ER mb proteins are assoc w/ cardiovascular disease	427
12-54950349-C-G (rs2171497)	7 (2, non-canonical)	Leu103Phe	0.64 E ASN to 0.05 AFR/AA	ulcerative colitis	428			BMI	397
12-54961249-C-T (rs997173)	8 (5)	Leu496Lys	0.63 E ASN to 0.06 AFR/AA	Kuru and sCJD (prion diseases)	429				
		Disease Disparity: although TESPA1 expresssion is upregulated in several cancers, the most dramatic increase in expression occurs in acute myeloid leukemia (AML) [426], a cancer which shows ethnic disparities [430]							
TVP23C		TGN vesicle protein 23 homolog C, FAM18B2		gene is an integration site for HBV in liver cancer	431	plasma protein assoc w/ colorectal cancer	432	bioinformatic feature gene assoc w/ ischemic stroke	433
				platelet granule secretion, chronic immune thrombocytopenia	434	data mining prognostic marker for liver cancer	435	readthrough translation with CDRT4 downregulated in obese individuals	436
				associated with CD4 Tex (exhausted T) cells	437	fusion CDRT4 found in pancreatic cancer	438		
17-15502927-A-C (rs73289533)	5 (1)	Ser256Arg	0.24 AFR/AA to 0.00 E ASN						

(Continued)

TABLE 6 Continued

Gene (SNP)	Affected Transcripts	Name/ Function	Population MAF Range	Associated w/ Immunity	Ref	Associated w/ Cancer	Ref	Associated w/ Metabolic Disease	Ref
17-15540420-A-G (rs200768112)	12 (1)	Trp202Arg	0.54 E ASN to 0.28 S ASN			choriocarcinoma	439		
17-15540428-C-G (rs2302252)	12 (1)	Ser199Thr	0.54 E ASN to 0.28 S ASN						
		Disease Disparity: Choriocarcinoma incidence rate 10-fold higher in Southeast Asia than in the West [439]							
ZNF23		KOX16, ZNF359, ZNF612		correlation with pathogenic environment	49	downregulated in cancer	440	mitochondrial dysregulation in melanoma	441
16-71453303-T-C (rs2070832)	9 (7)	Ser28Gly	0.94 AFR/AA to 0.29 E ASN	partial epilepsies	405			BMI	323
		Disease Disparity: reduced expression of this tumor repressor gene in ovarian and endometrial cancers [440]**;** oviarian cancers show ethnic disparities [364]							
		Predicted Impact: variant occurs in a putative N-terminal strong transcriptional repressor KRAB domain [442], loss of Ser may alter activity and/or binding interactions							
		Note: ZNF23 KRAB domain is truncated and does not appear to alter repressor activity [440], however not all ZNF23 interactors (such as mitochondrial ATPAF2. keratin-associated KRTAP10-8, myelin-associated MOBP, growth factor signaling regulators SPRED1 and SPRY1, and TNFR associated adaptor TRAF1), are transcription factors							
ZNF267		Zinc Finger Protein 267, HZF2		P. gingivalis infection	443	hepatic, colorectal cancer, B-cell lymphoma	444–446	liver disease (cirhhosis), NAFLD	447, 448
16-31915298-G-A (rs3850114)	2 (1)	Cys350Tyr	1.0 E ASN to 0.61 AFR/AA	serum IgE	323				
		Disease Disparity: hepatic and colorectal cancers show ethnic disparities [340, 449]							
ZNF628		Zinc Finger Protein 628, ZEC		target gene protamine inhibits microbial infection	450–452	protamine 1 marker for leukemia and colorectal cancer	453, 454	protamine alters BP, mitochondrial function	455
19-55481893-A-G (rs34864744)	2 (2)	Thr234Ala	0.93 AFR/AA to 0.45 E ASN						
		Disease Disparity: ethnic disparities observed in colorectal cancers [449]							
		Predicted Impact: variant alters potential phosphorylation status (-Thr) in a disordered region of this transcription activator [344] between two zinc finger clusters of the canonical protein that bind DNA independently [456]							

Genes listed have been associated with innate immunity/inflammation, cancer, and cardio-metabolic disease and have at least one variant in the human genome that occurs in at least 20% (Minor Allele Frequency (MAF) ≥ 0.2) of one or more populations. Missense variants are described by their location in the GRCh38 reference genome (accessed from gnomAD v3.1.2), rs number (reference SNP cluster ID), and amino acid location numbers and identities of the original and coded replacement. Populations are defined by Karczewski 2020 (15): African/African American (AFR/AA), East Asian (E ASN), non-Finnish European (EUR), Latino/Latina (LAT), Middle Eastern (MID E), and South Asian (S ASN). The number of affected transcripts listed include total transcripts (first number) and transcripts with missense mutations (in parentheses) that contain the gene variant, but do not include transcripts of any overlapping genes.

barriers in epithelia and auditory neurosensory hair cells (459), mediates fatty acid and lipoprotein-stimulated cholecystokinin secretion in the small intestine (460), regulates water homeostasis in kidney (461), and interferes with phospholipid scramblase (PLSCR1) anti-viral activity (374). Protein Disulfide Isomerase Family A Member 6 (PDIA6) inhibits intracellular aggregation of misfolded proteins and extracellular aggregation of platelets (381). Replication Protein A Interacting Protein (RPAIN) participates in

DNA metabolism, nuclear import, and response to UV light. The Semaphorin 6D (*SEMA6D*) gene codes for an integral membrane protein member of the semaphorin family whose members collectively sculpt axonal paths, branches, conduction, and target selection; the distribution of nine *SEMA6D* transcript isoforms varies according to developmental stage and tissue type. Tre-2/BUB2/CDC16 (TBC) Domain Family Member 4 (TBC1D4, also referred to as Akt Substrate of 160 kD or AS160) is a Rab-GTPase activator with multiple transcript variants; isoform 2 promotes SLC2A4/GLUT4 presentation at the plasma membrane to increase cellular glucose uptake (344). Thymocyte Expressed, Positive Selection Associated 1 (*TESPA1*) interacts with COP9 and TCR signalsomes and participates in T cell differentiation and T cell receptor signaling. Three zinc finger (ZNF) proteins ZNF23, ZNF267, and ZNF628 localize to the nucleus and regulate transcription. Parent genes and the corresponding population-enriched variants of the common cytokine receptor beta chain *CSF2RB* and the transcription co-repressor *RB1* are both discussed below.

3.3.2.1 CSF2RB

Colony stimulating factor 2 receptor beta (CSF2RB, CD131) forms dimers with the alpha receptor subunits for cytokines IL-3, IL-5, and GM-CSF (CSF2). As noted above, a population-enriched variant of the IL3RA subunit also exists, although the population distributions of these two variants are very different: the Val323Leu *IL3RA* variant is found least frequently among Africans/African Americans (MAF = 0.06, Table 4), whereas the Glu249Gln *CSF2RB* variant is more predominant in Africans/African Americans than any other population (MAF = 0.21).

CSF2RB is associated with pulmonary alveolar proteinosis (PAP), which involves the accumulation of surfactant and macrophage dysfunction in alveoli (reviewed in 462). Although studies so far have not suggested geographic or population differences in PAP occurrence, the most common PAP co-morbidities include cardiovascular disease, type 2 diabetes, and hypertension, all of which are unevenly distributed among populations. Further, a rare Arg461Cys *CSF2RB* variant (MAF< 0.001, not listed in Table 6) was found in individual patients with leukemia (355) and breast cancer (356). Notably, both of these cancers show racial and ethnic disparities [430 and 352 respectively].

3.3.2.2 RB1

Retinoblastoma (RB1) was one of the first tumor suppressors to be identified. Alterations in the expression and sequence of the *RB1* gene have been implicated in several cancers besides retinoblastoma where they were originally characterized (reviewed in 391). More than 40 years of extensive research indicates that regulation of and by RB1 is highly complex, linked with multiple signaling pathways, and varies with context. Not surprisingly, the number of proteins shown to interact with RB1 is more than 30 as curated by UniProt (344) and more than 150 as curated in BioGRID (463) and IntAct (464). The functional diversity of the binding partners of RB1 is consistent with its pleiotropic effects, which extend beyond transcription and cell cycle control to include progenitor maturation, terminal differentiation, and immune evasion (391).

Five protein coding transcripts of *RB1* have been identified. These include 1) the MANE select (canonical) protein composed of 27 exons encoding a total of 928 aa residues; 2) a closely related transcript that is 5 as shorter and differs from the canonical protein by 18 of its last 19 C-terminal residues; and 3) three much shorter transcripts (coding for 53, 103 or 110 aa peptides) which include all or portions of only 2 or 3 exons of the canonical protein. Of these shorter transcripts, the two shortest are derived from the N-terminal portion of RB1. In contrast, the 110 aa non-canonical transcript codes for an unidentified N-terminal residue equivalent to the Ser501 residue of the canonical protein and then aligns with all canonical residues up through Ser565; the remaining non-canonical aa residues 66-110 are located downstream of the canonical C-terminal residue 928. It is in this extra-exonic portion of the non-canonical 110 aa *RB1* isoform that the Leu99Ser population-enriched variant, which introduces a potential phosphorylation site, is found. In spite of the high number of aa residues ($n \geq 105$) in the canonical RB1 protein that are known to be post-translationally modified, within the aa 501-565 residue range that overlaps with the first 65 residues of the 110 aa isoforms, only two potential ubiquitination sites have been identified in the vicinity of aa 550) (391).

4 Conclusion

Population studies have traditionally focused on querying individual diseases or combinations of diseases, including cancer and cardio-metabolic disease, which frequently show disparate prevalence and/or severity in non-European populations. In this perspective, we have introduced a complementary approach that explores the intersection of innate immunity, cancer, and cardio-metabolic diseases. The effective elimination of disease disparities will involve not only addressing the profound social and behavioral determinants of health, but also identifying and treating the biological contributors of disease that include novel genes as well as previously characterized genes that participate in novel pathways.

We suggest that careful evaluation of population differences in conventional and unconventional innate immune genes and their related pathways will provide key insights into the underlying mechanisms that connect cancer and cardio-metabolic diseases. At the same time, the genes we have identified in this study that are associated with both cancer and cardio-metabolic diseases may play critical roles in under-appreciated facets of innate immunity and their contribution to disease disparities. Further, we predict that the geographic ancestral distribution of innate immune gene variants will match the geographical distribution of the environmental stressors (including but not limited to infectious agents) that they are designed to mitigate as described above for *HbS* and *DARC* variants with malaria (Section 1.3).

The genes we have identified serve as potential targets for diagnostics and/or therapeutic interventions. Notably, the development and clinical use of therapeutics targeting these candidate genes is likely to require a nuanced approach since variations in these genes across different global populations are likely to alter the activity and/or expression of their coded proteins, with the subsequent potential to impact therapeutic outcomes. Assessing the prevalence of specific target variants in one or more major populations and, more precisely, the presence of these specific target variants in individuals is a consequential step towards increasing the safety and effectiveness of emerging therapies. This perspective highlights the importance of 1) considering genetic diversity in identifying and developing treatments and 2) continuing to incorporate ongoing GWAS projects as they identify and characterize new or understudied genes and their population-enriched variants associated with complex and infectious diseases.

Author contributions

SY: Conceptualization, Data curation, Writing – original draft. DH: Data curation, Writing – original draft. KW: Data curation, Writing – original draft. NL: Writing – review & editing. KSK: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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