# Donor-derived hypouricemia in irrelevant recipients caused by kidney transplantation

Lisha Teng<sup>1,2,3#</sup>, Yanling Zhang<sup>1,2,3,4#</sup>, Luxi Ye<sup>1,2,3#</sup>, Junhao Lv<sup>1,2,3</sup>, Youying Mao<sup>5</sup>, Ronen Schneider<sup>6</sup>, Jianghua Chen<sup>1,2,3</sup>, Hong Jiang<sup>1,2,3</sup>, Jianyong Wu<sup>1,2,3</sup>

<sup>1</sup>Department of the Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China; <sup>2</sup>Key Laboratory of Kidney Disease Prevention and Control Technology, Hangzhou 310003, China; <sup>3</sup>The Third-Grade Laboratory under the National State, Administration of Traditional Chinese Medicine, Hangzhou 310000, China; <sup>4</sup>Department of Nephrology, The Second Hospital of Shaoxing, Shaoxing 312000, China; <sup>5</sup>Nephrology Department, Shanghai Children's Medical Center, Shanghai Jiao Tong University, Shanghai 200240, China; <sup>6</sup>Division of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

*Contributions:* (I) Conception and design: J Wu, H Jiang; (II) Administrative support: J Wu; (III) Provision of study materials: J Wu; (IV) Collection and assembly of data: Y Zhang, L Ye; (V) Data analysis and interpretation: L Teng, L Ye; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

"These authors have contributed equally to this work.

*Correspondence to:* Jianyong Wu; Hong Jiang. Department of the Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China. Email: wujianyong1964@zju.edu.cn; jianghong961106@zju.edu.cn.

**Background:** Hereditary renal hypouricemia (HRH) is a genetically heterogenetic disease. Patients with HRH are almost asymptomatic; but some may experience exercise-induced acute kidney injury (EAKI) and nephrolithiasis which may bring concerns regarding the risk-benefit ratio as marginal kidney donors. This study examined the pathogenic mutations of hypouricemia in two recipients after receiving kidney transplantation, providing preliminary evidence for the mechanism of hypouricemia.

**Methods:** Two participants underwent detailed biochemical examinations. DNA and RNA were extracted from transplant specimens for sequencing. The whole-genome sequencing and polymerase chain reaction (PCR) amplification were performed to confirm the pathogenic genes. Functional effects of mutant proteins were verified by bioinformatics analysis. RNA-sequencing (RNA-seq) was used to study the transcriptome of hypouricemia.

**Results:** Both of the recipients had the low serum uric acid (UA) (45–65 µmol/l), high fraction excretion of UA (44% and 75%) and an increase in the UA clearance (35.9 and 73.3 mL/min) with a functioning graft. The sequencing analyses revealed 7 kinds of potential mutational genes in this case, two novel mutations p.R89H and p.L181V in SLC22A12 gene which were revealed by bioinformatics could be pathogenic in nature.

**Conclusions:** Two novel mutations of SLC22A12 were identified. Preliminary functional analysis revealed a potential deleterious effect of these mutations in the grafts derived from the donor and sequencing analysis expand the molecular mechanisms of renal hypouricemia.

**Keywords:** Hereditary renal hypouricemia (HRH); single nucleotide polymorphism (SNP); kidney transplantation; SLC22A12

Submitted Dec 04, 2019. Accepted for publication Feb 05, 2020. doi: 10.21037/atm.2020.02.140 View this article at: http://dx.doi.org/10.21037/atm.2020.02.140

#### Page 2 of 10

## Introduction

Hereditary renal hypouricemia (HRH) is a hereditary and heterogenetic disorder characterized by defective tubular uric acid (UA) transport, reabsorption insufficiency, and/ or increased renal urate clearance resulting from the loss-of-function mutations in UA transport genes (1). HRH patients are mostly asymptomatic but 10% of the patients are susceptible to exercise-induced acute renal failure (EIARF) and/or nephrolithiasis, while 20% of them are afflicted by hypercalciuria, which can lead to nephrocalcinosis in the distal tubules (2-4). Currently, two biochemical parameters are in use to diagnose HRH: (I) serum UA concentration less than 2 mg/dL (equivalent to 119 µmol/L), and (II) more than 10% fractional excretion of UA (5,6). In Japan, the rate of HRH incidence is reportedly about 2.54% among hospitalized patients and 0.12-0.72% in the general population (7-9).

The first successful genetically matched kidney transplantation for HRH was reported in 2006 (10). In 2016, a kidney transplant recipient patients with HRH reported a rare case of nephrocalcinosis in the distal tubules three months after transplant surgery (4). Other than these sporadic reports, there is a dearth of scientific data on the transmission of renal hypouricemia in irrelevant donorrecipient transplantation.

Over the past decade, genome-wide association studies and case reports have shown an increase in the number of genetic variants that influence serum UA concentrations, such as SLC2A9, SLC22A12, SLC17A3, and ABCG2 (11,12). Single nucleotide polymorphisms (SNPs) in regulatory regions (rSNPs) modulate levels of gene expression in an allele-specific manner; however, there is lack of such studies in kidney transplantation research. Further, majority of published studies on hypouricemia includes case report or case series, which lack essential statistical analysis and comparison with healthy controls. Herein, we present two unrelated recipients who had no history of hypouricemia before renal transplantation but experienced sudden and unexpected hypouricemia after receiving transplants from a donor of different genetic background. We performed a DNA sequencing analysis in one healthy control and two kidney transplant recipients and followed up for 3.5 years after their surgery. Our results showed differential gene expression profile between healthy individuals and HRH patients and indicated possible pathogenic pathways associated with disease onset and progression.

Teng et al. Irrelevant kidney transplantation and hypouricemia

# **Methods**

#### Biochemical and ultrasound evaluation

To evaluate the factors associated with hypouricemia, we checked parameters such as blood biochemistry and urine routine for the UA metabolism, renal tubular acidosis and urine electrolytes, and the liver was examined by ultrasound.

# Tissue samples

Two of the three transplant specimens were collected at the time of transplantation and preserved at the hospital, while the other transplant specimen was collected in recipient 1 followed up for 3.5 years after transplantation surgery. Renal biopsy tissue was obtained from a live healthy renal transplant-recipient and the sample was used as the healthy control (Figure 1A). The study details were explained to all the participants, and a signed informed consent was obtained after their agreement. Extraction of DNA was performed using the Axyprep<sup>™</sup> Blood Genomic DNA Miniprep Kit (Axyprep, USA) following the manufacturer's recommendations. DNA was eluted in approximately 100 µL of buffer AE. DNA integrity was checked on 1% agarose gel and purity were checked using the NanoPhotometer<sup>®</sup> spectrophotometer (IMPLEN, CA, USA). DNA was quantified using Oubit<sup>®</sup> DNA Assay Kit in Qubit<sup>®</sup> 2.0 Flurometer (Life Technologies, CA, USA).

# Library preparation and sequencing

A total of 700 ng DNA from each sample was used as the input material for the DNA library preparations. Sequencing libraries were generated using NEB Next® Ultra DNA Library Prep Kit for Illumina® (NEB, USA) following manufacturer's recommendations and index codes were added to attribute sequences to each sample. The NEB Next Adaptor with hairpin loop structure were ligated to 3' adenvlated DNA fragments to prepare for hybridization and electrophoresis was carried out to select DNA fragments of specified length. Subsequently, 3 µL USER Enzyme (NEB, USA) was used with size-selected DNA at 37 °C for 15 min and 95 °C 5 min before carrying out polymerase chain reaction (PCR). PCR was performed with Phusion High-Fidelity DNA polymerase, Universal PCR primers, and Index (X) Primer to enrich final adaptor modified fragmented sample. Finally, the library fragments were purified using AMPure XP system (Beckman Coulter, Beverly, USA). The clustering of the index-coded samples

#### Annals of Translational Medicine, Vol 8, No 6 March 2020



Figure 1 Clinical data of the patients. (A) We collected the implants transplanted into the two recipients immediately (S1 and S2) and followed for three and a half years post-transplantation (S3) and a healthy control (HC). Variation of serum creatinine (B) and uric acid (C) within years of follow-up in the two recipients.

was performed on a cBot Cluster Generation System using HiSeq 2500 PE Cluster Kit (Illumina) according to the manufacturer's instructions. After cluster generation, the library preparations were sequenced on an Illumina Hiseq 2500 platform.

## PCR amplification and sequence analysis

The genomic DNA was isolated from the transplant samples obtained from the recipients and live donors using the AxyprepTM Blood Genomic DNA Miniprep Kit (Axyprep, USA). Seven pairs of oligonucleotide

#### Page 4 of 10

Table 1 Laboratory data on admission

Biochemical date	Recipient 1	Recipient 2
Gender	Male	Female
Age (years)	41	37
Complete blood cell count		
WBC (×10 <sup>9</sup> /L)	7.6	6.3
Hemoglobin (g/dL)	118	83
Hematocrit (%)	35.7	26.7
Platelets (×10 <sup>9</sup> /L)	145	128
Serum chemistries		
Total protein (g/L)	87.6	-
Albumin (g/L)	50.7	45
BUN (mg/dL)	17.1	17.6
Cr (µmol/L)	1004	823
Uric acid (µmol/L)	378	431
Sodium (mmol/L)	137	132
Potassium (mmol/L)	4.97	3.7
Chloride (mmol/L)	97	89
Calcium (mmol/L)	2.75	2.5
Phosphorus (mmol/L)	2.29	1.6
Urinalysis		
рН	5.5	8.5
Specific gravity	1.014	1.008
Protein	++	++
Occult blood	+++	+++
WBC sediment (/HPF)	1–3	0–2

primers were generated to amplify the different regions obtained from DNA sequencing and were sequenced directly. A total of 80 ng of genomic DNA was amplified in 20  $\mu$ L reaction volume containing 10  $\mu$ L Premix Taq (TaKaRa) and 0.8  $\mu$ M primers. Amplification products were purified on 1.5% agarose gel using 0.5× TBE buffer and Wizard SV gel and Gel/PCR DNA Fragments Extraction Kit (Promega, USA). DNA sequencing was performed with an automated DNA sequencer (Applied Biosystems 3730-Avant Genetic Analyzer; Applied Biosystems, USA).

#### Teng et al. Irrelevant kidney transplantation and hypouricemia

#### RNA isolation and cDNA library construction

Total RNA was extracted from implants of two kidney transplant recipient using Trizol reagent (Invitrogen, USA), and RNase-free DNase I (TaKaRa, Japan) following the manufacturer's protocol. One was the healthy control and the other was recipient1 after three and a half years posttransplantation. A total of 1.5 µg of RNA per sample was used as input material for RNA sample reparations. The differentially expressed genes were detected using an Affymetrix Mouse Genome 430 2.0 microarray (Thermo Fisher Scientific). The experimental procedures for microarray were performed at the Hangzhou Tianke Corporation (Hangzhou, China). The clustering of the indexcoded samples was performed on a cBot Cluster Generation System using the TruSeq SR Cluster Kit v3-cBot-HS (Illumina) according to the manufacturer's instructions. After the cluster generation, the library preparations were sequenced on an Illumina HiSeq 2500 platform.

# **Results**

#### Clinical and biochemical investigations

On September 2012, a 41-year-old male (recipient 1) and a 37-year-old female (recipient 2) with end-stage renal disease caused by chronic kidney disease (CKD) received renal transplantation from a deceased donor who had died from craniocerebral injury. On admission, they had a serum creatinine of 1,004 and 823 µmol/L (Table 1). Recipient 1 had a gradually increased serum creatinine (S-Cr) level beginning in 2000 diagnosed as IgA nephritis and started on hemodialysis at the age of 34 years. Serum creatinine level gradually increased in recipient 2 for 8 years and she began hemodialysis at the age of 35 years. The donor was a 30-year-old male (serum creatinine: 79 µmol/L) with no significant past medical history (Figure 1A). Within the first week of transplant, the serum creatinine levels decreased to 76 and 49 µmol/L respectively (Figure 1B). In addition, their physical examination, laboratory examination and grafts biopsy at zero time were uneventful and they were released from the hospital after great recovery. Both of them received triple immunosuppressive therapy consisting of cortico-steroids, mycophenolate mofetil, and tacrolimus. Since then, the two recipients have reported fluctuating low serum UA levels (patient 1: 55-65 µmol/L, normal serum creatinine: 70-80 µmol/L; patient 2: 45-55 µmol/L, normal

serum creatinine 60–70 µmol/L) (*Figure 1C*). We confirmed a well-functioning kidney graft (serum creatinine 82 µmol/L, eGFR 102 mL/min and serum creatinine 60 µmol/L, eGFR 109 mL/min respectively) with no proteinuria or haematuria after three years the transplantation except for the high fraction excretion of UA (FEUA) of 44% and 75% (normal <10%) and UA clearance of 35.9 and 73.3 mL/min (normal 7.3–14.7 mL/min). We reviewed the results of preoperative laboratory examinations of donor and found that the donor had a very low serum UA of 48 µmol/L. Our findings suggested that the low serum UA in two recipients could be associated with HRH, and therefore, molecular genetic analysis was performed to confirm the same.

# UA transporter genes analysis

PCR followed by DNA sequence analysis revealed 7 types of mutations. Probands were heterozygous for the unpublished missense mutation p.Q141K(c.C421A) in exon 5 and p.Q126X(c.C376T) in exon 4 in the ABCG2 and heterozygous for the unidentified missense mutation p.R89H(c.G266A) and p.L181V(c.C541G) in exon 1 in the *SLC22A12* gene. Variants p.R89H and p.L181V are novel and have not yet been identified in *SLC22A12* gene. Moreover, the nature of these mutations appears pathogenic as per the PolyPhen software (http://genetics.bwh.harvard.edu/pph2/) indicates that substitutions in *SLC22A12* were probably damaging (score of 0.809; sensitivity 0.84; specificity 0.93 and score of 0.996; sensitivity 0.55; specificity 0.98, respectively).

Other variations, one homozygous exon variant (p.R294H) and one heterozygous exon variant (p.A100T) have been previously reported (*Figure 2, Table 2*).

# Gene expression analysis by RNA-sequencing (RNA-seq)

To study the effect of mutations on the gene expression, we analyzed the transcriptomes of the transplant tissues by RNA-seq (*Table S1*). Analysis of the RNA-seq data revealed that a total of 57 genes were differentially regulated among the hypouricemia patients and the healthy controls (fold change >2, P value <0.05). Out of 57 gene, 21 were upregulated, while 36 genes were down regulated. We used unsupervised clustering hierarchy (*Figure 3A*) and the details of the differentially expressed genes are given in *Table 3*. KEGG pathway analysis revealed that the differentially expressed genes were played roles in hematopoietic cell lineage, T cell receptor signaling pathway, and other important

regulatory processes (Figure 3B).

#### Relationship between gene mutation and expression levels

We tried to elucidate the relationship between SNPs, gene expression, and phenotypes together. Mutation analysis findings point towards epithelial growth factor (EGF) receptor (EGFR), IL-7 receptor (IL7R) and growth hormone receptor (GHR) which could implicate the important role in transcriptional regulation through cancer related pathways, MAPK signaling pathway, regulation of actin cytoskeleton cytokine-cytokine receptor interaction, hematopoietic cell lineage, and Jak-STAT signaling pathway to exert their influence on the phenotypes (*Table 3*).

#### Discussion

HRH, is defined arbitrarily as serum UA concentration less than 119 µmol/L and increased fractional excretion of uric acid (FEUA) and/or uric acid clearance (CUA), with exclusion of other diseases that present hypouricemia as a symptom (13). Loss-of-function mutations in the SLC22A12 gene coding the UA transporter 1 (URAT1) and SLC2A9 gene coding the glucose transporter (GLUT9) caused type 1 (RHUC1) and 2 (RHUC2), respectively. Most renal hypouricemia is caused by mutations in the SLC22A12 gene. The high incidence of RHUC1 has been reported in the Asia region and Roma ethnicity. The allele frequency of c.774G>A (p.W258X) and c.269G>A (p.R90H) were 2.37% and 0.40 % in SLC22A12 among Japanese and Koreans (14,15). Frequencies of the c.1245 1253del and c.1400C>T variants were present in the Roma population at 1.87% and 5.56%, respectively (16,17). Several GWAS have indicated a substantial association between urate concentration and SNPs at 10 genetic loci including transporter-coding genes such as SLC2A9 (GLUT9), ABCG2 (BCRP), SLC17A1 (NPT1), SLC17A3 (NPT4), SLC17A4 (provisionally named as NPT5), SLC22A11 (OAT4), SLC22A12 (URAT1), and SLC16A9 (MCT9) as well as urate transport related scaffolding protein PDZK1 (18). However, Hurba et al. (19) reported the non-synonymous allelic variants on of GLUT9 were not related to urate uptake activity. But several studies reported clear function impact of GLUT9 variants in patients with renal hypouricemia 2 (20-22). For example, Dinour et al. (23) reported that homozygous mutations of GLUT9 cause a total defect of UA absorption and are associated with a high incidence of renal calculus and EIAKI and nephrolithiasis. Previously, a successful



**Figure 2** Mutations found in implants (S1, S2, S3) with hereditary hypouricemia. (A) The homozygous mutation of SLC2A9-p.R294H (c.G881A) discovered in the implants (S1, S2, S3) and the healthy control had happened to find the heterozygous mutation as well; (B) the other mutations discovered in this study; (C) SLC22A12 p.R89H mutation is predicted to be possibly damaging with a score of 0.809 (sensitivity: 0.84; specificity: 0.93); p.L181V mutation is predicted to be probably damaging with a score of 0.996 (sensitivity: 0.55; specificity: 0.98).

living-related kidney transplant has been reported in HRH. Both the donor and the recipient had the same disorder of urate metabolism and were homozygous for G774A before kidney transplantation (10). Another rare case reported nephrocalcinosis in the distal tubules caused by HRH in a living-donor renal transplantation. Genetic analysis revealed a heterozygous nonsense mutation of C889T in exon 5 of the urate transporter 1 (*URAT1*) gene in both, the donor and the recipient (4). In this study, we present a rather rare case of donor-derived HRH. To the best of our knowledge, this is the first report to show that unrelated recipients can acquire unexpected hypouricemia after kidney transplantation from the same donor with a different genetic background.

DNA analysis was performed on the tissue before being transplanted into the two recipients. The cases and a control

#### Annals of Translational Medicine, Vol 8, No 6 March 2020

#### Page 7 of 10

**Table 2** Sequence variations of coding regions in candidate genes between the implants transplanted into the two recipients immediately (S1 and S2) and followed for three and a half years post-transplantation (S3) and a healthy control (HC)

Chr	Exon	SNP	Nucleotide change	Amino acid change	HC	S1	S2	S3	Gene	Previously reported
4	7	C>T	c.G881A	p.R294H	Heter	Homo	Homo	Homo	SLC2A9	Yes
4	5	G>T	c.C421A	p.Q141K	None	Heter	Heter	Heter	ABCG2	No
4	4	G>A	c.C376T	p.Q126X	None	Heter	Heter	Heter	ABCG2	No
6	3	C>T	c.G298A	p.A100T	None	Heter	Heter	Heter	SLC17A3	Yes
11	1	G>A	c.G266A	p.R89H	None	Heter	Heter	Heter	SLC22A12	No
11	1	C>G	c.C541G	p.L181V	None	Heter	Heter	Heter	SLC22A12	No
13	8	C>A	c.G912T	p.K304N	None	Heter	Heter	Heter	ABCC4	No

SNP, single nucleotide polymorphism.



**Figure 3** Screening for differentially expressed genes in hypouricemia. (A) The clustering of differential genes in heatmap. The color in the heatmap represents the log 2-fold change of expression values. Text on the right of heatmap indicates the enriched gene ontology terms for each cluster of genes; (B) top 30 pathways from Kyoto Encyclopedia of Genes and Genomes enrichment analysis. The x-axis represents KEGG enrichment scores and the y-axis represents pathway terms. The colors of circle indicate P values and the size of circle indicates the numbers of differential RNAs. The circle with redder and larger indicating that the enrichment of the pathway is higher and differential RNAs number is larger in the pathway.

Gene	SNP ID	Chr	Risk allele	Possible pathway
EGFR	rs62452902	7	A	Pathways in cancer
				MAPK signaling pathway
				Regulation of actin cytoskeleton
				Cytokine-cytokine receptor interaction
IL7R	rs10058453	5	Т	Hematopoietic cell lineage
				Jak-STAT signaling pathway
				Cytokine-cytokine receptor interaction
GHR	rs4146624	5	А	Jak-STAT signaling pathway
				Cytokine-cytokine receptor interaction

Table 3 Other SNP sites found in transplants and possible pathways

SNP, single nucleotide polymorphism; GHR, growth hormone receptor.

were followed for 3.5 years post-transplantation. Our results showed that the mutated genes in the grafts of the donor remained unchanged after transplantation in a different un-URH environment up to the follow-up duration of 3.5 years. Many non-pathogenic single point mutations identified in the present study have been reported earlier and included the homozygous missense mutation, p.R294H in SLC2A9 in exon 7 (24) and a heterozygous sequence variant, p.A100T in SLC17A3 in exon 3 (25). We could not confirm the nosogenetic mutations from the family of the deceased donor. Therefore, the effect of previously unreported mutations on the hypouricemia remains unknown and needs to be answered in future. Genetic variants have been associated with many human diseases. However, about 88% of the GWAS-nominated SNPs are in intronic or intergenic regions suggesting that the noncoding regions of the genome can contribute to the disease risk, and may be involved in gene regulation. However, the underlying mechanism by remains unclear (26). SNPs can modulate the gene expression through a change in chromatic structure to distance a gene from its enhancers and by altering the copy number (27). Within each susceptibility locus, candidate risk genes have been prioritized based largely on bioinformatic evaluations of the relationships among genes, the presence of coding SNPs, or the gene expression-genotype correlations (28-30). Regulatory and coding variants often modify the functional impact of each other that can be detected by the sequencing data. Characterizing these mutual effects might help us understand functional mechanisms behind genetic associations to human phenotypes (31). For example mutational signatures related to liver carcinogenesis revealed frequently mutated coding and noncoding regions, such as long intergenic noncoding RNA genes (NEAT1 and MALAT1), promoters, CTCF-binding sites, and regulatory regions (32). Biswajit et al. unveiled rs2279590 at PTK2B-CLU locus, a risk factor previously associated with Alzheimer's disease, to have an enhancer effect on two nearby genes coding for protein tyrosine kinase 2 beta (PTK2B) and epoxide hydrolase-2 (EPHX2) (33). Based on these results, we speculate that defects in DNA sequences could probably affect tubule function through differential RNA expression. DNA mutation analysis have identified three risk loci that increase renal hypouricemia risk: (I) SNP (rs62452902) at EGFR locus, (II) SNP (rs10058453) at IL7R locus, (III) SNP (rs4146624) at GHR. We performed enrichment analysis from the data of the differentially expressed genes and identified that pathways related to cancers, MAPK signaling, regulation of actin cytoskeleton, cytokine-cytokine receptor interaction, hematopoietic cell lineage, and Jak-STAT signaling were significantly altered in hypouricemia transplant tissue, indicating that these pathway may be involved in the disease. EGF risk alleles may upregulate pathways related to cancer, MAPK signaling, alter actin cytoskeleton, and cytokine-cytokine receptor interactions to promote elevated blood UA by impacting UA metabolism and inhibiting UA excretion. Though our study presents interesting findings, its limitations include small number of cases and therefore requirement of further work to validate this work.

Teng et al. Irrelevant kidney transplantation and hypouricemia

### Conclusions

We report a renal transplantation case of donor-derived

#### Annals of Translational Medicine, Vol 8, No 6 March 2020

hypouricemia caused by mutations in the transplant tissue of donor with HRH. Seven kinds of potent mutations were discovered in this case, including two novel mutations which could be pathogenic in nature. However, further studies are needed to prove the role of these mutations in HRH pathogenicity.

# **Acknowledgments**

*Funding:* This study was supported by the National Natural Science Foundation of China (No. 81970647).

# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study details were explained to all the participants, and a signed informed consent was obtained after their agreement.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

## References

- Stiburkova B, Sebesta I, Ichida K, et al. Novel allelic variants and evidence for a prevalent mutation in URAT1 causing renal hypouricemia: biochemical, genetics and functional analysis. Eur J Hum Genet 2013;21:1067-73.
- Ichida K, Hosoyamada M, Hisatome I, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. J Am Soc Nephrol 2004;15:164-73.
- Ochi A, Takei T, Ichikawa A, et al. A case of acute renal failure after exercise with renal hypouricemia demonstrated compound heterozygous mutations of uric acid transporter 1. Clin Exp Nephrol 2012;16:316-9.

- Okabayashi Y, Yamamoto I, Komatsuzaki Y, et al. Rare case of nephrocalcinosis in the distal tubules caused by hereditary renal hypouricaemia 3 months after kidney transplantation. Nephrology (Carlton) 2016;21 Suppl 1:67-71.
- Sebesta I, Stiburkova B, Bartl J, et al. Diagnostic tests for primary renal hypouricemia. Nucleosides Nucleotides Nucleic Acids 2011;30:1112-6.
- 6. Shen H, Feng C, Jin X, et al. Recurrent exercise-induced acute kidney injury by idiopathic renal hypouricemia with a novel mutation in the SLC2A9 gene and literature review. BMC Pediatr 2014;14:73.
- 7. Hisatome I, Ogino K, Kotake H, et al. Cause of persistent hypouricemia in outpatients. Nephron 1989;51:13-6.
- Takahashi T, Tsuchida S, Oyamada T, et al. Recurrent URAT1 gene mutations and prevalence of renal hypouricemia in Japanese. Pediatr Nephrol 2005;20:576-8.
- Wakasugi M, Kazama JJ, Narita I, et al. Association between hypouricemia and reduced kidney function: a cross-sectional population-based study in Japan. Am J Nephrol 2015;41:138-46.
- Yamamoto I, Yamamoto H, Ichida K, et al. Successful living-related kidney transplantation in hereditary renal hypouricaemia. Nephrol Dial Transplant 2006;21:2041.
- Enomoto A, Kimura H, Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 2002;417:447-52.
- Dehghan A, Köttgen A, Yang Q, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet 2008;372:1953-61.
- Nakayama A, Matsuo H, Ohtahara A, et al. Clinical practice guideline for renal hypouricemia (1st edition). Hum Cell 2019;32:83-7.
- Iwai N, Mino Y, Hosoyamada M, et al. A high prevalence of renal hypouricemia caused by inactive SLC22A12 in Japanese. Kidney Int 2004;66:935-44.
- Cheong HI, Kang JH, Lee JH, et al. Mutational analysis of idiopathic renal hypouricemia in Korea. Pediatr Nephrol 2005;20:886-90.
- Stiburkova B, Gabrikova D, Čepek P, et al. Prevalence of URAT1 allelic variants in the Roma population. Nucleosides Nucleotides Nucleic Acids 2016;35:529-35.
- Gabrikova D, Bernasovska J, Sokolova J, et al. High frequency of SLC22A12 variants causing renal hypouricemia 1 in the Czech and Slovak Roma population; simple and rapid detection method by allele-specific polymerase chain reaction. Urolithiasis 2015;43:441-5.
- 18. Anzai N, Jutabha P, Amonpatumrat-Takahashi S, et al.

#### Teng et al. Irrelevant kidney transplantation and hypouricemia

#### Page 10 of 10

Recent advances in renal urate transport: characterization of candidate transporters indicated by genome-wide association studies. Clin Exp Nephrol 2012;16:89-95.

- Hurba O, Mancikova A, Krylov V, et al. Complex analysis of urate transporters SLC2A9, SLC22A12 and functional characterization of non-synonymous allelic variants of GLUT9 in the Czech population: no evidence of effect on hyperuricemia and gout. PLoS One 2014;9:e107902.
- Dinour D, Gray NK, Ganon L, et al. Two novel homozygous SLC2A9 mutations cause renal hypouricemia type 2. Nephrol Dial Transplant 2012;27:1035-41.
- 21. Matsuo H, Chiba T, Nagamori S, et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. Am J Hum Genet 2008;83:744-51.
- Ruiz A, Gautschi I, Schild L, et al. Human Mutations in SLC2A9 (Glut9) Affect Transport Capacity for Urate. Front Physiol 2018;9:476.
- 23. Dinour D, Gray NK, Campbell S, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. J Am Soc Nephrol 2010;21: 64-72.
- 24. Stiburkova B, Taylor J, Marinaki AM, et al. Acute kidney injury in two children caused by renal hypouricaemia type 2. Pediatr Nephrol 2012;27:1411-5.
- Stiburkova B, Ichida K, Sebesta I. Novel homozygous insertion in SLC2A9 gene caused renal hypouricemia. Mol Genet Metab 2011;102:430-5.
- 26. Hindorff LA, Sethupathy P, Junkins HA, et al. Potential etiologic and functional implications of genome-wide

**Cite this article as:** Teng L, Zhang Y, Ye L, Lv J, Mao Y, Schneider R, Chen J, Jiang H, Wu J. Donor-derived hypouricemia in irrelevant recipients caused by kidney transplantation. Ann Transl Med 2020;8(6):330. doi: 10.21037/ atm.2020.02.140

association loci for human diseases and traits. Proc Natl Acad Sci U S A 2009;106:9362-7.

- 27. Weischenfeldt J, Symmons O, Spitz F, et al. Phenotypic impact of genomic structural variation: insights from and for human disease. Nat Rev Genet 2013;14:125-38.
- Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119-24.
- Anderson CA, Boucher G, Lees CW, et al. Metaanalysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet 2011;43:246-52.
- Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40:955-62.
- Lappalainen T, Montgomery SB, Nica AC, et al. Epistatic selection between coding and regulatory variation in human evolution and disease. Am J Hum Genet 2011;89:459-63.
- Fujimoto A, Furuta M, Totoki Y, et al. Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. Nat Genet 2016;48:500-9.
- 33. Padhy B, Hayat B, Nanda GG, et al. Pseudoexfoliation and Alzheimer's associated CLU risk variant, rs2279590, lies within an enhancer element and regulates CLU, EPHX2 and PTK2B gene expression. Hum Mol Genet 2017;26:4519-29.

# Supplementary

# ${\bf Table \ S1} \ {\bf The \ value \ of \ differentially \ expressed \ genes \ in \ hypouricemia}$

Arth9.19800.958750.768750	Gene symbol	Value control	Value renal hypouricemia	log2 (fold change)	P value	Biological process
PTPNESPATePERPSPERPSPERPSPERPSSTOM4.3981377.84.49870.0214Dividia to mesor fund elicity inguinarySTOM4.3981377.84.49810.0374Dividia to mesor fund elicity inguinarySTOM2.91344.4684.41980.0374Dividia to mesor fund elicity status inguinaryCRT21.7234.45844.60900.0374Dividia to mesor fund elicity status inguinaryCRT21.7234.45844.60900.0374Dividia to mesor fund elicity inguinaryMAC4.73074.6497-0.4697Dividia to mesor fund elicity inguinaryMAC4.73074.6497-0.4697Dividia to mesor fund elicity inguinaryMAC4.70374.6497-0.4697Dividia to mesor fund elicity inguinaryMAC4.70374.6497-0.4697Dividia to mesor fund elicity inguinaryMAC4.70471.564-0.6774Dividia to mesor fund elicity inguinaryMAC4.70471.564-0.6774Dividia to mesor fund elicity inguinaryMAC1.512-0.6774Dividia to mesor fund elicity inguinaryMAC1.512-1.512Dividia to mesor fund elicity inguinaryMAC1.512-1.512Dividia to mesor fund elicity inguinaryMAC1.512-1.512Dividia to mesor fund elicity inguinaryMAC1.512Dividia to mesor fund elicity inguinaryMAC1.512Dividia to mesor fund elicity inguinaryMAC1.512Divi	AK4	80.8162	0.391208	-7.69057	0.043357	ATP metabolic process
ChiChiChiDescional conception instruction status algoing pathwayMCH197401.1284-1.68640.0074Mich conception instruction status algoing instruction coll cycle andMCT1.12900.0384-1.68040.0174Mich conception instruction coll cycle andMCT1.12900.0384-1.68040.01744Mich conception and the cycle	PTPRC	3.75744	767.974	7.67517	0.015972	Immunoglobulin biosynthetic process
SNMCS1572S. 502S. 502Planial to maxed prival to summaking to sub sub sumskame resurg and optical meansLPT2.001444.08A. 001001.51 mediate terms/LPT1.00555.0014A. 50201.00100Regulars resords, sub to nuclear the sub sub servation and optical mediate terms/LPT1.00550.00294-7.20170.00100Regulars regular sub to to presso the presso terms busine to presso the presso terms busine to presso terms busine to presso terms busine to presso terms busineSNAC0.00294-0.00294-0.00294Regulars regular sub to to presso terms busineSNAC0.0017-0.0017-0.0100Regulars regular sub to to presso terms busineSNAC0.0017-0.0117-0.0100Regulars regular sub to presso terms busineSNAC0.0017-0.0117-0.0110Regulars regular sub to presso terms busineSNAC0.0017-0.0117-0.0110Regulars regular sub to presso terms busine terms busineSNAC0.00171.0027Regulars regular to regular sub to presso terms busine termsSNAC0.00171.0027Regulars regular to regular sub to presso terms busineSNAC0.00171.0027Regulars regular to regular sub to presso terms busineSNAC0.00171.0027Regulars regular to regular to regular sub to presso terms busineSNAC0.00171.0027Regulars regular to regular t	CR1	1.03823	38.5892	5.21599	0.043357	Complement receptor mediated signaling pathway
MACT11/24011/2441.00//140Not angle response, signit conduction by skip dia as media transpin to exploye angleCUT1.73045.6466.200Not angleNot angle response, signit conduction by skip dia as media transpin to exploye angleCUT1.73045.6406.200Not angle response by lance started to angle response by lance	S100A4	43.3991	3757.78	6.43607	0.027141	Epithelial to mesenchymal transition
List2.64544.46894.46890.0858Tail mediae immunip.159.0021.03050.53390.53390.03599Magadam regulator of a patiencia159.0021.03050.25390.6359Magadam regulator of a patiencia169.1022.8470.4407-0.42070.0459Magadam regulator of a patiencia176.1020.86310.6407-0.42070.0459Magadam regulator of a patiencia176.1020.86110.6407Magadam regulator of a patienciaMagadam regulator of a patiencia176.1020.64070.6407Magadam regulator of a patienciaMagadam regulator of a patiencia176.1020.64070.6407Magadam regulator of a patienciaMagadam regulator of a patiencia176.1020.74170.6407Magadam regulator of a patienciaMagadam regulator of a patiencia176.1020.74170.6407Magadam regulator of a patienciaMagadam regulator of a patiencia176.1020.74170.64370.0774Magadam regulator of a patiencia176.1020.74170.74380.0774Magadam regulator of a patiencia176.1020.74170.74370.0724Magadam regulator of a patiencia176.1020.74170.74370.0724Magadam regulator of a patiencia176.1020.7410.74370.0724Magadam regulator of a patiencia176.1020.74170.74440.0724Magadam regulator of a patiencia176.1020.74170.74570.7457Magadam regulator	MUC1	137.403	1.12964	-6.92641	0.007747	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
Ch.T.2No.2	LYST	2.09134	44.666	4.41668	0.018538	T cell mediated immunity
TistANC1.20060.2007-0.40070.4	CELF2	1.17293	89.9344	6.26068	0.007747	RNA processing
MAVEC. 1002C. 1003C. 1003C. 1004Monical protein starting home appress home	TSPAN32	1.03685	50.396	5.60303	0.035989	Negative regulation of cell proliferation
Cirules2.4376.4036.4047-7.40570.4048Mediadis procesKOV6.36410.40477-4.20740.4048Mediadis procesMediaKOV1.40471.9549-6.2080.4049Mediadis procesMediadis procesSLCAV1.40471.9549-6.208Mediadis procesMediadis procesMediadis processional process	NAV2	6.79902	0.032998	-7.68679	0.018538	Regulation of systemic arterial blood pressure by baroreceptor feedback
SINGSINGDistrictDistrictDistrictConstructSICAL1054110543AD0402740Konsy designing metaple signing analysis,SICAL1.111211134AD141DistrictConstructSICAL1.111211134AD141DistrictDistrictAD4041.0114AD141DistrictDistrictSingian metaple signing analysis,TA4.014AD142DistrictDistrictDistrictSICALAD141AD143DistrictDistrictDistrictSICALAD142AD143DistrictDistrictDistrictSICALAD142AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD144AD143AD143DistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD143AD143DistrictDistrictDistrictSICALAD144AD143DistrictDistrictDistrictSICALAD144AD143Distr	C11orf54	243.97	5.42007	-5.49225	0.048447	Metabolic process
KNUSinthOxfordOxfordGordGordGordMuchally conjuned designedSLCAT14.14214.164A.1640A.0358Pattern scoprint needor signaling pathwayAMGAU2.00414.178A.1640A.0374Pattern scoprint needor signaling pathwayAMGAU3.178A.1630A.0374Pattern scoprint needor signaling pathwayNDR3.178A.1630A.0374Pattern scoprint needor signaling pathwaySLGAARA.1781A.1630A.0374Pattern scoprint needor signaling pathwaySLGAARA.1781A.1631A.0374Pattern scoprint needor signaling pathwayMAC4.868A.2481A.1781A.0374Pattern scoprint needor signaling pathwayMAGA4.868A.2481A.1781A.0374Pattern scoprint needor signaling pathwayMAGA4.868A.2481A.2481A.0471Pattern scoprint needor signaling pathwayMAGAA.1691A.1692A.1692A.1792Pattern scoprint needor signaling pathwayMAGAA.1692A.2481A.0493A.0471Intern scoprint needor signaling pathwayMAGAA.1692A.1692A.1692A.1692A.1692MAGAA.1692A.1692A.1692A.1692A.1692MAGAA.1692A.1692A.1692A.1692A.1692MAGAA.1692A.1692A.1692A.1692A.1692MAGAA.1692A.1692A.1692A.1692A.1692MAGAA.1	STK33	3.86033	0.047077	-6.35757	0.044526	Protein autophosphorylation
SLC2AV1,40071,5001,50700,5070Mites magnation developmentCLE/AV1,419211,1941,41970,00774Sind gapas mediated sign handlationTAA1,61740,11820,10740,00774Sind gapas mediated sign handlationTAA0,71340,11820,40370,00774Peaker sequition orgation incident signing pathwaySLCA/AV27,50471,82550,53510,0077Peaker sequition of relation patheticsNAGC1,84670,24570,54720,0077Peaker sequition of relations patheticsNAGC1,84670,54720,54720,0070Peaker sequition of edi gavaNAGCA1,84670,54760,0070NAGCA1,84670,74740,47420,0070-NAGCA0,41720,74740,47430,0070-NAGCA0,41820,9071-1,51840,0074-NAGCA0,41920,9072-1,51840,0074-NAGCA0,41920,9072-1,51840,0074-NAGCA0,41920,9072-1,51840,0074-NAGCA0,41920,9072-1,51840,0074-NAGCA0,41920,9072-1,51840,0074-NAGCA0,41920,40130,40140,40140,4014NAGCA0,4190,41930,40140,4014-NAGCA0,4290,40140,40140,4014-NAGCA <td< td=""><td>KCNJ1</td><td>53.6641</td><td>0.363949</td><td>-7.20408</td><td>0.027141</td><td>Kidney development</td></td<>	KCNJ1	53.6641	0.363949	-7.20408	0.027141	Kidney development
CLECK1.14121.14181.71810.50399Form cognitor necopir agring nativagating pathwayARHGAP90.50391.417806.14070.5037Sinal agrina intraductionARHGAP1.51316.75846.14030.0077-NARG20.75971.2825-5.53730.0077Pathia complication of syckine packationNARG30.84440.24360.53730.0077Pathia complication of syckine packationNARG40.48860.23850.53730.0077Pathia complication of syckine packationNARG50.84840.74790.54080.0077-NARG40.54190.54080.0077-NARG50.54130.5028NARG50.54130.5029NARG50.54140.54180.0101-NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG51.54190.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG50.54140.5419NARG5<	SLC2A14	1.40047	136.596	6.60786	0.028838	Multicellular organismal development
AMMAC2.00441.01490.01774Montpace mediate signal transductionTMA16.0150.0150Magite equidion of cybine productionSICAMO75.0471.0250-4.20310.01374Magite equidion of cybine productionSICAMO75.0471.0250-6.30730.00774Potros regulation of type larterform-stated signal gatiney attemptFMAC4.8800.2325-6.5730.0124Potros regulation of type larterform-stated signal gatiney attemptFMAC4.8800.2325-6.5730.0124Potros regulation of type larterform-stated signal gatiney attemptFMAC4.8800.2417Potros regulation of type larterform-stated signal gatiney attemptPotros regulation of type larterform-stated signal gatiney attemptFMAC4.8800.6418-0.0174Potros regulation of type larterform-stated signal gatiney attempt74762-040.4847-0.6419-0.0174Potros regulation of type larterform-stated signal gatiney attempt74762-050.4443-0.6419-0.0174Potros regulation of two regulation process74762-050.4443-0.6419-0.0174Potros regulation of two regulation process74762-050.4419-0.4418-0.0174Potros regulation of two regulati	CLEC7A	1.14152	181.946	7.31641	0.035989	Pattern recognition receptor signaling pathway
TAA18.17318.19831.9.19830.07777-NDR025.71393.1828-1.42350.00777Nepate regulation clyckine productionNLCG3.8441.4255-3.31730.00777Pater complex samerbyNLCG3.8443.42413.73730.00777Pater complex samerbyNLCG1.84570.20380.00777Pater complex samerbyNLCG1.84790.20380.00777Pater complex samerbyNLCG1.84710.81070.01610.01719Pater complex samerbyNLCG1.84710.81070.01719Pater complex samerbyNLCG0.81920.9040-2.33570.0171Imma regorseNLCG0.81420.02030.02719Pater complex samerbyNLCG0.34440.20390.02719Pater complex samerbyNLCG0.34440.20390.02719Pater complex samerbyNLCG0.34440.20390.02719Pater complex samerbyNLCG0.34440.42390.0241Imma regorseNLCG0.22490.02041.43010.0077Pater complex samerbyNLCG0.41430.42410.0139Pater complex samerbyNLCG0.41430.42410.0141Pater complex samerbyNLCG0.41430.41410.0174Pater complex samerbyNLCG0.11250.11250.0174Pater complex samerbyNLCG0.11250.11250.0174Pater complex samerby <td>ARHGAP9</td> <td>2.00949</td> <td>141.798</td> <td>6.14087</td> <td>0.007747</td> <td>Small gtpase mediated signal transduction</td>	ARHGAP9	2.00949	141.798	6.14087	0.007747	Small gtpase mediated signal transduction
NPR626.7.5876.1.8255-1.4.20310.40337Poster complex security8.6.04.0471.8.255-5.3.6130.00774Poster complex securityNMC60.84846.3.6431-0.5.7.530.01294Poster complex securityNMC74.88692.6.3.570.01294Orderal diry sylashedin organizationNMC81.6.9576.9.17.76.9.17.9Poster complexityNMC81.6.9576.9.17.10.01294Poster complexityNMC800.61510.00401-0.02001-NMC800.61520.00401-0.02001-NMC800.21630.01214Poster complexity-NMC800.61520.00401-0.02001-NMC800.61520.00401NMC800.22080.80610.02071-NMC800.4163-0.01710.00401-NMC801.61730.1629-0.0171-NMC801.61730.1629-0.0171-NMC801.61730.1629-0.0171-NMC801.61730.1629-0.0171-NMC801.61730.1629-0.0171-NMC801.61730.1629-0.0171-NMC901.61730.1629-0.0171-NMC901.61730.1629-0.0171-NMC901.61730.1629-0.0174-NMC901.61730.1629-0.0140-NMC90 <td< td=""><td>TRA</td><td>18.6176</td><td>679.856</td><td>5.19049</td><td>0.007747</td><td>-</td></td<>	TRA	18.6176	679.856	5.19049	0.007747	-
SicA3677.50877.50877.50870.00774Pedia complix asamilyNRAC3.849456.4915.71850.00747Pedia regulation of type 1 interform-mediatal signaling pathwayNRAC2.19796.71975.47590.02808Pequation of coll growthNRAC3.19716.81070.5108Pequation of coll growthNRAC6.19716.81075.10880.02171Peruis regulation of cocytosis2.78720.81020.78846.20280.021741Immune response2.78720.814210.0000-3.20570.021741Immune response2.78720.814210.0000-3.20570.021741Immune response2.78720.814210.0000-3.20570.00774Adapter immune responseNRAD0.22282.800.415.402140.03038Immune responseNRAD0.127300.16729-1.13010.00774Adapter immune responseNRAD1.61735.1328-4.71350.03048PerusNRAD1.61735.1328-4.71350.03048PerusNRAD1.61735.1328-4.71350.03049PerusNRAD1.61931.61930.04049PerusPerusNRAD1.61930.61930.04049PerusPerusNRAD1.61930.04140.64049PerusPerusNRAD1.61930.04150.64049PerusPerusNRAD1.61930.04150.64049Per	NDRG2	63.7139	3.18928	-4.32031	0.043357	Negative regulation of cytokine production
N.R.GS3.88445.4.4313.7.530.007747Peable regulation of regulation regulation insplantationP.M.C4.88922.0.5236.0.7530.00124Ordinal antin splosehead on signalizationU.NC1301.64675.8.14475.1.40680.02179Peable regulation of exceptasisU.NC1306.8.15210.0.64670.0.2170Peable regulation of exceptasisU.NC1300.5.15410.0.6460U.NC1300.5.15410.0.6400U.NC2010.5.15410.0.6400U.NC2010.5.15410.0.6400U.NC2010.2.24440.9.6910U.NC2010.2.24410.9.6910U.NC2012.7.34515.2.6.517.5.570.00774Nagabe immune responseU.U71A042.7.490.6.2782U.U71A15.1.2269U.U71A15.1.226U.U71A21.4.6424.0.133U.U71A31.4.623U.U71A41.4.6424.0.133U.U71A41.4.6424.0.133U.U71A41.4.6424.0.133U.U71A41.4.6424.0.133U.U71A41.4.6424.0.133U.U71A1.4.6424.0.133	SLC9A3R2	75.0647	1.82555	-5.36173	0.007747	Protein complex assembly
HM.1488828385.730.1224Critica cita rycolacietan organizationTMC2.19399.7975.47600.0559Replation of cal growhTMCR0.4816.14876.14870.0207Replation of cal growhTMCR0.4816.14970.20270.0218Immun regione citaguiant of exclosionTMR0.4810.54840.20300.22370.0217Immun regione citaguiant of exclosionDMR00.24480.24086.20320.0217Immun regioneDMR00.24480.50400.4182Immun regioneDMR00.22380.60210.4182Immun regioneDMR00.23480.50317.5010.00747Replation of errorisDMR00.23480.50310.50140.00747Replation of errorisDGR10.23480.40230.47180.0304Pasalition intraneo regioneDGR10.45490.41320.40140.0014Pasalition of errorisDGR10.54590.12620.15230.0014Pasalition of errorisDGR21.14920.40140.0014Pasalition of errorisDGR21.14920.40140.0014Pasalition of errorisDGR31.14920.41330.0014Pasalition of errorisDGR41.14920.41330.0014Pasalition of errorisDGR41.14920.41340.0014Pasalition of errorisDGR41.14920.00140.0014Pasalition of errorisDGR40	NLRC5	3.88494	53.4241	3.78153	0.007747	Positive regulation of type I interferon-mediated signaling pathway
TMG22197399.77975.479200.03598Regulation of cell growthUMC1301.64930.514910.514080.021719Politer engulation of encogolisTMC6E-ASI0.515210.60406-3.23570.02714Imman response2878700.515210.00405-3.23570.02714Imman responseVMC800.244040.67002-4.54040.07074-VMR900.22032.600.40.542140.03038Immanory responseVLR9100.22032.600.47.5870.00774Algebre imune responseVLR9110.51320.520.57.5870.00747Maghre imune responseVLR9120.41315.1326-7.5870.00747Maghre imune responseVLR9141.41320.42030.4038-0.00408-VLR9140.41324.40380.00408VLR9140.4132-3.94180.00408VLR9140.5132-3.94180.00408VLR9140.5132-3.94180.00408VLR9140.5132-3.94180.00402Poltacium in transportVLR9140.5132-0.0143-3.94180.00402Poltacium in transportVLR9140.5132-3.94180.00402Poltacium in transportVLR9140.5132-3.94180.00402Poltacium in transportVLR9140.52320.0143-3.94180.00402Poltacium into Hole Acidation in transport </td <td>FMNL1</td> <td>4.68808</td> <td>223.525</td> <td>5.5753</td> <td>0.012214</td> <td>Cortical actin cytoskeleton organization</td>	FMNL1	4.68808	223.525	5.5753	0.012214	Cortical actin cytoskeleton organization
LNC13D1.48875.4.4845.4.1980.02170Poather regulation of exceptatisTNRC6A2N8.19216.7.4443.4.21750.03020-ZH77C0.515100.94040-2.4.5900.00774Imume responseKNR20L0.44440.7012-4.51640.04181-LNRS2.7.3452.6.00.1-4.51640.04181-KNR301.2.3252.6.00.1-5.51640.04181-LNRS2.7.3452.6.00.1-7.517Naghve regulation of steroid metabolic processUGT144.7.3030.10278-1.1.3010.00747Naghve regulation of steroid metabolic processUGT451.4.4924.0.312-4.7.1730.00084Polatiskim in transportGR2A511.4.4924.0.313-4.9.1730.00184Regulation of intransport processGR70.51821.5.128-3.9.5180.01012Adonien catabolic processGR70.51821.5.1284.91560.01021Adonien catabolic processGR70.51820.1053-5.54140.04182Regulation of Mach signaling pathwayGR70.14290.60695-7.90160.04357Cell growth incole catabolicationGR70.14290.60695-7.90160.04357Cell growth incole catabolicationGR70.14290.60695-7.90160.03747Cell growth incole catabolicationGR70.52924.6119-5.66460.03740Homphilocial adhesion ring bagen mediated ging at Tinsduction <td>TMC8</td> <td>2.19739</td> <td>97.797</td> <td>5.47592</td> <td>0.035989</td> <td>Regulation of cell growth</td>	TMC8	2.19739	97.797	5.47592	0.035989	Regulation of cell growth
NNCRC-ASI8.197219.784489.3421730.032078-ZBTB20.6814910.000405-3.238570.02714Immune responseNKRDL0.3444342.0400.03012-DKKN22.41400.97012-4.51840.01420-NKRDL62.20028.00.485.422140.03024Infarmatory sponseULRB362.20028.00.485.422140.03024Infarmatory sponseULRB442.9030.027877.00774Negative regulation of stexici metabolic processKCM/r14.01735.1269-4.71360.03024Patasium in transportKCM/r14.01735.1269-4.71360.03024Patasium in transportKCM/r16.012211.328-4.91480.04024Regulation of immune system processCEGR15.132211.328-4.91580.04024Activation of embrace splating pathwaySOR8212.1650.05085-7.90150.04337Cell growth involved in calific schartate adhesionSOR8212.1650.05085-7.90150.03747Regulation of MbA-S signaling pathwaySOR9212.1650.05085-7.90150.03747Regulation of MbA-S signaling pathwaySOR9212.1650.05085-7.90150.07747Regulation of MbA-S signaling pathwaySOR9212.1650.05085-7.90150.07747Regulation of Indico calify a signaling pathwaySOR9212.1650.05085-7.16470.07747Regulation of Indico calify	UNC13D	1.64857	58.1647	5.14086	0.021719	Positive regulation of exocytosis
Z8787C0.8918210.090406-3.23570.027141Immune responseKR2D20.3444362.60020.00747-DMKN2.241400.76012-4.514640.04182-LR8D362.2006280.047.58570.00747Kalpitvi immune responseLLR832.7345152.00517.58570.00747Kalpitvi immune responseUGT/A42.0030.162788-11.36010.00747Kalpitvi immune responseUGT/A1.464224.0133-1.000044Polesium in transport17632-AS11.464224.01334.005880.03048-0GT120.56513.256-3.56140.04121Regulation of encidental process0GT120.56520.0163-3.65410.04024Politve regulation of encidental chasion0GT83.14293.68410.34530.00276Politve regulation of DNA-5 signaling pathway0GT81.18600.57320.6453Politve regulation of DNA-5 signaling pathway0GT81.18615.69321.57520.6453Politve regulation of DNA-5 signaling pathway0GT81.18615.6932-3.66460.03749Relation of enail of transit chasion0GT80.027495.894210.00774Nelation of enail of transit chasion0GT80.028481.18600.02749Nelation of enail of transit chasion0GT80.02941-3.69460.03749Nelation of enail of transit chasion0GT80.029510.02741Nelati	TNRC6C-AS1	8.19721	87.8446	3.42175	0.032078	-
KR2DL30.3444325.4080.623280.007747-DMKN22.4140.076012-1.51840.04182-MKRB62.22082800.485.402140.04180Infammatory responseURB32.73845260.617.58770.00777Adaptive immune responseUGT1/48427.9030.16278-1.13610.007747Maptive immune responseUGT1/4814.01735.1289-4.71350.00364Potastime in transportIFGB2-AS71.64923.1429-4.01350.00142Regulation of istenid metabolic processGGT1205.4661.326-4.91560.04091Regulation of immune system processCECR15.0192151.3284.91560.04091Regulation of Immune system processCECR15.01920.01453-5.90410.04045Positive regulation of Moh-5 signaling pathwayDX6603.75920.01453-6.9152O.04358Cell growth involved in cardiac muscle cell developmentL7740.829865.26026.15720.04358Cell growth involved in cardiac muscle cell developmentL7740.829865.26026.15720.04452Regulation of Moh-cost patientionFGD22.798166.51854.557430.01747Regulation of shord signal membrane adhesion moleculesFG22.798166.51854.557430.01747Regulation of shord indisionFG22.798166.51854.557430.00774Cill metabolic proces/metabolic proces/metabolic proces/meta	ZBTB7C	0.851521	0.090405	-3.23557	0.027141	Immune response
DMKN22.41490.78012-4.518400.04182-NKBD6.22062800.446.42140.3003Inflamatory responseLLRB32.73945326.0517.6800.007747Adative imune responseUGTA4427.9030.062786-11.3010.00767Megaluk regulation of stenid metabolic processKCNJ514.01735.13269-4.771350.03062Potassum ion transportITGB2-AS11.44624.0.91334.803690.03062-GGT125.465.01453-4.81560.04182Regulation of imune system processGGT45.0139215.128.0.49163Adenosire catabolic processAB/B6P5.27652.0.01453-8.504410.04645Positive regulation of CA-5 signaling pathwayDX603.142936.694.5.6532.0.04355Positive regulation of DNA-5 signaling pathwaySORB212.1655.0.056095.7.90105.0.007347Steletal system developmentIC7A0.82966.5.2522.6.1572.0.00747Steletal system developmentVCAN1.1801.57360.6.3733.0.00747Negaluk regulation of Imploycy poliferationVGAN.0.25951.6.56722.6.1574.0.00747Negaluk regulation of Imploycy poliferationVGAN.0.35818.1.3568.4.56733.0.00747Negaluk regulation of Imployce to regulation of Imploymerase Il promoter <tr< td=""><td>KIR2DL3</td><td>0.344843</td><td>25.4095</td><td>6.20328</td><td>0.007747</td><td>-</td></tr<>	KIR2DL3	0.344843	25.4095	6.20328	0.007747	-
NF6BD62208280.485.492140.03438Inflammatory responseLLRB32.73945526.0517.5670.00774Agative impulation of steriol immetable processUGT1A47.0300.16278-1.13010.00744Negative regulation of steriol imetabolic processIGR2-AS11.464240.91334.40360.03408-GGT1205.46513.256-3.954180.041821Regulation of immune system processGGT15.0192151.324.91650.04092Access catabolic processDGK03.14298.66440.54380.03307Positive regulation of AD-5 signaling pathwaySOR5212.16550.050965-7.901050.043357Cell growth involved in cardiac muscle cell developmentSOR5212.16550.050965-7.901050.043357Cell growth involved in cardiac muscle cell developmentSOR5212.16550.050965-7.901050.043357Cell growth involved in cardiac muscle cell developmentSOR5212.1650.050965-7.901050.04357Skeleta system developmentSOR5212.1650.050965-7.901050.00774Skeleta system developmentSOR5212.85636.91864.56730.01747Skeleta system developmentSOR5212.85613.2666-4.15680.00774Regulation of steriol functional signal mathematiceSOR5212.85636.81884.56730.01747Skeleta system developmentSOR5213.2666-4.15680.00774 </td <td>DMKN</td> <td>22.4149</td> <td>0.978012</td> <td>-4.51846</td> <td>0.041821</td> <td>-</td>	DMKN	22.4149	0.978012	-4.51846	0.041821	-
LILRB32.73845526.0517.58770.007747Adaptive immune responseUGT1A84.279330.162788-11.3010.007747Negative regulation of steroid metabolic processKCNJ151401735.132894.713500.030628-IGB2-A511.446924.0334.803680.030638-GGT120546513.2563954180.04091Adenosine catabolic processGGT45.01392151.3284.91660.04091Adenosine catabolic processABI3B75.76520.01453-8.50410.04081Positive regulation of tell-substrate adhesionDX6003.14290.05095-7.901050.04337Positive regulation of MDA-5 signaling pathwaySORB5212.16550.05095-7.901050.04337Cell growth involved in cardiac muscle cell developmentUCMA1.180157.3098.91570.007747Sequilation of MDA-5 signaling pathwayVCMA1.180157.3098.91570.007747Negative regulation of signal membrane adhesion moleculesIST15.507224.51184.957430.00774Negative regulation of signal regulation adhesion via plasm amembrane adhesion moleculesIST22.7951665.81584.557430.00774Negative regulation of mind optase mediated signal transductionIST21.30581.3056-7.16470.00774Negative regulation of mind optase mediated signal transductionIST20.6465558.61866.50220.00774Negative regulation of mind optas	NFKBID	62.2206	2800.48	5.49214	0.034038	Inflammatory response
UG71A8427.9330.162788-11.36010.007747Negative regulation of steroid metabolic processKCNUT5140.1735.13269-4.771350.030624Potasium ion transpotITGB2-AS11.464240.91334.403680.034038-GG71205.46513.256-3.954180.041821Regulation of immune system processGG715.0139215.1328-4.91560.040492Adenosine catabolic processABJSPP5.276520.01453-8.50410.04645Positive regulation of cell-substrate adhesionDX6003.142936.6943.545380.032078Positive regulation of DNA-6 signaling pathwaySORB201.16550.05696-7.901650.044326Regulation of DNA ecombinationVCAV1.1880153.26226.157220.044526Regulation of DNA ecombinationVCAV1.1880153.2692-3.664660.03744Homphilic cell adhesion via plasma membrane adhesion moleculesVCAV1.1880155.765246.41196.397030.007747Negative regulation of mitoch cell cycleVCMV1.286565.81584.556730.007747Olditar instition of mitoch cell cycleVCMV1.80030.40207-7.16470.007747Olditar englation of mitoch cell cycleVCM1.956558.61866.502420.04912Lymphocyte differentiationVCM1.95696.817245.02210.007747Pative regulation of hydrogen peroxide-mediated programmed cell deathVFT	LILRB3	2.73845	526.051	7.5857	0.007747	Adaptive immune response
KCN/I5140.1735.1289-4.771350.030624Potasium ion transportITGB2-AS11.4640240.91334.803680.034038-GGT1205.46513.266-3.954180.041821Regulation of immue system processGECR15.01392151.3284.91560.040912Adenosine catabolic processBLBBP5.276520.01453-8.504410.04645Positive regulation of cell-substrate adhesionDX603.142936.6843.54580.0377Positive regulation of DNA- signaling pathwaySORB5212.16550.050895-7.901050.043357Cell growth involved in cardiac muscle cell developmentL7R0.82996659.26236.157920.04456Regulation of DNA recombinationVCAN1.1801573.6098.915370.007747Steletal system developmentPCDF0A13.23422.5504-3.646660.037849Homophilic cell adhesion via plasma membrane adhesion moleculesFGD22.735166.51584.557430.007747Negative regulation of mitocit cell cycleST5.50722464.1196.307240.007747Positive regulation of mitocit cell cycleM7B0.0358181.135684.96570.007747Positive regulation of mitocit cell cycleKZF10.5665658.61866.502420.007747-KZF20.46665558.61866.502420.007747-KZF10.5665658.61866.502420.007747-KZF1	UGT1A8	427.903	0.162788	-11.3601	0.007747	Negative regulation of steroid metabolic process
ITGB2-AS11.464924.0.91334.803680.034038-GGT1205.46513.266-3.954180.041821Regulation of immune system processCECR15.01392151.3284.91560.040912Adenosine catabolic processABI3B75.276520.01453-8.504410.04645Positive regulation of cell-substrate adhesionDX603.14296.6644-5.545380.004655Positive regulation of DAA-signaling pathwaySORBS212.16550.050955-7.901050.04337Cell growth involved in cardiac nuscle cell developmentIL7R0.82996659.26236.157920.04452Regulation of DNA recombinationVCAN1.1801573.6098.915370.007747Skeletal system developmentFCDHGA13.24322.55042-3.664660.03784Homophilic cell adhesion via plasm membrane adhesion moleculesLS715.50722464.1196.397330.007747Regulation of small cybase mediated signal transductionM780.0358181.135684.98670.00774Regulation of small cybase mediated signal transductionM7840.646655.8.61866.502420.00774Istrastion of mitoch cell cycleM7870.862640.04797-7.16470.00774Pative regulation of mitoch cell cycleRFZ70.666555.8.61866.502420.00774Istrastion of mitoch cell cycleRFZ70.682640.047297-7.16470.00774Istrastion of mitoch cell cycleRFZ7	KCNJ15	140.173	5.13269	-4.77135	0.030624	Potassium ion transport
GG71205.46513.256-3.954180.04182Regulation of immune system processCECR15.01392151.3284.91560.040912Adenosine catabolic processAB/BBP5.275520.01453-8.504410.04645Positive regulation of cell-substrate adhesionDX603.142936.6943.545380.032078Positive regulation of DNA-5 signaling pathwaySORB212.1550.050895-7.901050.043357Cell growth involved in cardiac muscle cell developmentL/R0.82966692623-6.157920.007747Skeletal system developmentVCAN1.1801573.6098.915370.007747Skeletal system developmentFCDHGA132.34222.55042-3.664660.03744Homophilic cell adhesion via plasma membrane adhesion moleculesLST15.50722464.1196.397030.007747Regulation of small gtpase mediated signal transductionFGD22.7951665.81584.557430.01744Regulation of small gtpase mediated signal transductionFGD22.795161.26056-4.115660.007747G1/S transition of mitoic cell cycleDXF0.466555.618486.602420.40097-FG701178.705260.17052-5.673850.007747-FG701178.705260.170523-5.673850.007747-FG701178.682940.404729-7.507190.02714Negative regulation of hydrogen peroxide-mediated programmed cell deathFG701171.5629	ITGB2-AS1	1.46492	40.9133	4.80368	0.034038	-
CECR15.01392151.2824.91560.04091Admosine catabolic processAB/3BP5.276520.01453-8.50410.04645Positive regulation of cell-substrate adhesionDDX603.14293.6.9443.545380.032078Positive regulation of MDA-5 signaling pathwaySORB212.16550.050995-7.910160.04327Cell growth involved in cardiac muscle cell developmentL/TR0.82996859.26236.157920.04452Regulation of DNA recombinationVCAN1.180157.36098.915370.00774Keletal system developmentPCDHGA12.3322464.1196.397300.00774Negative regulation of Jwphocyte proliferationFCDHGA15.5722464.1196.397300.00774Negative regulation of small gtpase mediated signal transductionFGD22.7951665.81584.557430.01214Regulation of small gtpase mediated signal transductionFGD22.7951665.81584.59670.007747G1/S transition of mitotic cell cycleFG71178.76520.042097-7.16470.007747Postive regulation of hydrogen peroxide-mediated programmed cell deathFG701178.76520.047729-7.507190.007747-FG701778.682940.047729-7.507190.027141FG701778.682940.047729-7.507190.027141FG701771.52420.054565-4.80380.04337FG701771.52420.054565-4.803980.04337FG7017	GGT1	205.465	13.256	-3.95418	0.041821	Regulation of immune system process
ABJ3BP5.276520.01453-8.504410.04645Positive regulation of cell-substrate adhesionDDX603.142936.6943.545380.03278Positive regulation of MDA-5 signaling pathwaySORB5212.16550.050895-7.901050.043357Cell growth involved in cardiac muscle cell developmentL/R0.8296659.26236.157920.044526Regulation of DNA recombinationVCAN1.1801573.6098.915370.007747Skeletal system developmentPCDHGA13.24322.55042-3.664600.03784Homophilic cell adhesion via plasma membrana dhesion moleculesLST15.50722464.1196.397030.007747Skeletal system developmentFGD22.795165.81584.557430.01224Regulation of imphocyte proliferationMYB0.0388181.135664.567430.01274Regulation of mitotic cell cycleDST21.5551.26056-4.115860.02784G1/S transition of mitotic cell cyclePARK26.040090.042077-7.16470.007747Positive regulation of mitotic cell cycleIKZF10.64656558.61866.502420.007747-FGD21.95696.57.245.02210.007747-IKZF10.562540.04729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV25119.5629635.7245.022210.007747-FTV11.51420.0543316.190340.44337	CECR1	5.01392	151.328	4.9156	0.040912	Adenosine catabolic process
DX603.142936.6943.545380.03078Positive regulation of MDA-5 signaling pathwaySORBS212.16550.050895-7.901050.043357Cell growth involved in cardiac muscle cell developmentIL/R0.82996659.26236.157920.044526Regulation of DNA recombinationVCAN1.1801573.6098.915370.007747Skeletal system developmentPCDHGA132.34322.55042-3.664660.037849Homophilic cell adhesion via plasma membrane adhesion moleculesLST15.50722444.1196.397030.007747Negative regulation of small gtpase mediated signal transductionFGD22.795166.681584.557430.012214Regulation of small gtpase mediated signal transductionM7B0.0358181.136864.96670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.02888Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionIKZF10.64656558.61866.502420.007747-IKZF10.64656558.61866.502420.007747-IKZF10.64656558.61866.502420.007747-IKZF10.562920.107523-5.673850.007747-IKZF10.562920.507260.007747-IKZF10.562930.007747IKZF10.562940.007747 <td>ABI3BP</td> <td>5.27652</td> <td>0.01453</td> <td>-8.50441</td> <td>0.04645</td> <td>Positive regulation of cell-substrate adhesion</td>	ABI3BP	5.27652	0.01453	-8.50441	0.04645	Positive regulation of cell-substrate adhesion
SORBS212.16550.050995-7.90150.043357Cell growth involved in cardiac muscle cell developmentIL7R0.82996659.26236.157920.044526Regulation of DNA recombinationVCAN1.1801573.6098.915370.007747Skeletal system developmentPCDHGA132.34322.55042-3.664660.037849Homophilic cell adhesion via plasma membrane adhesion moleculesLST15.50722464.1196.397030.007747Negative regulation of lymphocyte proliferationFGD22.7951665.81584.557430.01214Regulation of small gtpase mediated signal transductionM7B0.0358181.135684.96670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.22838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitotic cell cycleIKZF10.64666558.61866.502420.04912Lymphocyte differentiationKZF18.682940.047729-7.507190.027141Negative regulation of transcription from RNA polymerase II promoterTCRBV2S119.5629635.7245.02210.007747-FTV11.524240.05655-4.803960.043357Positive regulation of transcription from RNA polymerase II promoterFW01G1.31113157.8216.911330.041821Fe-gamma receptor signaling pathway involved in phagocytosisFW312.16870.00914-10.37020.03	DDX60	3.1429	36.694	3.54538	0.032078	Positive regulation of MDA-5 signaling pathway
IL7R   0.829966   59.2623   6.15792   0.04452   Regulation of DNA recombination     VCAN   1.1801   573.609   8.91537   0.007747   Skeltal system development     PCDHGA1   32.342   2.55042   -3.66466   0.037849   Homophilic cell adhesion via plasma membrane adhesion molecules     LST1   5.5072   464.119   6.39703   0.00747   Negativor egulation of lymphocyte proliferation     FGD2   2.79516   65.8158   4.55743   0.01244   Regulation of small gpase mediated signal transduction     MYB   0.035818   1.13568   4.9867   0.00747   Regulation of mitotic cell cycle     DST   21.8556   1.26056   -4.11586   0.02888   Maintenance of cell polarity     PARK2   6.4009   0.42097   -7.1647   0.00747   Positive regulation of mitochondrial fusion     IKZF1   0.646565   58.6186   6.50242   0.40912   Lymphocyte differentiation     IKZF1   0.646565   58.6186   6.50242   0.00747   -     ICRBV2S1   19.5629   635.724 <td< td=""><td>SORBS2</td><td>12.1655</td><td>0.050895</td><td>-7.90105</td><td>0.043357</td><td>Cell growth involved in cardiac muscle cell development</td></td<>	SORBS2	12.1655	0.050895	-7.90105	0.043357	Cell growth involved in cardiac muscle cell development
VCAN1.18801573.6098.915370.007747Skeletal system developmentPCDHGA132.34222.55042-3.664660.037849Homophilic cell adhesion via plasma membrane adhesion moleculesLST15.50722464.1196.397030.007747Negative regulation of lymphocyte proliferationFGD22.7951665.81584.557430.01224Regulation of small gtpase mediated signal transductionM7B0.0358181.135684.98670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.02888Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionKZF10.64665558.61866.502420.040912Lymphocyte differentiationFG701178.705260.170523-5.673850.007747-CRBv2S119.5629635.7245.02210.007747-FT/11.524240.054565-4.803980.43357Positive regulation of transcription from RNA polymerase II promoterMV01G1.3113157.8216.911330.041821Fe-gamma receptor signaling pathway involved in phagocytosisGLIPRA22.8190120.53336.190840.04526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.00914-10.37020.037849Sensory perception of temperature stimulus	IL7R	0.829966	59.2623	6.15792	0.044526	Regulation of DNA recombination
PCDHGA132.34322.55042-3.664660.037849Homophilic cell adhesion via plasma membrane adhesion moleculesLST15.50722464.1196.397030.007747Negative regulation of lymphocyte proliferationFGD22.7951665.81584.557430.012214Regulation of small gtpase mediated signal transductionMYB0.0358181.135684.98670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.028838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionKZF10.64656558.61866.502420.40912Lymphocyte differentiationKZF18.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.022210.007747-ETV11.524240.054565-4.803980.43357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.3113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.04526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	VCAN	1.18801	573.609	8.91537	0.007747	Skeletal system development
LST15.50722464.1196.397030.007747Negative regulation of lymphocyte proliferationFGD22.7951665.81584.557430.012214Regulation of small gtpase mediated signal transductionMYB0.0358181.135684.98670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.028838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochodrial fusionKZF10.64656558.61866.502420.040912Lymphocyte differentiationFF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S11.524240.054565-4.803980.04357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.3113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPP22.81901205.9336.190840.044526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	PCDHGA1	32.3432	2.55042	-3.66466	0.037849	Homophilic cell adhesion via plasma membrane adhesion molecules
FGD22.7951665.81584.557430.012214Regulation of small gtpase mediated signal transductionMYB0.0358181.135684.98670.007747G1/S transition of mitotic cell cycleDST21.85561.20056-4.115860.028838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionIKZF10.64656558.61866.502420.04912Lymphocyte differentiationFF0701178.705260.170523-5.673850.007747-TCRBV2S119.5629635.7245.02210.007747-FTV11.524240.054565-4.80380.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPPR22.81901205.9336.190840.04526Positive regulation of emperature stimulusTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	LST1	5.50722	464.119	6.39703	0.007747	Negative regulation of lymphocyte proliferation
MYB0.0358181.135684.98670.007747G1/S transition of mitotic cell cycleDST21.85561.26056-4.115860.02838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionIKZF10.64656558.61866.502420.040912Lymphocyte differentiationEF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.022210.007747-FTV11.524240.054565-4.803880.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.04526Positive regulation of temperature stimulus	FGD2	2.79516	65.8158	4.55743	0.012214	Regulation of small gtpase mediated signal transduction
DST21.85561.26056-4.115860.028838Maintenance of cell polarityPARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionIKZF10.64656558.61866.502420.040912Lymphocyte differentiationEF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.022210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPPA22.81901205.9336.190840.043529Positive regulation of temperature stimulusTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	MYB	0.035818	1.13568	4.9867	0.007747	G1/S transition of mitotic cell cycle
PARK26.040090.042097-7.16470.007747Positive regulation of mitochondrial fusionIKZF10.64656558.61866.502420.040912Lymphocyte differentiationEF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.022210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.044526Positive regulation of temperature stimulusTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	DST	21.8556	1.26056	-4.11586	0.028838	Maintenance of cell polarity
IKZF10.64656558.61866.502420.040912Lymphocyte differentiationEF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.02210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.04526Positive regulation of temperature stimulusTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	PARK2	6.04009	0.042097	-7.1647	0.007747	Positive regulation of mitochondrial fusion
EF0701178.705260.170523-5.673850.007747-MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.022210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.043526Positive regulation of temperature stimulus	IKZF1	0.646565	58.6186	6.50242	0.040912	Lymphocyte differentiation
MET8.682940.047729-7.507190.027141Negative regulation of hydrogen peroxide-mediated programmed cell deathTCRBV2S119.5629635.7245.02210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.044526Positive regulation of temperature stimulusTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	EF070117	8.70526	0.170523	-5.67385	0.007747	
TCRBV2S119.5629635.7245.022210.007747-ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.044526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	MET	8.68294	0.047729	-7.50719	0.027141	Negative regulation of hydrogen peroxide-mediated programmed cell death
ETV11.524240.054565-4.803980.043357Positive regulation of transcription from RNA polymerase II promoterMYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.044526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	TCRBV2S1	19.5629	635.724	5.02221	0.007747	
MYO1G1.31113157.8216.911330.041821Fc-gamma receptor signaling pathway involved in phagocytosisGLIPR22.81901205.9336.190840.044526Positive regulation of epithelial to mesenchymal transitionTRPM312.16870.009194-10.37020.037849Sensory perception of temperature stimulus	ETV1	1.52424	0.054565	-4.80398	0.043357	Positive regulation of transcription from RNA polymerase II promoter
GLIPR2 2.81901 205.933 6.19084 0.044526 Positive regulation of epithelial to mesenchymal transition   TRPM3 12.1687 0.009194 -10.3702 0.037849 Sensory perception of temperature stimulus	MYO1G	1.31113	157.821	6.91133	0.041821	Fc-gamma receptor signaling pathway involved in phagocytosis
TRPM3   12.1687   0.009194   -10.3702   0.037849   Sensory perception of temperature stimulus	GLIPR2	2.81901	205.933	6.19084	0.044526	Positive regulation of epithelial to mesenchymal transition
	TRPM3	12.1687	0.009194	-10.3702	0.037849	Sensory perception of temperature stimulus