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The contribution of natural selection to present-day susceptibility to chronic inflammatory and autoimmune disease

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Abstract

Chronic inflammatory and autoimmune diseases have been the focus of many genome-wide association studies (GWAS) because they represent a significant cause of illness and morbidity, and many are heritable. Almost a decade of GWAS studies suggests that the pathological inflammation associated with these diseases is controlled by a limited number of networked immune system genes. Chronic inflammatory and autoimmune diseases are enigmatic from an evolutionary perspective because they exert a negative affect on reproductive fitness. The persistence of these conditions may be partially explained by the important roles the implicated immune genes play in pathogen defense and other functions thought to be under strong natural selection in humans. The evolutionary reasons for chronic inflammatory and autoimmune disease persistence and uneven distribution across populations are the focus of this review.

Introduction

Like all other organisms, humans are the transient outcome of eons of ancestral creatures affected by evolutionary forces. It has long been considered that chief amongst the factors that influence human physiological composition is natural selection exerted on the immune system [1,2]. As our primary interface with the environment, our immune system is thought to have been under severe selective pressure mediated by pathogens [3–7,8••,9–14,15••]. Indeed, studies examining human genomes for signs of positive selection, or 'selection for' particular traits, repeatedly find an overrepresentation of immune system genes associated with these signatures [16–21]. While we would expect the individuals of our young species to be phenotypically very similar, humans considerably vary in their capacity to manifest chronic diseases characterized by long-term, overt and pathological inflammation such as chronic inflammatory and many autoimmune diseases (Table 1). The persistence and increasing incidence of conditions characterized by pathological inflammation is a particularly enigmatic aspect of the diversification of human immunity, as many manifest in pre- and peri-reproductive individuals and negatively affect reproductive fitness. The factors contributing to disparate chronic inflammatory and autoimmune disease incidence are

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myriad and include both genetic as well as current environmental factors. Here, we consider how past human immune system adaptation may have contributed to current disease disparities between individuals and human populations.

The genetic basis of susceptibility to autoimmune and inflammatory disorders

With the advent of whole-genome genotyping arrays, examinations of the entire genome for associations with complex phenotypes have become common practice. In less than a decade, such genome-wide association studies (GWAS) have found hundreds of loci associated with chronic inflammatory and autoimmune diseases. The hundreds of genes implicated in the progression of these diseases by GWAS have revealed two major patterns that make the persistence and uneven distribution of chronic conditions characterized by pathological inflammation particularly intriguing. First, genes implicated in infectious disease susceptibility overlap considerably those associated with chronic inflammatory and autoimmune diseases [22•,23•,24,25••,26]. Such observations have forced a shift from disease models that emphasize individual inflammatory disease pathways, to a model of pathological inflammation regulated by a tightly regulated network of genes that are implicated in multiple diseases [24,27,28]. A recent assessment of risk allele sharing across seven chronic inflammatory and autoimmune diseases (celiac disease, multiple sclerosis, rheumatoid arthritis, Crohn's disease, psoriasis and systemic lupus erythematosus) found that over 40% of the associated single nucleotide polymorphisms (SNPs) were shared across multiple, though not by all seven, conditions [22•]. Via a large meta-analysis of multiple GWAS for inflammatory bowel disease (IBD), Jostins *et al*. found that 66 of 154 of loci associated with IBD were also associated with other 'immune-mediated diseases', including 8 loci associated with ankylosing spondylitis, and 14 loci associated with psoriasis [23•].

The overlap between chronic inflammatory and autoimmune implicated loci makes sense in the context of disease pathogenesis because such diseases tend to manifest in pairs and share expression of minor pathologies. For example, approximately 50% of patients with the axial skeleton arthritis ankylosing spondylitis (AS) acquire small gut lesions that, in 10% of patients, develop into Crohn's disease (CD) [29,30]. Other such diseases that co-manifest include Crohn's disease with psoriasis/arthritis, as well as IBD with multiple sclerosis/optic neuritis/rheumatoid arthritis/asthma [31•] (reviewed in Ref. [32]). A model of similar or shared mechanisms regulating the pathological inflammation of these conditions is further supported by the observation that anti-TNFa (infliximab) treatment for Crohn's disease significantly influences the risk of developing psoriasis [33–36]. Disease-associated gene overlap, disease co-occurrence and the influence that neutralizing a single but ubiquitous proinflammatory cytokine can have on the manifestation of multiple and seemingly diverse pathologies suggest that the essential mechanism of pathological inflammation across conditions is conserved and that such disease is the outcome of regulatory perturbations of a tightly regulated network of genes [22•,25••]. Importantly, the effect size of most GWAS identified loci appear to be rather small, suggesting that the manifestation of most chronic inflammatory and autoimmune diseases occurs via a combination of genetic risk loci and

environmental triggers (e.g., gluten consumption in celiac disease development) that lead to various small shifts in the expression of these gene networks in an individual [37••].

Natural selection as a contributing factor to disease susceptibility

The second major pattern noted for GWAS data is that many GWAS 'hits' occur proximal to immune genes in regions with signatures of positive natural selection [15••,38–41]. For this review we gathered a measure of recent positive selection, Integrated Haplotype Scores (iHS), from Hapmap phase II data for the most recent catalogue of all GWAS implicated loci (Figure 1) [21]. When we examined GWAS loci with an absolute iHS value greater than the 99th percentile of the genomewide distribution we found the European sample to have >2-fold increase ($P = 0.048$) in the number of positively selected alleles among GWAS SNPs associated with autoimmune diseases, while the African sample's strongest signals of positive selection occurred at loci associated with infectious disease ($P = 0.001$) (Figure 1a). This observation suggests that at least some of the present-day autoimmune risk loci have been adaptive and conferred some sort of functional benefit to Europeans in the past.

Interestingly, the African sample exhibits less of a signal for positive selection than the European sample overall, which may indicate disparate types of selection acting on these populations. Indeed, no signatures of selection on GWAS-associated SNPs appear to be shared between Europeans and Africans. Moreover, fifty-three percent of GWAS-associated SNPs showing evidence of recent selection in the European sample are either completely absent or found at very low frequency (minimum allele frequency <5%) within the African sample. We note, however, that virtually all GWAS studies to date have focused exclusively on individuals of European ancestry [42]. It is therefore possible that the genetic determinants of susceptibility to chronic inflammatory and autoimmune diseases in individuals of African descent are distinct from those found among Europeans and that, if we were to identify those variants, they would also show evidence of selection in Africans. Fortunately, an increasing number of cohorts of individuals of diverse ancestries are being assembled. Hopefully these data will soon allow less biased evaluations of the relative contribution of past selection to susceptibility to chronic inflammatory and autoimmune diseases in large array of human populations.

Asymmetrical interbreeding between archaic human and modern human populations is an interesting possibility that may have contributed to differences in the repertoires of disease-causing loci of African and European descended individuals. The temporal overlap between modern humans and Neanderthals in Europe has been estimated as 2600–5400 years, between ~35 000 and 40 000 years ago [43]. Interestingly, recent sequence studies of ancient DNA from Neanderthals suggests that some of the alleles presently associated with susceptibility to Crohn's disease, systemic lupus erythematosus, IL-18 levels and type-II diabetes in Europeans have been introduced in non-African populations via interbreeding of modern humans with archaic Neanderthal species at the time of the Out-of Africa exodus [44]. Similarly, an analysis of human leukocyte antigen (HLA) class I sequences from Denisovan, Vindija Neanderthal and modern human genomes revealed that several of the most common and functionally distinct HLA haplotypes found in Eurasian populations (e.g., HLA-C12:02, HLA-C15 and HLA-A11) were also present in the archaic genomes, which

suggests that these alleles came into modern Eurasian populations through admixture with archaic humans [45•]. The shared presence of these alleles in modern and archaic populations opens up the possibility that adaptive introgression of archaic alleles into modern human genetic diversity is amongst the factors contributing to the diversification of the immune system between populations.

To more formally assess if European and African populations have significantly differentiated disease-associated loci, we collected the levels of population differentiation (Fst) at GWAS-SNPs between European and African populations using the allele frequencies reported by the 1000 Genomes Project [46]. We found many GWAS-SNPs highly differentiated between the two populations (Fst values >0.4). SNPs associated with important inflammatory pathways appear to have very rapidly differentiated in humans. The most extremely differentiated SNPs (Fst >0.6) in the European and African samples occur proximal to genes that are the regulators of NFKB activation or are known to be expressed after NFKB regulation (i.e., *PRKCH*, *TNIP1*, *TRAF3IP2*) or occur in the chemokine cluster on chromosome 4q13.3 (Figure 2). Generally, SNPs associated with the NFKB and JAK-STAT (i.e., *REL*, *STAT3*, *STAT4*) pathway are well represented amongst polymorphisms highly differentiated between European- and African-descent individuals.

Within the European sample, multiple GWAS identified loci associated with a signature of positive selection are implicated repeatedly across several auto-immune conditions (i.e., *HLA-DRB1*, *SH2B3*), including celiac disease, type 1 diabetes, rheumatoid arthritis (Figure 1b). Previous authors have noted signatures of positive selection at these GWAS loci and suggested pathogens as the potential selective factor [6,15••,47]. The possible link between infectious and chronic inflammatory diseases is further supported by reports that some pathogens may be a contributing and possibly causal factor in chronic inflammatory and autoimmune disease (e.g., Epstein–Barr virus and SLE, RA and MS; *Mycobacterium avium* and Crohn's disease, *Yersinia enterocolica* and IBD) [48–55]. However, the relationship between infection with a present day pathogen and the co-occurrence of a chronic disease is very difficult to interpret in terms of past selective events, as the original mitigating factors of allele fixation can only be vaguely reconstructed. *Mycobacterium* species are, perhaps, the most well supported candidates for pathogen-mediated selection altering inflammatory pathways and increasing the frequency of chronic disease alleles in humans [2,23•,56]. That virtually all identified *Mycobacterium leprae* risk loci are also associated with genes implicated in IBD progression (e.g., *NOD2*, *LRRK2*, *TNFSF15*) [57••] hints at a possible evolutionary trade off between the probability of reproductive success after acquiring a pathogen with epitopes or tropism similar to *M. leprae*, and the likelihood of long-term pathological inflammation that may affect reproduction. Caution must be taken with such an interpretation; however, because it assumes that any other role an implicated gene might play in any other biological process is less important to ensure reproductive success than the process of surviving an infection. While pathogens are likely a very important factor driving an increase in chronic inflammatory and autoimmune disease risk loci, the relationship between the two is far from straight forward.

Discerning the influential factors in an evolutionary trade off

Most of our evidence of an association between chronic inflammatory/autoimmune risk alleles and adaptation to past infectious disease is diffuse, primarily because the etiological agent(s) at core of this question is/are fundamentally unknowable. Most of the support for specific pathogens exerting a past evolutionary effect leading to chronic disease consists of genes implicated in chronic disease progression also being implicated in host responses to *present day* pathogens [23•,57••,58–60]. For all of the attempts to connect historical pathogen exposure to present day human immune characteristics, it's worth noting the physiological promiscuity of the immune system. Many immune genes are cross-referenced and fulfill functions in other bodily systems thought to be under strong selective pressure, including reproduction, lung maintenance and embryonic and brain development [61–64]. An examination of the 20 GWAS implicated genes associated with the strongest signatures of positive selection reveals that along with host responses to infection, these genes are also involved other activities extremely important for reproductive success, such as embryo implantation into the uterine lining, embryonic morphogenesis and hematopoiesis (Table 2). Chronic inflammatory and autoimmune disease risk alleles associated with signatures of positive selection could indicate such alleles conferred greater reproductive success via a broader range of beneficial phenotypes than simply infection survival.

A good example of the complicated business of interpreting the evolutionary meaning of risk loci shared between chronic inflammatory and infectious diseases can be found in a celiac disease risk allele (exonic SNP rs3184504-A). This SNP is associated with *SH2B3*, a gene which encodes an adaptor important to T-cell activation and occurs in a region of 12q24 with a strong signature of positive selection. In 2010 Zhernakova *et al*. suggested that bacterial pathogens had acted as selective factors for rs3184504-A based on findings that peripheral blood mononuclear cells isolated from individuals homozygous for the selected allele under-expressed a mutated *SH2B3* and exhibited increased pro-inflammatory cytokine production when challenged with ligands for the bacterial detecting receptor NOD2 [15••]. Although this observation is compatible with selection driven by bacterial pathogens the identity of what *SH2B3* phenotype may be under selection is fogged by the pleiotropic nature of the gene. SH2B3 also acts as a regulator of two processes assumed to be under very high selective pressure — structural organization and development of platelets and endothelial cells (reviewed in Ref. [65]). Furthermore, the SNP rs3184504 is well known to co-segregate with intronic SNP (rs653178-C) in neighbouring RNA processing and amylosing lateral sclerosis (Lou Gherig's) risk gene *ATXN2* [66–69]. Both variants are found in high frequencies in Europeans, and are virtually non-existent in African populations (Figure 2b). The combination of both alleles is associated with multiple chronic diseases and, therefore, a wide range of pathologies (i.e., celiac disease, rheumatoid arthritis, psoriasis, cardiovascular disease, type 2 diabetes and thrombotic antiphospholipid syndrome) [24,70–73]. It seems very possible that signatures of positive selection in the region could be associated with other unknown beneficial variants that are being co-inherited within, at least, the 125Kb space between the *SH2B3* and *ATXN2* alleles, if not the entire >1 Megabase region of linkage disequilibrium that encompasses the two genes [66]. This might include *ATXN2* variants that limit neurodegenerative disease and which have

previously been proposed to be the target of positive selection [66]. Given the pleiotropy of most immune genes, and that natural selection is more easily detected in regions of high linkage disequilibrium, discerning the precise phenotypes in an evolutionary trade off can be a daunting task. Success could require extensive characterization of how putatively selected genetic variants might impact the multiple functions of the gene(s) located within the boundaries of the selected locus.

The rapid differentiation of chronic inflammatory risk alleles in humans

How pathogens, such as an ancestral *Mycobacterium*, may have exerted sufficient selective pressure to rapidly and significantly differentiate Eurasian and African populations at multiple chronic inflammatory and autoimmune disease risk loci is of significant interest. Our Fst analysis found 41 GWAS-implicated loci highly differentiated between European and Africans, with 8 loci exhibiting extreme Fst values (>0.6). It seems likely that in the ~60 000 years since these populations separated, major cultural shifts, such as the Mesolithic (~10 000–5000) transition from hunting-gathering to an agricultural lifestyle in Eurasia, to the initial exclusion of sub-Saharan Africa, would have profoundly affected human health and disease [74,75]. Pre-agricultural life after the end of Pleistocene was likely small group based, migratory or semi-sedentary, hunter-gatherer lifestyle. Most subarctic populations would have maintained a diverse diet and fairly egalitarian social structure (reviewed in Ref. [76•]). A shift to an agricultural economy would have led to significant changes in human ecology that altered the relationships between humans and pathogens. The advent of agriculture likely affected human immune phenotypes by encouraging many humans to live close together in large groups, with some suffering malnourishment due to eating an unevenly distributed and fairly homogenous diet of novel foods. With the emergence of moderate scale animal husbandry mixed and, potentially, stressed human and animal communities likely provided continuous stretches of human and nonhuman animal hosts for particular pathogens. The ease of pathogen transmission from one host to another also likely benefited from large and drastic alterations of the environment via mass waste accumulation, land clearance for farming, and diversion or development of local water supplies. All of these cultural and environmental changes would have contributed to the emergence of new infectious pathogens, nutritional deficiencies and ‘crowd diseases’ such as measles (reviewed in Ref. [77•]).

The dietary shifts associated with an agricultural economy likely transiently altered immune phenotypes on which selection could act. Efficient digestion of new foods could have conferred a selective advantage to agricultural populations via increased energy and indirectly affected the evolution of immunity. Novel foods likely also contributed to pathological immune phenotypes that reduce reproductive fitness. For example, with the emergence of cereal processing ~20 000 years ago, human populations began to consume considerable quantities gluten for, likely, the first time. It is the innovation of cereal processing that introduces many humans to high levels of the triggering antigen for celiac disease [78]. The negative effects of celiac disease, therefore, have only affected the human genome very recently. The likely ‘‘newness’’ of celiac disease may explain why the number of positively selected variants associated with the condition is high.

Similarly, the emergence of alcohol as a food stuff could have improved daily caloric intake, but might have also reduced reproductive fitness. Alcohol dehydrogenase (*ADH*) alleles that enhance alcohol metabolism are thought to have been under positive selection starting at the dawn of the Mesolithic [79–81]. Increased consumption or metabolism of alcohol, however, alters immune traits by changing innate immune modulation, triggering liver inflammation and promoting tumor development [82–88]. Similar arguments can be made about the indirect impact of other putative dietary adaptations such as the rise of multiple alleles upstream of the transcription start site for the gene that expresses Lactase/Lactase-Phlorizin Hydrolase (*LCT*) alleles in European populations approximately 2000–20 000 years ago [89,90]. These alleles confer lactase persistence and allow continued consumption of dairy products into old age. Milk, however, is iron poor, can cause gut microbleeding in human infants and toddlers (cow milk), and can disrupt iron absorption contributing to iron deficiency and potentially altering immune function [91–95]. After the Mesolithic–Neolithic transition, as agricultural practices disseminate, there is an increase in Eurasian skeletons with pathologies associated with nutritional disruptions such as increased carbohydrate and milk consumption including caries, cribia orbitalia and cranial pitting associated with anemia [96–100]. It is reasonable to expect that shifts in diet altered immune and, specifically, inflammatory phenotypes that later came under selective pressure via other factors.

Conclusion

The recent development of both high throughput sequencing and genotyping technologies, have led to a plethora of GWAS and genome-wide analyses of natural selection. These studies have revolutionized our understanding of how and why chronic inflammatory and autoimmune diseases manifest. Signatures of positive selection associated with risk alleles within a small network of, often, pleiotropic genes regulating these diseases, suggests that chronic inflammatory and autoimmune disease manifestation could be the outcome of an evolutionary trade off. While increased protection against pathogens seems a likely benefit, it is very possible that other traits such as anti-inflammatory conditions *in utero*, skin color and hypoxic responses associated with these genes could have been strong drivers of positive selection and contributed to increased frequencies of chronic disease risk alleles. The recent advent of new genome-editing technologies such as CRISPR together with induced pluripotent stem cells (known as iPS cells) open new exciting avenues to functionally test the impact of the selected alleles in different cell types and under different cellular conditions (e.g., in response to different pathogens, hypoxia, etc.) [101–104]. Determining which phenotypes might have been under selection in the past will allow us to delineate the immune functions that have been and still are essential for host survival, as well as help clarify the mechanisms contributing to pathological inflammation in contemporary human populations.

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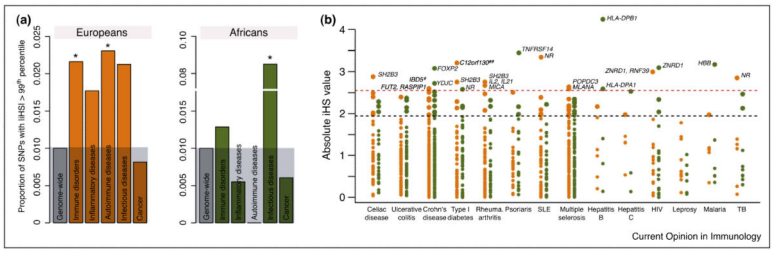

Figure 1.

Recent positive selection targeting SNPs associated with susceptibility to chronic inflammatory, autoimmune and infectious diseases. **(a)** The proportion of GWAS SNPs that present evidence for recent positive selection, as attested by the Integrated Haplotype Score (iHS) statistic [21]. The complete list of GWAS-associated SNPs was obtained from the NIH Catalog of Published Genome-Wide Association Studies [105], which reports all SNP trait associations with a *p*-values $<1.0 \times 10^{-5}$. For the purpose of the current analyses we used all GWAS SNPs with an association at a significance threshold $<1.0 \times 10^{-6}$. We note, however, that the results are qualitatively similar if using more stringent cutoffs for the GWAS data. The *y*-axis represents the proportion of SNPs that present an absolute iHS values above the 99th percentile of the HapMap phase II genome-wide distribution for Europeans (left side — orange bars) and Africans (right side — green bars). Diseases were grouped into broader groups: the set of inflammatory disorders includes Crohn's disease, ulcerative colitis and celiac disease. The set of autoimmune diseases includes rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, and psoriasis. The set of 'Immune disorders' encompasses both inflammatory and autoimmune diseases. The set of infectious diseases includes HIV/AIDS, Hepatitis B and C, Leprosy, Malaria and Tuberculosis. As a control we also looked at enrichment for signatures of selection among all cancer-related diseases. **(b)** iHS values for Europeans (orange) and Africans (green) for SNPs associated with several immune-related diseases by different GWAS studies. The genes reported by the GWAS as the most likely associated with the SNPs with absolute iHS values above the ninety-fifth percentile (orange dashed line) are reported. 'NR' stands for non-reported. # intergenic region. ## This is the same locus of *SH2B3*.

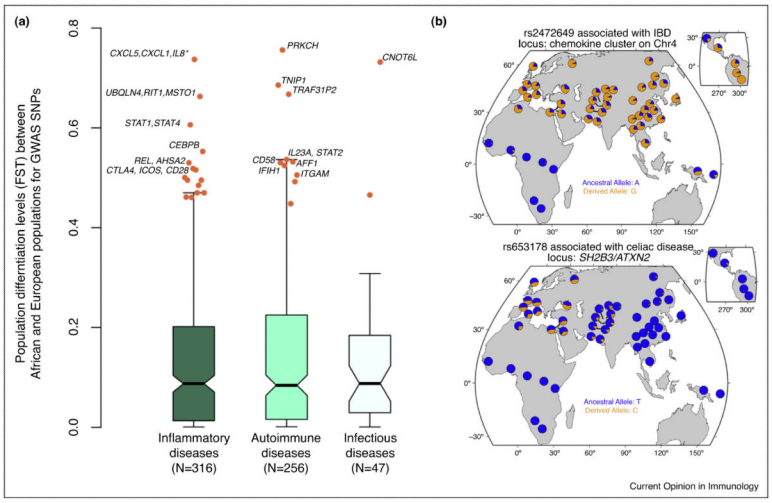

Figure 2.

Levels of population differentiation at GWAS SNPs for immune-related diseases. **(a)** Boxplots of Fst values between European- (CEU) and African-descent individuals (YRI) based on the data from the 1000 Genomes Project. The Fst statistic examines variation in SNP allele frequencies between populations. Under neutrality, Fst is determined by genetic drift, which affects all loci across the genome similarly. Conversely, positive selection will cause an increase in Fst values in the population where selection occurs. Orange dots highlight highly differentiated GWAS SNPs with an Fst value above the 95th percentile of the genome-wide distribution. **(b)** Worldwide frequency distribution of two highly differentiated SNPs. The top panel shows the worldwide distribution of allele frequencies for rs2472649, an SNP associated with IBD located in a chemokine cluster on chromosome 4 (e.g., *CXCL5*,*CXCL1*,*CXCL3*,*IL8*,*CXCL6*,*PF4*,*CXCL2*,*PF4V1*) and the bottom panel shows the worldwide distribution of allele frequencies for rs653178 an SNP associated with celiac disease linking the SH2B3/ATXN2 locus with susceptibility to celiac disease.

Table 1

Prevalence of select chronic Inflammatory and autoimmune diseases per 1000 individuals, by United States population. Data represents the combined sex prevalence rate normalized to 1000 Individuals unless otherwise noted. All data here was collected on populations within the United States after 1994, with the exception of some data for Native North Americans, which pre-dates 1994 and Includes Canadian groups. With the understanding that the defined population names used here encompass heterogeneous populations that may overlap, population group names were chosen based on the majority use In publications, with few exceptions: 'African American' and 'Black' are aggregated with 'non-Hispanic Black', Puerto Rican Hispanics and 'Latino American' are aggregated with 'Hispanic', 'White' and 'Caucasian' are aggregated with 'Non-Hispanic White', 'Alaskan Eskimo' is lumped under 'Native North American and Inuit'

Per 1000 individuals	Non-hispanic white Mean (range)	Non-hispanic black Mean (range)	Hispanic American Mean (range)	Asian American and Pacific Islander Mean (range)	Native North American/Inuit Mean (range)
Type 1 diabetes	2.13[a] (1.86–2.55) [106,107]	1.65[a] (1.29–2.04) [106,108]	1.12[a] (0.96–1.29) [106]	0.62[a] (0.50–0.77) [106,109]	0.32[a] (0.35–0.30) [106]
Psoriasis	30.5[b] (25–36) [110,111]	16.0[b] (13–19) [110,111]	12[b] (8–16) [111,112]	–	–
Multiple sclerosis	0.83[c] (0.56–0.99) [113]	0.56[c] (0.22–0.90) [113]	0.35[c] (0.11–0.56) [113,114]	–	–
Celiac disease	0.1 [115]	–	–	–	–
Ulcerative colitis (UC)	1.94 [116]	0.78 (0.07–1.5) [116,117]	0.56 (0.12–1.0) [116,13]	1.00 [116]	1.15 [116]
Crohn's disease (CD)	1.3 [116]	0.51 (0.12–0.89) [116,117]	0.26 (0.058–0.47) [116,118]	0.62 [116]	1.09 [116]
Inflammatory bowel disease (UC and CD combined)	3.24 [116]	2.39 [116]	0.53 (0.06–1.47) [116,118]	1.62 [116]	2.24 [116]
Systemic lupus erythematosus (SLE)	0.72 (0.34–1.11) [119,120] 1.19[d] (0.62–2.03) [119–121]	1.69 (1.16–2.23) [119,120] 3.78[d] (1.97–6.94) [119–122]	1.29 (1.03–1.59) [120,123] 1.81[d](1.38–2.44) [120,121]	1.75 [120] 1.5[d] (0.92–2.55) [120,121]	1.71 (1.65–1.78) [120,124] 2.13[d] [120]

[a] Age–adjusted rate 15–19 years of age, or as close to 19 years of age as possible.

[b] Age–adjusted to ≥20.

[c] Average of non-contiguous U.S. regions.

[d] Female only. Combined sex rates listed immediately above.

Table 2

Non-immune functions of genes associated with 20 SNPs with the strongest signatures of positive selection (IHS scores) and implicated in chronic inflammatory and autoimmune disease

GWAS gene	Physiological system/role	Process
NAA25	Universal	Cell cycle progression [125]
SH2B3	Embryonic development	Embryonic hematopoiesis[a] [61,126]
	Wound healing/haematological	Platelet architecture [61]
PTPN11	Reproduction	Genitalia development [127]
	Embryonic development	Genitalia development [127], heart development [128], growth plate architecture [129], brain development [130,62], face morphogenesis [130]
	Growth and development	Growth plate architecture [129], brain development [130], face morphogenesis [7]
	Digestive/metabolism	Insulin reception [128], energy metabolism [128,131]
ZNRD1	Reproduction	Testis (expressed in) [132,133]
IL2	Locomotion/cognitive	Sensorimotor gating [134]
IRF1	Reproduction	Uterine remodeling [135,63]
	Skeletal	Bone remodeling [136]
	DNA maintenance/repair	Telomere maintenance[a] [137]
IL13	Respiration	Regulator of lung cilia cell and goblet cell differentiation [64]
CSF2	Reproduction	Trophoblast differentiation [138], placenta development [138]
SLC22A4	Haematological/respiration	Haeme biosynthesis [139]
IL4	Reproduction	Regulates decidua [140], downregulates placental inflammation [141], contributes to normal maternal blood pressure [141], prevents reproductive failure[a] [142–144]
IL3	Brain development	Nervous system development [145], determinant of brain volume [145]
PDLIM4	Skeletal	Osteoblast development/function [146]
SLC22A5	Digestive	Maintenance of gut epithelial barrier[a] [147]
ACSL6	Brain development/cognitive	Neuronal cell proliferation [148]
	Growth and maintenance	Lipid synthesis/degradation [149,150]
GNA12	Reproduction	Sperm development [151]
TNXB	Growth and maintenance	Dermal collagen fibril development and organization [152]
POPDC3	Embryonic development	Heart development [153]
	Growth and maintenance	Skeletal muscle development [153]
RASIP1	Embryonic development	Vasculogenesis[a] [154], angiogenesis[a] [154]
MLANA	Skin colour	Melanogensis [155]
CPEB4	Digestive	Glucose metabolism/proinsulin production [156]
ETS1	Embryonic development	Angiogenesis [157], fetal membrane remodeling [158]
	Reproduction	Uterine decidualization [159]
	Respiration/cardiac/growth and maintenance	Response to hypoxia [160]

[a] Process with dual role in immunity.