ORIGINAL ARTICLE

CISH and Susceptibility to Infectious Diseases

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ABSTRACT

BACKGROUND

The interleukin-2–mediated immune response is critical for host defense against infectious pathogens. Cytokine-inducible SRC homology 2 (SH2) domain protein (CISH), a suppressor of cytokine signaling, controls interleukin-2 signaling.

METHODS

Using a case–control design, we tested for an association between *CISH* polymorphisms and susceptibility to major infectious diseases (bacteremia, tuberculosis, and severe malaria) in blood samples from 8402 persons in Gambia, Hong Kong, Kenya, Malawi, and Vietnam. We had previously tested 20 other immune-related genes in one or more of these sample collections.

RESULTS

We observed associations between variant alleles of multiple *CISH* polymorphisms and increased susceptibility to each infectious disease in each of the study populations. When all five single-nucleotide polymorphisms (SNPs) (at positions –639, –292, –163, +1320, and +3415 [all relative to *CISH*]) within the *CISH*-associated locus were considered together in a multiple-SNP score, we found an association between *CISH* genetic variants and susceptibility to bacteremia, malaria, and tuberculosis ($P=3.8\times10^{-11}$ for all comparisons), with –292 accounting for most of the association signal ($P=4.58\times10^{-7}$). Peripheral-blood mononuclear cells obtained from adult subjects carrying the –292 variant, as compared with wild-type cells, showed a muted response to the stimulation of interleukin-2 production — that is, 25 to 40% less *CISH* expression.

CONCLUSIONS

Variants of *CISH* are associated with susceptibility to diseases caused by diverse infectious pathogens, suggesting that negative regulators of cytokine signaling have a role in immunity against various infectious diseases. The overall risk of one of these infectious diseases was increased by at least 18% among persons carrying the variant *CISH* alleles.

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Tuberculosis, malaria, and invasive bacterial disease together account for more than 5 million deaths annually in the developing world. Although a significant proportion of interindividual variation in disease susceptibility can be attributed to environmental factors such as malnutrition and infection with the human immunodeficiency virus (HIV), a substantial portion is unexplained. Comparative studies involving twins and adopted persons suggest a genetic component,[1] and genes that, when mutated, result in primary immunodeficiency states have been identified. Such immunodeficiencies are extremely rare, however, and the current understanding of common host genetic factors influencing susceptibility to major infectious diseases at the population level is limited.

A principal feature of the host immune response to infection by structurally diverse pathogens is the inflammatory cytokine response.[2-4] The proinflammatory cytokine interleukin-2 determines the magnitude and duration of the T-cell response immediately after antigen encounter[5] and assists in the maturation of macrophages and the proliferation of B cells and natural killer cells[6] in the early stages of the adaptive immune response. Interleukin-2 also regulates the evolution of memory T cells after resolution of infection.[7] An excessive cytokine-mediated inflammatory response can be harmful to the host, resulting in severe forms of malaria and sepsis.[8-11]

Control of cytokine signaling in humans is mediated in part by negative feedback from the suppressor of cytokine signaling (SOCS) family of proteins. Cytokine-inducible SRC homology 2 (SH2) domain protein (CISH) was the first member of the SOCS family to be described.[12,13] *CISH* is the gene most consistently up-regulated by interleukin-2 stimulation in humans,[14] and it appears to be critical for T-cell proliferation and survival[15] in response to infection. CISH controls the signaling of a variety of cytokines, in particular interleukin-2. Unlike the other members of the SOCS family, CISH binds to the phosphorylated tyrosine residues of cytokine receptors and masks sites at which the signal transducer and activator of transcription 5 (STAT5) would otherwise dock.[12,16-19] Thus, increased CISH activity blocks the cytoplasmic docking and activation of STAT5 and thereby inhibits downstream cytokine signaling. Given the central role of CISH in controlling interleukin-2 signaling, we hypothesized that variation in *CISH* influences susceptibility to common infectious diseases.

Methods

Subjects

We analyzed data on 8402 persons from seven case–control series (Table 1). These persons included Kenyan children with bacteremia[20]; persons with tuberculosis from Malawi,[21] Hong Kong,[22] and Gambia[23]; and persons with severe malaria from Gambia,[24] Kenya,[25] and Vietnam.[8] We obtained written informed consent from the study participants or their parents or guardians and ethics approval from the relevant national authorities for all study collections (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We obtained blood samples from which we extracted DNA (see the Supplementary Appendix). Controls were geographically matched to the cases. Twenty other immune-related genes have been studied previously in one or more of these sample collections (see the Supplementary Appendix).

Genotyping, Cell Stimulation, and Gene Expression

We used standard methods for genotyping (see the Supplementary Appendix). We purified peripheral-blood mononuclear cells (PBMCs) from whole blood obtained from the subjects, cultured these cells, and then stimulated them with interleukin-2 or interleukin-3. We harvested the PBMCs at 0, 30, 60, and 120 minutes after the addition of interleukin; extracted RNA using a standard method; and synthesized and assayed complementary DNA using a real-time polymerase-chain-reaction assay (Supplementary Appendix).

Statistical Analysis

Power calculations for all case–control studies are included in Figure 1 in the Supplementary Appendix. A comparison of allele frequencies according to the different genetic patterns of inheritance between case subjects and controls was performed with Pearson's chi-square test. The most likely pattern of inheritance was determined on the basis of the best-fitting model with the use of logistic regression. Detailed descriptions of the statistical procedures, as well as of the various patterns of inheritance, are included in the Supplementary Appendix. Analysis of pair-

Table 1. Characteristics of the 8402 Subjects Enrolled in the Study.

Case–Control Series	Country	Region or City	Case Subjects (N=4866)	Control Subjects (N=3536)	Reference
			number		
Kenyan Bacteremia Study	Kenya	Kilifi coastal area	770	560*	Berkley et al.[20]
Malawian Tuberculosis Study	Malawi	Karonga District	335	450	Crampin et al.[21]
Hong Kong Tuberculosis Study	China	Hong Kong city	907	784	Tang et al.[22]
Gambian Tuberculosis Study	Gambia	Banjul coastal area	1309	1427	Lienhardt et al.[23]
Gambian Malaria Study	Gambia	Banjul coastal area	485	210	Hill et al.[24]
Kenyan Malaria Study	Kenya	Kilifi coastal area	685	560*	Marsh et al.[25]
Vietnam Malaria Study	Vietnam	Ho Chi Minh City	375	105	Khor et al.[8]

* Shared controls were used for the Kenyan Bacteremia Study and the Kenyan Malaria Study.[8]

wise linkage disequilibrium between single-nucleotide polymorphisms (SNPs) was performed with the use of the r^2 algorithm in Haploview software, version 3.2.[26] The multiple-SNP score was analyzed as previously described for case–control populations.[27] Subjects were classified according to the number of risk alleles they carried (0, 1, 2, 3, or ≥4). A trend test for association was then performed.[28] Our analysis of gene-expression data is included in the Supplementary Appendix.

RESULTS

GENETIC ANALYSIS OF *CISH*

CISH comprises four exons, of which exons 2 to 4 encode the CISH protein. We sequenced *CISH* (1000 bp upstream of the transcription start to the end of exon 4, including introns) in 24 case subjects and 24 controls from the Kenyan Bacteremia Study. The power to detect SNPs with a minor-allele frequency of 0.05 was 99.3% (Fig. 2 in the Supplementary Appendix). We identified eight SNPs with a minor-allele frequency greater than 5% (Fig. 3A in the Supplementary Appendix), and we did not detect any new coding changes or predicted splice-junction variants. We then genotyped these eight SNPs in the case–control Kenyan Bacteremia Study. Four of these SNPs (at positions −639, −292, −163, and +3415) showed evidence of association ($P=0.02$ to $P=1.0\times10^{-3}$) (Fig. 1 and Table 2); the variant alleles at each SNP were associated with an increased susceptibility to bacteremia. Adjustment for HIV status, malnutrition, and age did not significantly affect these associations.

We observed low pairwise linkage disequilibrium between SNPs at positions −639 and +3415, between these SNPs and those that lie between them, and between the SNPs that lie between them ($r^2<0.50$) (Fig. 3B in the Supplementary Appendix). We also observed associations between multiple SNPs and susceptibility to disease, and bearing in mind the low pairwise linkage disequilibrium between these SNPs, we hypothesized that the risk alleles at these SNPs confer susceptibility independently of one another. To investigate whether the risk of disease increased in an allele dose-dependent manner with respect to the number of risk alleles, we determined multiple-SNP scores for the five SNPs.[26] We observed that the risk of bacteremia was proportionate to the number of risk alleles carried ($P=5.1\times10^{-5}$) (see the Supplementary Appendix). The haplotype analysis was uninformative, presumably because of the low intermarker linkage disequilibrium. We did not observe any significant interaction among the five SNPs, and we went on to genotype them in the remaining six case–control studies.

In the Malawian Tuberculosis Study, the minor alleles of three SNPs (−292, +1320, and +3415) were associated with increased susceptibility to tuberculosis ($P=0.01$ to $P=5.0\times10^{-3}$) (Fig. 1 and Table 2). For +1320 ($P=6.0\times10^{-3}$), the effect of the risk allele appeared to be strongest with a recessive pattern of inheritance. Persons who were homozygous for the risk allele were significantly more susceptible to tuberculosis than matched controls (5.6% of case subjects were homozygous for the risk allele, as compared with 1.9% of controls; $P=5.0\times10^{-3}$). Adjustment

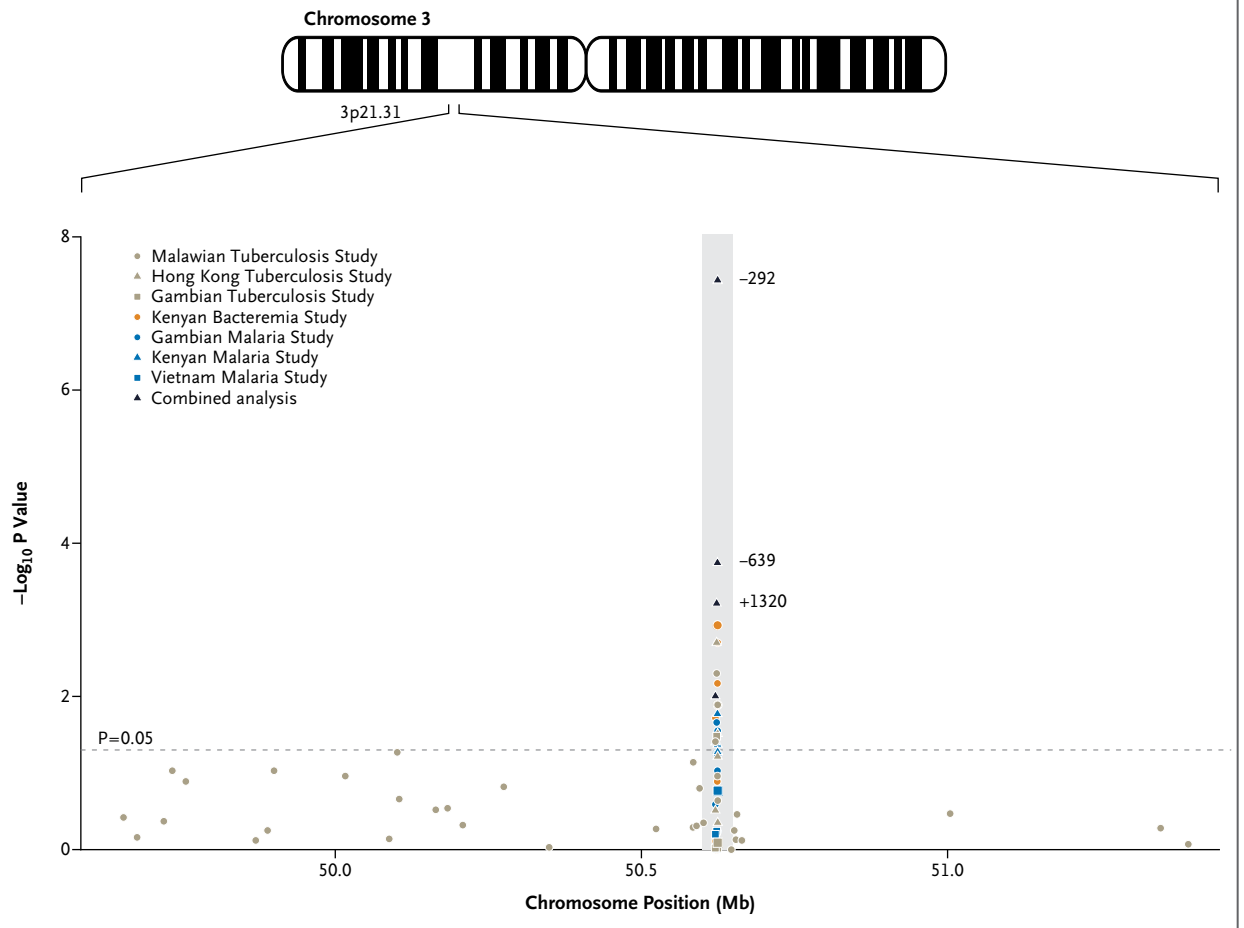

Figure 1. Single-Nucleotide Polymorphisms Genotyped within *CISH* and Its 2-Mb Flanking Region.
CISH is highlighted in gray. The dashed horizontal line indicates a P value of 0.05. P values are for the association with disease risk.

for the potential confounding effects of age, sex, and race or ethnic group did not affect the degree of statistical significance or odds ratio for each SNP. The trend test also showed an increase in the risk of disease with an increase in the number of risk alleles (P=0.03) (see the Supplementary Appendix). In the Hong Kong Tuberculosis Study, persons with tuberculosis were more likely to carry variant *CISH* alleles (at positions −292 and +1320) than were unaffected persons (P=0.03 and $P=2.0\times10^{-3}$, respectively). In the case–control Gambian Tuberculosis Study, we observed an association between the *CISH* +1320 variant allele (but not the −292 SNP variant allele) and susceptibility to clinical tuberculosis (P=0.03). The positive trend test for tuberculosis observed in the Malawian Tuberculosis Study was replicated in both the Hong Kong Tuberculosis Study (P=0.01) and the Gambian Tuberculosis Study (P=0.03).

We genotyped the five *CISH* SNPs in three sample collections obtained from subjects with severe malaria in the Gambian Malaria Study, the Kenyan Malaria Study, and the Vietnam Malaria Study. The variant alleles at positions −639, −292, +1320, and +3415 showed a significant association with increased susceptibility to disease. In particular, the minor allele at position −292 showed a significant association with susceptibility to severe malaria in the Gambian Malaria Study, the Kenyan Malaria Study, and the smaller Vietnam Malaria Study (Table 2). The trend toward an increase in disease risk with an increasing number of *CISH* risk alleles observed in

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the bacteremia and tuberculosis studies was replicated in all three malaria studies (see the Supplementary Appendix).

To investigate the possibility that the associated SNPs might be in linkage disequilibrium with causative variants, we performed exclusion mapping by genotyping 28 additional SNPs spanning 2 million bp in the chromosome 3p21 region surrounding *CISH* in the Malawian Tuberculosis Study population. None of these 28 SNPs showed evidence of association with tuberculosis (Fig. 1).

On pooled analysis, the carriage of *CISH* risk alleles at −639, −292, −163, +1320, and +3415 was associated with increased susceptibility to the infectious diseases studied (Table 2), with −292 accounting for most of the association signal ($P=4.58\times10^{-7}$) (Table 2 and Fig. 2). Multiple-SNP scoring of the five SNPs in each case–control study revealed a correlation between the number of *CISH* risk alleles and the risk of disease ($P=3.8\times10^{-11}$ for trend) (see the Supplementary Appendix). In persons carrying one or more risk alleles, the overall risk was increased by at least 18%.

FUNCTIONAL ANALYSIS OF *CISH*

We studied the functional effects of the *CISH* promoter variants because these SNPs showed the strongest associations with disease and they are more likely to affect gene expression than intragenic SNPs. We genotyped the promoter SNPs at positions −639, −292, and −163 in 400 healthy adult subjects of Han Chinese descent. The observed risk-allele frequency for the SNPs at positions −292 and −163 was 41.5% and 6.1%, respectively, and only a single subject was homozygous for the variant allele at position −163; SNP −639 was not polymorphic in these persons, a finding that is consistent with observations from the Hong Kong Chinese case–control study. We first examined the individual effects of SNPs −292 and −163 on *CISH* gene expression in human PBMCs after stimulation with interleukin-2 at a final concentration of 100 U per milliliter. Since levels of expression of the wild-type *CISH* −292AA and carrier *CISH* −292AT genotypes did not differ significantly, we questioned whether this SNP might exert a recessive effect. As shown in Figure 3A, the 10 persons who were homozygous for the variant *CISH* −292TT risk genotype had significantly lower levels of *CISH* than the 5 persons who were homozygous for the alternative allele (AA) and the 10 heterozygous carriers (AT) at 30, 60, and 120 minutes after stimulation with interleukin-2. We did not observe any difference in *CISH* expression (with respect to the *CISH* −292 genotype) after stimulation with interleukin-3. Nor did we observe a significant genotype-specific difference according to allelic variation at position −163 after stimulating cells with either interleukin-2 or interleukin-3 (data not shown).

To test for an interactive effect between *CISH* −292 and *CISH* −163, we determined two SNP diplotypes, −292 and −163, for the subjects in whom *CISH* expression was assessed (with the chromosomal phase determined by subcloning and sequencing for persons with a chromosomal phase that was uncertain), and we then compared *CISH* expression between the −292 genotypes in response to interleukin-2 stimulation, using −163 as the conditioning locus. For persons who were homozygous for the major (nonrisk) allele at −163, carriage of the variant −292TT genotype resulted in markedly lower overall gene expression (25 to 40% lower) in response to interleukin-2 stimulation at all time points (Fig. 3B). We observed no significant differences in *CISH* expression after stimulation by interleukin-2 or interleukin-3 when we compared the other *CISH* diplotypes with one another (data not shown).

DISCUSSION

We identified a panel of five *CISH* SNPs associated with increased susceptibility to bacteremia, tuberculosis, and malaria, and we estimated that the overall risk of one of these infectious diseases was increased by 18% among persons carrying a single *CISH* "risk" allele. This risk increased to 81% among persons with four or more risk alleles (see the Supplementary Appendix).

Two important considerations in genetic association studies are population stratification and multiple testing. To assess the presence of population stratification, we examined 28 independent markers in the 2-Mb region flanking *CISH*, and we did not detect significant inflation of test statistics (genomic inflation factor, 1.03). Furthermore, the consistency of the association across multiple racial and ethnic groups argues against the results being a product of population stratification. To account for multiple testing, we evaluated *CISH* in the context of 20 other immune-

related genes (analyzing a total of 187 SNPs) previously tested in one or more of these sample collections (see the Supplementary Appendix); the single-point observation with *CISH* –292 ($P=4.58\times10^{-7}$) remained significant after correction for all the genes and SNPs tested (the threshold P value after correction for multiple testing is 10^{-4}, with each of the 187 SNPs tested on average 2.7 times). The false positive report probability[29] for –292 was 10^{-4} or less even at previous probability levels of 10^{-5} or less. Further confidence is lent by the very low P value ($<5\times10^{-11}$) observed with the multiple-SNP score and the level of replication among study groups.

The pattern of association with *CISH* –292 was consistently reproducible across six of the seven

Table 2. Results of Single-Nucleotide Polymorphism (SNP) Analysis of *CISH*.*

SNP and Study Population	No. of Subjects	Best-Fitting Genetic Model	Risk-Allele Frequency†				Combined Analysis	
			Case Subjects	Control Subjects	P Value	Odds Ratio (95% CI)	P Value‡	Odds Ratio (95% CI)
–639								
KB	1326	Allelic	0.06	0.04	0.007	1.64 (1.14–2.35)		
MTB	607	Allelic	0.04	0.02	0.11	1.76 (0.87–3.53)		
HKTB	—	—	—	—	—	—		
GTB	2690	Allelic	0.02	0.02	0.88	1.03 (0.68–1.57)	1.8×10^{-4}	1.49 (1.22–1.83)
KM	1212	Allelic	0.06	0.04	0.02	1.57 (1.08–2.28)		
GM	660	Allelic	0.03	0.02	0.09	2.11 (0.87–5.11)		
VM	—	—	—	—	—	—		
–292								
KB	1293	Allelic	0.41	0.35	0.001	1.31 (1.11–1.55)		
MTB	749	Allelic	0.45	0.39	0.01	1.30 (1.06–1.61)		
HKTB	1677	Allelic	0.41	0.37	0.03	1.17 (1.01–1.34)		
GTB	2696	Allelic	0.28	0.28	0.81	0.99 (0.88–1.11)	4.6×10^{-7}	1.19 (1.12–1.25)
KM	1174	Allelic	0.39	0.35	0.04	1.19 (1.01–1.41)		
GM	675	Allelic	0.28	0.22	0.03	1.36 (1.03–1.78)		
VM	471	Dominant	0.41	0.34	0.03	1.60 (1.01–2.52)		
–163								
KB	1204	Allelic	0.17	0.12	0.002	1.50 (1.16–1.95)		
MTB	629	Allelic	0.16	0.14	0.23	1.21 (0.88–1.68)		
HKTB	1616	Allelic	0.17	0.18	0.45	0.93 (0.76–1.13)		
GTB§	2690	Allelic	0.20	0.19	0.64	1.04 (0.88–1.22)		
KM	1145	Allelic	0.24	0.12	<0.001¶	2.20 (1.72–2.84)		
GM	649	Allelic	0.13	0.12	0.58	1.11 (0.76–1.63)		
VM	—	—	—	—	—	—		
+1320								
KB	1200	Allelic	0.16	0.16	0.99	1.00 (0.74–1.35)		
MTB	819	Recessive	0.17	0.16	0.005	2.99 (1.27–7.18)		
HKTB	1691	Allelic	0.36	0.31	0.002	1.25 (1.08–1.44)		
GTB	2736	Allelic	0.06	0.05	0.03	1.28 (1.02–1.62)	6.1×10^{-4}	1.17 (1.07–1.28)
KM	1024	Allelic	0.16	0.16	0.99	1.00 (0.78–1.28)		
GM	689	Allelic	0.06	0.03	0.02	1.98 (1.09–3.57)		
VM	479	Allelic	0.33	0.31	0.58	1.10 (0.79–1.53)		

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Table 2. (Continued.)

SNP and Study Population	No. of Subjects	Best-Fitting Genetic Model	Risk-Allele Frequency†				Combined Analysis	
			Case Subjects	Control Subjects	P Value	Odds Ratio (95% CI)	P Value‡	Odds Ratio (95% CI)
+3415								
KB	1257	Allelic	0.24	0.20	0.02	1.26 (1.04–1.53)		
MTB	780	Allelic	0.29	0.24	0.04	1.27 (1.01–1.59)		
HKTB	1677	Allelic	0.06	0.06	0.31	0.86 (0.65–1.15)		
GTB	2702	Allelic	0.22	0.22	0.96	1.00 (0.88–1.13)	0.01	1.11 (1.03–1.20)
KM	1189	Allelic	0.24	0.20	0.04	1.23 (1.01–1.50)		
GM	684	Allelic	0.23	0.21	0.26	1.18 (0.89–1.56)		
VM	478	Allelic	0.06	0.05	0.63	1.19 (0.59–2.42)		

* Dashes indicate that the marker was not polymorphic in the specific population. GM denotes Gambian Malaria Study, GTB Gambian Tuberculosis Study, HKTB Hong Kong Tuberculosis Study, KB Kenyan Bacteremia Study, KM Kenyan Malaria Study, MTB Malawian Tuberculosis Study, and VM Vietnam Malaria Study.

† The risk-allele frequency is the minor-allele frequency for each SNP genotyped. This value is the actual allelic frequency and not the result of prediction programs. It was calculated as the number of mutant alleles divided by the total number of alleles.

‡ Both the Tarone and Breslow–Day tests for homogeneity showed no significant differences across the study populations for *CISH* –639, –292, and +3415, indicating that the pooled odds ratio and accompanying pooled P value were applicable across all populations. However, for *CISH* –292, inclusion of the GTB data resulted in tests of homogeneity that showed borderline significance (P=0.06). Thus, we performed a secondary analysis for –292, which did not include the GTB data ($P=3.9\times10^{-8}$; odds ratio, 1.23; 95% CI, 1.19 to 1.34).

§ The Tarone and Breslow–Day tests for homogeneity showed marked significance (P<0.001) for *CISH* –163; thus, pooling should not be performed for this SNP. However, for pooling performed for the sake of information, $P=3.0\times10^{-7}$.

¶ Since this was an apparently highly significant single-point observation, we confirmed the concordance of genotype calls between two investigators who were unaware of the case–control assignments. The concordance rate was 100%, arguing against genotyping error as the cause of this observation.

study groups, with the exception of the Gambian Tuberculosis Study. One possible explanation for this heterogeneity is that disease susceptibility was accounted for by more than one SNP within the five-SNP panel, thus rendering the single-SNP analysis incomplete. A second reason might relate to the underlying population structure, where different *CISH* SNPs may tag the informative variants in each distinct population. A third possibility is that there remain unidentified functional SNPs within the region of association delineated by the five-SNP panel that also account for association with disease. This last possibility is unlikely, however, since direct sequencing did not detect additional putatively functional polymorphisms. To explore the first and second possibilities, we used multiple-SNP scoring for all five associated SNPs. The risk of disease increased markedly with an increase in the number of risk alleles carried in each population. Since this multiple-SNP analysis was more informative, with respect to risk, than analyses of single SNPs in isolation, the first two possibilities remain plausible explanations. The mechanisms underlying an association between the *CISH* multiple-SNP score and the accompanying dose-dependent effect on disease susceptibility probably reflect the potential regulatory effect of these polymorphisms within a "multiple-hit model," whereby each "hit" affects gene expression cumulatively in aggregate. Such a process contrasts with that of structural variants, in which the presence of one deleterious mutation may be sufficient to account for disease.

In the ex vivo study, carriage of the –292 allele reduced *CISH* expression after stimulation with interleukin-2. However, this study lacked power to detect significant differences in gene expression in persons with 0, 1, 2, 3, and 4 or more risk alleles. Although –292 showed associations with multiple infectious diseases and could be a true functional variant, +1320 showed a stronger association with susceptibility to tuberculosis, and we found this association in each of the tuberculosis studies. Perhaps variation at +1320 affects transcript expression; position +1320 is located in the untranslated portion of exon 2.[30]

Stimulation by interleukin-2 may enhance

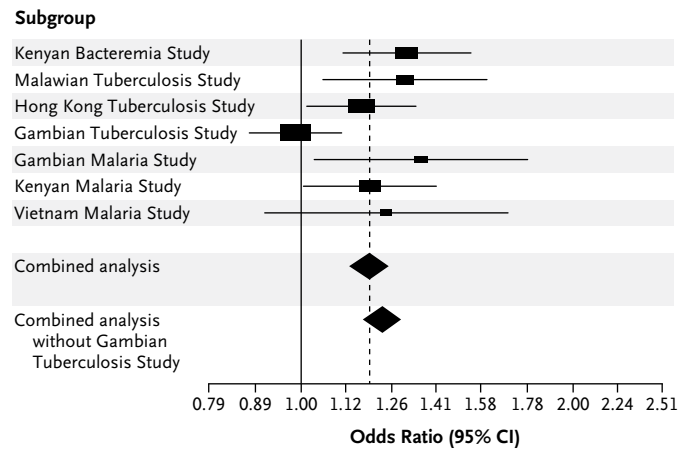

Figure 2. Odds Ratio for the Variant Allele *CISH* –292, According to Study Population.

Results of the overall pooled analysis and case–control analyses were generated with the use of the allelic test. The oblongs represent point estimates, with the height of the oblongs inversely proportional to the standard error of the estimate. The horizontal lines indicate the 95% confidence intervals for the estimates. The diamonds represent the summary odds ratios, with the width indicating the 95% confidence interval.

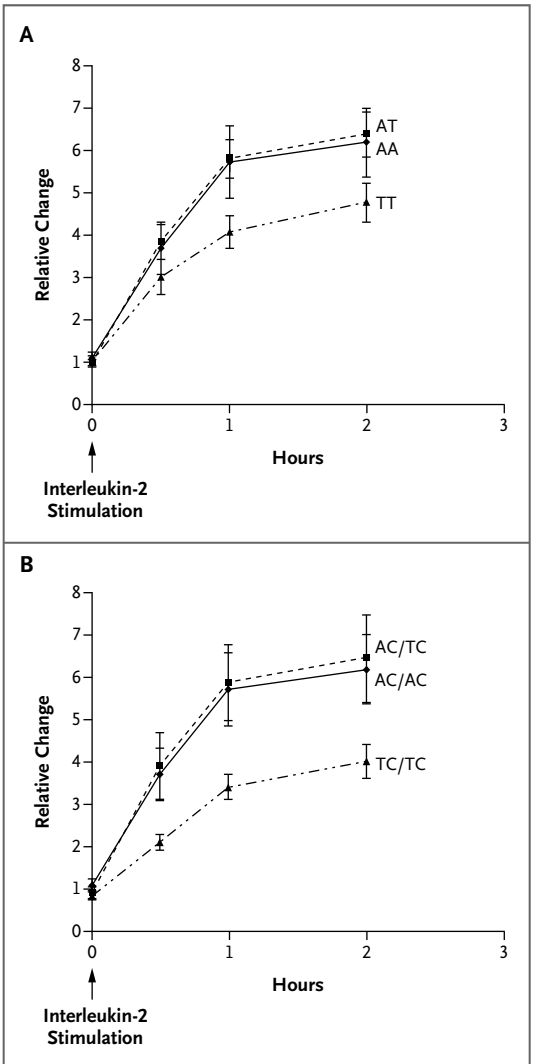

Figure 3. Expression of *CISH* –292 in Response to Stimulation with Interleukin-2.

Panel A shows differential expression of 5 wild-type (AA), 10 heterozygous (AT), and 10 homozygous mutant (TT) forms of *CISH* –292 in response to interleukin-2 stimulation. Panel B shows differential expression of five wild-type (AC/AC), five heterozygous (AC/TC), and five homozygous mutant (TC/TC) forms of the *CISH* –292 –163 diplotype in response to interleukin-2 stimulation in persons who were homozygous for the wild-type form at the –163 locus. I bars indicate standard errors.

microbial and viral replication,[31] and its effect may be further dependent on the presence of other immune cells. For example, clinical trials of interleukin-2 infusion in HIV-positive patients have shown different effects on individual persons depending on their CD4+ counts.[32,33] Although it is perhaps unexpected that common variation within a single gene influences susceptibility to a diverse range of infectious diseases, there is increasing evidence that disparate infections are recognized by a common host inflammatory pathway.[8,34-36]

The observation that the risk alleles occur at appreciable allele frequencies in each of the study populations is surprising, given data that suggest an evolutionary selective pressure exerted by some infectious diseases.[37,38] One explanation may be that the variant alleles associate with decreased susceptibility against other major causes of death in these populations. For example, immune modulation at the interleukin-2 receptor axis may protect against type 1 diabetes mellitus.[39] A possible role of *CISH* polymorphisms in the development of inflammatory as well as infectious diseases merits further study.

Current clinical management of bacteremia, malaria, and tuberculosis relies primarily on antimicrobial agents that are specifically targeted to the likely pathogen. Our findings implicate *CISH* in multiple-pathogen susceptibility and raise the possibility that pharmacologic manipulation of the SOCS pathway may have an effect on the treatment of multiple, diverse infectious diseases.

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CISH variants may also influence responses to existing immunotherapies such as interleukin-2 therapy in renal-cell cancer, which is associated with wide and largely unexplained variations in interindividual response rates.[40,41] Study of longitudinal immune responses together with responses to antimicrobial agents and clinical outcome in patients with infectious diseases may further define the risk model for *CISH* SNPs. The integration of such a model with environmental and other host genetic factors may improve the prediction of treatment responses and disease outcomes.

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No potential conflict of interest relevant to this article was reported.

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APPENDIX

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