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Genetic immune and inflammatory markers associated with diabetes in solid organ transplant recipients

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ABSTRACT

New-onset diabetes after transplantation (NODAT) is a complication following solid organ transplantation (SOT) and may be related to immune or inflammatory responses. We investigated whether single nucleotide polymorphisms (SNPs) within 158 immune- or inflammation-related genes contribute to NODAT in SOT recipients. The association between 263 SNPs and NODAT were investigated in a discovery sample of SOT recipients from the Swiss Transplant Cohort Study (STCS, n_1=696). Positive results were tested in a first STCS replication sample (n_2=489) and SNPs remaining significant after multiple test corrections were tested in a second SOT replication sample (n_3=156). Associations with diabetic traits were further tested in several large general population-based samples (n>480'000). Only *SP110 rs2114592C>T* remained associated with NODAT in the STCS replication sample. Carriers of r*s2114592-TT* had 9.9 times (95%C.I.:3.22-30.5, p=0.00006) higher risk for NODAT in the combined STCS samples (n=1184). *rs2114592C>T* was further associated with NODAT in the second SOT sample (OR:4.8, 95%C.I.:1.55-14.6, p=0.006). On the other hand, *SP110 rs2114592C>T* was not associated with diabetic traits in population-based samples, suggesting a specific gene-environment interaction, possibly due to the use of specific medications (i.e. immunosuppressants) in transplant patients and/or to the illness that may unmask the gene effect.

INTRODUCTION

New onset diabetes mellitus after transplantation (NODAT) is a serious complication following solid organ transplantation (SOT)(1) affecting 2-53% of transplanted patients(2). It is considered that NODAT alone is associated with increased 3-year mortality and a significant reduction of graft survival(2). NODAT is also associated with increased cardiovascular events, infectious complications, and graft loss(3), which justifies the great interest in understanding the underlying mechanisms and risk factors contributing to the development of this disease. Obesity, increased age, hepatitis C (HCV) infection, family history of diabetes mellitus, African-American or Hispanic descent are among the risk factors of NODAT(4). Immunosuppressive drugs such as corticosteroids and calcineurin inhibitors, in particular tacrolimus, are also associated with an increased risk of NODAT(1, 2).

Both infections and NODAT are frequent complications in SOT and may be related to altered innate immune responses(5). The innate immune system is the first line of defence against infections with offending pathogens. Cytokines released from immune cells can elicit local and systemic inflammatory responses which can contribute to the development of type 2 diabetes by enhancing insulin resistance. Several proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interferon gamma (IFNγ), were previously shown to decrease the expression of insulin-sensitive glucose transporters, insulin signalling and to promote insulin resistance(6). Also, in the absence of infection, obesity (pre- and post-transplant) is associated with chronic low-grade inflammation driven by adipokines derived from adipose tissue, which can lead to insulin resistance(7) and the development of NODAT(8). Genome-wide association studies (GWAS) conducted to date explain only 10% of type 2 diabetes heritability and more diabetes susceptibility genes remain to be discovered(9). Regarding the genetics of NODAT, little is known and many inconsistent associations have been reported and are reviewed(10). Therefore, we aimed to examine whether single nucleotide polymorphisms (SNPs) located in different genes mainly implicated in inflammation or in the immune responses to infectious diseases may contribute to the development of

NODAT in SOT recipients. As control, analyses were extended to samples of the general population.

MATERIAL AND METHODS

Samples description:

The Swiss Transplant Cohort Study (STCS) (discovery and first replication samples)

STCS is an ongoing prospective multicenter nationwide cohort project with an extensive and structured data collection(11, 12). Full description of this nationwide Swiss cohort (Basel, Bern, Geneva, Lausanne, St. Gallen and Zurich) is published elsewhere(13). Briefly, all SOT recipients in Switzerland are prospectively registered since May 2008. All patients with an allotransplant are included and are followed in their respective centers. Clinical data are collected at baseline, at 6, 12 months and yearly thereafter. For the discovery STCS cohort, patients transplanted from May 2008 to 8th of May 2011 were included in the analyses (n=1294). Patients from the STCS transplanted from 9th of May 2011 to May 2013 were included in the first replication cohort (n=759). Non Caucasian patients and patients who were diagnosed with glucose intolerance or diabetes before transplantation, as reported in the medical files, were excluded from NODAT analyses. Recipients younger than 18 years old and recipients with multiple organ transplantation were excluded from our study. If a patient received more than one transplantation during the inclusion period, only data from the first SOT was included in the analyses. NODAT was diagnosed if a patient needed anti-diabetic treatments following transplantation or if such new metabolic event was reported in the case report forms. For the combined STCS sample, new-onset hyperlipidemia was diagnosed if patients needed hypolipidemic treatment post-SOT. Patients with previous hyperlipidemia, as reported in the medical files, were excluded from the new-onset hyperlipidemia analyses. Blood samples were obtained from all SOT recipients at the time of transplantation. The study was approved by the corresponding ethics committee and all patients gave their written informed consent to participate in the study.

Second replication SOT sample

A full description of this cohort is published elsewhere(13-15). Briefly, a total of 200 patients were enrolled between 2003 and 2005 from the outpatient clinic of the Transplant Center of the University Hospital of Lausanne, Switzerland. Clinical data were collected retrospectively

from the medical files at the time of transplantation, at 1, 3, 6, 9 and 12 month post-transplantation and yearly after until 5-year post-transplantation. Non Caucasian patients and patients who had glucose intolerance or diabetes before transplantation, as reported in the medical files, were excluded from the present study. NODAT was diagnosed if a patient needed anti-diabetic treatment (either insulin or oral anti-diabetic agents) following transplantation or fulfilled the criteria given by the WHO and ADA consensuses(16), including fasting blood glucose (FBG) ≥ 7.0 mmol/l in ≥ two occasions) and/or 2 hours plasma glucose ≥ 11.1 mmol/l during oral glucose tolerance test. The study was approved by the ethics committee of the University of Lausanne and all patients gave their written informed consent to participate in the study.

Overall, 1294, 759 and 200 patients from the STCS discovery sample, the first STCS replication sample and the second SOT replication sample, respectively, were included in the study. After excluding patients younger than 18 years of age, patients with multiple organ transplantation, patients with previous diabetes or prediabetes, and keeping patients with both clinical and genetic data available, 696, 489 and 156 patients, respectively, remained included in the NODAT analysis.

Population based samples

Significant SNPs were tested for association with diabetes development in the general Caucasian population (UK biobank (6'117 type 2 diabetes cases and 109'942 controls), the MAGIC (Meta-Analyses of Glucose and Insulin-related traits) consortium (n=46'186), and the DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) consortium (n=69'033; 12'171 T2D cases and 56'862 controls). Associations with obesity markers in the GIANT (Genetic Investigation of ANthropometric Traits) consortium (n=250'596), lipid markers in the Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides (n>100'000) and with different metabolic parameters in the Cohorte Lausannoise (CoLaus, n=5338) were also tested. More information are given in Supplementary data.

Polymorphisms selection:

287 SNPs within 158 different genes (Supplementary Table 1) implicated in the immune response to infectious pathogens or inflammation were selected from customized 384 Golden Gate Genotyping Assay (Ilumina, San Diego, California, USA). More information about Polymorphisms selection and genotyping are given in Supplementary data.

Statistical analyses:

Quantitative data are presented as median and range unless otherwise mentioned, while qualitative data are presented as frequency and percentage. For association studies, the chi-square (Chi^2) test or the Fisher exact test for binomial variables were used. Differences in allele and genotype frequencies as well as deviation from Hardy-Weinberg equilibrium (HWE) were assessed using chi-square test. Data were analyzed using Stata 13 (StataCorp, College Station TX, USA) and R version 2.13.0 software (http://www.R-project.org).

STCS samples (discovery and first replication sample)

NODAT in the STCS samples was analyzed using logistic regression models adjusted for recipient's age at transplantation, sex, HCV status, baseline BMI, and the type of calcineurin inhibitor (variables identified through the univariate analysis with p-values <0.10, Table 1). Associations between NODAT and selected SNPs with p-values <0.01 in the STCS discovery sample were retained and analyzed in the STCS replication sample and in other cohorts as described. No correction for multiple testing was applied for the discovery sample as it was only used to explore associations between the selected SNPs and NODAT, and these associations were only considered significant if replicated in another cohort. Bonferroni correction for multiple testing, however, was applied for the replication cohorts.

In the combined STCS sample, logistic regression models adjusted for recipient's age at transplantation, sex, and baseline BMI were used to analyze other metabolic parameters including new-onset hyperlipidemia after transplantation. Due to nonlinearity of BMI and HDL-cholesterol models and the absence of any linear transformation, the association between the SNPs with BMI and HDL-cholesterol levels was assessed by fitting a Generalized Additive Mixed Model (GAMM) to allow a smooth trend for the response in time based on multiple observations for each patient (using a thin plate regression spline basis) adjusting for

recipient's age at transplantation, sex and baseline BMI (also adjusted for the use of hypolipidemic drugs for analysis of HDL-cholesterol). GAMMs were fitted using the mgcv package of R (settings were fixed at package defaults). In order to be more conservative, the uncertainty of estimated parameters was assessed by 1000 bootstraps at the subject level. Linear mixed models were used for total blood cholesterol and LDL-cholesterol analyses. These models were adjusted for recipient's age at transplantation, sex, baseline BMI, and hypolipidemic drugs intake.

Second replication SOT sample

Logistic regression models were applied for NODAT analyses adjusted for recipient's age at transplantation, sex, baseline BMI and type of calcineurin inhibitors.

Population-based samples

SNPs significantly associated with different metabolic traits in SOT samples were analyzed in population-based samples. Multivariate linear regression with allele dosage in which potential confounding factors such as age, sex, batch effect, five ancestry principal components and smoking status were used. FBG, oral glucose tolerance test, the surrogate estimates of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) were analyzed in the MAGIC study, while FBG was investigated in the CoLaus study.

BMI, waist circumference and waist-to hip ratio were the only adiposity traits analyzed by the GIANT Consortium. Triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol were analyzed in the "Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides" study(17).

Estimation of the functional activity of the significant SNPs:

The RegulomeDB(18) database was used to estimate the functional activity of the significant SNPs. This database annotates SNPs with known and predicted regulatory elements in the intergenic regions of the Homo sapiens genome and reveals known and predicted regulatory DNA elements including regions of DNase hypersensitivity, binding sites of transcription factors, and promoter regions that have been biochemically characterized to regulate

transcription. Source of these data include public datasets from GEO, the ENCODE project, and the published literature.

RESULTS

General characteristics of the study populations

The incidence of NODAT in the discovery sample was 21.8%. NODAT patients were older with higher baseline BMI and were more often prescribed then tacrolimus-based maintenance immunosuppression compared to non-NODAT patients. A detailed description of this sample is presented in Table 1. Similar descriptions for the replication samples are presented in Supplementary Tables 2 and 3.

Polymorphisms in immune related genes and NODAT in the STCS and the replication samples

The minor allele frequency (MAF) was <5% for 12 SNPs in our discovery sample and they were removed from the analyses. Additionally, 12 SNPs did not meet HWE ($p<0.05$), therefore, a total of 263 SNPs were finally analyzed (Supplementary Table 1, Part. A,B,C). Among these SNPs, 10 polymorphisms were associated with NODAT (p-value<0.01 in additive models and/or allele dosage; Supplementary Table 4). These SNPs were used for replication in the first replication sample (second subset of the STCS sample).

Among these 10 SNPs only one SNP, the *SP110 nuclear body protein* (*SP110) rs2114592C>T,* was associated with NODAT in the first replication sample after correction for multiple testing (Table 2) and was therefore investigated in the second SOT replication sample and in other population based samples. A significant observation was also noticed when combining both STCS samples, with *SP110 rs2114592-TT* genotype carriers having 9.9 (95%C.I.: 3.22-30.5, p=0.00006) higher risk of developing NODAT compared to reference genotype carriers (Table 2). Importantly, *SP110 rs2114592C>T* SNP was also associated with NODAT in the second SOT replication sample (n=156, OR:4.8, 95%C.I.:1.55-14.6, p=0.006). Time to NODAT in the combined STCS sample by *SP110* genotype is shown in Figure 1, with an increased incidence of NODAT during the first year in *SP110 rs2114592-TT* genotype carriers (p=0.003) compared to other genotypes.

A second SNP (*rs2907749A>G*) within the *nucleotide-binding oligomerization domain containing 1 (NOD1)* was associated with NODAT in the discovery and in the first replication samples, but this association did not remain significant after multiple testing correction (Supplementary Table 5a). This SNP was not significantly associated with NODAT in the second SOT replication sample (data not shown), but was significantly associated with NODAT (n=1156), new-onset hyperlipidemia (n=1051), lower HDL-cholesterol (n=1051), and higher total cholesterol levels (n=1051) in the combined STCS sample (Supplementary Table 5a and 5b).

***SP110 rs2114592C>T* SNP and other metabolic syndrome complications in the combined STCS sample**

The associations between *SP110 rs2114592C>T* SNP and other metabolic syndrome complications were investigated in the combined STCS sample (n=1071). No association was observed between *SP110 rs2114592C>T* SNP and BMI (dichotomized into normal versus overweight or obese) at 12 months post-SOT or when analyzing the evolution of BMI over time between different genotype groups (data not shown). Carriers of *SP110 rs2114592-TT* genotype presented 3 times higher risk of developing new-onset hyperlipidemia after transplantation (OR:3.41, 95%C.I.:1.06-11.0, p=0.04) when compared to the reference genotype (*SP110 rs2114592-CC)*, but this genotype was not associated with differences of lipid blood levels (Supplementary Table 6).

***SP110 rs2114592C>T* SNP and metabolic markers in population-based samples**

In the population-based samples, SP110 *rs2114592C>T* SNP was not associated with the different metabolic markers investigated, including available diabetes markers (Supplementary Table 7).

Tagging SNPs of *SP110* gene:

Twenty-six tagging SNPs within the *SP110* gene were found using HapMap Genome Browser (Supplementary Table 8). Only *SP110 rs7580900T>C* SNP was associated with NODAT in the

discovery sample (n=695, OR:0.72, 95%C.I.:0.55-0.95, p=0.02 in additive model and OR=0.43, 95%C.I.:0.23-0.80, p=0.007 for *rs7580900-CC* genotype compared to the reference genotype). This significant association between *SP110 rs7580900T>C* SNP and NODAT was not replicated in the different replication samples (data not shown).

Estimation of the functional activity of *SP110 rs2114592C>T* SNP

The functional activity of *SP110 rs2114592C>T* SNP was investigated using the RegulomeDB database(18). We found 22 SNPs to be in complete linkage disequilibrium (r^2=1) with *SP110 rs2114592C>T* SNP (intronic variant), among them the *SP110 rs75411703* SNP which shows a deoxyribonuclease sensitivity quantitative trait loci (dsQTL) effect and is linked to the expression of the target gene(19). Additionally, by using the eQTL gene browser-gene network database(20), *SP110 rs2114592-T* allele is associated with a decrease of *SP110* expression in the blood (p-value=3.87E-26). Altogether, these data suggest that S*P110 rs2114592C>T* SNP might have important regulatory functions.

DISCUSSION:

Inflammation is intimately linked with the development of diabetes in the general population (reviewed in(21, 22)) and recipients of SOT(5). In our study ten polymorphisms within 10 different genes primarily implicated in the innate immune response or inflammation were significantly ($p<0.01$) associated with NODAT in a discovery cohort of 696 patients from the STCS without a previous history of diabetes or glucose intolerance before SOT. These significant results were tested for replication in 2 samples with SOT (a second subset of the STCS and a third independent sample with SOT) and only one polymorphism in the intronic region of *SP110* gene *(rs2114592C>T)* was found to be significantly associated with NODAT in both replication samples. Carriers of the *rs2114592-TT* genotype had nearly 10 times increased risk of NODAT in the combined STCS sample. They also showed an increased risk of new-onset hyperlipidemia. However, *SP110 rs2114592C>T* was not associated with diabetes in large population-based samples.

SP110 nuclear body protein (encoded by the *SP110* gene) is an activator of gene transcription and may serve as a nuclear hormone receptor coactivator(23). This gene is a member of the SP100/SP140 family of nuclear body proteins and is involved in several cellular processes such as apoptosis, cell cycle control, and a prototype type I interferon-induced gene that regulates immune responses in particular in myeloid cells differentiation. Most of the studies investigating SP110 have shown its role in immunoprotective defenses against infectious organisms in humans, mainly tuberculosis(24). Human SP110 is the closest homolog of mouse intracellular pathogen resistance-1 (Ipr1) protein, and previous animal studies showed that the expression of the *Ipr1* transgene in macrophages limits the multiplication of M. tuberculosis and switches the infected macrophages towards an apoptotic cell death pathway(24). Several studies in human investigated the association between polymorphisms of *SP110* (among them the *rs2114592C>T*) and the risk of developing pulmonary tuberculosis, but results were inconsistent(25, 26). No previous studies related *SP110* or its polymorphisms to diabetes or NODAT. Interestingly, SP110, as a transcriptional coactivator, enhances transcription of genes

with retinoic acid response elements(23) and several of these genes such as *IL2RA, PEPCK1, UCP1 and CD38*(27) are known candidate genes for type 1 and type 2 diabetes. Retinoids are important in glucose and lipid metabolism and the activation of the retinoic acid cascade through the retinoic acid response elements has been previously related to the development of diabetes, adipogenesis and insulin resistance (reviewed in(28)). Functional activity of *SP110 rs2114592C>T* was investigated and was linked to the expression of the target gene. Moreover, it has several histone marks and influences the binding of several proteins, among them some important immune regulatory proteins (e.g.: IRF-4 and NF-ATc1), but also the transcription factor E2-alpha (encoded by TCF3). TCF3 is a transcriptional regulator that binds to IEB1 and IEB2 which are short DNA sequences in the insulin gene transcription control region providing a new possible mechanism relating *SP110* to the development of diabetes and/or NODAT.

Homozygous loss of function mutations in *SP110* in humans cause Hepatic Veno-occlusive Disease with Immunodeficiency (VODI), a monogenic autosomal recessive primary immunodeficiency associated with hepatic vascular occlusion and fibrosis(29) and a severe combined immunodeficiency despite normal lymphocyte numbers. VODI is associated with high mortality either due to hepatic failure but also to life threatening infections, often pneumocystis(29). SP110 deficient B cells have reduced ability to respond to T cell dependent signals and to differentiate into plasmablasts which might be the explanation for the observed hypogammaglobulinemia in VODI(30). Metabolic alterations, especially diabetes, are not hallmarks of VODI; however, these patients often die within the first 12 months of life, so long long-term metabolic complications of SP110 deficiency might be missed(29). These data altogether suggest that SNPs within the *SP110* gene may be linked in populations at risk with an altered inflammatory response, leading to the development of NODAT.

We also tested whether the associations between *SP110 rs2114592C>T* SNP and diabetes are present in the general population. No effect was observed in two large population-based samples and a large case-control sample of patients with type 2 diabetes, pointing out the implication of this SNP only in populations at high risk of developing metabolic diseases

including diabetes. Although there is a strong correlation between inflammation and Type 2 diabetes in the general population, our results suggest a specific gene-environment interaction, possibly due to the use of specific medications (i.e. immunosuppressants) in transplant patients and/or to the illness that may unmask the gene effect.

This study has several limitations and strengths. One of the major limitations of genetic studies in this field is the different definitions used for NODAT. However, it should be noted that NODAT definition in the discovery and second STCS replication samples was the same and the closest to the criteria given by the WHO and ADA consensuses (16), which is a strength in our study. Even though the association between *SP110 rs2114592C>T* and NODAT were replicated in two cohorts, they are modest in size and not truly independent. The present finding must therefore be confirmed by future studies. The selection of the SNPs was based on SNPs already associated with infections and inflammation in the literature and does not cover all variants within these genes, so unknown variants within these candidate genes with important associations with NODAT or novel pro-inflammatory variants may have been missed. Our findings on Caucasian samples cannot be extrapolated to other ethnicities. The present results do not allow determining whether *SP110 rs2114592C>T* SNP is the causative variant or merely a proxy of one or more yet unidentified variants. Despite the important regulatory functions suggested by the RegulomeDB and the eQTL databases, further studies are needed to elucidate which precise mechanisms underlie the observed associations. Another limitation is the low allelic frequency of *SP110 rs2114592C>T* with only few homozygote carriers of *TT* genotype being observed (see supplementary Table 9). Thus *SP110 rs2114592C>T* contributes only to a small fraction of new onset diabetes in the analyzed populations. On the other hand, the fact that these results were replicated in two independent samples with SOT strengthens the validity of our data. In addition, the high observed ORs suggest important clinical implications of *SP110 rs2114592C>T* SNP. Well-designed prospective clinical trials should therefore be conducted to test whether genetic testing before transplantation may offer more precise new onset diabetes risk stratification. In

addition, SP110 may be even more relevant in predicting diabetes in specific subgroups of at-risk SOT patients (e.g. HCV-infected transplant recipients, or overweight patients), but this remains to be analyzed.

In conclusion, our results link for the first time the *SP110* gene in the development of diabetes and other metabolic complications in SOT recipients. While the pathway by which the *SP110 rs2114592C>T* SNP is associated with diabetes remain unraveled, our study opens the door for further investigation of this SNP and provides a promising new candidate gene for diabetes development. Ultimately, an important question will be to determine whether personalized strategies based on genetic testing in pre-transplant patients may help to reduce the risk of developing diabetes.

Declaration of interests:

IB received honoraria for advisory committee and study sponsoring from Alexion, Boehringer-Ingelheim, and Lophius

CBE received honoraria for conferences or teaching CME courses from Astra Zeneca, Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Mepha, Otsuka, Servier and Vifor-Pharma in the past 3 years, and for writing a review article for the journal “Dialogues in clinical neurosciences” (Servier) He received an unrestricted educational research grant from Takeda in the past 3 years.

JFD received honoraria for advisory committees from Bayer, BMS, Gilead Science, Janssen Cilag, Jennerex, Merck, Novartis, Roche and for speaking and teaching from Bayer, Boehringer-Ingelheim, Novartis, and Roche

SC received honoraria for teaching CME courses from Forum für Medizinische Fortbildung

NM received honoraria for advisory committee from Basliea and travel support from Astellas and Gilead.

RL reports personal fees from Lectures for AZ, NovoNordisk, Boehringer-Ingelheim, Sanofi, Servier, Medtronic, MSD.

MR reports personal fees from Baxalta and CSL Behring

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Footnote

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Authors' contributions:

All authors reviewed, revised and approved the final version of the manuscript.

LQ obtained funding, did the statistical analysis, interpreted the data and wrote the manuscript

WA did the genetic analysis (STCS cohort) and interpreted the data

PYB obtained funding, designed the genetic analysis (STCS cohort) and interpreted the data.

SC collected and interpreted the data (second replication SOT sample)

JPV, OM, DG, RL, NJM, IB, CvD, JS, PM, JFD, PMS, MP obtained funding, designed the STCS study, collected and interpreted the data

ZK supervised the statistical analysis and did the statistical analysis for the population based cohorts

PMV, MR, CH and FV interpreted the data

PV collected and interpreted the data

CBE was the chief investigator, obtained funding, designed the study, and interpreted the data.

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Figure 1. Time to new onset diabetes after transplantation (NODAT) in the combined Swiss Transplant Cohort Study (STCS) sample by SP110 genotype for the rs2114592 polymorphism.

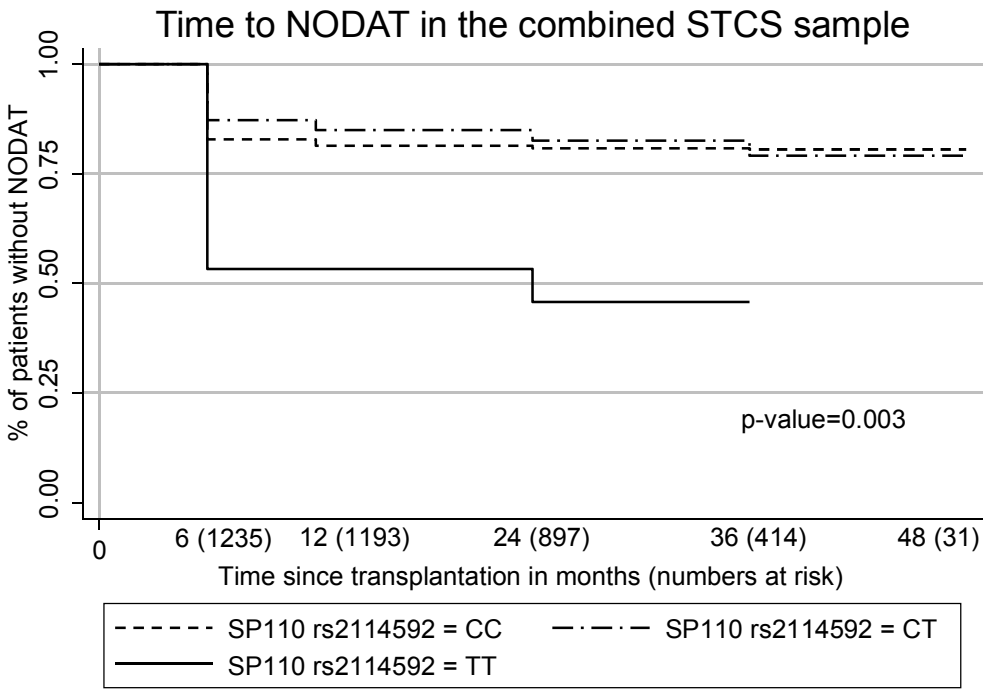

Table 1: Clinical characteristics of the solid organ transplantation discovery sample (Swiss transplant cohort study first sample).

Characteristic	***Total***	***Non-NODAT***	***NODAT***	***p-value***
Sample size (%)	696	544 (78.2)	152 (21.8)	
Age at transplantation (years), median (range)	52 (18-79)	51 (18-79)	56 (19-73)	0.0003
Recipient sex (Male) [%]	65.6	63.7	72.4	0.05
Living donor [%]	32.7	33.7	29.0	0.27
Donor age (years) median (range)	52 (1-86)	52 (1-85)	54 (14-86)	0.73
Donor sex (Male) [%]	53.3	54.8	48.0	0.14
Recipients anti-HCV [% of HCV positive]	7.7	6.5	11.8	0.03
Organ [%]				0.15
Kidney	69.1	70.6	63.8	
Liver	15.5	15.1	17.1	
Lung	9.2	9.2	9.2	
Heart	6.2	5.1	9.9	
Body mass index (kg/m^2), median (range)				
Pre-transplant	24.4 (13.7-41.2)	24.2 (13.7-39.1)	25.8 (15.2-41.2)	0.0001
One year follow-up	25.1 (15.4-44.4)	24.7 (15.4-44.4)	26.6 (17.3-44.3)	0.0005
Calcineurin inhibitors, [%]				0.004
Tacrolimus	66.5	64.1	75.0	
Cyclosporine	26.2	29.1	15.8	
None	7.3	6.8	9.2	

NODAT: New-onset diabetes after transplantation, HCV: hepatitis C.

Table 2: Association between *SP110 rs2114592 C>T* genotypes and new-onset diabetes after transplantation in the Swiss transplant cohort study (STCS) replication sample and the combined sample.

	CC	**CT**	**TT**	**T allele dosage**
STCS replication sample				
Sample size	376	105	8	
Odds ratio (95% CI)	1 (Ref.)	1.26 (0.72 - 2.20)	8.90 (1.97 - 40.0)	1.70 (1.08 - 2.66)
P-corrected value*		1.0	0.04	0.20
Combined STCS samples				
Sample size	935	234	15	
Odds ratio (95% CI)	1 (Ref.)	1.16 (0.81 - 1.65)	9.90 (3.22 - 30.5)	1.53 (1.13 - 2.06)
P-value		0.42	0.00006	0.005

Results are expressed as odds ratio and (95% confidence interval). Statistical analysis by logistic regression adjusting for age of recipient at transplantation (continuous variable), sex of the recipient, baseline BMI (continuous variable), type of calcineurin inhibitor (no calcineurin inhibitor / tacrolimus / cyclosporine). No adjustement was done for HCV status (as in the discovery sample) because data were not available.

*P- values were corrected using Bonferroni correction for multiple testing (corrected P-value = original p-value * 10)

SUPPLEMENTARY INFORMATIONS

Population based samples description:

The Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)

MAGIC is a large-scale meta-analysis of genome-wide data for continuous diabetes-related traits in participants without diabetes(1). Meta-analyses of ~2.5 million directly genotyped or imputed autosomal single nucleotide polymorphisms (SNPs) were performed from genome-wide association studies (GWAS). These cohorts include up to 46'186 non-diabetic participants of European descent informative for FBG, the surrogate estimates of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) derived from fasting variables by homeostasis model assessment and up to 15'234 non-diabetic individuals informative for 2 hour oral glucose tolerance test(2).

The UK biobank for diabetes

UK Biobank recruited 500,000 participants aged between 40-69 years in 2006-2010 from across the country to take part in this project. They have undergone measures, provided blood, urine and saliva samples for future analysis, detailed information about themselves and agreed to have their health followed. The UK biobank has type 2 diabetes status (diagnosed by the doctors) in 116,059 individuals of white British ancestry.

The DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) consortium

The DIAGRAM consortium is a meta-analysis of GWAS data in 12'171 type 2 diabetes cases vs. 56'862 controls in individuals of European ancestry(3).

Genetic Investigation of ANtropometric Traits (GIANT) consortium

The GIANT consortium performed a meta-analysis of GWAS data with a discovery set of 123'865 individuals of European ancestry from 46 studies for height, BMI and waist-to hip ratio(4, 5).

Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides

Data on lipid traits have been downloaded from “Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides” website which is a meta-analysis of 46 lipid GWASs. These studies together comprise >100,000 individuals of European descent (maximum sample size 100,184 for Total Cholesterol, 95,454 for LDL-C, 99,900 for HDL-C and 96,598 for triglycerides), ascertained in the United States, Europe or Australia(6, 7).

Cohorte Lausannoise (CoLaus)

Participants aged 35 to 75 years in this population-based study (CoLaus) were recruited between June 2003 and May 2006 as previously described(8). The assessment included cardiovascular risk factors such as the BMI, fat mass, waist circumference, blood pressure, blood glucose, triglycerides and HDL-C. In addition, all Caucasians (91% of the sample) underwent a genetic exam (n=5338). Of note, CoLaus is part of the MAGIC and GIANT studies.

Polymorphism selection and genotyping:

The SNPs from genes previously associated with infectious phenotypes or inflammation were selected based on the literature search using Medline database until June 2012. SNPs from genes that were not studied so far were selected based on tagging SNP approach.

Genomic DNA was extracted from blood specimens using the Gentra Puregene Blood Kit (Qiagen). Genotyping was performed using a customized GoldenGate Genotyping Assay on Veracode platform (Illumina, San Diego, California), unless otherwise indicated. Results were analyzed on a BeadXpress Reader according to standard protocols and quality controls. Additional SNPs in the discovery sample and all the SNPs from the first replication sample were genotyped using the Competitive Allele-Specific PCR system (KASP™ technology, LGC Genomics, UK) on QuantStudio™ 12K Flex system or ABI 7500 Fast real-time thermocycler (Applied Biosystems) according to the manufacturer's protocol. The KASP primers were designed by Kraken™ assay design and workflow management software and further validated by the manufacturer (LGC Genomics, UK).

Genotypes of the second replication were exported from the Illumina 200K cardiometabochip(9). The CardioMetabochip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200'000 SNPs from regions identified by large scale meta-analyses of GWAS for metabolic and cardiovascular traits. Customized SNPs were added to the CardioMetabochip which included the SNP significantly associated with NODAT in the STCS cohorts. CardioMetabochip genotyping was performed at the iGE3 genomics platform of the University of Geneva (10). Genotyping for the CoLaus subjects was performed using the Affymetrix GeneChipR Human Mapping 500K array set.

Supplementary table 1 (Part A): Selected genetic polymorphisms, allelic variants and chromosomal positions

rs_number	Alleles	Position	Gene	Chromosome
rs1033638	C/T	11026660	MASP2	1
rs1061622	G/T	12192898	TNFRSF1B	1
rs631090	C/T	22659910	C1QB	1
rs7530511	C/T	67219704	IL23R	1
rs2476601	A/G	113834946	PTPN22	1
rs1016140	G/T	116533925	CD58	1
rs1205	C/T	159712443	CRP	1
rs1801274	C/T	161509955	FCGR2A	1
rs10800098	A/G	165439858	RXRG	1
rs3024493	G/T	206770623	IL10	1
rs1800871	C/T	206773289	IL10	1
rs1800896	A/G	206773552	IL10	1
rs1800890	A/T	206776020	IL10	1
rs1518108	C/T	206869829	IL20	1
rs3813946	A/G	207454348	CR2	1
rs1048971	A/G	207472977	CR2	1
rs17615	A/G	207473117	CR2	1
rs6656401	A/G	207518704	CR1	1
rs851193	A/G	223121509	TLR5	1
rs5744105	C/G	223142735	TLR5	1
rs3806265	C/T	247423034	NLRP3	1
rs4612666	C/T	247435768	NLRP3	1
rs10754558	C/G	247448734	NLRP3	1
rs212706	C/T	32226063	NLRC4	2
rs408813	G/T	32251321	NLRC4	2
rs385076	C/T	32264782	NLRC4	2
rs2272127	C/G	102423413	IL18RAP	2
rs917997	A/G	102454108	IL18RAP	2
rs1800587	C/T	112785383	IL1A	2
rs1143634	C/T	112832813	IL1B	2
rs1143633	A/G	112832890	IL1B	2
rs1143627	C/T	112836810	IL1B	2
rs4251961	C/T	113116890	IL1RN	2
rs419598	C/T	113129630	IL1RN	2
rs3806496	C/T	118940998	MARCO	2
rs1318645	C/G	118942009	MARCO	2
rs6761637	C/T	118981487	MARCO	2
rs13432	C/G	159769216	CD302	2
rs1921310	A/G	161192690	TANK	2
rs1990760	C/T	162267541	IFIH1	2
rs2280235	C/T	190979104	STAT1	2

rs1547550	C/G	190980999	STAT1	2
rs2280233	A/G	190985840	STAT1	2
rs2066802	C/T	191009941	STAT1	2
rs231775	A/G	203867991	CTLA4	2
rs3087243	A/G	203874196	CTLA4	2
rs2276631	A/G	218384290	SLC11A1	2
rs17221959	C/T	218387907	SLC11A1	2
rs1059823	A/G	218395121	SLC11A1	2
rs2114592	C/T	230210491	SP110	2
rs11556887	C/T	230212961	SP110	2
rs35060588	C/G	10213318	IRAK2	3
rs3844283	C/G	10222796	IRAK2	3
rs708035	A/T	10234479	IRAK2	3
rs1801282	C/G	12351626	PPARG	3
rs6853	A/G	38142879	MYD88	3
rs3732378	A/G	39265671	CX3CR1	3
rs3732379	C/T	39265765	CX3CR1	3
rs1799864	A/G	46357717	CCR2	3
rs1799987	A/G	46370444	CCR5	3
rs414171	A/T	50612068	CISH	3
rs352139	A/G	52224356	TLR9	3
rs600718	A/T	101851531	NFKBIZ	3
rs1129055	A/G	122119472	CD86	3
rs1840680	A/G	157438240	PTX3	3
rs11096955	A/C	38774486	TLR10	4
rs11096956	G/T	38774559	TLR10	4
rs5743618	G/T	38797027	TLR1	4
rs4833095	C/T	38798089	TLR1	4
rs5743611	C/G	38798593	TLR1	4
rs5743818	G/T	38827542	TLR6	4
rs5743810	C/T	38828729	TLR6	4
rs2227306	C/T	73741338	IL8	4
rs1554013	C/T	76012331	CXCL10	4
rs1585215	A/G	102523317	NFKB1	4
rs1585213	A/G	102523541	NFKB1	4
rs230547	C/T	102615104	NFKB1	4
rs2069762	G/T	122456825	IL2	4
rs4833837	A/G	122615808	IL21	4
rs4696480	A/T	153685974	TLR2	4
rs3804099	C/T	153703504	TLR2	4
rs3804100	C/T	153704257	TLR2	4
rs5743303	A/T	186067699	TLR3	4
rs5743305	A/T	186068179	TLR3	4
rs3775291	A/G	186082920	TLR3	4
rs1494555	C/T	35871088	IL7R	5

rs10512747	C/T	40841639	CARD6	5
rs17473484	C/T	115579763	TICAM2	5
rs2288384	C/T	115580331	TICAM2	5
rs256996	A/G	115580393	TICAM2	5
rs2070721	A/C	132490150	IRF1	5
rs2549009	A/G	132491073	IRF1	5
rs1295686	A/G	132660151	IL13	5
rs2070874	C/T	132674018	IL4	5
rs7380824	C/T	139477397	TMEM173	5
rs1131769	A/G	139478334	TMEM173	5
rs2569190	A/G	140633331	CD14	5
rs5744455	C/T	140633722	CD14	5
rs3212227	A/C	159315942	IL12B	5
rs2853696	A/G	159317652	IL12B	5
rs6887695	C/G	159395637	IL12B	5
rs12211228	C/G	408833	IRF4	6
rs9391981	C/G	3086772	RIPK1	6
rs1048412	A/G	30064718	ZNRD1	6
rs2071592	A/T	31547563	NFKBIL1	6
rs1800629	A/G	31575254	TNF	6
rs3093662	A/G	31576412	TNF	6
rs7453920	A/G	32762235	HLADQB2	6
rs2228396	A/G	32830032	TAP2	6
rs1057141	A/G	32850997	TAP1	6
rs3077	C/T	33065245	HLADPA1	6
rs9277535	A/G	33087084	HLADPB1	6
rs529948	A/G	44268632	NFKBIE	6
rs1974226	A/G	52190537	IL17A	6
rs2397084	C/T	52237046	IL17F	6
rs1800795	C/G	22727026	IL6	7
rs2907748	C/T	30433407	NOD1	7
rs2907749	A/G	30446125	NOD1	7
rs2075818	C/G	30456766	NOD1	7
rs1334512	G/T	80638588	CD36	7
rs4728142	A/G	128933913	IRF5	7
rs1800972	C/G	6877901	DEFB1	8
rs42490	A/G	89766285	RIPK2	8
rs40457	A/G	89811459	RIPK2	8
rs9695310	C/G	32464137	DDX58	9
rs10813831	A/G	32526148	DDX58	9
rs10982385	G/T	114730737	TNFSF15	9
rs4574921	C/T	114776054	TNFSF15	9
rs3810936	C/T	114790605	TNFSF15	9
rs6478108	C/T	114796423	TNFSF15	9
rs2737190	A/G	117701903	TLR4	9

rs10759932	C/T	117702866	TLR4	9
rs11536889	C/G	117715853	TLR4	9
rs10818488	A/G	120942809	TRAF1	9
rs2900180	C/T	120944104	TRAF1	9
rs2300929	C/T	120954562	C5	9
rs2269066	C/T	120974740	C5	9
rs17611	A/G	121006922	C5	9
rs17514136	A/G	134880818	FCN2	9
rs1801157	A/G	44372809	CXCL12	10
rs1800450	A/G	52771475	MBL2	10
rs7095891	A/G	52771701	MBL2	10
rs7096206	C/G	52771925	MBL2	10
rs11003125	C/G	52772254	MBL2	10
rs5744034	C/T	1275007	TOLLIP	11
rs4963060	A/G	1299830	TOLLIP	11
rs7937602	A/C	35170144	CD44	11
rs5030419	C/G	36509193	TRAF6	11
rs2227973	A/G	36575763	RAG1	11
rs4151040	C/T	36577519	RAG1	11
rs1056403	C/T	36579620	RAG1	11
rs501192	A/G	105029658	CASP1	11
rs1946518	G/T	112164735	IL18	11
rs2228055	A/G	117994131	IL10RA	11
rs2229114	C/T	117999163	IL10RA	11
rs8177352	A/G	126283948	TIRAP	11
rs611953	A/G	126293796	TIRAP	11
rs740839	C/T	6229471	CD9	12
rs4149570	G/T	6342424	TNFRSF1A	12
rs2024301	A/T	8125585	CLEC4A	12
rs1133104	G/T	8138526	CLEC4A	12
rs4296104	A/G	8454092	CLEC6A	12
rs10841845	A/G	8533837	CLEC4E	12
rs11046143	A/G	8542421	CLEC4E	12
rs526680	C/T	9916703	CLEC2A	12
rs580960	C/T	9930538	CLEC2A	12
rs479499	A/C	9984958	CLEC12A	12
rs581949	C/T	9996807	CLEC1B	12
rs11053560	C/T	10029855	CLEC9A	12
rs7315231	A/G	10054326	CLEC9A	12
rs16910526	G/T	10118488	CLEC7A	12
rs7959064	A/G	10131559	CLEC7A	12
rs2617160	A/T	10392998	KLRC4	12
rs4251520	C/T	43781535	IRAK4	12
rs11465955	C/T	66209619	IRAK3	12
rs1370128	C/T	66224858	IRAK3	12

rs2069707	C/G	68160508	IFNG	12
rs2069705	C/T	68161231	IFNG	12
rs741344	A/G	68203306	IL26	12
rs2227485	C/T	68253933	IL22	12
rs11106877	A/G	77827755	NAV3	12
rs4761403	A/G	77843176	NAV3	12
rs1131454	C/T	112911065	OAS1	12
rs10774671	A/G	112919388	OAS1	12
rs2072136	C/T	112961114	OAS3	12
rs2010604	C/G	112970403	OAS3	12
rs2072138	C/G	112987088	OAS2	12
rs2072137	A/G	113003116	OAS2	12
rs2240185	C/G	113006312	OAS2	12
rs1169279	A/G	121018070	OASL	12
rs2393799	C/T	121132209	P2RX7	12
rs1718119	C/T	121177300	P2RX7	12
rs3751143	G/T	121184501	P2RX7	12
rs3764147	A/G	43883789	C13orf31	13
rs10507522	A/G	43904864	CR13ORF31	13
rs2582869	A/G	108259797	TNFSF13B	13
rs8904	C/T	35402011	NFKBIA	14
rs3138053	A/G	35405648	NFKBIA	14
rs6572335	A/G	45965382		14
rs1131877	A/G	102875712	TRAF3	14
rs4774	C/G	10906991	CIITA	16
rs2903692	A/G	11144926	CLEC16A	16
rs6498169	A/G	11155472	CLEC16A	16
rs11074956	G/T	11243864	CLEC16A	16
rs1805015	C/T	27362859	IL4R	16
rs4243232	C/T	30503402	ITGAL	16
rs2230433	C/G	30506720	ITGAL	16
rs9302752	C/T	50685192	NOD2	16
rs7194886	C/T	50691282	NOD2	16
rs2066843	C/T	50711288	NOD2	16
rs5743289	C/T	50722863	NOD2	16
rs5743291	A/G	50723365	NOD2	16
rs1024611	C/T	34252769	CCL2	17
rs4586	C/T	34256250	CCL2	17
rs1133763	A/C	34320812	CCL8	17
rs2280789	C/T	35879999	CCL5	17
rs2107538	C/T	35880776	CCL5	17
rs2227319	A/G	40014592	CSF3	17
rs2293152	C/G	42329511	STAT3	17
rs9891119	A/C	42355962	STAT3	17
rs4794067	C/T	47731462	TBX21	17

rs17244587	A/G	47745669	TBX21	17
rs2287886	A/G	7747650	CD209	19
rs4804803	A/G	7747847	CD209	19
rs735240	A/G	7748450	CD209	19
rs2277998	A/G	7766742	CLEC4M	19
rs5498	A/G	10285007	ICAM1	19
rs11575934	A/G	18075808	IL12RB1	19
rs436857	A/G	18086825	IL12RB1	19
rs12980275	A/G	39241143	IL28B	19
rs8099917	G/T	39252525	IL28AB	19
rs10418239	C/G	48219568	CARD8	19
rs2288877	A/G	48234294	CARD8	19
rs2043211	A/T	48234449	CARD8	19
rs2304204	A/G	49665763	IRF3	19
rs1043680	C/G	55000979	NLRP2	19
rs299170	C/T	55805104	NLRP11	19
rs1363758	A/C	55818381	NLRP11	19
rs379327	A/G	55858800	NLRP4	19
rs306487	A/G	55971826	NLRP8	19
rs8116776	C/T	3858160	MAVS	20
rs7262903	A/G	3862380	MAVS	20
rs2232571	C/T	38345681	LBP	20
rs2232582	C/T	38350862	LBP	20
rs1883832	C/T	46118343	CD40	20
rs3765459	A/G	46128768	CD40	20
rs7341	G/T	58994761	CTSZ	20
rs236729	C/T	59004920	CTSZ	20
rs3208008	A/C	63694757	TNFRSF6B	20
rs2834167	A/G	33268483	IL10RB	21
rs1012335	C/G	33341701	IFNAR1	21
rs2284553	A/G	33404389	IFNGR2	21
rs2268241	A/G	33408744	IFNGR2	21
rs879574	A/T	17107415	IL17RA	22
rs879577	A/G	17108319	IL17RA	22
rs755622	C/G	23894205	MIF	22
rs4821544	C/T	36862461	NCF4	22
rs729749	C/T	36867804	NCF4	22
rs864058	C/T	12887911	TLR7	X
rs3764880	A/G	12906707	TLR8	X
rs1548731	C/T	12909828	TLR8	X
rs5744080	C/T	12919685	TLR8	X
rs7061789	A/G	154015024	IRAK1	X

Supplementary table 1 (Part B): Excluded genetic polymorphisms (not meeting Hardy-Weinberg equilibrium with p<0.05), allelic variants and chromosomal positions

rs_number	Alleles	Position	Gene	Chromosome
rs12033074	C/G	22640116	C1Q	1
rs35829419	A/C	247425556	NLRP3	1
rs2239704	G/T	31572364	LTA	6
rs10870077	C/G	136369439	CARD9	9
rs266093	C/G	44370760	CXCL12	10
rs5030737	C/T	52771482	MBL2	10
rs353644	A/G	35160066	CD44	11
rs12813085	C/T	68224048	IL26	12
rs3087456	A/G	10877045	CIITA	16
rs1634517	A/C	36105010	CCL4	17
rs6503695	C/T	42347515	STAT3	17
rs882643	C/G	17110933	IL17RA	22

Supplementary table 1 (Part C): Excluded genetic polymorphisms (minor allele frequency <5%), allelic variants and chromosomal positions

rs_number	Alleles	Position	Gene	Chromosome
rs72550870	AG	11046609	MASP2	1
rs5743708	AG	153705165	TLR2	4
rs763780	CT	52236941	IL17F	6
rs4986790	AG	117713024	TLR4	9
rs4986791	CT	117713324	TLR4	9
rs1800451	AG	52771466	MBL2	10
rs5743856	AG	1308608	TOLLIP	11
rs2066807	CG	56346898	STAT2	12
rs2066844	CT	50712015	NOD2	16
rs2066845	CG	50722629	NOD2	16
rs2302267	GT	12867459	TLR7	X
rs5744043	CT	12906628	TLR8	X

Supplementary table 2: Clinical characteristics of the solid organ transplantation first replication sample (Swiss transplant cohort study second sample)

Characteristic	Total	Non-NODAT	NODAT	p-value
Sample size	489	398	91	
Age at transplantation (years), median (range)	51 (18 – 75)	50 (18 – 75)	54.5 (20 – 72)	0.03
Recipient sex (Males) [%]	64.0	63.9	64.4	0.92
Living donor [%]	26.5	27.8	21.1	0.19
Donor sex (Males) [%]	52.9	52.0	56.7	0.42
Recipients anti-HCV [%]	8.3	8.1	8.9	0.81
Organ, [%]				0.28
Kidney	56.5	54.8	63.7	
Liver	19.6	21.1	13.1	
Lung	15.5	15.6	15.4	
Heart	8.4	8.5	7.8	
Body mass index (kg/m^2), median (range)				
Pre-transplant	24.6 (13.4 – 43.5)	24.5 (13.4 – 43.5)	25.5 (16.3 – 41.0)	0.21
One year follow-up	24.8 (13.7 – 41.7)	24.7 (14.9 – 41.1)	25.5 (13.7 – 41.7)	0.20
Calcineurin inhibitors, tacrolimus [%]	56.7	52.8	72.4	0.007

NODAT: New-onset diabetes after transplantation, HCV: hepatitis C

Supplementary table 3: Clinical characteristics of the solid organ transplantation second replication sample

Characteristic	Total	Non-NODAT	NODAT	p-value
Sample size	156	111	45	
Age at transplantation (years), median (range)	48 (22 – 68)	46 (22 – 68)	53 (28 – 68)	0.002
Recipient sex (Males) [%]	60.9	55.9	73.3	0.048
Living donor [%]	11.5	11.7	11.1	0.915
Donor age (years), median (range)	43.5 (10 – 73)	41 (10 – 73)	48 (13 – 69)	0.043
Donor sex (Males) [%]	56.8	63.2	54.8	0.06
Organ, [%]				0.46
Kidney	102 [65.4]	75 [67.6]	27 [60.0]	
Liver	37 [23.7]	26 [23.4]	11 [24.4]	
Lung	17 [10.9]	10 [9.0]	7 [15.6]	
Body mass index (kg/m^2), median (range)				
Pre-transplant	23.5 (15.8 – 37.3)	22.3 (15.8 – 36.2)	26.4 (18.8 – 37.3)	0.0003
One year follow-up	26.0 (16.7 – 43.6)	25.5 (16.7 – 43.6)	27.1 (19.9 – 42.3)	0.099
Calcineurin inhibitors, n [%]				<0.001
Tacrolimus	54 [34.6]	29 [26.1]	25 [55.6]	
Cyclosporine	102 [65.4]	82 [73.9]	20 [44.4]	

SOT: solid organ transplantation; NODAT: New-onset diabetes after transplantation

Supplementary table 4: Association between different genotypes and new-onset diabetes after transplantation in a discovery sample of solid organ transplant recipients from the Swiss transplant cohort study

Gene, SNP, function	NODAT	p-value
ICAM1, rs5498, missense		
AA (n=229)	1 (Ref.)	
AG (n=341)	0.64 (0.43 - 0.96)	0.03
GG (n=146)	0.43 (0.24 - 0.78)	0.005
G Allele dosage	0.65 (0.50 - 0.86)	0.003
CTSZ, rs7341, near Gene-3		
GG (n=251)	1 Ref.	
GT (n=313)	1.02 (0.68 - 1.50)	0.93
TT (n=129)	0.33 (0.17 - 0.63)	0.001
T Allele dosage	0.67 (0.51 - 0.88)	0.004
C1QB, rs631090, intron variant		
TT (n=581)	1 (Ref.)	
TC (n=103)	1.55 (0.93 - 2.58)	0.10
CC (n=8)	25.1 (2.80 - 25.6)	0.004
C Allele dosage	2.04 (1.32 - 3.13)	0.001
NOD1, rs2907749, near Gene-3		
AA (n=326)	1 (Ref.)	
AG (n=303)	1.27 (0.85 - 1.91)	0.25
GG (n=63)	3.15 (1.70 - 5.87)	0.0003
G Allele dosage	1.60 (1.20 - 2.14)	0.001
SP110, rs2114592, intron variant		
CC (n=559)	1 (Ref.)	
CT (n=129)	1.08 (0.67- 1.73)	0.75
TT (n=7)	11.5 (2.07- 63.3)	0.005
T Allele dosage	1.42 (0.94 - 2.12)	0.09
TLR10, rs11096956, cds-synon		
GG (n=365)	1 (Ref.)	
GT (270)	1.73 (1.17 - 2.56)	0.006
TT (n=61)	2.13 (1.13 - 4.04)	0.02
T Allele dosage	1.52 (1.15 - 2.02)	0.003
TNF, rs3093662, intron variant		
AA (n=585)	1 (Ref.)	
AG (n=102)	1.89 (1.15 - 3.10)	0.01
GG (n=5)	3.09 (0.48 - 20.0)	0.24
G Allele dosage	1.86 (1.19 - 2.91)	0.006
P2RX7, rs2393799, near Gene-5		
CC (n=411)	1 (Ref.)	
CT (n=239)	1.48 (0.99 - 2.22)	0.06
TT (n=42)	2.38 (1.14 - 4.98)	0.02
T Allele dosage	1.52 (1.12 - 2.05)	0.007
TLR4, rs10759932, near Gene-5		
TT (n=515)	1 (Ref.)	
TC (n=170)	0.53 (0.32 - 0.85)	0.01
CC (n=8)	0.38 (0.04 - 3.21)	0.37
C Allele dosage	0.54 (0.34 - 0.85)	0.007
rs6572335, intergenic		
AA (n=172)	1 (Ref.)	
AG (n=362)	1.30 (0.80 - 2.11)	0.28
GG (n=161)	2.10 (1.23 - 3.59)	0.006
G Allele dosage	1.46 (1.12 - 1.91)	0.005

NODAT, new-onset diabetes after transplantation. Results are expressed as odds ratio and (95% confidence interval). Statistical analysis by logistic regression adjusting for age of recipient at transplantation, sex of the recipient, baseline body mass index (continuous variable), type of calcineurin inhibitor (no calcineurin inhibitor / tacrolimus / cyclosporine) and hepatitis C virus status (positive / negative).

Supplementary table 5a: Association between NOD1 rs2907749A>G single nucleotide polymorphism and new-onset diabetes after transplantation in the Swiss transplant cohort study (STCS) replication sample and the combined sample

	AA	**AG**	**GG**	**G allele dosage**
STCS replication sample				
Sample size	250	176	38	
Odds ratio (95% CI)	1 (ref.)	1.15 (0.69 - 1.92)	2.31 (1.06 - 5.00)	1.39 (0.97 - 1.98)
P-corrected value*		1.0	0.30	0.70
Combined STCS samples				
Sample size	576	479	101	
Odds ratio (95% CI)	1 (ref.)	1.19 (0.87 - 1.63)	2.77 (1.72 - 4.44)	1.49 (1.20 - 1.86)
P-value		0.27	**0.00003**	**0.0004**

CI: confidence interval

Statistical analysis by logistic regression adjusting for age of recipient at transplantation (continuous variable), sex of the recipient, baseline BMI (continuous variable), and type of calcineurin inhibitor (no calcineurin inhibitor / tacrolimus / cyclosporine).

*P- values were corrected using Bonferroni correction for multiple testing (corrected P-value = original p-value x 10)

Supplementary table 5b: Association between NOD1 rs2907749 A>G single nucleotide polymorphism and lipid markers in the combined Swiss transplant cohort study sample

	AA	AG	GG	G allele dosage
Sample size	538	427	86	
New-onset hyperlipidemia	1 (ref.)	1.51 (1.12-2.03)	1.33 (0.79-2.25)	1.29 (1.04-1.60)
P-value		**0.006**	0.29	**0.02**
Differences (mmol/L)				
Total cholesterol	Ref.	-0.13 (-0.47; 0.22)	0.98 (0.38-1.59)	0.23 (-0.02; 0.49)
P-value		0.47	**0.002**	0.07
LDL-cholesterol	Ref.	0.00 (-0.10; 0.10)	-0.02 (-0.20; 0.16)	-0.01 (-0.08; 0.07)
P-value		0.99	0.79	0.85
HDL-cholesterol	Ref.	-0.04 (-0.08; -0.003)	-0.12 (-0.19; -0.05)	-0.05 (-0.08; -0.02)
P-value		**0.02**	**0.001**	**0.001**

Results are expressed as odds ratio and (95% confidence interval) for new-onset hyperlipidemia and for difference relative to the AA genotype. Statistical analysis performed using logistic regression for new-onset hyperlipidemia and for differences in lipid levels, adjusted for age of recipient at transplantation (continuous variable), sex of the recipient, baseline BMI (continuous variable) and intake of hypolipidemic drugs (positive / negative coding)

Supplementary table 6: Association between *SP110 rs2114592 C>T* genotypes and lipid complications in the combined Swiss transplant cohort study sample

	CC	CT	TT	T allele dosage
Sample size	840	219	12	
New-onset hyperlipidemia	1 (ref.)	1.03 (0.73; 1.46)	3.41 (1.06; 11.0)	1.18 (0.87; 1.61)
P-value		0.85	**0.04**	0.28
Differences (mmol/L)				
Total cholesterol	Ref.	0.01 (-0.39; 0.42)	1.31 (-0.06; 2.67)	0.17 (-0.19; 0.53)
P-value		0.94	0.06	0.35
LDL-cholesterol	Ref.	0.08 (-0.04; 0.20)	0.05 (-0.36; 0.45)	0.06 (-0.04; 0.17)
P-value		0.20	0.82	0.23
HDL-cholesterol	Ref.	0.02 (-0.04; 0.04)	-0.07(-0.19; 0.10)	0.00 (0.03; 0.02)
P-value		0.41	0.19	0.40

Results are expressed as odds ratio and (95% confidence interval) for new-onset hyperlipidemia and for difference relative to the CC genotype. Statistical analysis performed using logistic regression for new-onset hyperlipidemia and for differences in lipid levels, adjusted for age of recipient at transplantation (continuous variable), sex of the recipient, baseline BMI (continuous variable) and intake of hypolipidemic drugs (positive/negative coding).

Supplementary table 7: Associations between SP110 rs2114592 single nucleotide polymorphism and different metabolic parameters in the population-based samples

Phenotype	Sample size	Beta (95% CI)	P-value
Body mass index			
CoLaus	5'409	0.001 (-0.077 – 0.079)	0.98
GIANT	250'596	0.0003 (-0.0114 – 0.0120)	0.96
Waist/hip ratio			
CoLaus	5'406	0.014 (-0.053 – 0.081)	0.68
GIANT	156'804	0.009 (-0.004 – 0.022)	0.16
Glucose			
CoLaus	5'400	-0.029 (-0.098 – 0.040)	0.41
MAGIC	46'186	0.006 (-0.007 – 0.019)	0.35
2 hours glucose			
MAGIC	15'234	-0.067 (-0.131 – -0.003)	0.04
HOMA-B			
MAGIC	46'186	-0.001 (-0.017 – 0.015)	0.90
HOMA-IR			
MAGIC	46'186	0.007 (-0.007 – 0.021)	0.34
Total cholesterol			
CoLaus	5'433	0.050 (-0.015 – 0.115)	0.13
GWAS	100'176	-0.002 (-0.009 – 0.005)	0.58
HDL-cholestererol			
CoLaus	5'433	-0.005 (-0.027 – 0.017)	0.66
GWAS	99'892	-0.003 (-0.010 – 0.004)	0.38
LDL-cholesterol			
CoLaus	5'358	0.063 (0.006 – 0.120)	0.03
GWAS	95'446	0.002 (-0.006 – 0.010)	0.64
Triglycerides			
CoLaus	5'433	-0.014 (-0.085 – 0.057)	0.70
GWAS	96'590	-0.002 (-0.007 – 0.003)	0.46

HOMA-IR: surrogate estimates of insulin resistance, HOMA-B: surrogate estimates of beta-cell function, GWAS: GWAS for total cholesterol, HDL-C, LDL-C, and triglycerides. Additionally, SP110 rs2114592 was not associated with type 2 diabetes in 116'059 individuals from the UK biobank, and no recessive effect was detected (data not shown). No significant increase in the prevalence of type 2 diabetes was found in the *rs2114592 TT* carriers when compared to the other genotypes (5.25% versus 5.27%, respectively, covariate adjusted P=0.87). SP110 rs2114592 was also not associated with type 2 diabetes in the DIAGRAM consortium, a meta-analysis of case-control samples with type 2 diabetes (data not shown).

Supplementary table 8: Functional tagging single nucleotide polymorphisms (SNP) of SP110 gene

Gene	rs_number	Allele	Position	MAF	HWE (p-value)
SP110	rs3948463	G>A	230172144	9	0.06
	rs3948464	C>T	230185999	13	0.48
	rs1135791	T>C	230177560	50	0.14
	rs7580900	T>C	230216669	46	0.27
	rs10210254	G>A	230167656	29	0.35
	rs722555	A>G	230168800	40	0.25
	rs9784019	A>G	230170859	11	0.89
	rs28445040	C>T	230245867	18	0.66

Functional tagging SNPs selected using HapMap Genome Browser by limiting the search to SNPs with a MAF>5% in the Caucasian population and r^2 cutoff of 0.8. By further limiting the selection to SNPs within the coding region, 5-UTR and 3'UTR, eight SP110 tagging SNPs were selected and analyzed (see above)

MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium

Supplementary table 9: Diagnosis of new-onset diabetes after transplantation (NODAT, transplant population) in patients with *SP110 rs2114592-TT* versus CT/CC genotype groups

Groups	TT	CT/CC
Discovery STCS cohort	5 over 7 (71.4%)	147 over 688 (21.4%)
First STCS replication sample	5 over 8 (62.5%)	85 over 481 (17.7%)
Second replication sample	2 over 2 (100%)	26 over 154 (16.9%)
Combined transplantation sample	12 over 17 (70.6%)[&]	258 over 1323 (19.5%)

NODAT: New-onset diabetes after transplantation.

Results are expressed as number of patients with NODAT or diabetes among all subjects with specific genotypes, [%]

[&] 17 patients have the *rs2114592-TT* genotype, among them 12 patients (70.6%) are diagnosed with NODAT

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