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Plasma levels of sIL-2Rα: associations with clinical cardiovascular events and genome- wide association scan

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Abstract

Objective—Interleukin-2 receptor subunit alpha (IL-2Rα) regulates lymphocyte activation, which plays an important role in atherosclerosis. Associations between soluble IL-2Rα and cardiovascular disease (CVD) have not been widely studied and little is known about the genetic determinants of sIL-2Rα levels.

Approach and Results—We measured baseline levels of sIL- 2Rα in 4408 European-American (EA) and 766 African-American (AA) adults from the Cardiovascular Health Study (CHS) and examined associations with baseline CVD risk factors, subclinical CVD and incident CVD events. We also performed a genome-wide association study (GWAS) for sIL-2Rα in CHS (2964 EAs and 683 AAs) and further combined CHS EA results with those from two other EA cohorts in a meta-analysis (N=4464 EAs). In age, sex- and race- adjusted models, sIL-2Rα was positively associated with current smoking, type 2 diabetes, hypertension, insulin, waist circumference, C-reactive protein, interleukin-6, fibrinogen, internal carotid wall thickness, all-cause mortality, CVD mortality, and incident CVD, stroke and heart failure. When adjusted for baseline CVD risk factors and subclinical CVD, associations with all- cause mortality, CVD mortality and heart failure remained significant in both EAs and AAs. In the EA GWAS analysis, we observed 52 single nucleotide polymorphisms (SNPs) in the chromosome 10p15-14 region, which contains *IL2RA*, *IL15RA* and *RMB17*, that reached genome-wide significance ($p<5\times10^{-8}$).

The most significant SNP was rs7911500 ($p=1.31\times10^{-75}$). The EA meta-analysis results were highly consistent with CHS-only results. No SNPs reached statistical significance in the AAs.

Conclusions—These results support a role for sIL-2Rα in atherosclerosis and provide evidence for multiple associated SNPs at chromosome 10p15-14.

Keywords

IL-2Ra; Inflammation; Atherosclerosis; Genome-wide association

Introduction

Interleukin (IL)-2 and IL-2 receptor (IL-2R) signaling play an important role in regulating both tolerance and immunity. IL-2 is a T cell growth factor, inducing the proliferation and differentiation of antigen-activated T cells[1,2], and is particularly important in the development of regulatory T cells in the thymus[3]. The IL-2R is a trimeric receptor composed of the IL-2Rα subunit (CD25), the IL-2Rβ subunit (CD122), and the IL-2γc subunit (CD132). IL-2Rα is specific for IL-2R, while IL-2Rβ and IL-2Rγc are shared components of other cytokine receptors (e.g., IL-15)[4,5]. sIL-2Rα results from the proteolytic cleavage of IL-2Rα at the cell surface by a membrane metalloproteinase (ectodomain shedding)[6]; which is encoded by *IL2RA* on human chromosome 10. The function of sIL-2Rα has not been fully elucidated. Since the sIL-2Rα has IL-2 binding kinetics similar to the membrane form, sIL-2Rα may serve to mitigate the immune responses by binding and sequestering IL-2[7].

High plasma levels of sIL-2Rα have been associated with autoimmune diseases including Crohn's disease[8], rheumatoid arthritis[9], and multiple sclerosis[10] and higher levels have been observed in patients with coronary artery disease[11]. Murine models have shown that IL-2 increases regulatory T cell numbers in atherosclerotic plaques and also reduces the size of those plaques[12]. When the IL-2 receptor is blocked in the same model, the plaque reduction is negated.

Despite its potential importance in the immune system and cardiovascular disease (CVD), sIL-2Rα has not been widely investigated in large prospective population-based studies of CVD. A 2003 study in the Health, Aging and Body Composition (Health ABC) study did not result in evidence for a significant association between sIL-2Rα and CVD; however, sIL-2Rα measurements were only available in a subset of N=499 participants. In addition, little is known about the genetic determinants for sIL-2Rα levels. While genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in the *IL-2RA* gene for several autoimmune diseases[10], there have been no published reports for GWAS of serum levels of sIL- 2Rα.

In the current study, we examined sIL-2Rα levels in the Cardiovascular Health Study (CHS), a cohort of older adults with follow-up for incident clinical CVD and mortality for up to 20 years. We examined the relationships between sIL-2Rα at baseline and incident events as well as cross-sectionally with other CVD and inflammatory markers (fibrinogen, C-reactive protein [CRP], and IL-6). We then conducted a GWAS and region-specific conditional analyses to identify genetic variants associated with sIL-2Rα levels. Finally, we performed a

GWAS meta- analysis, including results from two additional studies: the Health ABC study and the Multi- Ethnic Study of Atherosclerosis (MESA), to increase our power to detect associated variants not detected in CHS alone.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Associations between sIL2Rα and baseline CVD risk factors and other inflammation biomarkers

The characteristics of the 5174 CHS participants with sIL-2Rα measurements at the baseline exam are summarized in Table 1, and Spearman correlation coefficients for sIL-2Ra with each continuous CVD risk factor and IMT are given in Supplemental Table I. sIL-2Rα levels were on average higher in older individuals, higher in men, and higher in EAs. At baseline, mean sIL-2Rα levels were 1146.4 pg/mL (standard deviation (SD)=507.5 pg/mL) and 1101.6 pg/mL (SD=556.4 pg/mL) in EA men and women, respectively; and 873.1 pg/mL (SD=505.5 pg/mL) and 910.9 pg/mL (SD=581.2 pg/mL) in AA men and women, respectively. In age-, race- and sex-adjusted models sIL-2Rα was additionally associated with current smoking, type 2 diabetes, hypertension, fasting insulin, waist circumference, CRP, IL-6, fibrinogen, and internal carotid wall IMT and negatively associated with LDL and high density lipoprotein (HDL) cholesterol. After further adjustment, sIL2Ra levels remained associated with age, race, smoking, hypertension, lipids, and inflammation.

Incident events analysis

We performed survival analysis in 4406 EAs and 768 AAs. There were 2985(EA)/451(AA) all- cause deaths; including 1202/186 cases of cardiovascular mortality. There were 1234/195 incident cases of CHD, 762/117 incident strokes, and 1246/199 incident cases of heart failure (fatal and non-fatal events). When minimally adjusted for age, sex, race, and study site, baseline sIL-2Rα was significantly associated with increased risk for all outcomes in both EAs and AAs (Table 2). Results were slight attenuated in EAs after additional adjustment for baseline risk factors except for stroke, and not attenuated at all in AAs. When further adjustment was made for inflammation status and measures of subclinical CVD, all-cause mortality and heart failure remained significant for both the EAs and AAs; cardiovascular mortality remained significant only for EAs; and stroke remained significant only for AAs. Effect estimates were mostly similar between EAs and AAs (sIL-2Rα as a continuous predictor). In analyses where sIL-2Rα was modeled in quartiles, the risk of increased sIL-2Rα for stroke in AAs appears to be driven by the highest quartile of sIL-2Rα as compared to a more graded effect in EAs. We estimated a 63%(EA)/67% (AA) increased risk for all-cause mortality, and a 57%/71% increased risk of heart failure for individuals in the fourth quartile versus those in the first quartile, after adjustment for both established CVD risk factors, inflammation biomarkers and subclinical measures of CVD. For cardiovascular mortality, this estimated increased risk was 64% in EAs and not significant in AAs; and 28% in EAs and 130% in AAs for stroke.

Genome-wide association study of sIL-2Rα in CHS EA and AA

We conducted a race-stratified GWAS in 2964 EAs and 683 AAs from CHS that had both sIL- 2Rα measurement and GWAS data available. A total of 52 SNPs in the chromosome 10p15- p14 region (containing *IL2RA, IL15RA*, and *RBM17*) reached genomewide significance ($p<5\times10^{-8}$) in the EA analysis. The most significant SNP was rs7911500 ($p=1.31\times10^{-75}$), which is located between *IL2RA* and *IL15RA*. No other regions reached genome-wide significance in the EA analysis. No SNPs reached genome-wide significance in the AA analysis. The top findings in AAs were for an intergenic SNP between *BRE* and *FOSL2* on chromosome 2 (rs7602568, $p=5.8\times10^{-6}$) and an intronic SNP in *ADK* (rs12220238, $p=8.3\times10^{-6}$), nearly 70Mb from *IL2RA* on chromosome 10. *IL2RA* SNP rs7911500 (p=0.52) demonstrated no evidence for association in AAs, though the minor allele frequency for this variant in AAs was only 2.5% (compared to 13.4% in EAs). Several chromosome 10p15-p14 SNPs between *IL15RA* and *IL2RA* (lead SNP rs8177607, $p=3.2\times10^{-4}$) provided nominal evidence for an association in AAs. rs8177607 showed no evidence for association in EAs (p=0.65).

Conditional and multiple variant analysis of *IL2RA* region in CHS EA

In the CHS EAs, as described in Methods, we performed an iterative, forward-selection conditional analysis of the chromosome 10p14-15 region (approximately a 200 Kb span), beginning with conditioning on the rs7911500 SNP (Figure 1). The order of additional SNP conditioning was rs791590 ($p_{cond}=7.0\times10^{-35}$; an intronic SNP in *IL2RA*), rs8177757 ($p_{cond}=2.3\times10^{-10}$; located between *IL15RA and IL2RA*), rs10905716 ($p_{cond}=3.3\times10^{-9}$; located between *IL2RA* and *RBM17*), and finally rs7924005 ($p_{cond}=4.4\times10^{-10}$; located in *LOC101928080* downstream from *RBM17*). There was still nominal evidence for further association of SNPs in the region after adjusting for these five, although none reached genome-wide significance. The multiple variant penalized regression method LLARRMA identified six SNPs (Resample Model Inclusion Probability (RMIP) > 0.8; namely, rs2104286 (RMIP =1.00), rs7924005 (RMIP=0.995), rs10905716 (RMIP=0.995), rs4749955 (RMIP=0.911), rs11256497 (RMIP=0.899), and rs7898880 (RMIP=0.871)) that were consistently associated with sIL-2Rα levels across alternative resamplings of the data. Our top SNP in our initial GWAS, rs7911500 (RMIP = 0.002) was not predicted to be important in the multi-SNP LLARRMA model. However, LLARRMA did include the top variant, rs791590 (RMIP = 0.592), from the conditional analysis after conditioning on rs7911500, more often than not in the final multi-SNP model across different resamplings of the data.

The five index SNPs identified in the conditional analysis, in total explain approximately 14% of the variation in sIL-2Rα levels after adjusting for age, sex and PCs to account for population admixture. When we further examined these five SNPs individually for association with incident cardiovascular events in CHS, none of them was significant. We also observed no evidence for an association between a genetic risk score (equal to the sum of the alleles individually associated with increased sIL-2Rα for these five SNPs) and clinical events.

Meta-analysis of CHS, MESA and Health ABC EA

We conducted a meta-analysis combining GWAS results for CHS (N=2964), MESA (N=714) and Health ABC (N=786) EA participants to increase power to detect loci potentially missed in the CHS-only analysis. Meta-analysis results were highly consistent with those observed in the CHS-only analysis, where only variants in the chromosome 10p15-p14 region (*IL15RA*/*IL2RA*/*RBM17*) reached statistical significance (Figure 2). A total of 95 SNPs in this region were significant in the meta-analysis, and the most significant SNP remained rs7911500 ($p = 1.1 \times 10^{-100}$).

We assessed the evidence for association between sIL2r and 1093 variants reported as significant in prior GWAS studies, according to the NHGRI GWAS catalogue (https://www.genome.gov) for the traits listed in Table 1. Only our top two SNPs, rs7911500 and rs12722606, which were previously reported to be significantly associated with an inflammatory phenotype based on the IL-6 – CRP pattern, were statistically significant with the sIL2rα levels in this candidate variant analysis after Bonferroni correction for 1093 test ($p<4.6\times10^{-5}$). Additionally, we searched the CARDIoGRAM+C4D database containing data from multiple GWAS (63,746 case and 13,0681 controls) combined to determine variants associated with coronary artery disease and myocardial infarction (http://www.cardiogramplusc4d.org[14,15,16]). No significant associations (all $p>0.05$) between our SNPs and CVD were identified.

Discussion

We report the first large-scale assessment of sIL-2Rα for association with CVD related traits and events in a prospective cohort and the first GWAS for SNPs associated with sIL-2Rα levels. The major findings from this study are: A) sIL-2Rα levels are associated with a number of established CVD risk factors and carotid IMT, a measure of subclinical CVD. B) Plasma sIL- 2Rα predicted all-cause mortality and cardiovascular mortality independently of CVD risk factors and baseline subclinical CVD. C) In CHS alone (N=2961) we identified 52 SNPs in the chromosome 10p15-p14 region with genome-wide significance for association with plasma sIL- 2Rα levels; most significant was rs7911500, intergenic to *IL15RA* and *IL2RA*. D) Conditional analysis indicated that there are multiple SNPs independently associated in this region; the five most significant loci, in total explain approximately 14% of the variation in plasma sIL- 2Rα levels in CHS EAs. E) Combining results from EAs in CHS and two additional cohort studies, MESA and Health ABC (n=4464), did not result in any additional significantly associated loci. F) We did not identify any significant associations in the CHS AAs, although we did observe nominal evidence for association in the *IL15RA*/*IL2RA* region. G) There was no evidence that sIL-2Rα-associated SNPs were associated with incident clinical events in CHS; we also observed no evidence of association with coronary artery disease and myocardial infarction in a search of the CARDIoGRAM+C4D database results for these SNPs[14,15,16]

Activated T lymphocytes play an important role in atherosclerosis promoting chemokine secretion, inflammation, and eventually, the formation of atherosclerotic plaques. IL-2, produced by T helper 1 cells, has been found in plaques and contributes to the development of atherosclerosis by its interaction with the IL-2 receptor increasing lymphocyte

activation[13]. IL-2 stimulates the synthesis of interferon gamma thereby promoting an increased immune response and atherosclerotic progression. However, IL-2 also promotes regulatory T cells, and may have an atheroprotective role as well[12].

While sIL-2Rα is a strong biological candidate for use as a biomarker for CVD morbidity and mortality, epidemiologic studies have been limited. Analysis in the Health ABC study did not identify evidence for an association between sIL-2Rα and either subclinical (p=0.27) or clinical CVD (p=0.27), but measured sIL-2Rα levels were only available on a subset of 499 of the 3045 participants with incident event data. Although it was not statistically significant, median sIL-2Rα level was slightly higher in those with incident clinical CVD as compared to those with no CVD (1.4 mg/mL versus 1.2 mg/mL)[14]. Investigators from another study of 286 Japanese patients that underwent angiography (167 coronary artery disease [CAD] cases and 119 controls) reported a significant positive association of sIL-2Rα and cross-sectional CAD case status based on extreme quartiles of sIL-2Rα (p=0.005 for minimally adjusted model and p=0.035 for model with additional adjustment for CVD risk factors)[11]. The current study represents the first well- powered effort examining sIL-2Rα level prospectively with clinical CVD events and all-cause mortality. We observed statistically significant evidence for all incident events examined (all- cause mortality, CVD mortality, incident CHD, stroke and heart failure) in minimally adjusted models, and for all-cause mortality, CVD mortality and incident heart failure in fully adjusted models. We found sIL-2Rα levels to be significantly associated with carotid intima-media thickness in the minimally adjusted model; although this did not remain significant when other cardiovascular risk factors were added to the model.

Fifty-two chromosome 10p15-p14 SNPs were significantly associated ($p<5\times10^{-8}$) with plasma sIL-2Rα levels in CHS EAs; no other regions reached genome-wide significance. The most significant SNP, rs7911500, was located between *IL15RA* and *IL2RA*. Iterative conditional analyses identified a total of five significant “independent” SNPs across the region. LLARRMA identified six SNPs that were consistently associated with sIL-2Rα levels across alternative resamplings of the data. Both iterative conditional analyses and LLARRMA provide compelling evidence for the existence of multiple important causal variants in the region, though they did not agree with respect to the importance of our most significant SNP, rs7911500. Higher density genotype data, including both common haplotype-tagging variants and less-common putative functional variants, will be necessary to fine map the association signals in this region. Two of our significant SNPs in the region, rs2104286 ($p=4.9\times10^{-59}$; the top SNP identified by LLARRMA) and rs11594656 ($p=1.5\times10^{-41}$), have been shown to function in transcription factor binding. These SNPs have also been reported to be associated with sIL2Rα levels and type 1 diabetes and multiple sclerosis[15, 16].

No regions reached genome-wide significance in the smaller cohort of CHS AAs. Nominal evidence for association in AAs was detected between *IL15RA* and *IL2RA* (best result: rs8177607, $p=3.2\times10^{-4}$). The lead SNP in EAs, rs7911500, was less polymorphic in AAs and demonstrated no evidence for association. Similarly, no evidence for association was found for rs791590 (p=0.31) or rs10905716 (p=0.43), two significant variants in EAs in the conditional analyses. The two other significant SNPs in the conditional analyses, rs8177757

and rs7924005, were not successfully imputed in the AAs. The difference in findings between EAs and AAs could suggest different risk variants in the two populations, be reflective of different LD structures in the region that mask common underlying causal variants, or be the result of lower power in AAs. There are strong allele frequency differences between the two populations for many of the EA SNPs in the region (see Supplemental Table II for frequencies in HapMap CEU and YRI populations) and the AA sample size is considerably smaller than for EAs.

Interestingly, the top SNP from LLARRMA, rs2104286, in EAs was nominally significant in AAs (p=0.011) despite the lower estimated frequency of the minor allele in AAs (MAF=0.065) compared to EAs (MAF=0.27). The effect estimates for the SNP were similar in AAs (β = -0.17) and EAs (β =-0.15), where carriers of the minor allele were predicted to have lower sIL-2Rα levels.

Elevated sIL-2Rα levels have been shown to be associated with a number of autoimmune diseases and may predict a relapse of those diseases[7]. We found a number of *IL2RA* SNPs previously associated with autoimmune-related diseases to be significantly associated with sIL-2Rα levels. A number of our significant SNPs have also been observed to be associated in GWAS, fine mapping studies and SNP specific genotyping studies for autoimmune diseases including Graves' disease (rs11594656, Odds Ratio (OR)=1.54, p=0.0053)[17], vitiligo (rs706779 OR=1.27, $p=3\times10^{-9}$)[18], Crohn's disease (rs12722489, OR=1.11, $p=3\times10^{-9}$) [19], type 1 diabetes (rs7090530, OR=1.23, p=0.003)[20] and multiple sclerosis (rs2104286, OR=0.81, p=0.017)[20]. Our two most significant SNPs, rs7911500 and rs12722605, were found to be significantly associated with an inflammatory phenotype derived from the high-sensitivity CRP-interleukin-6 (IL-6) pattern in a G W A S o f the Genetics of Lipid Lowering Drugs and Diet Network ($p=5\times10^{-9}$ and $p=5\times10^{-8}$)[21]. The nature of this association is uncertain; it is possible that these variants or others in linkage disequilibrium with them are directly increasing the sIL-2Rα levels which in turn results in downstream increases in both IL-6 and CRP.

There are several limitations in the current study which should be noted. We only analyzed common variants; rare polymorphisms may account for much of the variability in the sIL-2Rα levels. Also, we had weak statistical power to detect associations in AAs. Finally, our study was focused on older adults and the results may not be generalizable to other populations.

Our findings suggest that serum sIL-2Rα, a surrogate marker of T lymphocyte activation, may be a valuable novel biomarker for all-cause mortality, cardiovascular morality, stroke and heart failure in older adults. Additional studies are needed to assess whether sIL-2Rα levels predict mortality in younger populations. Also, further studies are needed a) to identify the causal variants in the chromosomal region harboring *IL15RA* and *IL2RA* influencing sIL-2rα, b) to provide very large and multi-ethnic samples to identify additional genetic loci for this trait, and c) to determine the complex biology of the genetic control of IL-2/IL-2R interactions with respect to regulatory T cell promotion and pro-inflammatory cytokine production.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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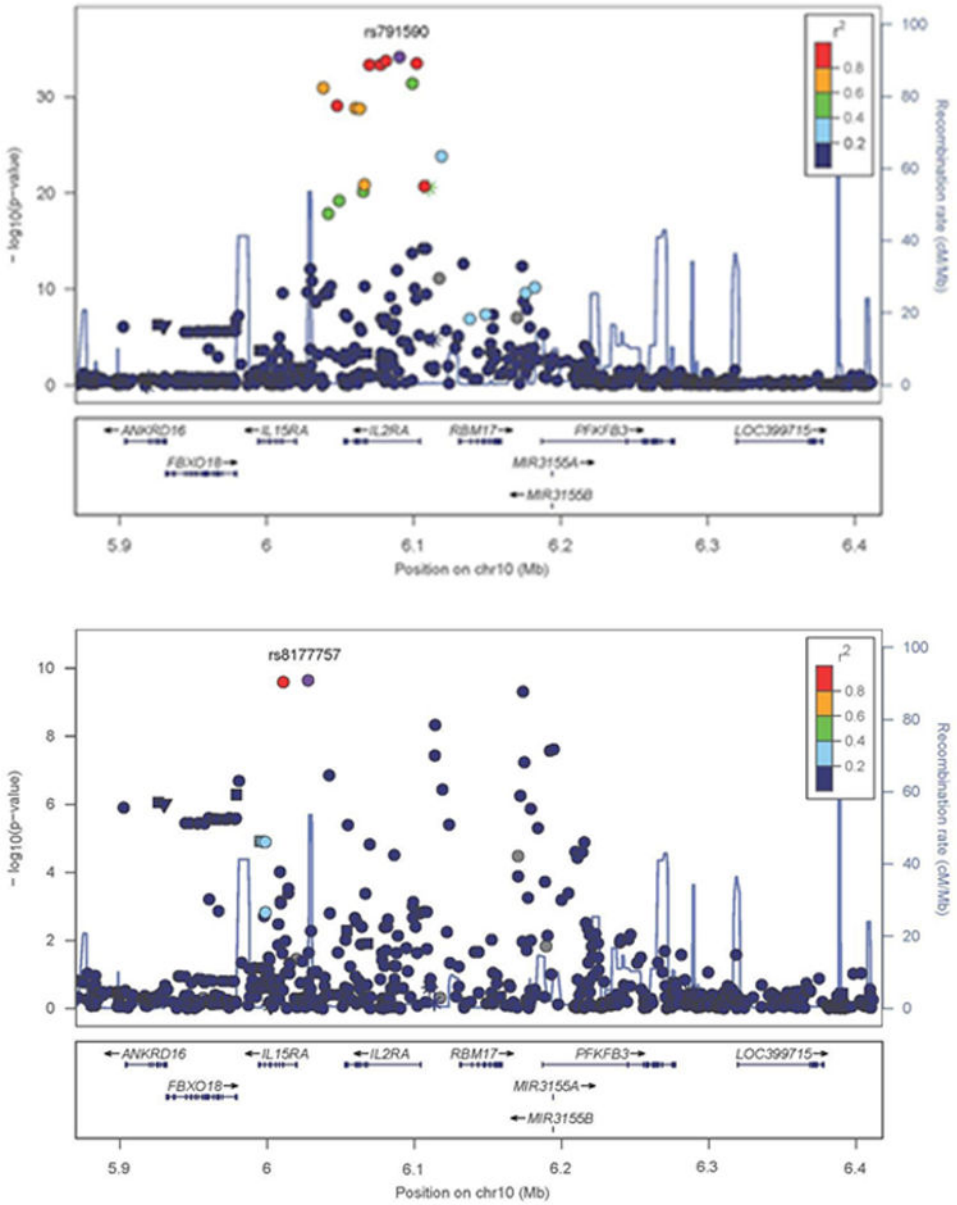
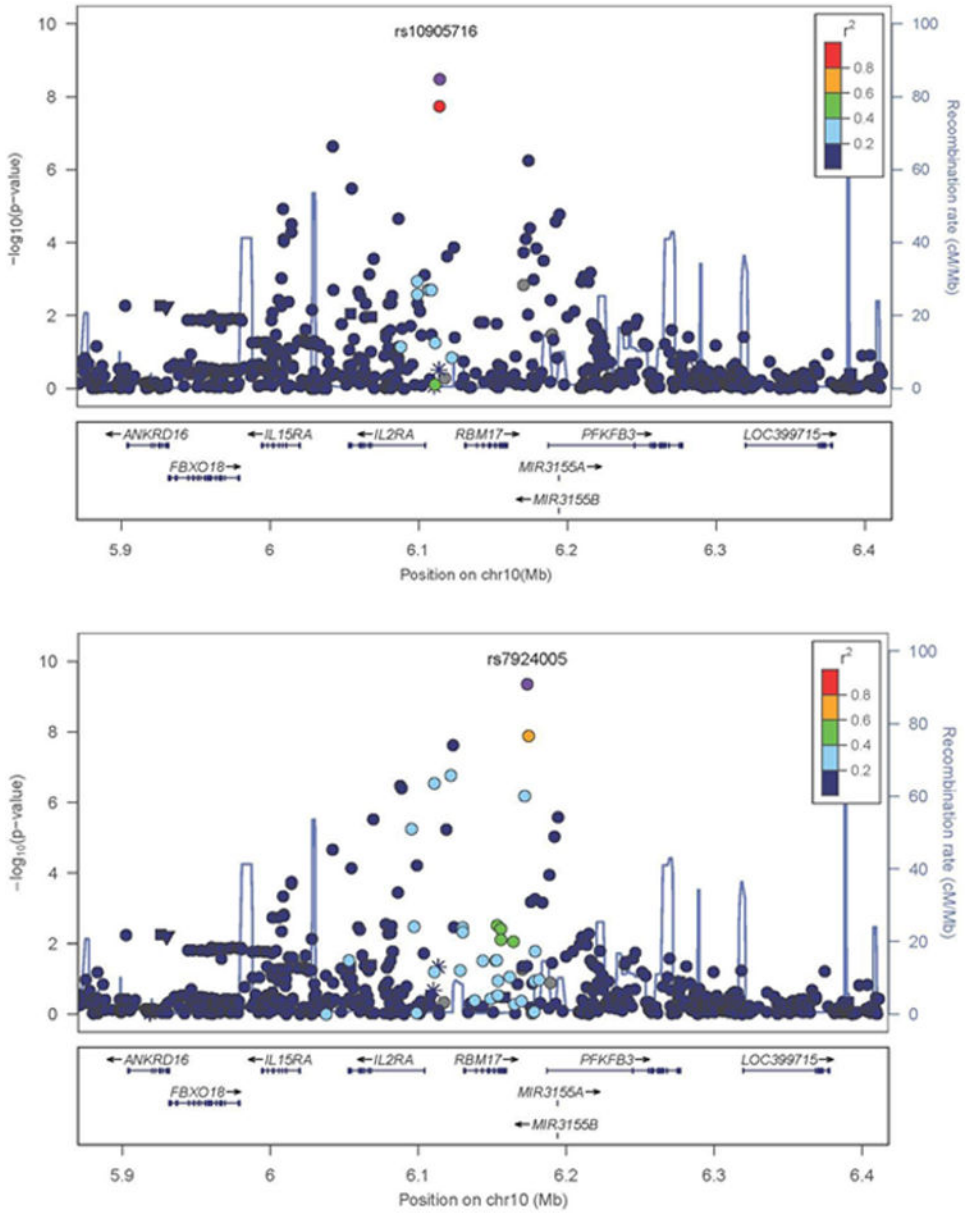
Abbreviations

IL-2	Interleukin-2
sIL-2Rα	Soluble interleukin-2 receptor alpha
CVD	Cardiovascular disease
EA	European-American
AA	African-American
CHS	Cardiovascular Health Study
GWAS	Genome-wide association study
SNP	Single nucleotide polymorphism
Health ABC	Health, Aging and Body Composition study
MESA	Multi-Ethnic Study of Atherosclerosis
QC	Quality control
IMT	Intima media thickness
CHD	Coronary heart disease
CHF	Congestive heart failure
SBP	Systolic blood pressure
LDL	Low density lipoprotein
CRP	C-reactive protein
IL-6	Interleukin-6
PCs	Principle components
SD	Standard deviation
HDL	High density lipoprotein
CAD	Coronary artery disease
BMI	Body mass index
OR	Odds ratio

Significance

This study found that sIL-2Rα, a regulator of white blood cells, is associated with a number of cardiovascular disease risk factors, as well as with all-cause mortality, cardiovascular disease mortality, and heart failure in the Cardiovascular Health Study. Analysis of genetic variants in European Americans found a number of variants in the chromosome 10 region containing the genes IL2RA, IL15RA, and RMB17 to be significantly associated with sIL-2Rα. These results provide support for a role of sIL-2Rα in atherosclerosis and cardiovascular disease.





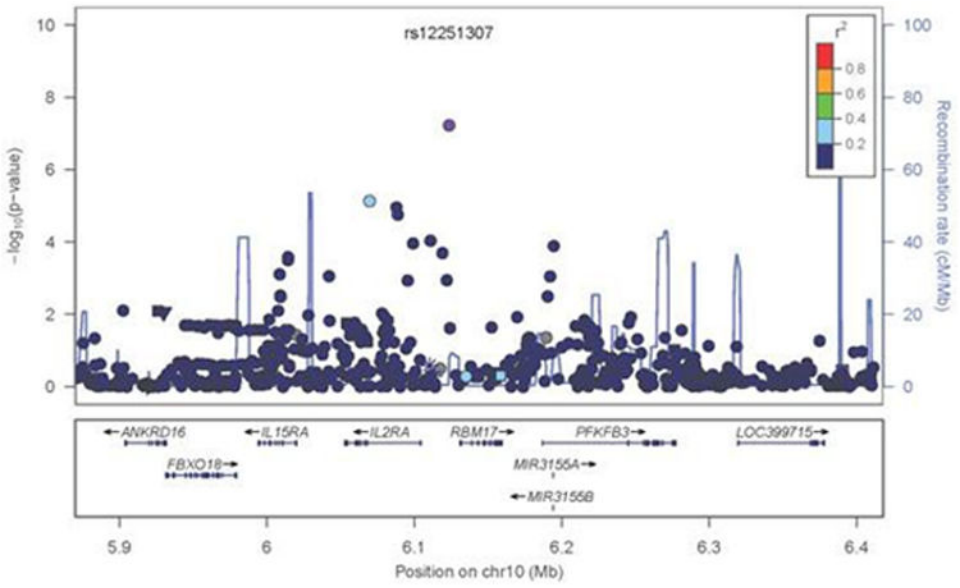


Figure 1.

Conditional analysis: A, Cardiovascular Health Study (CHS) interleukin (IL)2sR α adjusted by rs7911500. B, CHS IL2sR α adjusted by rs7911500 and rs791590. C, CHS IL2sR α adjusted by rs7911500, rs791590, and rs8177757. D, CHS IL2sR α adjusted by rs7911500, rs791590, rs8177757, and rs10905716. E, CHS IL2sR α adjusted by rs7911500, rs791590, rs8177757, rs10905716, and rs7924005.

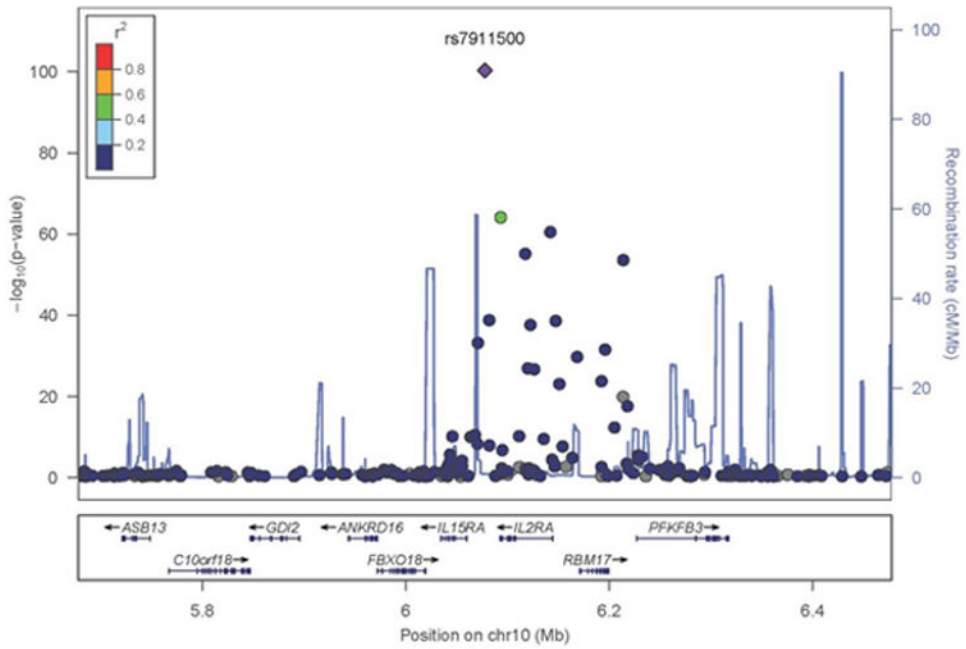


Figure 2.
Meta analysis of European Americans.

Table 1

Associations Between slL-2Rα and Other Cardiovascular Risk Factors and Atherosclerosis at the CHS Baseline Examination

Baseline Characteristics (Mean±SD or %)	Model A, β±SE	Model B, β±SE	Model C, β±SE
Age, y (5.6)	0.074±0.005***	0.078+0.006***	0.067±0.006***
Female sex (57.2%)	–0.029±0.011*	–0.031±0.011*	0,017±0012
Black race (14.8%)	–0.120±0.007***	–0.133±0.008***	–0.134±0.008***
Current smokIng (54.0%)	0.100±0.164***	0.108±0017***	0.079±0.017***
Type 2 diabetes mellitus (16.2%)	0.056±0.014**	0.042±0.015**	–0.002±0.015
Hypertension (44.5%)	0.Q42±0.006***	0.046±0.007***	0.030±0.007***
Systolic blood pressure, mm Hg (136.6±21.8)	0.013±0.005	–0.011±0.026	0.003±0.007
LDL cholesterol, mg/dL (129.8±35.6)	–0.030±0.005***	–0.030±0.005***	–0.032±0.007***
HDL cholesterol, mg/dL (54.2±15.7)	–0.055±0.006***	–0.050+.0.006***	–0.046±0.006***
Triglycerides, mg/dL (139.8±76.7)	0.007±0.005	–0.002±0.006	–0.025±0.008*
Glucose, mg/dL (111.1 ±35.9)	0.013+0.005	–0.009±0.008	–0.013±0.007
Insulin, IU/mL(17.4±27.4)	0.023±0.005***	0,017±0.005*	0.011±0.005
BMI. kg/m^2(26.6±4.7)	0.009±0.006	0.005±0.006	–0.016±0.006*
waist circumference, cm (94.4±13.1)	0.014±0.005*	0.016±0.010	0.003±0.010
C-reactive protein, mg/L (4.8±8.0)	0.083±0.005**	0.080±0.005***	0.043±0.008***
IL-6,pg/mL(2.2±1.8)	0.059±0.005***	0.051±0.005***	0.024+0.006***
Fibrinogen, mg/dL (323.8±67.3)	0.067±0.005**	0.063±0054***	0032±0-006***
Internal carotid wall thickness, mm (1.5±0.7)	0.027±0.006***	0.014±0.006	0.009±0.006

Each variable was examined for association with slL-2Ra in a separate model, adjusting for the variables listed in each model; the exception Is that a variable is not adjusted for Itself when it is being tested. β tor all measures except sex, race, diabetes mellitus, and hypertension are for a 1-SD change in the predictor. Model A: adjusted for age, race, and sex. Model B: adjusted for age, race, sex, smoking, diabetes mellitus, hypertension, systolic Mood pressure, and BMI. Model C: adjusted for age. race, sex, smoking, diabetes mellitus. hypertension, systolic blood pressure, BMI, LDL cholesterol, HDL cholesterol, C-reactive protein, IL-6, and fibrinogen. BMI indicates body mass index; CHS, Cardiovascular Health Study; IL, interieukin; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. sIL-2Rα in-transformed *P* values:

* *P*<0.01

** *P*<0.001

*** *P*<0.0001.

Table 2

Hazard Ratios Between sIL–2Rα and Incident Events In CHS

	All–Cause Mortality (n=29S5 events}	Cardiovascular Mortality (n=1202 events)	Coronary Heart Disease (n=i234 events)	Stroke (n=762 events)	Heart Failure (n=1246 events)
European Americans					
Model	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Minimal† (1)	1.17(1.14–1.19)***	1.16(1.11–1.20)**	1.11(1.05–1.15)***	1.08(1.01–1.14)*	1.16(1.12–1.21)***
Multivarian† (2)	1.16(1.13–1.19)***	1.15(1.10–1.20)***	1 10(1.05–1.15)***	1.06(099–1 14)	1.17(1.12–1.22)***
Subclinical† (3)	1.14(1.11–1.18)***	1.13(1.07–1.19)***	1.05(0.99–1.11)	1.03(0.95–1.12)	1.14(1.08–1.19)***
2nd Q vs 1st Q‡ (3)	1.17(1.04–1.32)*	1.19(0.98–1.45)	1.16(0.97–1.39)	1.46 (1.16–1.B4)**	1.17(0.97–1.401)
3rd Q vs 1st Q‡ (3)	1.25(1.11–1.41)***	1.38(1.10–1.62)**	1.23(1.03–1.46)*	1.38(1.09–1.74)*	1,16(0.97–1.40)
4th Q vs 1st Q‡ (3)	1.63(1.45–1.83)***	1.64 (1.36–1.99)***	1.16(0.97–1.402)	1.28(1.01–1.64)***	1.57(1.31–1.88)***
	All-Cause Mortality (n=451 events)	Cardiovascular Mortality (n=186 events)	Coronary Heart Disease (n=195 events)	Stroke (n=117 events)	Heart Failure (n=199 events)
African Americans					
Model	HF (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Mlrilmal† (1)	1.17(1.10–1.25)***	1.14(1.02–1.28)*	1 15(1.04–1.28)**	1.16 (1.02–1 33)*	1.18(1.07–1.29)**
Multivariable† (2)	1.17(1.04–1.26)***	1,15(1.02–1.31)*	1.19(1.06–1.33)**	1.21 (1.04–1.40)*	1.19(1.07–1.32)**
Subclinical† (3)	1.16(1.07–1.18)***	1.07(0.89–1.29)	1.12(0.96–1.31)	1.22(1.06–1.41)*	1.21 (1.09–1.35)***
2nd Q vs 1st Q† (3)	0.99 (0.76–1.29)	1,02 (0.67–1.55)	1.42(0.98–2.06)	0.94(0.55–1.61)	1.37(0.93–2.01)
3rd Q vs 1st Q‡ (3)	1.31 (0.99–1.73)	1.48(0.94–2.23)	1 50(0 99–2 29)	1.20(0.67–2.14)	1.84(1.23–2.77)**
4th Q vs lst Q‡ (3)	1.67(1.22–2.28)**	1,33 (0.79–2.25)	1.09(0.61–1.94)	2.30(1.34–3.95)**	1.71(1.05–2.80)*

Model 1: Adjusted for age, sex, and study site; Model 2: model 1+smoklng. diabetes mellitus. Hypertension, systolic blood pressure, low–density lipoprotein; Model 3: model 2+C-reactive protein, IL–6, fibrinogen, and carotid intima-media thickness. CI Indicates confidence Interval; CHS, Cardiovascular Health Study; HR, hazard ratio; and IL, interleukin.

*P< 05

**P<0.005

***P<0.0001.

†HRs for a 1-SD unit increase in slL–2R.

‡HRs comparing quartiles to first quartile of SIL-2R.