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A Single-Nucleotide Polymorphism (rs1131243) of the Transforming Growth Factor Beta Signaling Pathway Contributes to Risk of Acute Rejection in Chinese Renal Transplant Recipients

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Statistical Analysis C
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Background: Acute rejection (AR) is a common complication of kidney transplantation. The transforming growth factor beta (TGF-β) signaling pathway has been observed to be involved in several cellular functions. Our study aimed to investigate the correlations between single-nucleotide polymorphisms (SNPs) in TGF-β-related genes and the risk of AR in renal transplant recipients.

Material/Methods: This retrospective, single-center study included 200 Chinese renal transplant recipients. All exons, exon/intron boundaries, and flanking regions of the TGF-β signaling pathway were detected by targeting sequencing (TS) based on next-generation sequencing technology. Tagger SNPs and haplotypes were identified after adjustment. A general linear model (GLM) was used to explore the confounding effect of clinical variables. Five adjusted inheritance models were utilized to investigate the influence of SNPs on AR, and Banff score was applied to evaluate the effect of related SNPs on pathological changes.

Results: A total of 188 SNPs on *TGF*-β genes were detected. Analysis of adjustment led to identification of 31 tagger SNPs and 10 haplotype blocks. After the analysis of a general linear model and 5 sirolimus-adjusted multiple inheritance models, 1 of the SNPs – rs1131243 on the *TGF*-β*R3* gene – was observed to be significantly associated with the occurrence of AR. Based on Banff score, no significant association was observed between SNPs and pathological changes.

Conclusions: In this study, we observed that the SNP rs1131243 on the *TGF*-β*R3* gene was significantly associated with the occurrence of AR in Chinese renal transplant recipients.

MeSH Keywords: Kidney Transplantation • Polymorphism, Single Nucleotide • Transforming Growth Factor beta

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Background

Renal transplant is considered as the most effective therapeutic treatment for end-stage renal disease [1,2]. Compared with dialysis treatments, renal transplant allows patients to have a better quality of life and longer survival [3]. However, various complications, such as acute rejection (AR), chronic allograft dysfunction, and immunosuppressive agent-related nephrotoxicity, still strictly limit its wide application [4]. Graft loss, increased risk of chronic allograft dysfunction, and poor long-term outcomes are some of the clinical concerns related to AR [5,6]. Therefore, understanding the pathogenesis of AR is imperative for improving long-term and short-term prognosis in patients.

The TGF-β family of polypeptides includes 3 TGF-β isoforms, activins, nodal, and bone morphogenetic proteins (BMPs), and growth and differentiation factors (GDFs) [7]. In contrast to the large number of TGF-β ligands, SMAD proteins, as fewer receptors and downstream intracellular effectors, mediate the transduction of intracellular signaling. In mammals, 7 type I receptors and 5 type II receptors were identified and were shown to form a heteromeric complex of type I and type II transmembrane receptors [8–10].

The TGF-β signaling pathway is widely involved in regulation of cellular responses, including cell growth and differentiation, apoptosis, homeostasis, and many other cellular functions [11,12]. TGF-β has various regulatory functions which range from specifying tissue pattern formation as morphogens during embryonic development to maintaining physiological homeostasis as cytokines in adult organisms. It is now widely accepted that TGF-β is a bifunctional regulator. TGF-β is a suppressor of early-stage tumors and has also been observed to promote tumor growth and progression by inducing epithelial-to-mesenchymal transition (EMT) [13–15]. TGF-β has immune-suppressive functions in several diseases [16,17]. Moreover, TGF-β, as an immune-regulatory cytokine, plays a crucial role in the development, homeostasis, and tolerance of T cells [18]. The immune response meditated by T cells is the main cause of AR, but the association of the TGF-β signaling pathway with AR is yet to be fully determined.

A genome-wide association study (GWAS) identified genetic variants and their association with human diseases, which enables analysis of millions of single-nucleotide polymorphisms (SNPs) in the genome. GWAS may be applied to identify novel molecules and pathways involved in acute rejection and to predict transplant outcomes [19]. The aim of this retrospective, single-center study was to investigate the correlation between SNPs in TGF-β signaling pathway-related genes and the susceptibility to AR by use of target sequencing (TS) based on next-generation sequencing (NGS) at our center.

Material and Methods

Study design and population

This work is a retrospective, single-center, cohort study, which was carried out to explore the influence of SNPs in TGFB signaling pathway-related genes (*TGF-β1, TGF-β2, TGF-β3, TGF-βR1, TGF-βR2, TGF-βR3, SMAD2, SMAD3, SMAD4*) on the risk of AR in renal transplant recipients. The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved the protocols followed in this study (2016-SR-029). Written informed consents were obtained from all transplant recipients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Recipients in this study were strictly limited to living-related transplantation of donors to lineal or collateral relatives not beyond the third degree of kinship or transplantation of kidney donors after cardiac death, from 2011 to 2015.

This study included 200 renal transplant recipients who received renal transplant between 1 February 2011 and 1 December 2015 at the kidney transplant center of the Nanjing Medical University First Affiliated Hospital, as detailed in our previous study [20]. Briefly, we enrolled adult patients who underwent single-kidney transplantation, with or without AR period confirmed by biopsy. Medical records of enrolled patients were meticulously extracted and reviewed by 2 clinicians (ZJ Wang and RY Tan).

Clinical data on age, sex, height, AR incidence, delayed graft function (DGF), and immunosuppressive protocols were also extracted independently by 2 authors (Ming Zheng and Jiajun Zhou). AR after kidney transplantation was diagnosed by 2 independent pathologists through application of histological examination of hematoxylin-eosin staining and immunohistological staining based on the Banff 15 criteria [21]. AR scores were classified by the degree of interstitial infiltration and intimal arteritis according to the type/grade of AR based on the Banff 15 criteria.

Ethics approval and consent to participate

The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved the protocols followed in this study (2016-SR-029). Written informed consent was obtained from all transplant recipients. Peripheral blood samples (2 mL) from each recipient were collected. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration

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and its later amendments or comparable ethical standards. Recipients in this study were strictly limited to living-related transplantation of donors to lineal or collateral relatives not beyond the third degree of kinship or transplantation of kidney donors after cardiac death, from 2011 to 2015.

Immunosuppressive protocols

All recipients in our center underwent routine immunosuppressive protocols that included 3 or 4 drugs. Briefly, the basic protocol consisted of tacrolimus taken at an initial dosage of 0.2 mg/kg/day (*q12h*), with mycophenolate mofetil (MMF) at an initial dosage of 0.75–1.0 g/day (*q12h*) 24–48 h after transplantation, and prednisone, combined with or without sirolimus at an initial dosage of 1 mg/day (*qd*). The combined usage of sirolimus or not depended on drug concentrations, immunoreaction, and clinical symptoms of recipients. These dosages were later calibrated according to the serum creatinine levels and drug concentrations. As determined by the tolerance and response of recipients, tacrolimus could later be changed to cyclosporin A during follow-up. For patients who had AR episodes, methylprednisolone was administered intravenously at a dosage of 200 mg/day for 3–5 days. Detailed information on the immunosuppressive agents used in our center can be found in our previous study [22].

Sample collection, preparation, and TS

Peripheral blood samples (2 mL) from each recipient were collected. After DNA extraction, the concentration and purity of genomic DNA (gDNA) was quantitatively analyzed and gene integrity was accessed through application of agarose gel electrophoresis. A pool containing upstream and downstream oligonucleotides was selected as gDNA hybrids specific to target regions of interest. Then, the gDNA was fragmented and the adapter-ligated DNA was amplified through selective, limited-cycle polymerase chain reaction. The captured libraries were denatured and loaded into an Illumina cBot instrument as per the manufacturer's instructions. Then, sequencing data based on the human reference sequence UCSC hg19 assembly (NCBI build 37.2) was analyzed using the Genome Analysis Tool Kit, Picard software, and dbSNP 132. During this procedure, putative somatic variant cells with 2 separate programs – MuTect 1.1.5 and VarScan 2.3.6 – were also observed.

Statistical analysis

Data are presented as mean±standard deviation (SD) except when stated otherwise. We explored minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) by using R packages genetics (genetics: Population Genetics, R package version 1.3.8.1.). Linkage disequilibrium (LD) blocks were analyzed by using Haploview version 4.2 (Broad Institute, Cambridge, MA, USA). The general linear model (GLM) was applied to examine the influence of clinical variables on AR. We used R package SNPassoc (SNPassoc: SNPs-based whole-genome association studies, R package version 1.9-2.) to perform 5 sirolimus-adjusted multiple inheritance models, including codominant model 1 (major allele homozygotes *vs.* heterozygotes), codominant model 2 (major allele homozygotes *vs.* minor allele homozygotes), dominant model (major allele homozygotes *vs.* minor allele homozygotes plus heterozygotes), recessive model (major allele homozygotes plus heterozygotes *vs.* minor allele homozygotes), over-dominant model (heterozygotes *vs.* major allele homozygotes plus minor allele homozygotes), and log-additive model (major allele homozygotes *vs.* heterozygotes *vs.* minor allele homozygotes). The Bonferroni correction method (the α value for each comparison equal to the fixed α value divided by the total number of comparisons) was performed to avoid the inflation of p-values from multiple comparisons [23]. Chi-square analysis and exact chi-square analysis of variance were used to compare Banff score values when considering 2 or 3 genotypes. All data were analyzed by SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Table 1. Baseline characteristics of acute rejection and stable subjects.

Characteristics	Stable group	AR group
Case number	131	69
Age (years, mean±SD)	41.29±1.98	40.88±2.97
Male n(%)	82 (62.60)	42 (60.87)
Weight(kg)	59.45±9.12	62.69 ±8.76
Usage of Sir n(%)	5 (3.81)	19 (27.54)
PRA (%) before renal transplant	0.00	0.00
DGF(%)	34 (25.95)	32 (46.37)

AR – acute rejection; SD – standard deviation; Sir – sirolimus; PRA – panel reactive antibody; DGF – delayed graft function.

Results

Baseline characteristics of study participants

Table 1 presents the baseline clinical characteristics of the renal transplant recipients: age, sex, weight, and incidence of DGF. A total of 200 recipients (124 men and 76 women) who underwent first ABO-matched single-kidney transplantation were included in this study. Of these, 69 recipients (42 men and 27 women) had experienced at least 1 AR episode. None of

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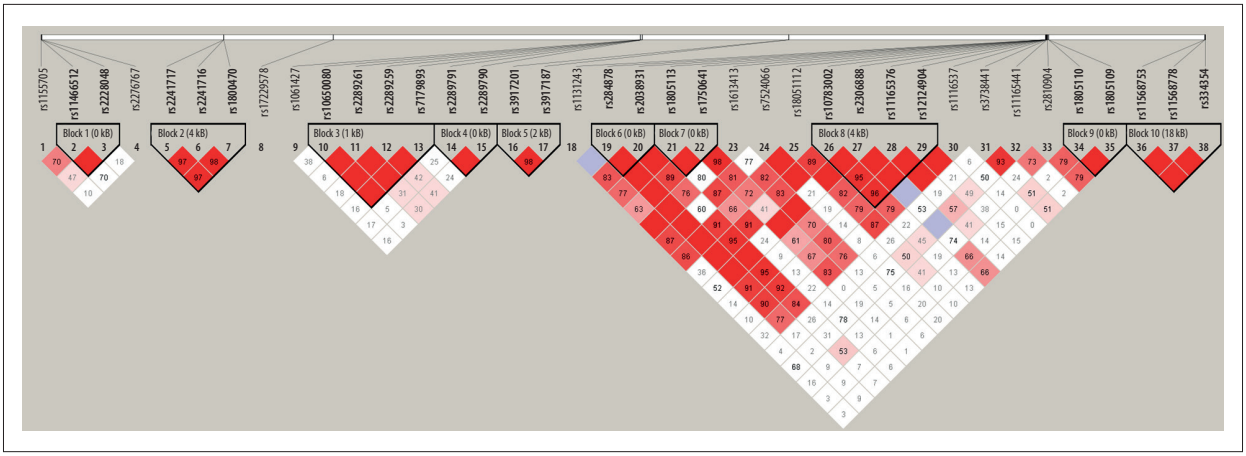

Figure 1. Haploblocks of 31 tagger SNPs.

Table 2. Results of logistic analysis of rs1131243 with the occurrence of acute rejection in 5 models adjusted by the usage of sirolimus.

SNP	Model	Genotype	AR n (%)	non-AR n (%)	OR	Lower	Upper	*P* value
rs1131243	Codominant	CC	38 (55.07)	104 (79.39)				0.00037
		CT	27 (39.13)	24 (18.32)	3.71	1.82	7.58	
		TT	4 (5.80)	3 (2.29)	5.41	1.14	25.75	
	Dominant	CC *vs.* TT+CT	38 (55.07)	27 (20.68)	3.9	1.97	7.72	7.79E-05
	Recessive	CC+CT *vs.* TT	65 (94.20)	3 (2.29)	3.57	0.77	16.54	0.11
	Overdominant	CT *vs.* CC+TT	27 (39.13)	107 (81.68)	3.31	1.65	6.65	0.00073
	Log-additive	CC *vs.* CT *vs.* TT	131 (65.50)	69 (34.50)	3.04	1.7	5.43	0.00011

Number of comparison: 5; Alpha: 0.05; Corrected Alpha: 0.01.

the 200 recipients had detected panel reactive antibody (PRA) before transplantation. Comprehensive and detailed information on recipients and other clinical information can be found in our previous study [20].

Association analysis between tagger SNPs and AR

A total of 188 SNPs on TGF-β signaling pathway genes were detected by target sequencing. Detailed information on chromosome, position, function, and details are presented in Supplementary Table 1. Among these, 47 novel SNPs were reported for the first time. SNPs with a MAF >0.05 were identified as normal frequency, whereas MAF <0.05 were considered as rare frequency SNPs. The analysis of HWE highlighted 38 SNPs with MAF >0.05 and HWE >0.05 (Supplementary Table 2). During the study, Haploview version 4.2 was used to further analyze haplotypes by evaluating LD block and haplotype among 38 SNPs. After the adjustment of LD analysis, 31 tagger SNPs with 10 blocks (Block1: rs11466512-rs2228048, Block2: rs2241716-rs2241717-rs1800470, Block3: rs1065080-rs2289261-rs2289259-rs7179893, Block4: rs2289790-rs2289791, Block5: rs3917187-rs3917201, Block6: rs284878-rs2038931, Block7: rs1805113-rs1750641, Block8: rs10783002-rs2306888-rs11165376-rs12124904, Block9: rs1805110-rs1805109, Block10: rs11568753-rs11568778-rs334354) were included for further research (Figure 1, Supplementary Figure 1, Supplementary Table 3). However, no significant correlation was observed between the haplotypes and AR.

GLM analysis was undertaken to investigate the influence of the distribution of various clinical variables on the occurrence of AR. The use of sirolimus or not was found to be significantly related with the distribution of AR with a *P* value of 0.015 after the analysis of Pillai's Trace, Wilks' Lambda, Hotelling's Trace, and Roy's Largest Root (Supplementary Table 4). Other clinical variables, including age, sex, weight, and DGF showed no significant relation with AR (Supplementary Table 4). Thereafter, 5 models adjusted by the use of sirolimus were used to analyze the effect of tagger SNPs on AR by a corrected statistically significant P value according to Bonferroni correction method (corrected-P=0.01).The tagger SNP rs1131243 on *TGF-β Receptor 3* (*TGFBR3*) gene exhibited significant correlation with

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Table 3. Association analysis of rs1131243 genotypes with Banff score (**A**) and combined Banff score (**B**).

A

Genotype	CC	%	CT	%	TT	%
Borderline	27	56.25	10	55.56	1	33.33
IA	18	37.50	4	22.22	2	66.66
IB	1	2.08	0	0	0	0
IIA	2	4.16	3	16.67	0	0
IIB	0	0	1	5.56	0	0
Sum	48	100	18	100	3	100

df=8, χ^2=8.386, P=0.40.

B

Genotype	CC	%	CT	%	TT	%
Borderline+IA+IB	46	95.83	14	77.78	3	100
IIA+IIB	2	4.16	4	22.22	0	0
Sum	48	100	18	100	3	100

df=2, exact χ^2=4.86, P=0.055.

the occurrence of AR in 4 of the 5 models as *P*=0.00037 in co-dominant model (OR1=3.71, 95% CI1: 1.82–7.58, OR2=5.41, 95% CI2: 1.14–25.75), *P*=7.79E-05 in dominant model (OR=3.9, 95% CI: 1.97–7.72), *P*=0.11 in recessive model (OR=3.57, 95% CI: 0.77–16.54), *P*=0.00073 in over-dominant model (OR=3.31, 95% CI: 1.65–6.65), and *P*=0.00011 in log-additive model (OR=3.04, 95% CI: 1.7–5.43) (Table 2). No corrected statistical significance was observed in the other 30 SNPs (Supplementary Table 5).

Effect of SNPs on histological examination outcome

Of the 200 recipients included in this study, 69 were diagnosed as having AR by allograft biopsy. The degree of AR was determined based on histological examination and according to Banff 15 criteria. Of these 69 recipients, 38 were classified as borderline, 24 were classified as Banff IA, 2 were classified as Banff I B and Banff IIB (1 recipient each), and 5 were classified as Banff IIA. No significant correlation was observed between the type of rs1131243 and the degree of AR (df=8, χ^2=8.386, *P*=0.3967, Table 3A). As the presence of endarteritis confirmed in biopsy is the criterion that distinguishes between I and II degree of AR by Banff 15, the level of AR was divided into 2 groups. The degree of borderline, IA, and IB were regarded as a single group and the degree of II and more than II was regarded as the other group. We found that recipients who carried the rs1131243 T variant were more likely to have endarteritis and a higher level of AR. However, no significant difference was identified between rs1131243 and the 2 groups with a *P* value of 0.055 (df=2, exact χ^2=4.86, Table 3B).

Discussion

In this study, TS assay was performed based on NGS technology to identify the associations of SNPs of the TGF-β signaling pathway with AR following kidney transplantation. Mutations on rs1131243 of *TGF-βR3* gene were observed for the first time and found to be significantly correlated with increasing risk of AR in renal transplant recipients.

Changes in *TGF-βR1* and *TGF-βR2* gene can lead to growth inhibition in cells by TGF-β signaling pathway mediation [24]. Kim et al. reported that a synonymous SNP – rs2228048 of the *TGF-βR2* gene – is associated with acute rejection in Korean renal transplant recipients [25]. In our study, we also detected SNP rs2228048 in Chinese recipients. However, the SNP rs2228048 showed a *P* value of 0.8146 based on the HWE analysis in our cohort, which indicated that equilibrium had been achieved. Variations of SNPs among human populations may be the reason for differences in these results.

TGF-βR3, also known as betaglycan, is the most abundant of the TGF-β receptors [26]. It has a high affinity for both homodimeric and heterodimer TGF-β1 and TGF-β2 [27]. Recent genetic studies of TGF-βR3 have reported its role in several diseases. According to Kao et al., SNP rs6696224 of *TGF-βR3* gene was significantly associated with heart failure and preserved ejection fraction in the Cardiovascular Health Study (CHS) [28]. The rs1192415 of *TGF-βR3* gene has been observed to be associated with primary open angle glaucoma among various

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human populations [29,30]. In the white population, a SNP rs1805110 on the *TGF-βR3* gene was found to be associated with Behçet's disease and idiopathic intermediate uveitis [31].

The present results show that rs1131243, an SNP on the *TGF-βR3* gene located in 3'-untranslated region sequences, is significantly correlated with the occurrence of post-transplantation AR episodes in first-time renal transplant patients. Recipients carrying the rs1131243 T variant appear to have a higher risk of AR after kidney transplantation. Kumar et al. stated that the *TGF-βR3* gene in acute rejection recipients was significantly upregulated among non-rejection recipients after intestinal transplantation in children based on quantitative real-time PCR [32]. TGF-βR3, which has no known signaling domain, is reported to regulate the TGF-β signaling pathway by enhancing the binding of TGF-β ligands to TGF-β type II receptors by binding TGF-β and presenting it to TGF-βR2 [33,34]. Variants of *TGF-βR3* can lead to the activation of diverse downstream substrates and regulatory proteins, influencing the transcription of various target genes that function in differentiation, proliferation, and activation of many types of immune cells [12]. Our research indicates that the rs1131243 variant of 3'-UTR on the *TGF-βR3* gene alters the function of TGF-βR3, thereby affecting the occurrence of AR.

This study did not observe any statistically significant difference between the genotype of rs1131243 and the level of AR in the 69 patients confirmed by histological examination. The results of the present study indicate that rs1131243 T variant causes a higher risk of AR but does not influence the severity. Since the presence of endarteritis confirmed by biopsy is the dividing criteria between Banff I and II degree of AR based on Banff 15, the AR patients were categorized into 2 groups. We observed that recipients who carried the rs1131243 T variant were more likely to have endarteritis and a higher level of AR. However, after analysis using the exact chi-square test, no statistically significant difference was observed with a P value of 0.055. The relatively low number of AR recipients may have contributed to the border line P value. More recipients confirmed by biopsy should be included in further research to verify the result.

This study has certain limitations. This was a single-center study of 200 patients from eastern China who received renal transplantation and it may not have comprehensively covered the influence of SNPs in AR. Some SNPs which occur in a specific cohort may have been inadvertently ignored in this study. Also, SNPs with a MAF <0.05 in the cohort of our center were not sufficiently included in this study and thus may have led us to miss certain crucial findings. Negative results of other TGF-β and SMAD genes in this study might not be adequate to rule out the function of related genes and downstream proteins in the occurrence of AR.

Conclusions

We found that an SNP – rs1131243 on the *TGF-βR3* gene – is significantly related to the risk of AR in renal transplant recipients but does not influence the severity of AR.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Genetic expression files are posted on the Sequence Read Archive (SRA) database (*https://www.ncbi.nlm.nih.gov/sra; SRP133091*).

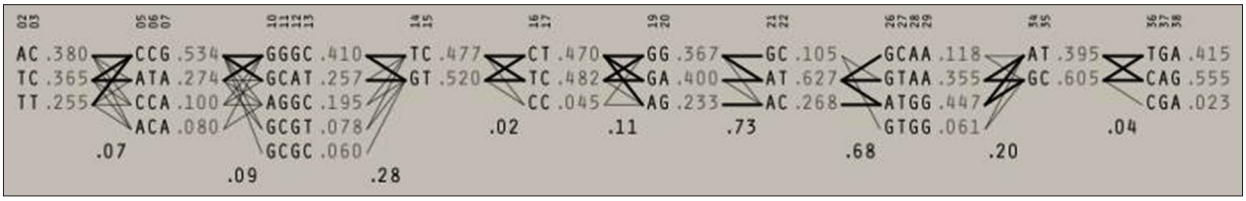
Conflict of interests

None.

Abbreviations

AR – acute rejection; TGF-β – transforming growth factor beta; TGF-βR – transforming growth factor beta receptor; SNPs – single-nucleotide polymorphisms; TS – targeting sequencing; GLM – general linear model; MAF – minor allele frequency; HWE – Hardy-Weinberg equilibrium; LD – linkage disequilibrium.

Supplementary Data



Supplementary Figure 1. Linkage disequilibrium analysis of tagger SNPs.

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Supplementary Table 1. Detailed information of 188 SNPs on TGF-β signaling pathway genes.

Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr18	45368162	C	T	SMAD2	UTR3	.	NM_001003652: c.*36G>A;NM_001135937: c.*36G>A;NM_005901: c.*36G>A
chr18	45368395	C	T	SMAD2	Intronic	.	.
chr18	45368457	C	T	SMAD2	Intronic	rs79502327	.
chr18	45371509	C	T	SMAD2	Intronic	rs1787186	.
chr18	45371546	T	G	SMAD2	Intronic	.	.
chr18	45371623	T	C	SMAD2	Intronic	rs781465847	.
chr18	45371791	C	T	SMAD2	Exonic	rs1804712	SMAD2: NM_001135937: exon9: c.G1110A: p.Q370Q,SMAD2: NM_001003652: exon10: c.G1200A: p.Q400Q,SMAD2: NM_005901: exon10: c.G1200A: p.Q400Q
chr18	45374824	C	T	SMAD2	Intronic	rs150503321	.
chr18	45375054	T	C	SMAD2	Exonic	rs2282656	SMAD2: NM_001135937: exon7: c.A699G: p.L233L,SMAD2: NM_001003652: exon8: c.A789G: p.L263L,SMAD2: NM_005901: exon8: c.A789G: p.L263L
chr18	45375138	C	T	SMAD2	Intronic	rs368276908	.
chr18	45377682	T	C	SMAD2	Exonic	rs146872557	SMAD2: NM_001135937: exon6: c.A657G: p.L219L,SMAD2: NM_001003652: exon7: c.A747G: p.L249L,SMAD2: NM_005901: exon7: c.A747G: p.L249L
chr18	45377752	G	A	SMAD2	Intronic	rs187015964	.
chr18	45391368	T	C	SMAD2	Intronic	.	.
chr18	45394653	G	A	SMAD2	Intronic	rs72661146	.
chr18	45394662	C	A	SMAD2	Intronic	rs72661145	.
chr18	45394919	T	C	SMAD2	Intronic	rs1787177	.
chr18	45395548	T	C	SMAD2	Intronic	.	.
chr18	45422862	T	C	SMAD2	Intronic	.	.
chr18	45423208	A	G	SMAD2	Intronic	.	.
chr15	67358470	C	T	SMAD3	UTR5	rs36221703	NM_005902: c.-23C>T
chr15	67358478	G	A	SMAD3	UTR5	rs1061427	NM_005902: c.-15G>A
chr15	67358558	G	A	SMAD3	Exonic	rs187952791	SMAD3: NM_005902: exon1: c.G66A: p.E22E
chr15	67391319	C	T	SMAD3	Intronic	rs760598093	.
chr15	67391336	C	T	SMAD3	Intronic	rs184408275	.
chr15	67391497	C	A	SMAD3	Intronic	rs1866319	.
chr15	67430223	T	C	SMAD3	Intronic	rs1866318	.
chr15	67430466	T	C	SMAD3	Intronic	.	.
chr15	67430492	A	G	SMAD3	Intronic	.	.
chr15	67430552	T	C	SMAD3	Intronic	rs12914140	.
chr15	67457335	A	G	SMAD3	Exonic	rs1065080	SMAD3: NM_001145103: exon2: c.A177G: p.L59L,SMAD3: NM_005902: exon2: c.A309G: p.L103L

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Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr15	67457485	G	C	SMAD3	Intronic	rs2289261	.
chr15	67457647	C	T	SMAD3	Exonic	rs145380987	SMAD3: NM_001145102: exon3: c.C142T: p.L48L,SMAD3: NM_001145103: exon3: c.C325T: p.L109L,SMAD3: NM_005902: exon3: c.C457T: p.L153L
chr15	67457807	C	T	SMAD3	Intronic	rs2289260	.
chr15	67457815	C	T	SMAD3	Intronic	.	.
chr15	67457840	G	A	SMAD3	Intronic	rs56336520	.
chr15	67457850	G	A	SMAD3	Intronic	rs2289259	.
chr15	67458930	C	T	SMAD3	Intronic	rs7179840	.
chr15	67459013	C	T	SMAD3	Intronic	rs7179893	.
chr15	67459307	A	T	SMAD3	Intronic	.	.
chr15	67462729	G	A	SMAD3	Intronic	rs3743341	.
chr15	67473847	C	T	SMAD3	Intronic	rs549919159	.
chr15	67476952	G	T	SMAD3	Intronic	rs2289791	.
chr15	67476970	T	C	SMAD3	Intronic	rs2289790	.
chr15	67476986	C	T	SMAD3	Intronic	rs545596731	.
chr15	67479198	C	T	SMAD3	Intronic	rs191278238	.
chr15	67479524	G	A	SMAD3	Intronic	.	.
chr15	67479591	G	A	SMAD3	Intronic	.	.
chr15	67482696	A	G	SMAD3	Intronic	rs28410524	.
chr18	48573689	A	G	SMAD4	Intronic	rs77389132	.
chr18	48573718	T	A	SMAD4	Intronic	.	.
chr18	48575389	T	C	SMAD4	Intronic	rs2276163	.
chr18	48575544	T	C	SMAD4	Intronic	.	.
chr18	48577782	G	C	SMAD4	Intronic	rs7229678	.
chr18	48577894	G	A	SMAD4	Intronic	rs118185031	.
chr18	48584863	T	G	SMAD4	Intronic	rs556951898	.
chr18	48586175	A	G	SMAD4	Intronic	.	.
chr18	48586184	A	G	SMAD4	Intronic	rs948589	.
chr18	48586328	T	A	SMAD4	Intronic	rs758408803	.
chr18	48586344	C	T	SMAD4	Intronic	rs948588	.
chr18	48593617	T	C	SMAD4	Intronic	rs139741673	.
chr19	41836947	G	C	T/GFB1	UTR3	.	NM_000660: c.*10C>G
chr19	41837123	C	T	T/GFB1	Splicing	rs199982059	NM_000660: exon8: c.1015-8G>A
chr19	41837997	C	T	T/GFB1	Intronic	rs570977266	.
chr19	41838174	C	T	T/GFB1	Exonic	rs190566789	T/GFB1: NM_000660: exon6: c.G873A: p.K291K
chr19	41838206	G	A	T/GFB1	Intronic	rs8179181	.
chr19	41838287	C	T	T/GFB1	Intronic	rs13306709	.
chr19	41847736	T	C	T/GFB1	Intronic	rs542695848	.
chr19	41847933	A	T	T/GFB1	Exonic	rs569594975	T/GFB1: NM_000660: exon5: c.T715A: p.F239I
chr19	41847956	G	A	T/GFB1	Intronic	rs763345073	.

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Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr19	41848038	C	T	T/GFB1	Intronic	rs200134934	.
chr19	41848075	C	T	T/GFB1	Exonic	.	T/GFB1: NM_000660: exon4: c.G712A: p.G238R
chr19	41850710	C	T	T/GFB1	Exonic	rs766221068	T/GFB1: NM_000660: exon3: c.G576A: p.S192S
chr19	41850742	G	A	T/GFB1	Exonic	rs753852676	T/GFB1: NM_000660: exon3: c.C544T: p.L182F
chr19	41850921	C	T	T/GFB1	Intronic	rs531039494	.
chr19	41854052	C	A	T/GFB1	Intronic	rs2241717	.
chr19	41854086	C	T	T/GFB1	Intronic	rs2241716	.
chr19	41854400	C	T	T/GFB1	Intronic	rs376729112	.
chr19	41854452	C	T	T/GFB1	Intronic	.	.
chr19	41854477	A	C	T/GFB1	Intronic	.	.
chr19	41854534	T	A	T/GFB1	Intronic	rs8108632	.
chr19	41858838	T	A	T/GFB1	Exonic	.	T/GFB1: NM_000660: exon1: c.A112T: p.M38L
chr19	41858867	G	A	T/GFB1	Exonic	.	T/GFB1: NM_000660: exon1: c.C83T: p.A28V
chr19	41858921	G	A	T/GFB1	Exonic	rs1800470	T/GFB1: NM_000660: exon1: c.C29T: p.P10L
chr19	41859047	A	C	T/GFB1	UTR5	.	NM_000660: c.-98T>G
chr1	218607317	G	A	T/GFB2	Intronic	.	.
chr1	218607796	C	T	T/GFB2	Splicing	.	NM_001135599: exon5: c.838+6C>T;NM_003238: exon4: c.754+6C>T
chr1	218607817	G	T	T/GFB2	Intronic	rs748386982	.
chr1	218607922	A	G	T/GFB2	Intronic	.	.
chr1	218610691	G	T	T/GFB2	Exonic	.	T/GFB2: NM_003238: exon6: c.G939T: p.V313V,T/GFB2: NM_001135599: exon7: c.G1023T: p.V341V
chr14	76425446	G	T	T/GFB3	UTR3	rs188123116	NM_003239: c.*84C>A
chr14	76427103	A	G	T/GFB3	Intronic	rs115411167	.
chr14	76427473	C	G	T/GFB3	Intronic	.	.
chr14	76429555	C	T	T/GFB3	Intronic	rs3917201	.
chr14	76429868	A	G	T/GFB3	Intronic	rs3917200	.
chr14	76431886	T	A	T/GFB3	Intronic	rs200111860	.
chr14	76432136	T	C	T/GFB3	Intronic	rs3917187	.
chr14	76437409	C	A	T/GFB3	Intronic	rs200181092	.
chr14	76437431	G	A	T/GFB3	Intronic	rs752520633	.
chr14	76437614	A	G	T/GFB3	Intronic	rs3917176	.
chr14	76437638	C	T	T/GFB3	Intronic	rs201310311	.
chr14	76437817	C	T	T/GFB3	Intronic	rs554067491	.
chr14	76438137	C	G	T/GFB3	Intronic	rs537980685	.
chr14	76446750	G	A	T/GFB3	Intronic	.	.

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chr14	76446782	G	C	T/GFB3	Intronic	.	.
chr14	76446943	C	T	T/GFB3	Exonic	rs778214495	T/GFB3: NM_003239: exon1: c.G294A: p.S98S
chr14	76447049	G	T	T/GFB3	Exonic	rs757664433	T/GFB3: NM_003239: exon1: c.C188A: p.T63N
chr9	101890227	C	T	T/GFBR1	Intronic	rs11568753	.
chr9	101890294	A	G	T/GFBR1	Intronic	rs189740990	.
chr9	101890980	A	G	T/GFBR1	Intronic	rs7041311	.
chr9	101891294	A	G	T/GFBR1	Exonic	.	T/GFBR1: NM_001130916: exon2: c.A255G: p.V85V,T/GFBR1: NM_004612: exon2: c.A255G: p.V85V
chr9	101891447	G	C	T/GFBR1	Intronic	rs56402414	.
chr9	101891478	C	T	T/GFBR1	Intronic	.	.
chr9	101900392	C	G	T/GFBR1	Intronic	.	.
chr9	101900410	A	G	T/GFBR1	Intronic	rs11568778	.
chr9	101907072	T	C	T/GFBR1	Exonic	rs192662552	T/GFBR1: NM_001130916: exon5: c.T801C: p.N267N,T/GFBR1: NM_004612: exon6: c.T1032C: p.N344N
chr9	101907222	C	T	T/GFBR1	Intronic	rs56251429	.
chr9	101908915	G	A	T/GFBR1	Intronic	rs334354	.
chr3	30648248	C	G	T/GFBR2	Utr5	rs2306856	NM_001024847: c.-128C>G;NM_003242: c.-128C>G
chr3	30648538	C	G	T/GFBR2	Intronic	.	.
chr3	30648636	T	G	T/GFBR2	Intronic	.	.
chr3	30664732	A	C	T/GFBR2	Exonic	rs200111443	T/GFBR2: NM_001024847: exon2: c.A136C: p.S46R
chr3	30664864	T	C	T/GFBR2	Intronic	rs117998227	.
chr3	30686107	A	C	T/GFBR2	Intronic	.	.
chr3	30686264	C	T	T/GFBR2	Exonic	rs769570752	T/GFBR2: NM_003242: exon2: c.C120T: p.D40D,T/GFBR2: NM_001024847: exon3: c.C195T: p.D65D
chr3	30686414	A	G	T/GFBR2	Splicing	rs1155705	NM_001024847: exon3: c.338+7A>G;NM_003242: exon2: c.263+7A>G
chr3	30691692	C	A	T/GFBR2	Intronic	.	.
chr3	30713126	T	A	T/GFBR2	Splicing	rs11466512	NM_001024847: exon5: c.530-4T>A;NM_003242: exon4: c.455-4T>A
chr3	30713246	G	A	T/GFBR2	Exonic	rs56105708	T/GFBR2: NM_003242: exon4: c.G571A: p.V191I,T/GFBR2: NM_001024847: exon5: c.G646A: p.V216I
chr3	30713292	C	T	T/GFBR2	Exonic	rs150022335	T/GFBR2: NM_003242: exon4: c.C617T: p.T206M,T/GFBR2: NM_001024847: exon5: c.C692T: p.T231M
chr3	30713314	C	T	T/GFBR2	Exonic	rs200332401	T/GFBR2: NM_003242: exon4: c.C639T: p.S213S,T/GFBR2: NM_001024847: exon5: c.C714T: p.S238S
chr3	30713619	C	T	T/GFBR2	Exonic	rs34833812	T/GFBR2: NM_003242: exon4: c.C944T: p.T315M,T/GFBR2: NM_001024847: exon5: c.C1019T: p.T340M

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Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr3	30713842	C	T	T/GFBR2	Exonic	rs2228048	T/GFBR2: NM_003242: exon4: c.C1167T: p.N389N,T/GFBR2: NM_001024847: exon5: c.C1242T: p.N414N
chr3	30713945	T	C	T/GFBR2	Intronic	rs45515293	.
chr3	30730096	G	A	T/GFBR2	Intronic	.	.
chr3	30732821	C	A	T/GFBR2	Intronic	rs2276767	.
chr3	30733100	G	A	T/GFBR2	UTR3	.	NM_001024847: c.*9G>A;NM_003242: c.*9G>A
chr3	30733102	G	A	T/GFBR2	UTR3	.	NM_001024847: c.*11G>A;NM_003242: c.*11G>A
chr1	92149139	C	T	T/GFBR3	UTR3	rs1805115	NM_001195683: c.*157G>A;NM_001195684: c.*157G>A;NM_003243: c.*157G>A
chr1	92149277	C	T	T/GFBR3	UTR3	rs1131243	NM_001195683: c.*19G>A;NM_001195684: c.*19G>A;NM_003243: c.*19G>A
chr1	92149503	A	T	T/GFBR3	Intronic	.	.
chr1	92161307	C	T	T/GFBR3	Exonic	rs141883791	T/GFBR3: NM_001195683: exon16: c.G2356A: p.V786M,T/GFBR3: NM_003243: exon16: c.G2359A: p.V787M,T/GFBR3: NM_001195684: exon17: c.G2356A: p.V786M
chr1	92161515	T	A	T/GFBR3	Intronic	rs2253316	.
chr1	92163682	C	G	T/GFBR3	Exonic	rs17882828	T/GFBR3: NM_001195683: exon15: c.G2290C: p.G764R,T/GFBR3: NM_003243: exon15: c.G2293C: p.G765R,T/GFBR3: NM_001195684: exon16: c.G2290C: p.G764R
chr1	92163786	G	T	T/GFBR3	Intronic	rs2296621	.
chr1	92174260	A	G	T/GFBR3	Exonic	rs284878	T/GFBR3: NM_001195683: exon14: c.T2244C: p.T748T,T/GFBR3: NM_003243: exon14: c.T2247C: p.T749T,T/GFBR3: NM_001195684: exon15: c.T2244C: p.T748T
chr1	92174383	A	G	T/GFBR3	Intronic	rs78893665	.
chr1	92174415	G	A	T/GFBR3	Intronic	rs2038931	.
chr1	92177740	C	T	T/GFBR3	Intronic	rs528216123	.
chr1	92177938	A	G	T/GFBR3	Exonic	rs1805113	T/GFBR3: NM_001195683: exon13: c.T2025C: p.F675F,T/GFBR3: NM_003243: exon13: c.T2028C: p.F676F,T/GFBR3: NM_001195684: exon14: c.T2025C: p.F675F
chr1	92178172	T	C	T/GFBR3	Intronic	rs573785401	.
chr1	92178259	C	T	T/GFBR3	Intronic	rs1750641	.
chr1	92178260	A	G	T/GFBR3	Intronic	rs1613413	.
chr1	92181670	C	A	T/GFBR3	Intronic	rs2029354	.
chr1	92181678	T	G	T/GFBR3	Intronic	rs2029355	.
chr1	92181746	T	C	T/GFBR3	Intronic	rs140473734	.
chr1	92184673	G	A	T/GFBR3	Intronic	rs4658260	.

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Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr1	92184744	C	T	T/GFBR3	Intronic	rs4658261	.
chr1	92184814	G	T	T/GFBR3	Intronic	rs7524066	.
chr1	92185059	A	T	T/GFBR3	Intronic	rs61748118	.
chr1	92185134	A	C	T/GFBR3	Intronic	rs186586693	.
chr1	92185136	C	T	T/GFBR3	Intronic	rs577773521	.
chr1	92185185	T	C	T/GFBR3	Intronic	rs2279455	.
chr1	92185657	C	T	T/GFBR3	Exonic	rs1805112	T/GFBR3: NM_001195683: exon9: c.G1203A: p.P401P,T/GFBR3: NM_003243: exon9: c.G1206A: p.P402P,T/GFBR3: NM_001195684: exon10: c.G1203A: p.P401P
chr1	92185715	A	G	T/GFBR3	Exonic	.	T/GFBR3: NM_001195683: exon9: c.T1145C: p.L382P,T/GFBR3: NM_003243: exon9: c.T1148C: p.L383P,T/GFBR3: NM_001195684: exon10: c.T1145C: p.L382P
chr1	92185881	G	A	T/GFBR3	Intronic	.	.
chr1	92195221	C	T	T/GFBR3	Intronic	.	.
chr1	92195229	C	T	T/GFBR3	Intronic	.	.
chr1	92195555	T	G	T/GFBR3	Intronic	.	.
chr1	92195601	G	A	T/GFBR3	Intronic	rs10783002	.
chr1	92195652	T	C	T/GFBR3	Intronic	rs11466584	.
chr1	92200376	G	A	T/GFBR3	Exonic	rs376528004	T/GFBR3: NM_001195683: exon5: c.C525T: p.T175T,T/GFBR3: NM_003243: exon5: c.C525T: p.T175T,T/GFBR3: NM_001195684: exon6: c.C525T: p.T175T
chr1	92200382	T	C	T/GFBR3	Exonic	rs2306888	T/GFBR3: NM_001195683: exon5: c.A519G: p.S173S,T/GFBR3: NM_003243: exon5: c.A519G: p.S173S,T/GFBR3: NM_001195684: exon6: c.A519G: p.S173S
chr1	92200389	A	G	T/GFBR3	Exonic	rs186259544	T/GFBR3: NM_001195683: exon5: c.T512C: p.V171A,T/GFBR3: NM_003243: exon5: c.T512C: p.V171A,T/GFBR3: NM_001195684: exon6: c.T512C: p.V171A
chr1	92200513	A	C	T/GFBR3	Exonic	rs759218481	T/GFBR3: NM_001195683: exon5: c.T388G: p.S130A,T/GFBR3: NM_003243: exon5: c.T388G: p.S130A,T/GFBR3: NM_001195684: exon6: c.T388G: p.S130A
chr1	92200520	G	C	T/GFBR3	Splicing	rs138007142	NM_001195683: exon6: c.385-4C>G;NM_001195684: exon7: c.385-4C>G;NM_003243: exon6: c.385-4C>G
chr1	92200593	A	G	T/GFBR3	Intronic	rs11165376	.
chr1	92200597	G	A	T/GFBR3	Intronic	rs12124904	.
chr1	92200601	T	G	T/GFBR3	Intronic	.	.
chr1	92200627	T	C	T/GFBR3	Intronic	rs10874913	.
chr1	92200634	C	T	T/GFBR3	Intronic	rs11165377	.
chr1	92224067	C	T	T/GFBR3	Intronic	rs3738441	.
chr1	92224347	G	A	T/GFBR3	Intronic	rs11165441	.

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Chromosome	Position	Reference allele	Alternation allele	Gene name	Function	avsnp144	Gene detail
chr1	92262874	T	C	T/GFBR3	Exonic	rs2810904	T/GFBR3: NM_001195683: exon3: c.A216G: p.A72A,T/GFBR3: NM_003243: exon3: c.A216G: p.A72A,T/GFBR3: NM_001195684: exon4: c.A216G: p.A72A
chr1	92263079	G	A	T/GFBR3	Intronic	rs17881268	.
chr1	92266656	A	G	T/GFBR3	Intronic	rs72716444	.
chr1	92266836	C	T	T/GFBR3	Intronic	rs12123363	.
chr1	92327045	G	A	T/GFBR3	Exonic	rs1805110	T/GFBR3: NM_001195683: exon2: c.C44T: p.S15F,T/GFBR3: NM_003243: exon2: c.C44T: p.S15F,T/GFBR3: NM_001195684: exon3: c.C44T: p.S15F
	92327126	C	T	T/GFBR3	UTR5	rs1805109	NM_001195683: c.-38G>A;NM_001195684: c.-38G>A;NM_003243: c.-38G>A

Supplementary Table 2. HWE and MAF analysis of 188 SNPs.

SNP	Position	HWE	MAF	REF: ALT
rs10874913	92200627	7.24E-58	0.45	C: T
rs1866319	67391497	2.86E-31	0.11	C: A
rs7179840	67458930	4.08E-22	0.15	C: T
rs1866318	67430223	8.54E-09	0.02	C: T
rs2253316	92161515	2.00E-04	0.028	T: A
rs1787186	45371509	6.00E-04	0.49	T: C
rs2279455	92185185	6.00E-04	0.092	T: C
rs2276163	48575389	0.0053	0.043	T: C
rs8108632	41854534	0.013	0.14	T: A
rs7041311	101890980	0.015	0.007	A: G
rs2029354	92181670	0.10	0.018	C: A
rs2029355	92181678	0.10	0.018	T: G
rs4658261	92184744	0.10	0.018	C: T
rs11165377	92200634	0.11	0.07	C: T
rs2810904	92262874	0.14	0.20	C: T
rs45515293	30713945	0.22	0.025	T: C
rs1805115	92149139	0.26	0.028	C: T
rs2038931	92174415	0.29	0.4	G: A
rs2289261	67457485	0.29	0.39	G: C
rs1131243	92149277	0.43	0.16	C: T
rs1805110	92327045	0.31	0.39	G: A
rs1805109	92327126	0.31	0.39	C: T
rs12124904	92200597	0.31	0.48	G: A
rs1613413	92178260	0.33	0.25	G: A
rs2241716	41854086	0.36	0.28	C: T
rs11165376	92200593	0.38	0.49	G: A
rs10783002	92195601	0.43	0.45	G: A

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SNP	Position	HWE	MAF	REF: ALT
rs2289791	67476952	0.47	0.48	G: T
rs11165441	92224347	0.49	0.22	G: A
rs11466512	30713126	0.50	0.38	T: A
rs2276767	30732821	0.50	0.11	C: A
rs7179893	67459013	0.56	0.33	C: T
rs2289790	67476970	0.57	0.47	T: C
rs2296621	92163786	0.60	0.043	G: T
rs2241717	41854052	0.60	0.36	C: A
rs1155705	30686414	0.63	0.33	G: A
rs1061427	67358478	0.67	0.20	G: A
rs3917201	76429555	0.68	0.48	C: T
rs11568753	101890227	0.73	0.41	C: T
rs1805113	92177938	0.73	0.10	A: G
rs3917187	76432136	0.77	0.47	C: T
rs334354	101908915	0.77	0.44	G: A
rs1750641	92178259	0.79	0.37	T: C
rs7229678	48577782	0.81	0.46	G: C
rs2228048	30713842	0.81	0.25	C: T
rs2289259	67457850	0.88	0.25	G: A
rs3738441	92224067	0.90	0.3	T: C
rs2306856	30648248	1	0.007	C: G
Chr3: 30648538	30648538	1	0.003	C: G
Chr3: 30648636	30648636	1	0.003	T: G
rs200111443	30664732	1	0.005	A: C
rs117998227	30664864	1	0.007	T: C
Chr3: 30686107	30686107	1	0.003	A: C
rs769570752	30686264	1	0.003	C: T
Chr3: 30691692	30691692	1	0.003	C: A
rs56105708	30713246	1	0.022	G: A
rs150022335	30713292	1	0.003	C: T
rs200332401	30713314	1	0.003	C: T
rs34833812	30713619	1	0.022	C: T
Chr3: 30730096	30730096	1	0.003	G: A
Chr3: 30733100	30733100	1	0.003	G: A
Chr3: 30733102	30733102	1	0.003	G: A
Chr19: 41836947	41836947	1	0.003	G: C
rs199982059	41837123	1	0.013	C: T
rs570977266	41837997	1	0.003	C: T
rs190566789	41838174	1	0.013	C: T
rs8179181	41838206	1	0.003	G: A
rs13306709	41838287	1	0.003	C: T
rs542695848	41847736	1	0.003	T: C
rs569594975	41847933	1	0.003	A: T

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SNP	Position	HWE	MAF	REF: ALT
rs763345073	41847956	1	0.003	G: A
rs200134934	41848038	1	0.005	C: T
Chr19: 41848075	41848075	1	0.003	C: T
rs766221068	41850710	1	0.003	C: T
rs753852676	41850742	1	0.003	G: A
rs531039494	41850921	1	0.003	C: T
rs376729112	41854400	1	0.003	C: T
Chr19: 41854452	41854452	1	0.003	C: T
Chr19: 41854477	41854477	1	0.003	A: C
Chr19: 41858838	41858838	1	0.003	T: A
Chr19: 41858867	41858867	1	0.003	G: A
rs1800470	41858921	1	0.46	G: A
Chr19: 41859047	41859047	1	0.003	A: C
Chr18: 45368162	45368162	1	0.003	C: T
Chr18: 45368395	45368395	1	0.003	C: T
rs79502327	45368457	1	0.005	C: T
Chr18: 45371546	45371546	1	0.003	T: G
rs781465847	45371623	1	0.003	T: C
rs1804712	45371791	1	0.003	C: T
rs150503321	45374824	1	0.003	C: T
rs2282656	45375054	1	0.003	T: C
rs368276908	45375138	1	0.003	C: T
rs146872557	45377682	1	0.003	T: C
rs187015964	45377752	1	0.003	G: A
Chr18: 45391368	45391368	1	0.003	T: C
rs72661146	45394653	1	0.02	G: A
rs72661145	45394662	1	0.02	C: A
rs1787177	45394919	1	0.015	T: C
Chr18: 45395548	45395548	1	0.003	T: C
Chr18: 45422862	45422862	1	0.003	T: C
Chr18: 45423208	45423208	1	0.003	A: G
rs77389132	48573689	1	0.02	A: G
Chr18: 48573718	48573718	1	0.003	T: A
Chr18: 48575544	48575544	1	0.003	T: C
rs118185031	48577894	1	0.015	G: A
rs556951898	48584863	1	0.003	T: G
Chr18: 48586175	48586175	1	0.003	A: G
rs948589	48586184	1	0.003	A: G
rs758408803	48586328	1	0.003	T: A
rs948588	48586344	1	0.043	C: T
rs139741673	48593617	1	0.03	T: C
rs36221703	67358470	1	0.025	C: T
rs187952791	67358558	1	0.02	G: A

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SNP	Position	HWE	MAF	REF: ALT
rs760598093	67391319	1	0.003	C: T
rs184408275	67391336	1	0.01	C: T
Chr15: 67430466	67430466	1	0.003	T: C
Chr15: 67430492	67430492	1	0.003	A: G
rs12914140	67430552	1	0.043	T: C
rs1065080	67457335	1	0.195	G: A
rs145380987	67457647	1	0.003	C: T
rs2289260	67457807	1	0.003	C: T
Chr15: 67457815	67457815	1	0.003	C: T
rs56336520	67457840	1	0.005	G: A
Chr15: 67459307	67459307	1	0.003	A: T
rs3743341	67462729	1	0.003	G: A
rs549919159	67473847	1	0.007	C: T
rs545596731	67476986	1	0.013	C: T
rs191278238	67479198	1	0.005	C: T
Chr15: 67479524	67479524	1	0.003	G: A
Chr15: 67479591	67479591	1	0.003	G: A
rs28410524	67482696	1	0.01	A: G
rs188123116	76425446	1	0.005	G: T
rs115411167	76427103	1	0.005	A: G
Chr14: 76427473	76427473	1	0.003	C: G
rs3917200	76429868	1	0.033	A: G
rs200111860	76431886	1	0.003	T: A
rs200181092	76437409	1	0.003	C: A
rs752520633	76437431	1	0.003	G: A
rs3917176	76437614	1	0.018	A: G
rs201310311	76437638	1	0.005	C: T
rs554067491	76437817	1	0.007	C: T
rs537980685	76438137	1	0.003	C: G
Chr14: 76446750	76446750	1	0.003	G: A
Chr14: 76446782	76446782	1	0.003	G: C
rs778214495	76446943	1	0.003	C: T
rs757664433	76447049	1	0.003	G: T
Chr1: 92149503	92149503	1	0.003	A: T
rs141883791	92161307	1	0.005	C: T
rs17882828	92163682	1	0.037	C: G
rs284878	92174260	1	0.23	G: A
rs78893665	92174383	1	0.01	A: G
rs528216123	92177740	1	0.003	C: T
rs573785401	92178172	1	0.007	T: C
rs140473734	92181746	1	0.003	T: C
rs4658260	92184673	1	0.003	G: A
rs7524066	92184814	1	0.092	G: T

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SNP	Position	HWE	MAF	REF: ALT
rs61748118	92185059	1	0.03	A: T
rs186586693	92185134	1	0.007	A: C
rs577773521	92185136	1	0.003	C: T
rs1805112	92185657	1	0.468	T: C
Chr1: 92185715	92185715	1	0.003	A: G
Chr1: 92185881	92185881	1	0.003	G: A
Chr1: 92195221	92195221	1	0.003	C: T
Chr1: 92195229	92195229	1	0.003	C: T
Chr1: 92195555	92195555	1	0.003	T: G
rs11466584	92195652	1	0.003	T: C
rs376528004	92200376	1	0.003	G: A
rs2306888	92200382	1	0.11	T: C
rs186259544	92200389	1	0.003	A: G
rs759218481	92200513	1	0.003	A: C
rs138007142	92200520	1	0.003	G: C
Chr1: 92200601	92200601	1	0.003	T: G
rs17881268	92263079	1	0.003	G: A
rs72716444	92266656	1	0.035	A: G
rs12123363	92266836	1	0.043	C: T
rs189740990	101890294	1	0.003	A: G
Chr9: 101891294	101891294	1	0.003	A: G
rs56402414	101891447	1	0.043	G: C
Chr9: 101891478	101891478	1	0.003	C: T
Chr9: 101900392	101900392	1	0.003	C: G
rs11568778	101900410	1	0.438	A: G
rs192662552	101907072	1	0.003	T: C
rs56251429	101907222	1	0.007	C: T
Chr1: 218607317	218607317	1	0.003	G: A
Chr1: 218607796	218607796	1	0.003	C: T
rs748386982	218607817	1	0.003	G: T
Chr1: 218607922	218607922	1	0.003	A: G
Chr1: 218610691	218610691	1	0.003	G: T

REF – referential allele; ALT – alterative allele.

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Supplementary Table 3. Detailed information of 31 tagger SNPs.

SNP	POS	HWE	MAF	REF: ALT
rs11165377	92200634	0.11	0.07	C: T
rs7524066	92184814	1	0.092	G: T
rs1805113	92177938	0.73	0.10	A: G
rs2276767	30732821	0.49	0.11	C: A
rs2306888	92200382	1	0.11	T: C
rs1131243	92149277	0.30	0.12	C: T
rs1065080	67457335	1	0.19	G: A
rs2810904	92262874	0.14	0.20	C: T
rs1061427	67358478	0.67	0.20	G: A
rs11165441	92224347	0.48	0.22	G: A
rs284878	92174260	1	0.23	G: A
rs2228048	30713842	0.81	0.25	C: T
rs2289259	67457850	0.88	0.25	G: A
rs2241716	41854086	0.35	0.28	C: T
rs3738441	92224067	0.90	0.3	T: C
rs1155705	30686414	0.62	0.33	G: A
rs7179893	67459013	0.56	0.33	C: T
rs2241717	41854052	0.60	0.36	C: A
rs1750641	92178259	0.79	0.37	T: C
rs11466512	30713126	0.49	0.38	T: A
rs2289261	67457485	0.28	0.39	G: C
rs1805109	92327126	0.31	0.39	C: T
rs2038931	92174415	0.28	0.4	G: A
rs11568753	101890227	0.73	0.41	C: T
rs10783002	92195601	0.43	0.45	G: A
rs1800470	41858921	1	0.46	G: A
rs7229678	48577782	0.81	0.46	G: C
rs1805112	92185657	1	0.46	T: C
rs3917187	76432136	0.77	0.47	C: T
rs2289791	67476952	0.47	0.48	G: T
rs11165376	92200593	0.37	0.49	G: A

REF – referential allele; ALT – alterative allele.

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Supplementary Table 4. General linear model for clinical variables on the occurrence of acute rejection.

Effect	Method	Value	F	*P* value
Intercept	Pillai's Trace	0.72	58.52	0
	Wilks' Lambda	0.28	58.52	0
	Hotelling's Trace	2.53	58.52	0
	Roy's Largest Root	2.53	58.52	0
Gender	Pillai's Trace	0.015	0.36	0.94
	Wilks' Lambda	0.99	0.36	0.94
	Hotelling's Trace	0.015	0.36	0.94
	Roy's Largest Root	0.015	0.36	0.94
Age	Pillai's Trace	0.027	0.65	0.74
	Wilks' Lambda	0.97	0.65	0.74
	Hotelling's Trace	0.028	0.65	0.74
	Roy's Largest Root	0.028	0.65	0.74
Weight	Pillai's Trace	0.042	1.02	0.42
	Wilks' Lambda	0.96	1.02	0.42
	Hotelling's Trace	0.061	1.02	0.42
	Roy's Largest Root	0.061	1.02	0.42
ISD	Pillai's Trace	0.057	1.40	0.20
	Wilks' Lambda	0.97	1.40	0.20
	Hotelling's Trace	0.034	1.40	0.20
	Roy's Largest Root	0.034	1.40	0.20
Duration	Pillai's Trace	0.033	0.78	0.62
	Wilks' Lambda	0.97	0.78	0.62
	Hotelling's Trace	0.034	0.78	0.62
	Roy's Largest Root	0.034	0.78	0.622
Sir	**Pillai's Trace**	**0.096**	**2.44**	**0.015**
	Wilks' Lambda	**0.91**	**2.44**	**0.015**
	Hotelling's Trace	**0.11**	**2.44**	**0.015**
	Roy's Largest Root	**0.11**	**2.44**	**0.015**
DGF	Pillai's Trace	0.071	1.77	0.085
	Wilks' Lambda	0.93	1.77	0.085
	Hotelling's Trace	0.077	1.77	0.085
	Roy's Largest Root	0.077	1.77	0.085

ISD – immunosuppressive drug; Sir – sirolimus; DGF – delayed graft function.

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Supplementary Table 5. Results of logistic analysis of 31 tagger SNPs in 5 model adjusted by the usage of sirolimus.

	Codominant	Dominant	Recessive	Overdominant	log-additive
rs1131243	0.00036	7.79E-05	0.10	0.00073	0.00011
rs1805113	0.049	0.021	0.16	0.055	0.01
rs1155705	0.062	0.026	0.13	0.22	0.01
rs7524066	0.11	0.040	0.51	0.055	0.04
rs2810904	0.24	0.15	0.18	0.43	0.09
rs3738441	0.28	0.12	0.43	0.26	0.12
rs1061427	0.39	0.17	0.66	0.21	0.18
rs2276767	0.016	0.054	0.09	0.014	0.19
rs1805112	0.085	0.79	0.04	0.065	0.33
rs3917187	0.23	0.11	0.92	0.14	0.3
rs7179893	0.60	0.52	0.35	0.95	0.35
rs2241717	0.083	0.85	0.04	0.10	0.36
rs2038931	0.61	0.54	0.34	0.89	0.36
rs1800470	0.35	0.98	0.17	0.26	0.41
rs11165376	0.44	0.90	0.22	0.34	0.42
rs2289259	0.70	0.40	0.75	0.48	0.43
rs10783002	0.14	0.68	0.09	0.08	0.49
rs11165377	0.80	0.51	0.85	0.53	0.54
rs11466512	0.16	0.71	0.09	0.15	0.58
rs284878	0.89	0.77	0.65	0.93	0.68
rs2289791	0.30	0.25	0.57	0.12	0.70
rs11568753	0.23	0.60	0.18	0.12	0.70
rs2289261	0.92	0.69	0.88	0.78	0.72
rs1750641	0.93	0.79	0.74	0.98	0.72
rs2306888	0.88	0.83	0.62	0.94	0.75
rs11165441	0.24	0.79	0.11	0.39	0.77
rs2228048	0.80	0.97	0.53	0.71	0.81
rs1065080	0.50	0.56	0.40	0.34	0.83
rs2241716	0.096	0.29	0.17	0.04	0.86
rs7229678	0.89	0.91	0.68	0.66	0.86
rs1805109	0.95	0.88	0.83	0.76	0.98

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