

Letter to the editor

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# Allele-specific expression analyses reveal immune divergences between ibex and goat species

**DEAR EDITOR,**

Understanding the different immune responses of wild and domestic caprid species is critical for addressing certain zoonotic diseases. In this study, we generated blood transcriptomes of 13 Siberian ibex and domestic goat hybrids and performed allele-specific expression and splicing analyses. Results showed that genes exhibiting significant imbalance between the ibex and goat were highly related to the Toll-like receptor (TLR), antigen recognition, and immune activation pathways. Comparative genomic analysis of the species revealed that immune function-related genes were under strong selection pressure in the domestic goat. These allelic imbalances in gene expression may be related to fixed divergent sites in *cis*-regulatory elements, which may affect the expression of immune-related genes and contribute to the adaptive diversity between ibex and goat species.

The Siberian ibex is a wild relative of the domestic goat and is distributed in the mountains of Central and East Asia. It is classified as a near-threatened species in the IUCN Red List (<https://www.iucnredlist.org>) and is considered an endangered species in the China Red Data Book of Endangered Animals. Siberian ibex and domestic goats, which are able to produce fertile offspring, often cohabitate in the same ecosystem and share multiple pathogens, such as petitis ruminants virus (Benfield et al., 2021). Understanding the differences between these wild and domestic species is critical to the safety of livestock and wildlife. Hybrid offspring between the ibex and goat provide an ideal model for transcriptional comparison between the species. In ibex-goat hybrids, allele-specific expression can directly reflect gene expression divergence in parental species, and indirectly assess the function of variations in *cis*-regulatory elements (Wittkopp et al., 2004).

In this study, we collected peripheral blood samples from 13 adult female ibex-goat hybrids (Figure 1A). Using a bin map of

the whole genome, we divided the 13 hybrids into three F1 and 10 F2 samples (Supplementary Methods). On average, for each sample, 11X re-sequencing data and 3.5 Gb of transcriptome data were generated, respectively. Ibex and goat genomes were downloaded for genomic comparison.

We first performed genomic comparison between the ibex and goat to provide insight into the effects of natural selection on these divergent species. We detected signals of positively selected genes (PSGs) and evaluated the number of substitutions per synonymous (*Ks*) and nonsynonymous (*Ka*) sites for both species based on their genomes. We identified 96 and 74 PSGs in the goat and ibex lineage, respectively (Supplementary Tables S1–S6). Pathway enrichment analysis indicated that the 96 goat PSGs were significantly enriched in two pathways (corrected *P*-value < 0.05), i.e., immune system and olfactory signaling pathways. In contrast, the 74 ibex PSGs were enriched in 13 pathways (Figure 1B). Comparison of the *Ka/Ks* ratios for each Gene Ontology (GO) category revealed that the elevated pairwise *Ka/Ks* ratios were enriched in immune-defense of domestic goats (Supplementary Figures S1–S3 and Table S7).

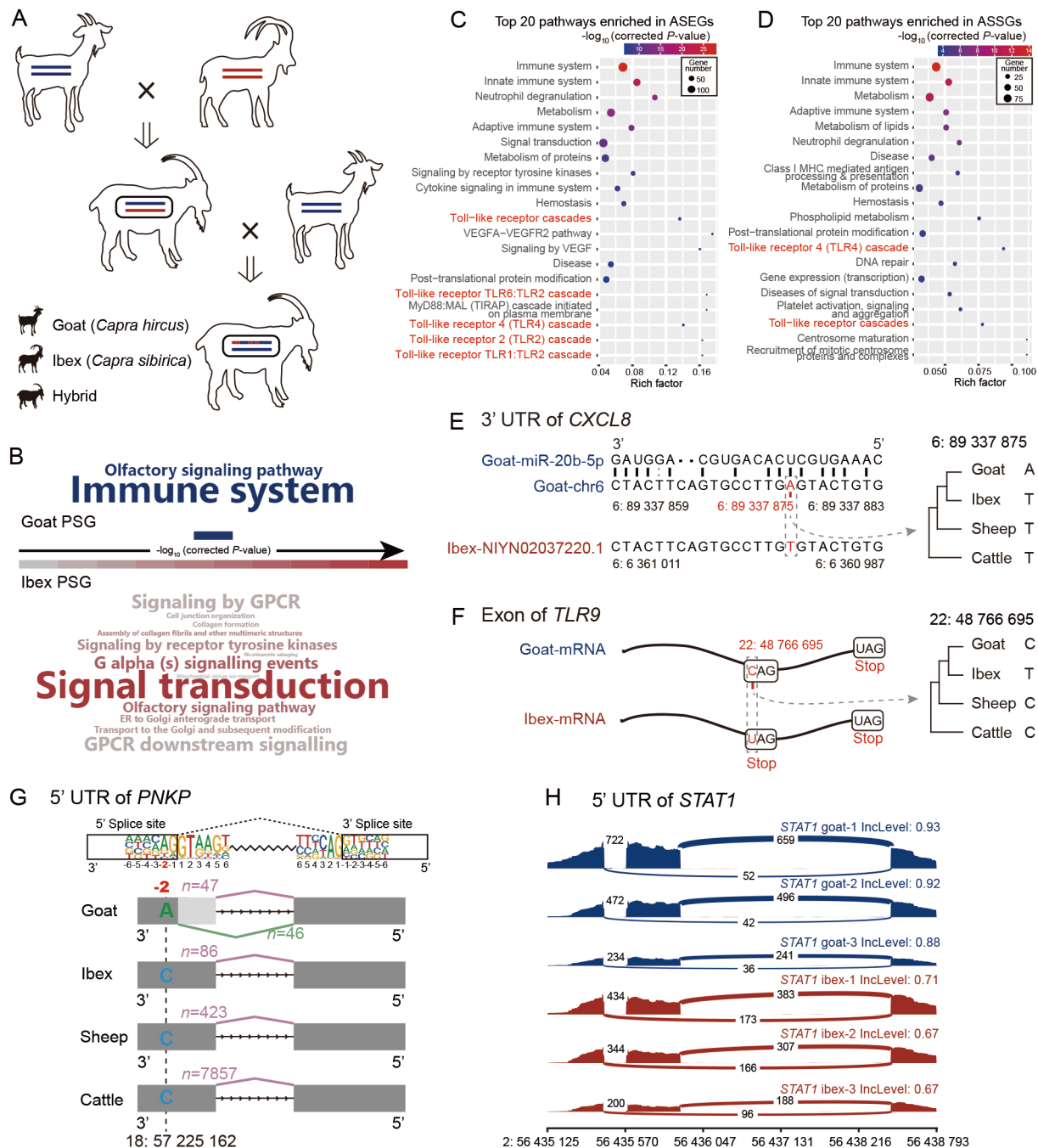
We next performed transcriptome analysis. To identify alleles between goat and ibex hybrids and reduce mapping bias, we first obtained ~5 Mb of fixed divergent sites (FDSs) between the two species (Supplementary Methods and Figure S4). A pseudogenome was then constructed by replacing the FDSs from the goat allele to the ibex allele (Supplementary Methods and Figure S5). After mapping to the goat genome and pseudogenome, the results were merged for allelic expression and splicing analyses. The expression ratios of goat and ibex alleles in the FDSs were calculated. The FDSs with imbalanced expression were filtered as allele-specific

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**Figure 1 Allelic imbalance expression and genomic divergence between ibex and goat**

A: Schematic of experimental design. B: Word clouds of significantly enriched pathways (corrected *P*-value<0.05) of positively selected genes in goat and ibex lineages. Input gene numbers are indicated by phrase text size, and gradient colors represent enriched significance in goat (blue) and ibex (red) lineages. C, D: Top 20 pathways enriched in ASEGs (C) and ASSGs (D), with TLR-related cascades highlighted in red. E: Predicted binding pattern of *CXCL8* and micro20b-5p, with comparison of key mutation in Bovidae in right panel. F: Mutation in ibex introduced a stop-codon in *TLR9*, with comparison of key mutation in Bovidae in right panel. G: Sequence log of nucleotide preference of splicing sites in whole genome. Bottom panel shows splicing patterns of *PNKP* in goat and other species. Frequencies of various splicing events are marked by "n". H: Differential splicing of *STAT1* in goats (blue) and ibex (red).

sites. Based on these allele-specific FDSs, we used a bin map to distinguish the ibex and goat fragments in the 13 hybrids for further analysis (Supplementary Methods and Supplementary Figure S6). A total of 896 genes with at least three allele-

specific sites were regarded as allele-specific expression genes (ASEGs) (Supplementary Figure S7), which included 853 protein-coding genes, 39 non-coding RNAs, and four pseudogenes. Allele-specific splicing genes (ASSGs) were

detected in three F1 hybrids. Transcriptome reads were divided into two genetic alleles. Splicing events were detected by rMATS v4.0.1 and tested using the likelihood-ratio method. In total, 827 statistically significant differential splicing events were found (Supplementary Methods and Figure S8).

Enrichment analyses of ASEs and ASSGs revealed significant associations with immune system-related pathways (Figure 1C, D; Supplementary Tables S8, S9), consistent with the goat PSG-enriched immune system pathway. We further explored the intersections between ASEs/ASSGs and published immune-related signaling pathways in Kyoto Encyclopedia of Genes and Genomes (KEGG). For the ASEs, TLR, a pattern recognition receptor (PRR), exhibited the highest intersections. For the ASSGs, RIG-I-like receptor cascade, another PRR, exhibited the highest intersections, followed by the TLR cascade (Supplementary Figure S9).

The ASEs in the TLR and immune-related pathways were analyzed in detail (Supplementary Table S10). *CXCL8* showed high ibex-preferred expression (Supplementary Figure S10A). One FDS in the 3' untranslated region (UTR) had a T-to-A mutation in goats (Figure 1E), which differs from that found in other bovine genomes (Fu et al., 2021). This mutation may increase the binding of mir20b-5p to the 3'UTR of *CXCL8* (Figure 1E) (Agarwal et al., 2015). For the *TLR9* gene, allele expression was lower in the ibex (Supplementary Figure S10B) and contained a C-to-T mutation, introducing a premature stop codon (Figure 1F) associated with nonsense-mediated mRNA decay (Lykke-Andersen & Jensen, 2015).

Among the identified ASSGs, *PNKP* plays an important role in DNA repair. It contained one fixed mutation at the -2 site in the 5' UTR, which showed high conservation among individuals (Figure 1G). This mutation (from G in Bovidae to T in goat) and splicing event are both novel in the goat genome (Figure 1G; Supplementary Figure S11). The *STAT1* gene showed one splicing variant, which generated an extended 5' isoform with a nuclear localization signal (Figure 1H; Supplementary Figure S12). This is a newly evolved isoform, conserved in multiple organisms (Supplementary Figures S13–S14).

We combined comparative genetics and functional allele-specific expression to provide multi-omics analysis of adaptive evolution in caprid species. Genomic analysis indicated that immune-related genes were under higher selection pressure in the domestic goat than in the ibex lineage. Transcriptome analysis indicated that the ASEs and ASSGs in the ibex-goat hybrids were also enriched in immune-related pathways. Thus, these results revealed the importance of immunity in the adaptive evolution of caprine, consistent with enhanced resistance of gastrointestinal nematodes (Zheng et al., 2020) and the brucellosis transmission model in early goat domestication (Fournié et al., 2017). We identified several immune-related pathways with high enrichment factors, such as the TLR cascade, which participates in pathogen recognition and immune activation. The effects of admixture and gene expression have also been studied in humans, with the Neanderthal haplotype associated with significantly increased expression of *TLR1* (McCoy et al., 2017). In conclusion, we identified several FDSs that likely affect transcriptome expression by regulating gene expression and

splicing, which may ultimately influence immune function. These findings should aid further epidemiological studies, especially the transmission of diseases between wild and domestic animals.

## DATA AVAILABILITY

All data used in the study are described in the manuscript and/or Supplementary Materials. The re-sequencing and transcriptome data were submitted to the Science Data Bank database (DOI: 10.57760/sciencedb.j00139.00004, 31253.11. sciencedb.j00139.00004), National Genomics Data Center (GSA: PRJCA009442, PRJCA009461), National Center for Biotechnology Information (NCBI BioProjectID: PRJNA836147, PRJNA836141), and China National GeneBank Database (CNGB: CNP0002452, CNP0002378).

## SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS' CONTRIBUTIONS

X.H.W., Y.J., and W.X.Z. designed and supervised the study; Ming Li, X.L.D., and Y.J.L. collected the hybrid samples; Z.R.Y. and J.X.L. performed the data analysis with contributions from Z.Q.Z., Ming Li, Y.W., and C.Z.; Z.R.Y., X.H.W., and H.A.N. drafted the manuscript; R.L., C.N.C., and Mao Li revised the manuscript. All authors read and approved the final version of the manuscript.

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## Supplementary Materials

### Supplementary Materials and Methods

#### Specimens and tissue samples

Samples were taken from 13 female ibex-goat hybrids (*Capra sibirica* and *Capra hircus*) (4–5 years old) from the Xinjiang Tianshan Wildlife Park, Karamay, China. All animals were born in the park and were in good health when the blood samples were taken. All samples were compared based on fixed divergent sites (FDSs) between ibex and goat to identify those fragments with ibex descent/lineage from the bin map (see “Lineage/descent/generation identification”).

#### Genome sequencing read alignment and single nucleotide polymorphism (SNP) calling

Genomic DNA was extracted from whole blood using the phenol-chloroform method. Purified libraries were constructed using at least 6 µg of genomic DNA following the standard library preparation protocols with 300–500 bp insert sizes for 150 bp paired-end sequencing. All libraries were then sequenced on the Illumina-HiSeq 2500 system with paired-end sequencing. To obtain high-quality reads, all reads were initially filtered using Trimmomatic v0.36 (Bolger et al., 2014). The leading or trailing stretches of Ns and bases below three were trimmed. Reads with an average quality of bases less than 16 and shorter than 36 bases were removed. High-quality reads were then aligned to the latest goat reference genome (GCF\_001704415.1) using BWA-MEM v0.7.15 with default parameters (Li, 2013). Picard v2.1 was used to filter potential polymerase chain reaction (PCR) duplicates and to sort reads. To reduce the influence of indels, all BAM files were realigned in the surrounding region using GATK v3.7.0 (McKenna et al., 2010). HaplotypeCaller in GATK was used to call SNPs, and VariantFiltration was used to filter SNPs with a filtering expression: “QD<2.0 || ReadPosRankSum<8.0 || FS>60.0 || MQ<40.0 || MQRankSum<-12.5”. All variants were finally annotated using ANNOVAR (Wang et al., 2010).

#### Evolutionary analysis

For genomic evolutionary analysis, we used the genomes of ibex (GCA\_001704415.1), goat (GCA\_003182615.2), and other eight bovine species, including sheep (GCA\_000298735.2), Tibetan antelope (GCA\_000400835.1), bohor reedbuck (GCA\_006410935.1), steenbok (GCA\_006410735.1), common duiker (GCA\_006408735.1), gerenuk (GCA\_006410535.1), yak (GCA\_000-298355.1), and cattle (GCA\_002263795.2). Each genome was aligned to the goat reference genome using the “lastal” command with default parameters. The phylogenetic tree structure (Supplementary Figure S1) and conserved genome synteny methodology referred to previous study (Chen et al., 2019), used to establish a high-confidence orthologous gene set.

Based on the orthologous set of 13 534 genes, evolutionary analyses were conducted using the Codeml program of PAML v4.10.0 (Yang, 2007), which includes branch-site and free-ratio models. The branch-site model was used to detect genes under positive selection (PSGs) (Supplementary Table S1, S2), estimated using the likelihood ratio test (LRT). The free-ratio model was used to calculate the values of  $K_a$  and  $K_s$  and the  $K_a/K_s$  ratio for each orthologous gene, while lineage-specific  $K_a/K_s$  values were estimated using 10 000 concatenated alignments constructed from 150 randomly chosen genes (Supplementary Figure S2). We collected the human Gene Ontology (GO) annotation results from Ensembl to assign GO categories. To ensure accuracy, categories with more than 20 genes were examined using a binomial test (Supplementary Figure S3) to determine whether they had a significant excess of nonsynonymous changes in either the ibex or goat lineage (Qiu et al., 2012).

#### Transcriptome sequencing and mapping

Total RNA was extracted using TRIzol reagent (Invitrogen, USA) following the manufacturer's protocols. Genomic DNA contamination was removed using RNA-free DNase I, and RNA quality was measured using a bioanalyzer (Agilent, USA). The RNA Integrity Number (RIN) was required to be greater than 7. mRNA was isolated from total RNA using a NEBNext® Ultra™ RNA Library Prep Kit for Illumina® (NEB, USA) according to the manufacturer's recommendations. cDNA fragments (300–500 bp) were used to construct the library. The Illumina X Ten platform was used to sequence the DNA library and generate 150 bp paired-end reads. Due to the unusually high frequency of some short partial sequences, we used Trimmomatic (Bolger et al., 2014) to remove adapters and reads. All high-quality reads were then aligned to GCF\_001704415.1 using STAR v2.7.9a with default parameters (Dobin et al., 2013). Expression levels were quantified using FPKM in Cufflinks v2.2.1 (Trapnell et al., 2010).

### **Divergent site definition and pseudogenome construction**

To define the FDSs between ibex and goat species, we used whole-genome resequencing data of 186 domestic goats and three Siberian ibex collected from a previous study (Zheng et al., 2020). Based on this worldwide dataset, we called divergent sites between ibex and goat groups by GATK v3.7.0, using a threshold of  $F_{ST}$  equal to 1. When assigning the initial divergent sites to the hybrid transcriptome, some sites still showed multi-polymorphism. After removing the sites with more than two genotypes in the hybrids, we finally obtained 5 560 781 FDSs. All divergent sites were then annotated by ANNOVAR (Supplementary Figure S4) (Wang et al., 2010).

The ibex pseudogenome was constructed by replacement of the FDSs without changing the genome coordinates, as per previous study (Wang et al., 2013). By merging the reads uniquely mapped to the genome and pseudogenome, we reduced the mapping bias caused by the FDSs. An in-house script was used to achieve construction. Effectiveness was tested by evaluating the mapping rate (Supplementary Figure S5).

### **Lineage/descent/generation identification**

The FDSs were used to judge fragments with ibex descent in the 13 hybrids with a bin map. We applied a 1 Mb window/bin with 500 kb steps to slide the whole genome using an in-house script. Using the FDS genotypes in each bin, the bins were tagged with “ibex-like” or “goat-like”, then merged with adjacent bins with the same tag. In F1 samples, all bins were “ibex-like”. In F2 samples, the “ibex-like” and “goat-like” bins were mixed due to partial and discontinuous recombination events (Supplementary Figure S6).

### **Identification of genes with allele-specific expression**

Genes with allele-specific expression were identified by comparing read counts between the two alleles. Fragments with ibex-like tags in F2 samples were partial and inconsistent with each other, so the FDSs were overlapped with the ibex-like fragments to obtain individual FDSs. Fragment information was obtained from resequencing the DNA data of each sample. In the transcriptome, individual FDSs with read depth below 10-fold and total depth (both alleles) below 30-fold were filtered out to avoid incorrect SNPs. Only sites passing these specific filters were used for further analysis.

The statistical significance of imbalance was calculated using a binomial test and Benjamin-Hochberg false discovery rate (FDR) correction (threshold of 0.05). Allele ratio ( $>0.65$  or  $<0.35$ ) and FDR ( $<0.05$ ) cut-off criteria were used to measure allele-specific expression genes (ASEGs), as in previous study (Wang et al., 2013). Due to the rarity of ibex samples, we could not remove imprinted genes by backcrossing, so we used intersections with currently known databases (<http://www.geneimprint.com/site/home>) to remove all possible imprinted genes. These genes, which

contained both goat-preferred and ibex-preferred expression sites, were regarded as unconcordant and removed. To improve the accuracy of the final ASEG list for further analysis, genes with at least three imbalanced expression alleles were retained (Cao et al., 2019). ASEGs were annotated with ANNOVAR using the annotated gtf-file downloaded from NCBI.

The ASEGs were used to mark the origin of each read and separate the whole transcriptome into three categories, i.e., ibex, goat, and unknown. The separated ibex and goat transcriptomes were used to calculate gene expression levels (Supplementary Figure S7) and for splicing analysis.

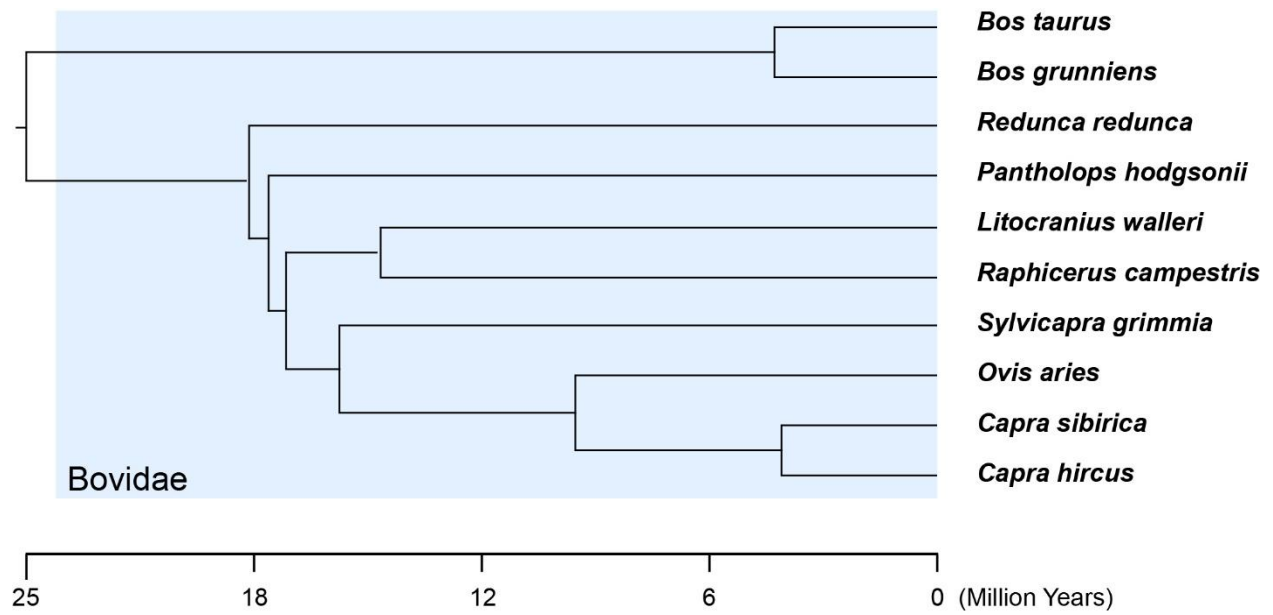
### **Identification of genes with allele-specific splicing**

Genes showing alternative (allele-specific) splicing events were defined as allele-specific splicing genes (ASSGs). Due to the random nature of recombination events, the hybrid fragments of ibex descent in the F2 samples were only partial fragments, which can affect accuracy when testing splicing ratios in the samples. To ensure the reliability of the three replicates in the experiments, ASS events were detected in the three F1 hybrids using replicate multivariate analysis of transcript splicing (rMATS) (Shen et al., 2014) with the separated genetic allele samples described in ASEG analysis. The five alternative splicing events include exon skipping (SE), mutually exclusive exons (MXEs), alternative 5' splice sites (A5SSs), alternative 3' splice sites (A3SSs), and retained introns (RIs). The likelihood-ratio method was applied to test significance of splicing events, using the exon-inclusion ratio ( $\psi$ value), also known as percent spliced in (PSI). Statistical criteria were applied to obtain the final ASS events (Supplementary Figure S8), i.e.,  $|\Delta\psi| > 10\%$  and  $FDR \leq 0.05\%$ .

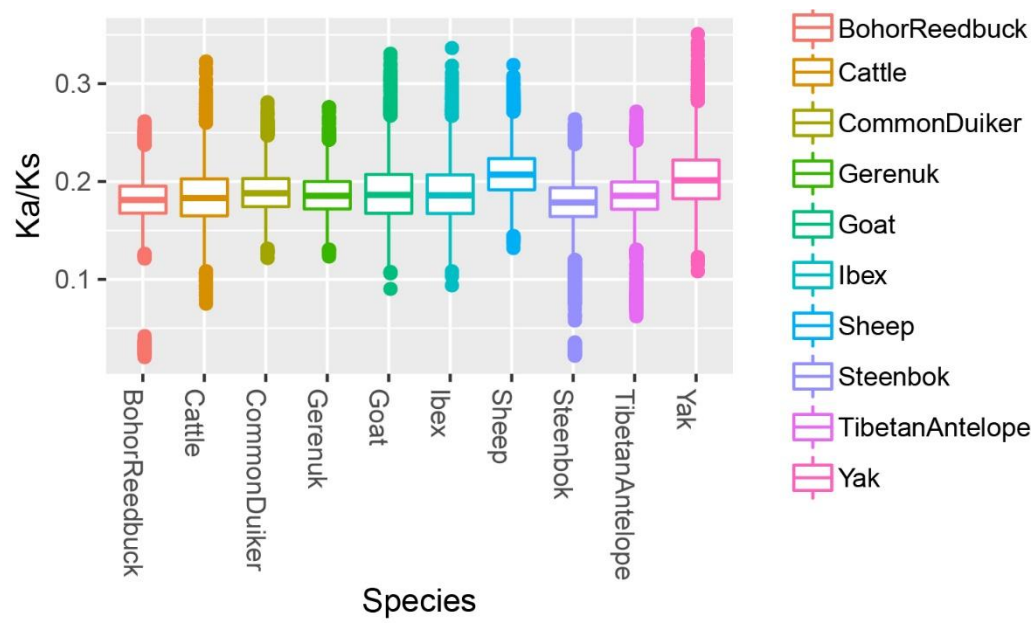
For some genes displaying both ASE and ASS events, we performed further tests to judge whether allele-specific expression was caused by allele-specific splicing. We ignored splicing regions within these genes and re-defined them following the ASEG criteria. Results showed that determination of ASS and ASE was independent.

### **Gene set enrichment analysis**

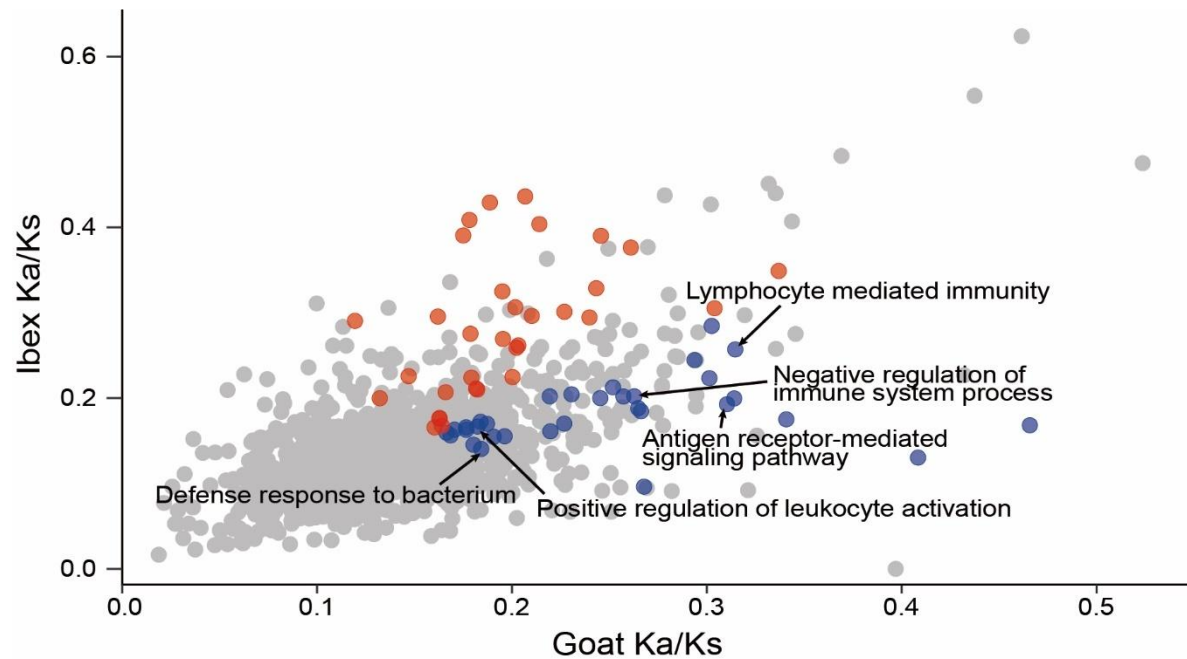
GO and Reactom enrichment analyses were performed using KOBAS. To increase the accuracy of enrichment, gene symbol IDs were converted into protein sequences, referring to GCF\_001704415.1. Fisher's exact test was used for statistical analysis and the Benjamin-Hochberg method was used for FDR correction.



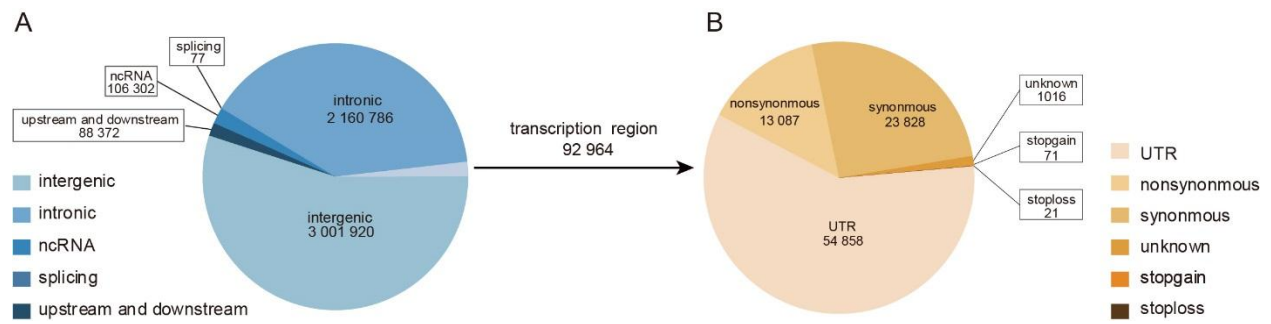
**Supplementary Figure S1 Phylogenetic tree used in positive selection analysis.**



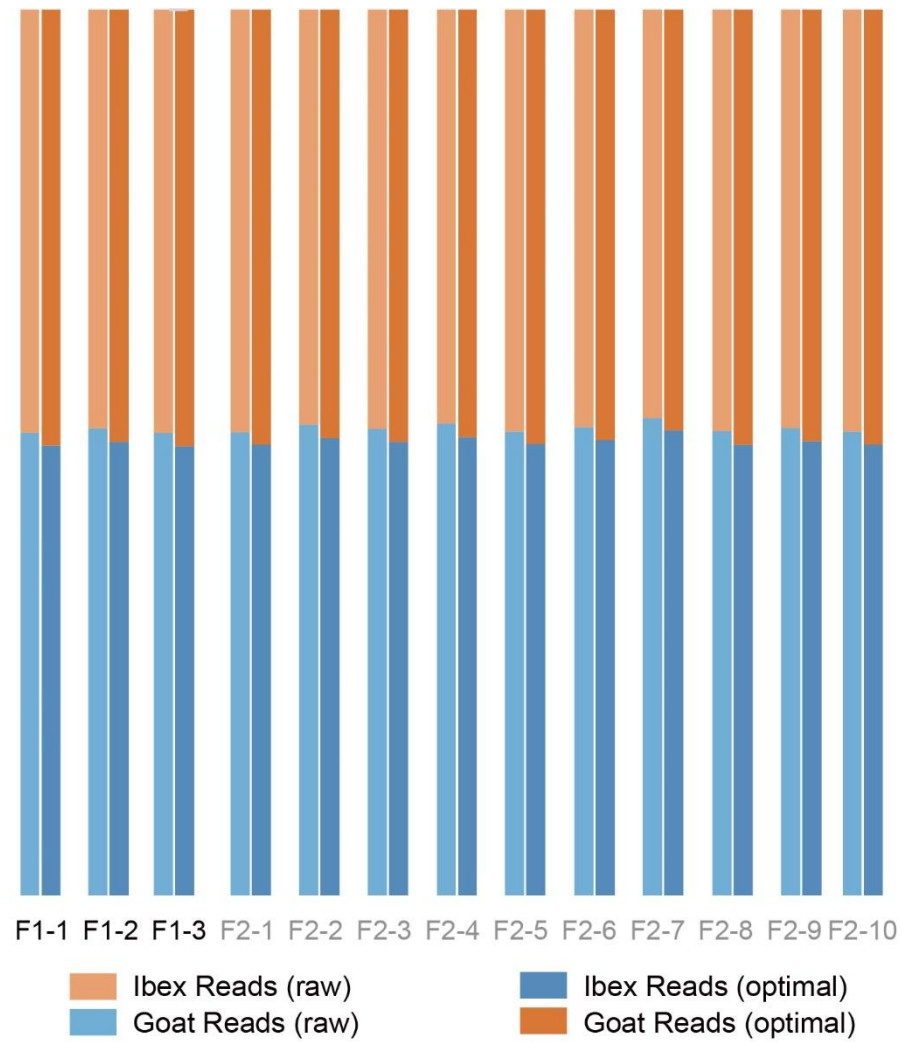
**Supplementary Figure S2  $Ka/Ks$  ratios of 10 species.** Box plot shows ratio of nonsynonymous to synonymous mutations ( $Ka/Ks$ ) for 10 species.



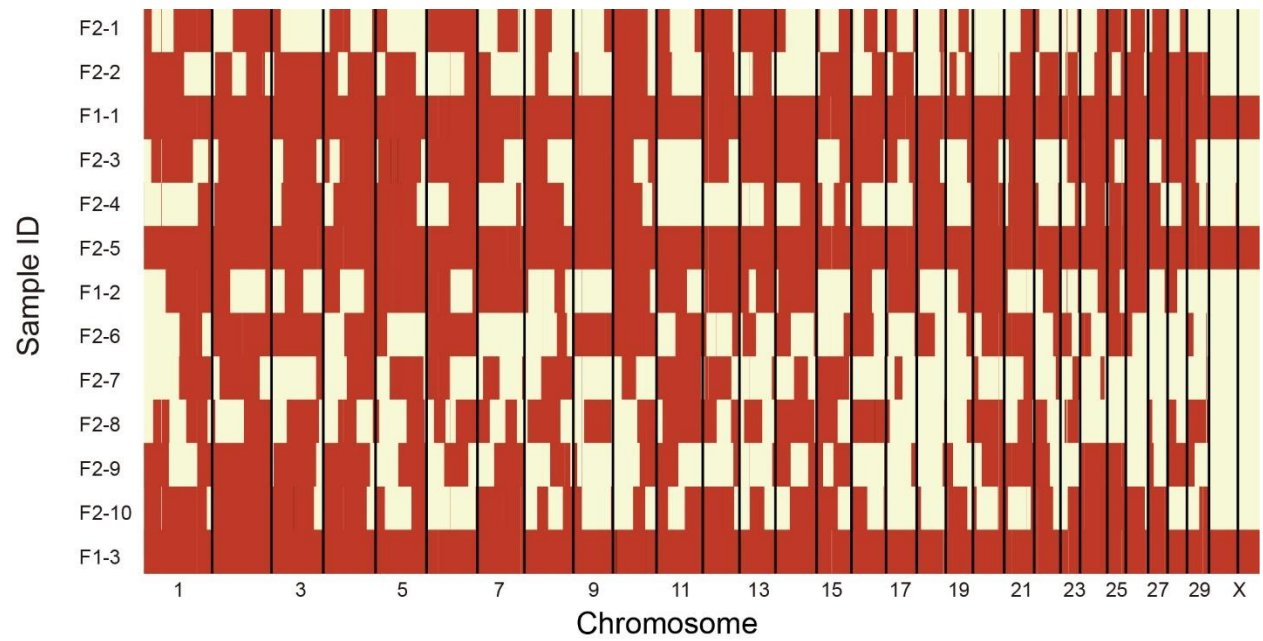
**Supplementary Figure S3 Mean *Ka/Ks* ratios of goat and ibex pairs for all 1 487 GO categories.** Bionomic tests were used to check reliability of putatively accelerated GO categories ( $P < 0.05$ ). Accelerated categories in ibex and goat lineages are highlighted by red and blue circles, respectively. Complete list of categories is provided in Supplementary Table S7.



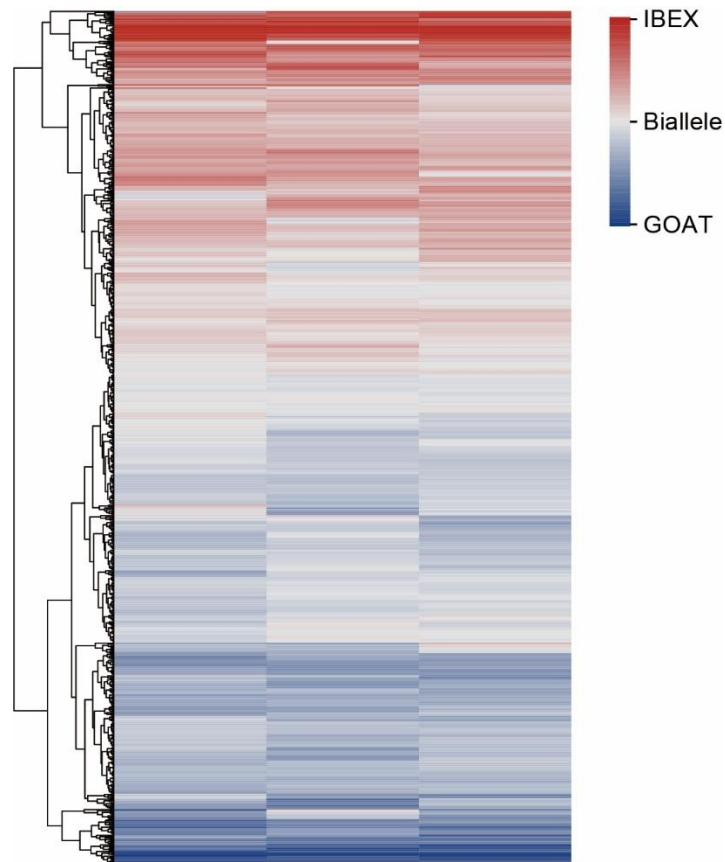
**Supplementary Figure S4 Distribution of fixed divergent sites.** (A) Functional annotation of fixed divergent sites in genes. (B) Functional annotation of fixed divergent sites in transcriptional region.



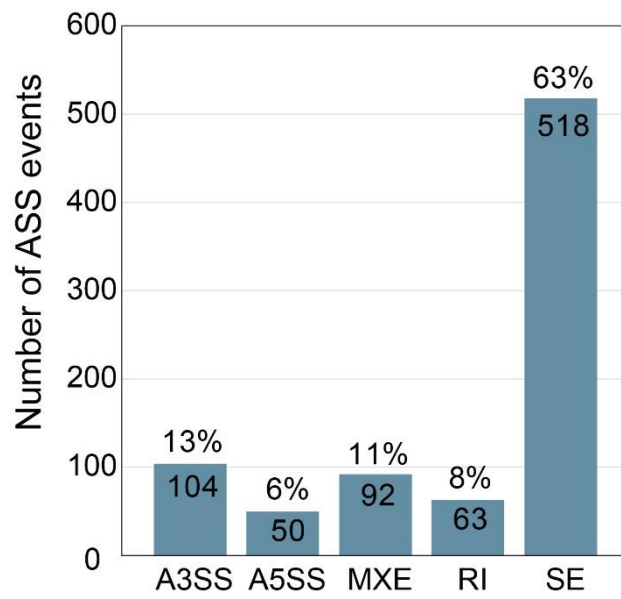
**Supplementary Figure S5 Adjustment of mapping bias in hybrid transcriptome.** Raw results represent initial mapping bias using goat as reference. Optimal results represent average mapping results of goat and pseudogenome.



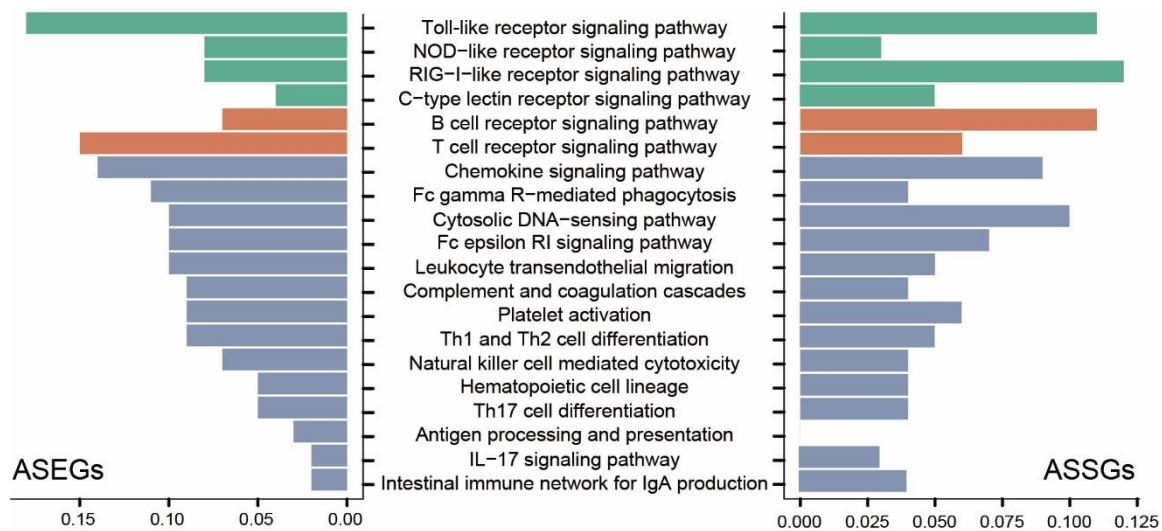
**Supplementary Figure S6 Distribution of fragments with ibex descent in 13 hybrids.** Descent of fragment was defined by fixed divergent sites. Heterozygous (ibex-like bins) and pure regions (goat-like bins) are represented in red and yellow, respectively.



**Supplementary Figure S7 Heatmap of gene expression of ASEGs in three F1 hybrids.**

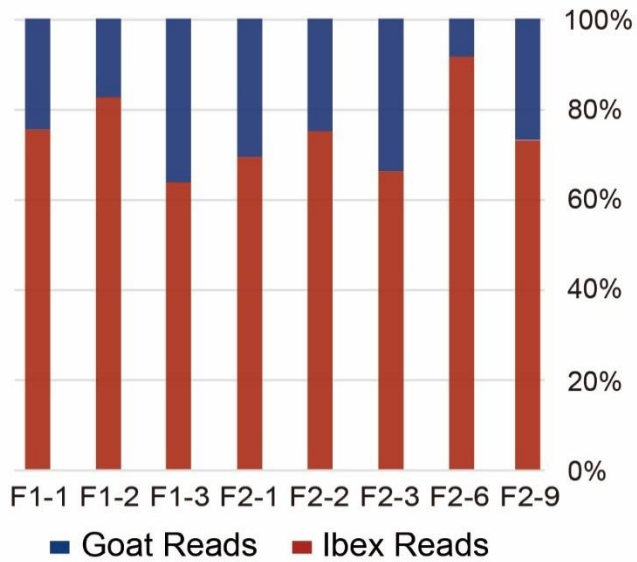


**Supplementary Figure S8 Statistical results of ASS events.**

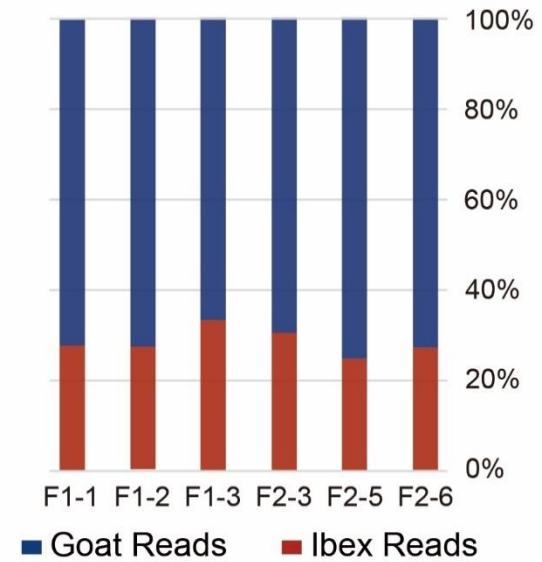


**Supplementary Figure S9 Proportion of ASEGs and ASSGs belonging to immune-related pathways in KEGG.** Pattern recognition receptor (PRP) pathways and other receptor pathways are marked in green and orange, respectively, while others are in gray.

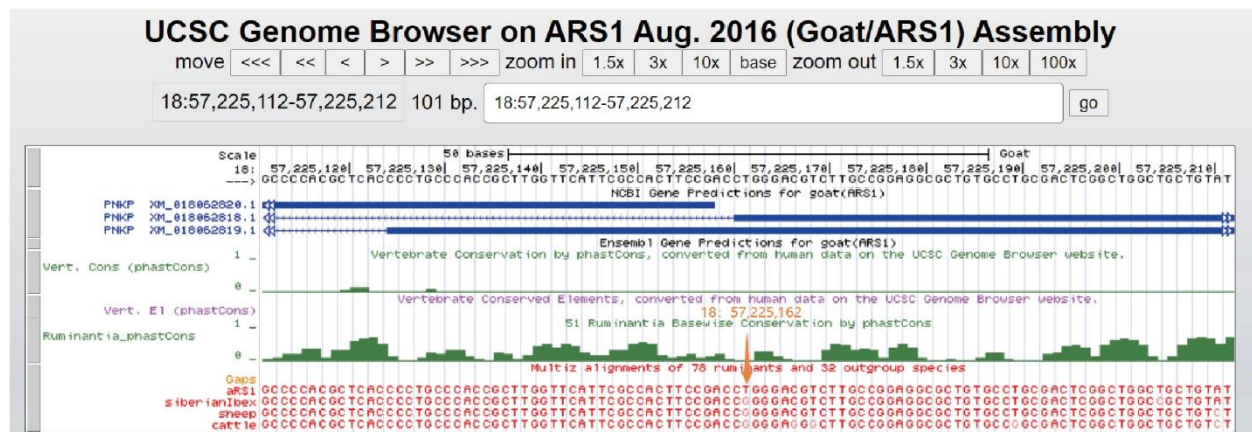
**A** *CXCL8* 6: 89335401-89338881



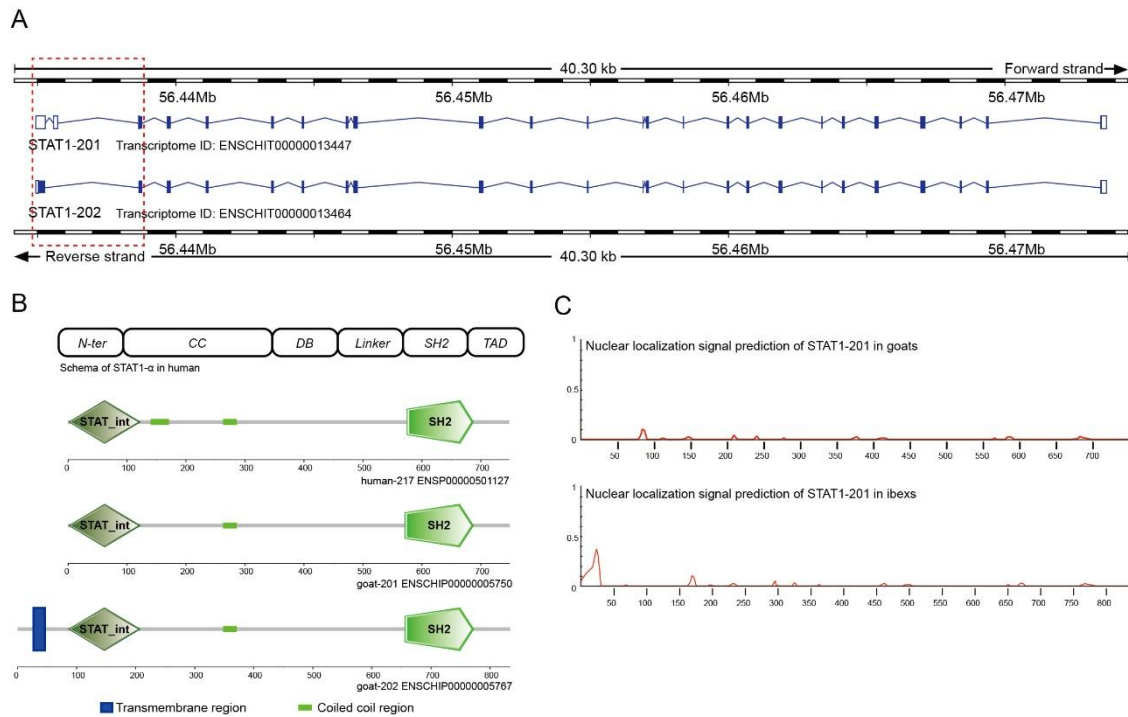
**B** *TLR9* 22: 48764919-48768006



**Supplementary Figure S10 Expression ratios of *CXCL8* and *TLR9* in hybrids.** (A, B) Allele-specific expression of *CXCL8* (A) and *TLR9* (B) in heterozygous individuals.

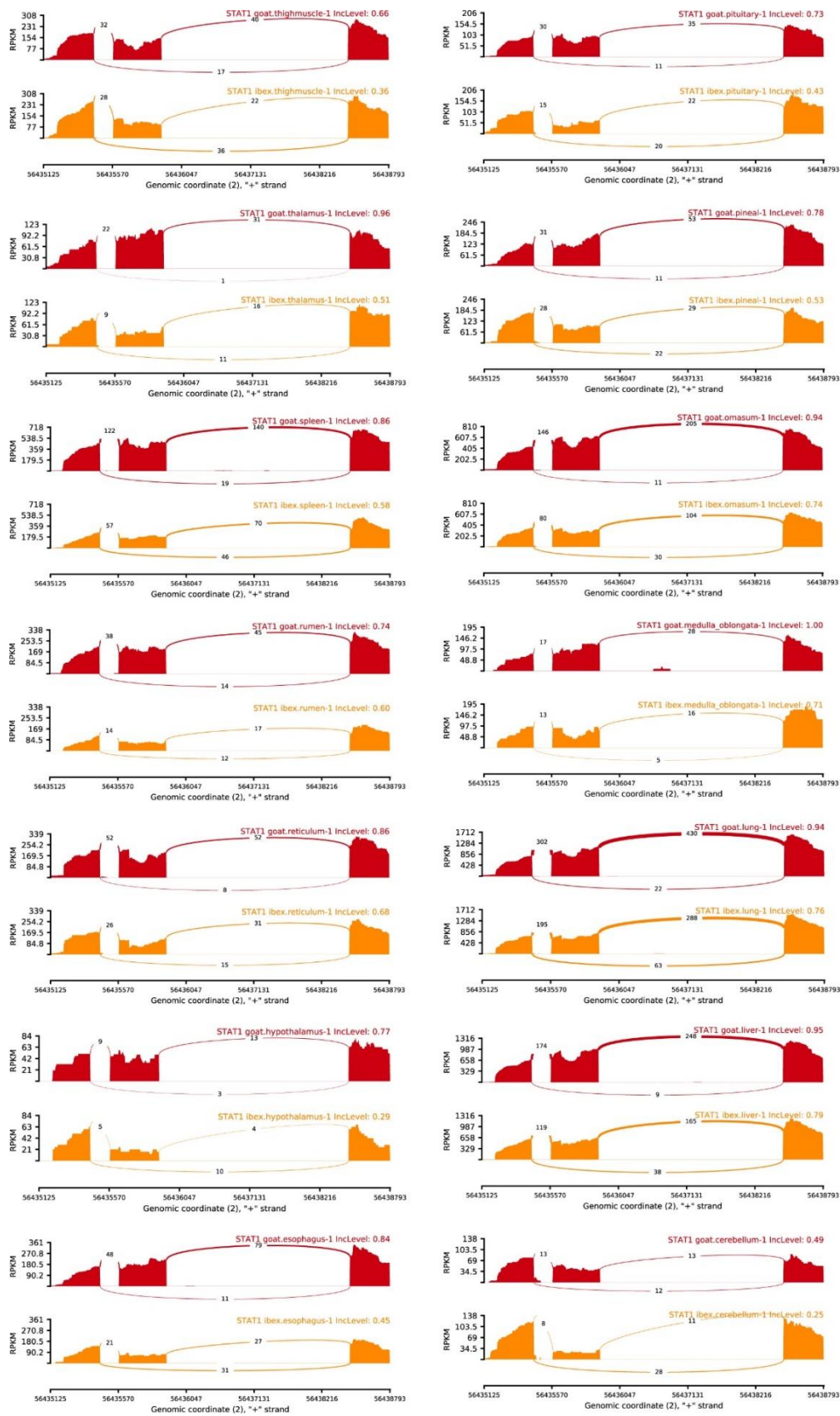


**Supplementary Figure S11 Adjacent 100 bp around *PNKP* alternative splicing event in UCSC Genome Browser. Orange arrow points to fixed divergent site (18: 57 225 162) in *PNKP*.**



**Supplementary Figure S12 Isoforms of *STAT1* in goat.** (A) Structures of two transcripts from Ensembl. (B) Predicted protein structure of two isoforms by SMART (Letunic & Bork, 2018), with human as a reference. (C) Nuclear localization signal prediction in goats showing the new N-terminal region of STAT1-202 contains a stronger nuclear localization signal, as predicted by NLStradamus (Ba et al., 2009).





**Supplementary Figure S14 Alternative splicing condition of new isoform.** Isoform exists in other tissues, such as thigh muscles, thalamus, pituitary, pineal, spleen, omasum, rumen, medulla-oblongata, reticulum, lung, hypothalamus, liver, esophagus, and cerebellum.

**Supplementary Table S1** Summary of positively selected genes in goat lineage. All gene IDs, transcript IDs, and peptide IDs are annotated from cattle.

| Gene ID                   | Transcript ID                   | Peptide ID             | Gene Symbol |
|---------------------------|---------------------------------|------------------------|-------------|
| gene:ENSBTAG00000013693.5 | transcript:ENSBTAT00000018202.4 | pep:ENSBTAP00000018202 | na          |
| gene:ENSBTAG00000043561.1 | transcript:ENSBTAT00000060569.1 | pep:ENSBTAP00000053147 | COX1        |
| gene:ENSBTAG00000014158.5 | transcript:ENSBTAT00000018816.4 | pep:ENSBTAP00000018816 | CCNT2       |
| gene:ENSBTAG00000023918.4 | transcript:ENSBTAT00000055181.2 | pep:ENSBTAP00000050989 | na          |
| gene:ENSBTAG00000046915.1 | transcript:ENSBTAT00000066040.1 | pep:ENSBTAP00000053954 | na          |
| gene:ENSBTAG00000047426.1 | transcript:ENSBTAT00000064259.1 | pep:ENSBTAP00000055421 | LYPD6       |
| gene:ENSBTAG00000021883.4 | transcript:ENSBTAT00000029169.4 | pep:ENSBTAP00000029169 | AP3M1       |
| gene:ENSBTAG00000021706.5 | transcript:ENSBTAT00000028930.5 | pep:ENSBTAP00000028930 | TBX3        |
| gene:ENSBTAG00000007441.4 | transcript:ENSBTAT00000009785.4 | pep:ENSBTAP00000009785 | SEC23IP     |
| gene:ENSBTAG00000008013.4 | transcript:ENSBTAT00000044459.1 | pep:ENSBTAP00000041953 | LRRC2       |
| gene:ENSBTAG00000006921.5 | transcript:ENSBTAT00000009089.5 | pep:ENSBTAP00000009089 | ABCA6       |
| gene:ENSBTAG00000013556.5 | transcript:ENSBTAT00000018027.5 | pep:ENSBTAP00000018027 | UNC13D      |
| gene:ENSBTAG00000044151.2 | transcript:ENSBTAT00000061288.2 | pep:ENSBTAP00000053262 | ANKDD1B     |
| gene:ENSBTAG00000046421.1 | transcript:ENSBTAT00000008579.5 | pep:ENSBTAP00000008579 | na          |
| gene:ENSBTAG00000045860.1 | transcript:ENSBTAT00000002951.5 | pep:ENSBTAP00000002951 | na          |
| gene:ENSBTAG00000013364.5 | transcript:ENSBTAT00000017778.5 | pep:ENSBTAP00000017778 | LIPM        |
| gene:ENSBTAG00000019007.3 | transcript:ENSBTAT00000025298.3 | pep:ENSBTAP00000048421 | na          |
| gene:ENSBTAG00000021337.5 | transcript:ENSBTAT00000028448.5 | pep:ENSBTAP00000028448 | SBF1        |
| gene:ENSBTAG00000035777.3 | transcript:ENSBTAT00000050265.3 | pep:ENSBTAP00000046998 | na          |
| gene:ENSBTAG00000002138.5 | transcript:ENSBTAT00000015977.5 | pep:ENSBTAP00000015977 | PADI1       |
| gene:ENSBTAG00000019555.4 | transcript:ENSBTAT00000026057.4 | pep:ENSBTAP00000026057 | ZSCAN20     |
| gene:ENSBTAG00000047862.1 | transcript:ENSBTAT00000063587.1 | pep:ENSBTAP00000055397 | na          |
| gene:ENSBTAG00000040323.2 | transcript:ENSBTAT00000057166.2 | pep:ENSBTAP00000052542 | na          |
| gene:ENSBTAG00000045731.1 | transcript:ENSBTAT00000063972.1 | pep:ENSBTAP00000054874 | na          |

| Gene ID                   | Transcript ID                   | Peptide ID             | Gene Symbol |
|---------------------------|---------------------------------|------------------------|-------------|
| gene:ENSBTAG00000046161.1 | transcript:ENSBTAT00000066127.1 | pep:ENSBTAP00000056562 | na          |
| gene:ENSBTAG00000017863.4 | transcript:ENSBTAT00000023743.4 | pep:ENSBTAP00000023743 | SRGN        |
| gene:ENSBTAG00000021721.5 | transcript:ENSBTAT00000028955.5 | pep:ENSBTAP00000028955 | CDSN        |
| gene:ENSBTAG00000047632.1 | transcript:ENSBTAT00000065204.1 | pep:ENSBTAP00000056315 | IGHE        |
| gene:ENSBTAG00000010504.5 | transcript:ENSBTAT00000013895.5 | pep:ENSBTAP00000013895 | TBRG4       |
| gene:ENSBTAG00000038576.2 | transcript:ENSBTAT00000053287.2 | pep:ENSBTAP00000052286 | na          |
| gene:ENSBTAG00000018237.4 | transcript:ENSBTAT00000024275.4 | pep:ENSBTAP00000024275 | MYO16       |
| gene:ENSBTAG00000011002.5 | transcript:ENSBTAT00000014612.5 | pep:ENSBTAP00000014612 | CCDC136     |
| gene:ENSBTAG00000039873.2 | transcript:ENSBTAT00000053102.2 | pep:ENSBTAP00000050775 | na          |
| gene:ENSBTAG00000007457.4 | transcript:ENSBTAT00000009810.4 | pep:ENSBTAP00000009810 | na          |
| gene:ENSBTAG00000015490.5 | transcript:ENSBTAT00000020581.5 | pep:ENSBTAP00000020580 | HS1BP3      |
| gene:ENSBTAG00000013378.4 | transcript:ENSBTAT00000017800.4 | pep:ENSBTAP00000017800 | na          |
| gene:ENSBTAG00000012215.5 | transcript:ENSBTAT00000016173.5 | pep:ENSBTAP00000016173 | CPNE7       |
| gene:ENSBTAG00000009764.5 | transcript:ENSBTAT00000012877.3 | pep:ENSBTAP00000012877 | na          |
| gene:ENSBTAG00000014368.3 | transcript:ENSBTAT00000034482.2 | pep:ENSBTAP00000034373 | SLAMF6      |
| gene:ENSBTAG00000002937.5 | transcript:ENSBTAT00000003821.5 | pep:ENSBTAP00000003821 | ADGRE3      |
| gene:ENSBTAG00000030714.3 | transcript:ENSBTAT00000043427.3 | pep:ENSBTAP00000041000 | na          |
| gene:ENSBTAG00000012817.5 | transcript:ENSBTAT00000009631.5 | pep:ENSBTAP00000009631 | JAG1        |
| gene:ENSBTAG00000009547.5 | transcript:ENSBTAT00000012560.5 | pep:ENSBTAP00000012560 | ZDHHC4      |
| gene:ENSBTAG00000021841.5 | transcript:ENSBTAT00000026607.5 | pep:ENSBTAP00000026607 | CHD7        |
| gene:ENSBTAG00000008330.5 | transcript:ENSBTAT00000010969.5 | pep:ENSBTAP00000010969 | RNF19B      |
| gene:ENSBTAG00000016804.5 | transcript:ENSBTAT00000022355.5 | pep:ENSBTAP00000022355 | LYST        |
| gene:ENSBTAG00000007580.3 | transcript:ENSBTAT00000009973.1 | pep:ENSBTAP00000009973 | ZSWIM2      |
| gene:ENSBTAG00000021414.5 | transcript:ENSBTAT00000028547.4 | pep:ENSBTAP00000028547 | na          |
| gene:ENSBTAG00000002331.5 | transcript:ENSBTAT00000003008.5 | pep:ENSBTAP00000003008 | DLGAP5      |

| Gene ID                   | Transcript ID                   | Peptide ID             | Gene Symbol |
|---------------------------|---------------------------------|------------------------|-------------|
| gene:ENSBTAG00000037882.1 | transcript:ENSBTAT00000054145.1 | pep:ENSBTAP00000049904 | ZNF584      |
| gene:ENSBTAG00000023258.2 | transcript:ENSBTAT00000031637.2 | pep:ENSBTAP00000031587 | na          |
| gene:ENSBTAG00000046461.1 | transcript:ENSBTAT00000066165.1 | pep:ENSBTAP00000055465 | na          |
| gene:ENSBTAG00000009171.5 | transcript:ENSBTAT00000023823.5 | pep:ENSBTAP00000023823 | na          |
| gene:ENSBTAG00000010382.5 | transcript:ENSBTAT00000013702.5 | pep:ENSBTAP00000013702 | MUC13       |
| gene:ENSBTAG00000000076.4 | transcript:ENSBTAT00000000084.4 | pep:ENSBTAP00000000084 | RECK        |
| gene:ENSBTAG00000027326.4 | transcript:ENSBTAT00000039179.4 | pep:ENSBTAP00000038979 | TP53RK      |
| gene:ENSBTAG00000046729.1 | transcript:ENSBTAT00000065674.1 | pep:ENSBTAP00000055770 | na          |
| gene:ENSBTAG00000005784.5 | transcript:ENSBTAT00000007609.5 | pep:ENSBTAP00000007609 | CSMD2       |
| gene:ENSBTAG00000011325.5 | transcript:ENSBTAT00000015052.5 | pep:ENSBTAP00000015052 | KHK         |
| gene:ENSBTAG00000022227.4 | transcript:ENSBTAT00000030005.4 | pep:ENSBTAP00000029993 | na          |
| gene:ENSBTAG00000008943.4 | transcript:ENSBTAT00000011774.4 | pep:ENSBTAP00000011774 | ZSCAN12     |
| gene:ENSBTAG00000040459.1 | transcript:ENSBTAT00000052426.1 | pep:ENSBTAP00000048758 | na          |
| gene:ENSBTAG00000011403.4 | transcript:ENSBTAT00000015156.4 | pep:ENSBTAP00000015156 | RUSC2       |
| gene:ENSBTAG00000015810.5 | transcript:ENSBTAT00000020999.5 | pep:ENSBTAP00000020999 | PLET1       |
| gene:ENSBTAG00000002773.5 | transcript:ENSBTAT00000003593.5 | pep:ENSBTAP00000003593 | na          |
| gene:ENSBTAG00000040392.2 | transcript:ENSBTAT00000010394.5 | pep:ENSBTAP00000010394 | na          |
| gene:ENSBTAG00000038368.2 | transcript:ENSBTAT00000056122.2 | pep:ENSBTAP00000051461 | SNRPG       |
| gene:ENSBTAG00000001810.4 | transcript:ENSBTAT00000002366.4 | pep:ENSBTAP00000002366 | SCAF11      |
| gene:ENSBTAG00000031355.1 | transcript:ENSBTAT00000044432.1 | pep:ENSBTAP00000041928 | na          |
| gene:ENSBTAG00000038286.1 | transcript:ENSBTAT00000055170.1 | pep:ENSBTAP00000048663 | na          |
| gene:ENSBTAG00000018290.4 | transcript:ENSBTAT00000024340.4 | pep:ENSBTAP00000024340 | IL9         |
| gene:ENSBTAG00000040367.1 | transcript:ENSBTAT00000044482.2 | pep:ENSBTAP00000048506 | na          |
| gene:ENSBTAG00000000697.5 | transcript:ENSBTAT00000039795.4 | pep:ENSBTAP00000039583 | RRP8        |
| gene:ENSBTAG00000033169.3 | transcript:ENSBTAT00000047111.2 | pep:ENSBTAP00000044341 | LAMB4       |

| Gene ID                    | Transcript ID                    | Peptide ID              | Gene Symbol |
|----------------------------|----------------------------------|-------------------------|-------------|
| gene:ENSBTAG00000015868.4  | transcript:ENSBTAT00000021092.4  | pep:ENSBTAP000000021092 | LIG4        |
| gene:ENSBTAG00000043990.2  | transcript:ENSBTAT00000061105.2  | pep:ENSBTAP000000053440 | KHDRBS2     |
| gene:ENSBTAG00000038794.2  | transcript:ENSBTAT000000053653.1 | pep:ENSBTAP000000047510 | TMEM245     |
| gene:ENSBTAG00000007823.4  | transcript:ENSBTAT000000010295.4 | pep:ENSBTAP000000010295 | TG          |
| gene:ENSBTAG00000001034.4  | transcript:ENSBTAT000000001371.4 | pep:ENSBTAP000000001371 | IL18R1      |
| gene:ENSBTAG000000012577.4 | transcript:ENSBTAT000000016697.4 | pep:ENSBTAP000000016697 | UVSSA       |
| gene:ENSBTAG000000015517.5 | transcript:ENSBTAT000000020621.4 | pep:ENSBTAP000000020621 | na          |
| gene:ENSBTAG000000045664.1 | transcript:ENSBTAT000000064452.1 | pep:ENSBTAP000000056252 | LRRC41      |
| gene:ENSBTAG000000015729.5 | transcript:ENSBTAT000000020879.5 | pep:ENSBTAP000000020879 | ADH7        |
| gene:ENSBTAG000000035710.4 | transcript:ENSBTAT000000061334.2 | pep:ENSBTAP000000053687 | ZBBX        |
| gene:ENSBTAG000000015839.5 | transcript:ENSBTAT000000021045.5 | pep:ENSBTAP000000021045 | MAP4        |
| gene:ENSBTAG000000019919.4 | transcript:ENSBTAT000000026536.4 | pep:ENSBTAP000000026536 | na          |
| gene:ENSBTAG000000002501.5 | transcript:ENSBTAT000000003250.5 | pep:ENSBTAP000000003250 | CUEDC2      |
| gene:ENSBTAG000000004585.5 | transcript:ENSBTAT000000006021.4 | pep:ENSBTAP000000006021 | CCDC30      |
| gene:ENSBTAG000000011481.5 | transcript:ENSBTAT000000065322.1 | pep:ENSBTAP000000056128 | IL12RB1     |
| gene:ENSBTAG000000011036.5 | transcript:ENSBTAT000000014658.5 | pep:ENSBTAP000000014658 | CEACAM20    |
| gene:ENSBTAG000000024891.4 | transcript:ENSBTAT000000034665.4 | pep:ENSBTAP000000034552 | na          |
| gene:ENSBTAG000000007955.5 | transcript:ENSBTAT000000010460.3 | pep:ENSBTAP000000010460 | SEZ6L2      |
| gene:ENSBTAG000000046727.1 | transcript:ENSBTAT000000062985.1 | pep:ENSBTAP000000055309 | na          |
| gene:ENSBTAG000000036297.3 | transcript:ENSBTAT000000050795.3 | pep:ENSBTAP000000047450 | RBFA        |
| gene:ENSBTAG000000019686.5 | transcript:ENSBTAT000000047448.3 | pep:ENSBTAP000000044656 | NCKAP1L     |
| gene:ENSBTAG000000005190.4 | transcript:ENSBTAT00000006842.4  | pep:ENSBTAP00000006842  | TSC1        |

**Supplementary Table S2** Summary of positively selected genes in ibex lineage. All gene IDs, transcript IDs, and peptide IDs are annotated from cattle.

| Gene ID                   | Transcript ID                   | Peptide ID             | Gene Symbol |
|---------------------------|---------------------------------|------------------------|-------------|
| gene:ENSBTAG00000020633.2 | transcript:ENSBTAT00000027497.2 | pep:ENSBTAP00000027497 | NOB1        |
| gene:ENSBTAG00000009850.3 | transcript:ENSBTAT00000039003.2 | pep:ENSBTAP00000038807 | na          |
| gene:ENSBTAG00000020573.5 | transcript:ENSBTAT00000027416.5 | pep:ENSBTAP00000027416 | SCUBE2      |
| gene:ENSBTAG00000016407.5 | transcript:ENSBTAT00000021815.5 | pep:ENSBTAP00000021815 | IRX6        |
| gene:ENSBTAG00000014762.5 | transcript:ENSBTAT00000065058.1 | pep:ENSBTAP00000056176 | ISG20       |
| gene:ENSBTAG00000020155.5 | transcript:ENSBTAT00000064867.1 | pep:ENSBTAP00000054813 | RP1L1       |
| gene:ENSBTAG00000044195.2 | transcript:ENSBTAT00000061463.2 | pep:ENSBTAP00000053549 | SDK2        |
| gene:ENSBTAG00000011349.5 | transcript:ENSBTAT00000015083.5 | pep:ENSBTAP00000015083 | CDH24       |
| gene:ENSBTAG00000021791.4 | transcript:ENSBTAT00000029045.4 | pep:ENSBTAP00000029045 | PARP9       |
| gene:ENSBTAG00000019231.4 | transcript:ENSBTAT00000025606.4 | pep:ENSBTAP00000025606 | MAIP1       |
| gene:ENSBTAG00000045606.1 | transcript:ENSBTAT00000066010.1 | pep:ENSBTAP00000054961 | na          |
| gene:ENSBTAG00000002539.4 | transcript:ENSBTAT00000042716.3 | pep:ENSBTAP00000040347 | TRIOBP      |
| gene:ENSBTAG00000021557.2 | transcript:ENSBTAT00000028720.2 | pep:ENSBTAP00000028720 | FUT2        |
| gene:ENSBTAG00000000799.4 | transcript:ENSBTAT00000001057.4 | pep:ENSBTAP00000001057 | ICA1        |
| gene:ENSBTAG00000005183.5 | transcript:ENSBTAT00000006828.5 | pep:ENSBTAP00000006828 | MVK         |
| gene:ENSBTAG00000040305.2 | transcript:ENSBTAT00000057213.2 | pep:ENSBTAP00000050373 | na          |
| gene:ENSBTAG00000023933.4 | transcript:ENSBTAT00000042743.3 | pep:ENSBTAP00000040372 | SEC16A      |
| gene:ENSBTAG00000014599.5 | transcript:ENSBTAT00000019433.5 | pep:ENSBTAP00000019433 | LRRC66      |
| gene:ENSBTAG00000012837.5 | transcript:ENSBTAT00000017057.5 | pep:ENSBTAP00000017057 | COL6A6      |
| gene:ENSBTAG00000037803.1 | transcript:ENSBTAT00000055475.1 | pep:ENSBTAP00000051224 | ZNF197      |
| gene:ENSBTAG00000009907.5 | transcript:ENSBTAT00000013073.5 | pep:ENSBTAP00000013073 | MAPK4       |
| gene:ENSBTAG00000026825.1 | transcript:ENSBTAT00000038349.1 | pep:ENSBTAP00000038164 | TMEM37      |
| gene:ENSBTAG00000006721.5 | transcript:ENSBTAT00000047621.3 | pep:ENSBTAP00000044811 | TWISTNB     |
| gene:ENSBTAG00000008253.5 | transcript:ENSBTAT00000010864.5 | pep:ENSBTAP00000010864 | EXPH5       |

| Gene ID                    | Transcript ID                    | Peptide ID              | Gene Symbol |
|----------------------------|----------------------------------|-------------------------|-------------|
| gene:ENSBTAG00000038267.2  | transcript:ENSBTAT00000052988.2  | pep:ENSBTAP00000050887  | na          |
| gene:ENSBTAG00000001618.5  | transcript:ENSBTAT00000002122.5  | pep:ENSBTAP00000002122  | ALPK3       |
| gene:ENSBTAG00000002868.3  | transcript:ENSBTAT00000003720.3  | pep:ENSBTAP00000003720  | GPR6        |
| gene:ENSBTAG00000009192.5  | transcript:ENSBTAT00000005973.5  | pep:ENSBTAP00000005973  | na          |
| gene:ENSBTAG00000006635.3  | transcript:ENSBTAT00000008720.3  | pep:ENSBTAP00000008720  | DBX2        |
| gene:ENSBTAG00000047943.1  | transcript:ENSBTAT000000064919.1 | pep:ENSBTAP00000054477  | na          |
| gene:ENSBTAG00000004423.5  | transcript:ENSBTAT00000005797.5  | pep:ENSBTAP00000005797  | ARHGAP42    |
| gene:ENSBTAG00000013245.5  | transcript:ENSBTAT000000053490.2 | pep:ENSBTAP000000047648 | ITPR3       |
| gene:ENSBTAG00000012682.5  | transcript:ENSBTAT000000047528.3 | pep:ENSBTAP000000044729 | UNC13A      |
| gene:ENSBTAG00000005753.5  | transcript:ENSBTAT00000007566.5  | pep:ENSBTAP00000007566  | PARP6       |
| gene:ENSBTAG000000047174.1 | transcript:ENSBTAT000000064843.1 | pep:ENSBTAP00000054472  | na          |
| gene:ENSBTAG00000004464.5  | transcript:ENSBTAT00000005861.5  | pep:ENSBTAP00000005861  | C17orf53    |
| gene:ENSBTAG000000046101.1 | transcript:ENSBTAT000000064558.1 | pep:ENSBTAP00000055450  | na          |
| gene:ENSBTAG000000032224.3 | transcript:ENSBTAT000000023466.5 | pep:ENSBTAP000000023466 | na          |
| gene:ENSBTAG000000021150.5 | transcript:ENSBTAT000000032152.4 | pep:ENSBTAP000000032090 | na          |
| gene:ENSBTAG000000032429.3 | transcript:ENSBTAT000000046004.3 | pep:ENSBTAP000000043341 | OR10AD1     |
| gene:ENSBTAG000000038327.2 | transcript:ENSBTAT000000052094.2 | pep:ENSBTAP000000050462 | na          |
| gene:ENSBTAG000000047078.1 | transcript:ENSBTAT000000064859.1 | pep:ENSBTAP000000054706 | NTF4        |
| gene:ENSBTAG00000000712.5  | transcript:ENSBTAT00000000956.5  | pep:ENSBTAP00000000956  | FBXW2       |
| gene:ENSBTAG00000011922.5  | transcript:ENSBTAT00000015828.4  | pep:ENSBTAP00000015828  | PLEC        |
| gene:ENSBTAG00000006240.3  | transcript:ENSBTAT00000008190.2  | pep:ENSBTAP00000008190  | TLR4        |
| gene:ENSBTAG00000017426.5  | transcript:ENSBTAT000000023165.5 | pep:ENSBTAP000000023165 | PDCD6IP     |
| gene:ENSBTAG00000007062.5  | transcript:ENSBTAT00000009285.5  | pep:ENSBTAP00000009285  | IGFBP5      |
| gene:ENSBTAG000000047569.1 | transcript:ENSBTAT000000065958.1 | pep:ENSBTAP00000055893  | na          |
| gene:ENSBTAG000000048135.1 | transcript:ENSBTAT000000066155.1 | pep:ENSBTAP00000055469  | na          |

| Gene ID                    | Transcript ID                    | Peptide ID              | Gene Symbol |
|----------------------------|----------------------------------|-------------------------|-------------|
| gene:ENSBTAG00000000237.4  | transcript:ENSBTAT00000000291.4  | pep:ENSBTAP000000042520 | na          |
| gene:ENSBTAG000000039615.2 | transcript:ENSBTAT000000054186.2 | pep:ENSBTAP000000049857 | na          |
| gene:ENSBTAG000000020532.5 | transcript:ENSBTAT000000027356.5 | pep:ENSBTAP000000048750 | na          |
| gene:ENSBTAG000000018872.4 | transcript:ENSBTAT000000025122.4 | pep:ENSBTAP000000025122 | F12         |
| gene:ENSBTAG000000018134.5 | transcript:ENSBTAT000000024140.4 | pep:ENSBTAP000000024140 | AREG        |
| gene:ENSBTAG000000003937.4 | transcript:ENSBTAT000000005143.4 | pep:ENSBTAP000000005143 | na          |
| gene:ENSBTAG000000021310.5 | transcript:ENSBTAT000000018302.5 | pep:ENSBTAP000000018302 | COL4A4      |
| gene:ENSBTAG000000005154.4 | transcript:ENSBTAT000000006789.4 | pep:ENSBTAP000000006789 | APCDD1      |
| gene:ENSBTAG000000040153.2 | transcript:ENSBTAT000000053199.2 | pep:ENSBTAP000000050564 | na          |
| gene:ENSBTAG000000030564.3 | transcript:ENSBTAT000000043163.3 | pep:ENSBTAP000000040753 | na          |
| gene:ENSBTAG000000014768.5 | transcript:ENSBTAT000000019646.5 | pep:ENSBTAP000000019646 | ZNF786      |
| gene:ENSBTAG000000046228.1 | transcript:ENSBTAT000000064530.1 | pep:ENSBTAP000000056226 | na          |
| gene:ENSBTAG000000046321.1 | transcript:ENSBTAT000000015433.5 | pep:ENSBTAP000000015433 | TSPOAP1     |
| gene:ENSBTAG000000006933.5 | transcript:ENSBTAT000000009104.5 | pep:ENSBTAP000000009104 | PPP1R10     |
| gene:ENSBTAG000000024545.4 | transcript:ENSBTAT000000017605.5 | pep:ENSBTAP000000017605 | DCHS2       |
| gene:ENSBTAG000000046313.1 | transcript:ENSBTAT000000063186.1 | pep:ENSBTAP000000055319 | CCDC54      |
| gene:ENSBTAG000000004232.5 | transcript:ENSBTAT000000005544.5 | pep:ENSBTAP000000005544 | TMIE        |
| gene:ENSBTAG000000002853.5 | transcript:ENSBTAT000000043065.2 | pep:ENSBTAP000000040660 | HRC         |
| gene:ENSBTAG000000027629.4 | transcript:ENSBTAT000000004244.5 | pep:ENSBTAP000000004244 | na          |
| gene:ENSBTAG000000025320.4 | transcript:ENSBTAT000000049153.3 | pep:ENSBTAP000000046086 | AKAP1       |
| gene:ENSBTAG000000012721.4 | transcript:ENSBTAT000000016909.4 | pep:ENSBTAP000000016909 | HOGA1       |
| gene:ENSBTAG000000048115.1 | transcript:ENSBTAT000000063444.1 | pep:ENSBTAP000000056282 | na          |
| gene:ENSBTAG000000025526.4 | transcript:ENSBTAT000000035900.4 | pep:ENSBTAP000000035767 | MDC1        |
| gene:ENSBTAG000000002962.5 | transcript:ENSBTAT000000003860.5 | pep:ENSBTAP000000003860 | na          |
| gene:ENSBTAG000000046138.1 | transcript:ENSBTAT000000063124.1 | pep:ENSBTAP000000056436 | C1orf68     |



**Supplementary Table S3** Enrichment results of positively selected genes in goats

| Terms                       | Database | ID           | Input number | Background number | P-Value     | Corrected P-Value | Input                                                                                                                                                                                                                                                                     |
|-----------------------------|----------|--------------|--------------|-------------------|-------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Olfactory Signaling Pathway | Reactome | R-HSA-381753 | 6            | 393               | 0.000383927 | 0.026174537       | ENSBTAP00000055309 ENSBTAP00000034552 ENSBTAP00000048758 ENSBTAP00000041000 ENSBTAP00000038888 ENSBTAP00000020621                                                                                                                                                         |
| Immune System               | Reactome | R-HSA-168256 | 14           | 2096              | 0.000435853 | 0.026174537       | ENSBTAP00000013702 ENSBTAP00000003593 ENSBTAP00000044656 ENSBTAP00000003821 ENSBTAP00000041928 ENSBTAP00000010969 ENSBTAP00000018027 ENSBTAP00000002951 ENSBTAP00000052286 ENSBTAP00000034373 ENSBTAP00000024340 ENSBTAP00000056252 ENSBTAP00000056128 ENSBTAP00000001371 |

**Supplementary Table S4** GO enrichment of positively selected genes in goats

| Terms                                           | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| leukocyte mediated immunity                     | Gene Ontology | GO:0002443 | 3            | 32                | 7.97E-05 | 0.024096          | ENSBTAP00000009631 ENSBTAP00000022355 ENSBTAP00000056315                                                                                                                                                                                                                                                             |
| negative regulation of cell cycle arrest        | Gene Ontology | GO:0071157 | 2            | 5                 | 0.000116 | 0.024096          | ENSBTAP00000055397 ENSBTAP00000055770                                                                                                                                                                                                                                                                                |
| L-amino acid transmembrane transporter activity | Gene Ontology | GO:0015179 | 2            | 5                 | 0.000116 | 0.024096          | ENSBTAP00000023823 ENSBTAP00000010394                                                                                                                                                                                                                                                                                |
| cellular anatomical entity                      | Gene Ontology | GO:0110165 | 18           | 2864              | 0.000128 | 0.024096          | ENSBTAP00000015977 ENSBTAP00000016173 ENSBTAP00000038979 ENSBTAP00000013702 ENSBTAP00000047510 ENSBTAP00000029169 ENSBTAP0000000084 ENSBTAP00000010969 ENSBTAP00000056315 ENSBTAP00000050989 ENSBTAP00000034373 ENSBTAP00000038888 ENSBTAP00000056252 ENSBTAP00000053954 ENSBTAP00000056128 ENSBTAP00000020621 ENSBT |

| Terms                                                         | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                               |
|---------------------------------------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                               |               |            |              |                   |          |                   | AP00000055421 ENSBTAP00000017800                                                                                                                                                                                                    |
| membrane                                                      | Gene Ontology | GO:0016020 | 12           | 1443              | 0.000167 | 0.024096          | ENSBTAP00000023823 ENSBTAP00000038979 ENSBTAP00000047510 ENSBTAP00000028547 ENSBTAP00000009631 ENSBTAP00000018027 ENSBTAP0000002538 ENSBTAP00000010394 ENSBTAP00000038888 ENSBTAP00000041928 ENSBTAP000000056252 ENSBTAP00000018202 |
| histone-lysine N-methyltransferase activity                   | Gene Ontology | GO:0018024 | 2            | 7                 | 0.000198 | 0.024096          | ENSBTAP00000055397 ENSBTAP00000055770                                                                                                                                                                                               |
| alpha-beta T cell differentiation involved in immune response | Gene Ontology | GO:0002293 | 2            | 7                 | 0.000198 | 0.024096          | ENSBTAP00000056128 ENSBTAP00000001371                                                                                                                                                                                               |
| histone methyltransferase activity                            | Gene Ontology | GO:0042054 | 2            | 9                 | 0.000301 | 0.025515          | ENSBTAP00000055397 ENSBTAP00000055770                                                                                                                                                                                               |
| site of                                                       | Gene          | GO:0035861 | 2            | 9                 | 0.000301 | 0.025515          | ENSBTAP00000055397 ENSBTAP00000055770                                                                                                                                                                                               |

| Terms                                      | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                 |
|--------------------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| double-strand break                        | Ontology      |            |              |                   |          |                   | P00000055770                                                                                                                                                                                                                          |
| L-alpha-amino acid transmembrane transport | Gene Ontology | GO:1902475 | 2            | 9                 | 0.000301 | 0.025515          | ENSBTAP00000023823 ENSBTAP00000010394                                                                                                                                                                                                 |
| nitrogen compound metabolic process        | Gene Ontology | GO:0006807 | 12           | 1541              | 0.000302 | 0.025515          | ENSBTAP00000016697 ENSBTAP00000009973 ENSBTAP00000048506 ENSBTAP00000048421 ENSBTAP00000010295 ENSBTAP00000009631 ENSBTAP00000009810 ENSBTAP00000018816 ENSBTAP00000002951 ENSBTAP00000039583 ENSBTAP000000052174 ENSBTAP000000028448 |
| single-stranded DNA binding                | Gene Ontology | GO:0003697 | 2            | 10                | 0.000361 | 0.026175          | ENSBTAP000000055397 ENSBTAP000000055770                                                                                                                                                                                               |
| positive regulation of ATPase activity     | Gene Ontology | GO:0032781 | 2            | 10                | 0.000361 | 0.026175          | ENSBTAP000000055397 ENSBTAP000000055770                                                                                                                                                                                               |
| DNA catabolic process                      | Gene Ontology | GO:0006308 | 2            | 11                | 0.000426 | 0.026175          | ENSBTAP000000055397 ENSBTAP000000055770                                                                                                                                                                                               |

| Terms                             | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                    |
|-----------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| positive regulation of cell cycle | Gene Ontology | GO:0045787 | 3            | 61                | 0.000483 | 0.026175          | ENSBTAP00000055397 ENSBTAP00000055770 ENSBTAP00000018816                                                                                                                                                                                 |
| TOR signaling                     | Gene Ontology | GO:0031929 | 2            | 12                | 0.000496 | 0.026175          | ENSBTAP00000023823 ENSBTAP00000010394                                                                                                                                                                                                    |
| ion binding                       | Gene Ontology | GO:0043167 | 9            | 962               | 0.000501 | 0.026175          | ENSBTAP00000020580 ENSBTAP00000038979 ENSBTAP00000003821 ENSBTAP00000010295 ENSBTAP00000009810 ENSBTAP00000015052 ENSBTAP000000052286 ENSBTAP00000015977 ENSBTAP00000024275                                                              |
| olfactory receptor activity       | Gene Ontology | GO:0004984 | 3            | 67                | 0.000628 | 0.028604          | ENSBTAP00000048758 ENSBTAP00000041000 ENSBTAP00000034552                                                                                                                                                                                 |
| binding                           | Gene Ontology | GO:0005488 | 14           | 2247              | 0.00086  | 0.034926          | ENSBTAP00000020580 ENSBTAP00000003008 ENSBTAP00000022355 ENSBTAP000000052542 ENSBTAP00000015052 ENSBTAP00000056315 ENSBTAP00000055397 ENSBTAP00000024340 ENSBTAP00000055770 ENSBTAP00000023743 ENSBTAP00000020621 ENSBTAP00000015977 ENS |

| Terms                                   | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                |
|-----------------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------|
|                                         |               |            |              |                   |          |                   | BTAP00000024275 ENSBTAP00000021092                                                                                                   |
| molecular function regulator            | Gene Ontology | GO:0098772 | 5            | 307               | 0.000901 | 0.035291          | ENSBTAP00000010295 ENSBTAP00000000084 ENSBTAP00000009631 ENSBTAP00000044656 ENSBTAP00000028448                                       |
| sensory perception of chemical stimulus | Gene Ontology | GO:0007606 | 3            | 78                | 0.00096  | 0.036324          | ENSBTAP00000041000 ENSBTAP00000034552 ENSBTAP00000038888                                                                             |
| embryonic appendage morphogenesis       | Gene Ontology | GO:0035113 | 2            | 18                | 0.001026 | 0.036577          | ENSBTAP00000026607 ENSBTAP00000000084                                                                                                |
| metal ion binding                       | Gene Ontology | GO:0046872 | 7            | 657               | 0.001034 | 0.036577          | ENSBTAP00000021092 ENSBTAP00000003821 ENSBTAP00000002366 ENSBTAP00000055397 ENSBTAP00000054874 ENSBTAP00000055770 ENSBTAP00000046998 |
| amino acid transmembrane transport      | Gene Ontology | GO:0003333 | 2            | 20                | 0.001243 | 0.042622          | ENSBTAP00000023823 ENSBTAP00000010394                                                                                                |
| cell migration                          | Gene          | GO:0016477 | 4            | 198               | 0.001389 | 0.045127          | ENSBTAP00000000084 ENSBTAP                                                                                                           |

| Terms                            | Database      | ID         | Input number | Background number | P-Value  | Corrected P-Value | Input                                              |
|----------------------------------|---------------|------------|--------------|-------------------|----------|-------------------|----------------------------------------------------|
|                                  | Ontology      |            |              |                   |          |                   | P00000020999 ENSBTAP00000029204 ENSBTAP00000041928 |
| stem cell population maintenance | Gene Ontology | GO:0019827 | 2            | 22                | 0.001481 | 0.045127          | ENSBTAP00000021092 ENSBTAP00000028930              |
| immune receptor activity         | Gene Ontology | GO:0140375 | 2            | 22                | 0.001481 | 0.045127          | ENSBTAP000000056128 ENSBTAP00000001371             |
| histone methylation              | Gene Ontology | GO:0016571 | 2            | 23                | 0.001607 | 0.047652          | ENSBTAP000000055397 ENSBTAP000000055770            |

**Supplementary Table S5** Enrichment results of positively selected genes in ibex

| Terms                         | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                           |
|-------------------------------|----------|--------------|--------------|-------------------|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Signal Transduction           | Reactome | R-HSA-162582 | 16           | 2689              | 4.67E-06 | 0.004741707       | ENSBTAP00000049857 ENSBTAP00000018302 ENSBTAP00000023466 ENSBTAP00000050887 ENSBTAP00000043341 ENSBTAP00000027416 ENSBTAP00000050373 ENSBTAP00000055893 ENSBTAP00000005797 ENSBTAP00000054961 ENSBTAP00000054706 ENSBTAP00000017057 ENSBTAP00000056282 ENSBTAP00000050462 ENSBTAP00000047648 ENSBTAP00000024140 |
| G alpha (s) signalling events | Reactome | R-HSA-418555 | 7            | 536               | 2.84E-05 | 0.009824554       | ENSBTAP00000049857 ENSBTAP00000023466 ENSBTAP00000050887 ENSBTAP00000043341 ENSBTAP00000050373 ENSBTAP00000054961 ENSBTAP00000056282                                                                                                                                                                            |
| Olfactory Signaling Pathway   | Reactome | R-HSA-381753 | 6            | 393               | 4.71E-05 | 0.012234788       | ENSBTAP00000023466 ENSBTAP00000050887 ENSBTAP00000043341 ENSBTAP00000050373 ENSBTAP00000054961 ENSBTAP00000056282                                                                                                                                                                                               |

| Terms                                                        | Database | ID            | Input number | Background number | P-Value     | Corrected P-Value | Input                                                                                                                             |
|--------------------------------------------------------------|----------|---------------|--------------|-------------------|-------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Signaling by Receptor Tyrosine Kinases                       | Reactome | R-HSA-9006934 | 6            | 458               | 0.000108032 | 0.018689559       | ENSBTAP00000018302 ENSBTAP00000054706 ENSBTAP00000047648 ENSBTAP00000055893 ENSBTAP00000017057 ENSBTAP00000024140                 |
| ER to Golgi Anterograde Transport                            | Reactome | R-HSA-199977  | 4            | 154               | 0.000130685 | 0.019378733       | ENSBTAP00000040753 ENSBTAP00000004244 ENSBTAP00000040372 ENSBTAP00000024140                                                       |
| Assembly of collagen fibrils and other multimeric structures | Reactome | R-HSA-2022090 | 3            | 60                | 0.00015104  | 0.019597417       | ENSBTAP00000015828 ENSBTAP00000018302 ENSBTAP00000017057                                                                          |
| Transport to the Golgi and subsequent modification           | Reactome | R-HSA-948021  | 4            | 185               | 0.00025935  | 0.022783787       | ENSBTAP00000040753 ENSBTAP00000004244 ENSBTAP00000040372 ENSBTAP00000024140                                                       |
| GPCR downstream signalling                                   | Reactome | R-HSA-388396  | 8            | 1108              | 0.000435324 | 0.030929016       | ENSBTAP00000049857 ENSBTAP00000023466 ENSBTAP00000050887 ENSBTAP00000043341 ENSBTAP00000050373 ENSBTAP00000054961 ENSBTAP00000005 |

| Terms                               | Database | ID            | Input number | Background number | P-Value     | Corrected P-Value | Input                                                                                                                                                   |
|-------------------------------------|----------|---------------|--------------|-------------------|-------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                     |          |               |              |                   |             |                   | 6282 ENSBTAP00000047648                                                                                                                                 |
| Collagen formation                  | Reactome | R-HSA-1474290 | 3            | 89                | 0.000461902 | 0.030929016       | ENSBTAP00000015828 ENSBTAP00000018302 ENSBTAP00000017057                                                                                                |
| Cell junction organization          | Reactome | R-HSA-446728  | 3            | 90                | 0.000476748 | 0.030929016       | ENSBTAP00000015083 ENSBTAP00000053549 ENSBTAP00000015828                                                                                                |
| Nicotinamide salvaging              | Reactome | R-HSA-197264  | 2            | 19                | 0.000533948 | 0.032602263       | ENSBTAP00000007566 ENSBTAP00000029045                                                                                                                   |
| Signaling by GPCR                   | Reactome | R-HSA-372790  | 8            | 1170              | 0.000621019 | 0.033927243       | ENSBTAP00000049857 ENSBTAP00000023466 ENSBTAP00000050887 ENSBTAP00000043341 ENSBTAP00000050373 ENSBTAP00000054961 ENSBTAP00000056282 ENSBTAP00000047648 |
| Mitochondrial calcium ion transport | Reactome | R-HSA-8949215 | 2            | 23                | 0.000759598 | 0.038926863       | ENSBTAP00000046086 ENSBTAP00000025606                                                                                                                   |

**Supplementary Table S6** GO ontology enrichment for Ibex Positive Selection Genes

| Term                                                          | Database      | ID         | Input number | Background number | P-Value     | Corrected P-Value | Input                                                                                                                                                                                                   |
|---------------------------------------------------------------|---------------|------------|--------------|-------------------|-------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| sensory perception                                            | Gene Ontology | GO:0007600 | 4            | 145               | 0.000104248 | 0.018689559       | ENSBTAP000000056282 ENSBTAP00000005544 ENSBTAP000000054961 ENSBTAP000000050887                                                                                                                          |
| DNA catabolic process                                         | Gene Ontology | GO:0006308 | 2            | 11                | 0.000199992 | 0.022783787       | ENSBTAP000000056176 ENSBTAP000000054477                                                                                                                                                                 |
| regulation of blood coagulation                               | Gene Ontology | GO:0030193 | 2            | 12                | 0.000233079 | 0.022783787       | ENSBTAP000000008190 ENSBTAP000000025122                                                                                                                                                                 |
| detection of chemical stimulus involved in sensory perception | Gene Ontology | GO:0050907 | 3            | 73                | 0.000263396 | 0.022783787       | ENSBTAP000000043341 ENSBTAP000000054961 ENSBTAP000000050887                                                                                                                                             |
| regulation of biological process                              | Gene Ontology | GO:0050789 | 10           | 1778              | 0.000576837 | 0.033264293       | ENSBTAP000000040660 ENSBTAP000000021815 ENSBTAP000000010864 ENSBTAP000000029045 ENSBTAP000000023165 ENSBTAP000000050373 ENSBTAP000000005797 ENSBTAP000000055450 ENSBTAP000000054477 ENSBTAP000000050564 |
| I band                                                        | Gene          | GO:003167  | 2            | 24                | 0.00082203  | 0.0389268         | ENSBTAP000000040660 ENSBTAP                                                                                                                                                                             |

|                            |               |            |    |      |             |             |                                                                                                                                                                                                  |
|----------------------------|---------------|------------|----|------|-------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            | Ontology      | 4          |    |      | 8           | 63          | 00000004244                                                                                                                                                                                      |
|                            |               |            |    |      |             |             | ENSBTAP000000040660 ENSBTAP00000027497 ENSBTAP00000005124 ENSBTAP00000016909 ENSBTAP000000025606 ENSBTAP00000055893 ENSBTAP00000015433 ENSBTAP000000046086 ENSBTAP0000050462 ENSBTAP000000054706 |
| intracellular organelle    | Gene Ontology | GO:0043229 | 10 | 1863 | 0.000825039 | 0.038926863 |                                                                                                                                                                                                  |
| collagen metabolic process | Gene Ontology | GO:0032963 | 2  | 27   | 0.001023699 | 0.046199984 | ENSBTAP00000018302 ENSBTAP00000017057                                                                                                                                                            |

**Supplementary Table S7** Summary of candidate accelerated GO categories in goat and ibex lineages

| Pathway ID | G-dNdS | I-dNdS | Group | Description                                          |
|------------|--------|--------|-------|------------------------------------------------------|
| GO:0030545 | 0.34   | 0.18   | Goat  | mitochondrial protein complex                        |
| GO:0045787 | 0.31   | 0.26   | Goat  | lymphocyte mediated immunity                         |
| GO:0002683 | 0.31   | 0.20   | Goat  | receptor regulator activity                          |
| GO:0002696 | 0.31   | 0.19   | Goat  | antigen receptor-mediated signaling pathway          |
| GO:0004518 | 0.30   | 0.28   | Goat  | spindle pole                                         |
| GO:0006869 | 0.29   | 0.24   | Goat  | sensory perception of chemical stimulus              |
| GO:0005764 | 0.27   | 0.18   | Goat  | carbohydrate binding                                 |
| GO:0002684 | 0.26   | 0.19   | Goat  | positive regulation of cell cycle                    |
| GO:0009314 | 0.26   | 0.20   | Goat  | negative regulation of immune system process         |
| GO:0034641 | 0.18   | 0.17   | Goat  | positive regulation of leukocyte activation          |
| GO:0001775 | 0.26   | 0.20   | Goat  | receptor-mediated endocytosis                        |
| GO:0003006 | 0.25   | 0.21   | Goat  | DNA biosynthetic process                             |
| GO:0016042 | 0.47   | 0.17   | Goat  | mitotic cell cycle checkpoint                        |
| GO:0045087 | 0.25   | 0.20   | Goat  | organelle outer membrane                             |
| GO:0046545 | 0.41   | 0.13   | Goat  | lipid transport                                      |
| GO:0006974 | 0.23   | 0.20   | Goat  | hydrolase activity, acting on glycosyl bonds         |
| GO:0030097 | 0.23   | 0.17   | Goat  | cytokine-mediated signaling pathway                  |
| GO:0006955 | 0.22   | 0.20   | Goat  | peptidase regulator activity                         |
| GO:0033554 | 0.20   | 0.16   | Goat  | monooxygenase activity                               |
| GO:0031982 | 0.19   | 0.15   | Goat  | detection of stimulus involved in sensory perception |
| GO:0002376 | 0.19   | 0.17   | Goat  | cellular component organization or biogenesis        |
| GO:0070062 | 0.18   | 0.14   | Goat  | defense response to bacterium                        |
| GO:1903561 | 0.18   | 0.17   | Goat  | vacuolar membrane                                    |
| GO:0034645 | 0.18   | 0.15   | Goat  | selective autophagy                                  |
| GO:0043229 | 0.18   | 0.16   | Goat  | myeloid cell differentiation                         |
| GO:0071944 | 0.18   | 0.17   | Goat  | establishment of localization                        |
| GO:0099503 | 0.30   | 0.22   | Goat  | positive regulation of mitophagy                     |
| GO:0007165 | 0.17   | 0.16   | Goat  | response to radiation                                |
| GO:0050794 | 0.17   | 0.16   | Goat  | peptidase inhibitor activity                         |
| GO:0046879 | 0.27   | 0.10   | Goat  | protein C-terminus binding                           |
| GO:0010817 | 0.22   | 0.16   | Goat  | cell activation                                      |
| GO:0031224 | 0.17   | 0.16   | Goat  | neurotransmitter transport                           |
| GO:0050851 | 0.34   | 0.35   | Ibex  | amino acid transport                                 |
| GO:0006898 | 0.30   | 0.31   | Ibex  | mitotic nuclear division                             |
| GO:0030879 | 0.26   | 0.38   | Ibex  | glycosaminoglycan binding                            |
| GO:0050663 | 0.25   | 0.39   | Ibex  | fatty acid metabolic process                         |
| GO:0050727 | 0.24   | 0.33   | Ibex  | active ion transmembrane transporter activity        |
| GO:0051656 | 0.24   | 0.29   | Ibex  | regulation of response to DNA damage stimulus        |
| GO:0002250 | 0.23   | 0.30   | Ibex  | response to nutrient                                 |
| GO:0031334 | 0.21   | 0.40   | Ibex  | small molecule catabolic process                     |
| GO:0051251 | 0.21   | 0.30   | Ibex  | response to other organism                           |

| Pathway ID | G-dNdS | I-dNdS | Group | Description                                               |
|------------|--------|--------|-------|-----------------------------------------------------------|
| GO:0016072 | 0.21   | 0.44   | Ibex  | negative regulation of cell adhesion                      |
| GO:0006281 | 0.20   | 0.26   | Ibex  | regulation of membrane potential                          |
| GO:0006310 | 0.20   | 0.31   | Ibex  | cellular response to stress                               |
| GO:0051707 | 0.20   | 0.22   | Ibex  | nuclear envelope                                          |
| GO:0002703 | 0.19   | 0.43   | Ibex  | regulation of transmembrane transport                     |
| GO:0038023 | 0.18   | 0.21   | Ibex  | cellular macromolecule biosynthetic process               |
| GO:0060089 | 0.18   | 0.21   | Ibex  | guanyl-nucleotide exchange factor activity                |
| GO:0016301 | 0.17   | 0.21   | Ibex  | response to biotic stimulus                               |
| GO:0009607 | 0.18   | 0.22   | Ibex  | RNA splicing, via transesterification reactions           |
| GO:0098687 | 0.18   | 0.28   | Ibex  | regulation of cellular component size                     |
| GO:0006364 | 0.18   | 0.39   | Ibex  | cell adhesion                                             |
| GO:0007186 | 0.20   | 0.26   | Ibex  | oxoacid metabolic process                                 |
| GO:0051345 | 0.15   | 0.23   | Ibex  | cellular response to toxic substance                      |
| GO:0043167 | 0.16   | 0.17   | Ibex  | inorganic ion homeostasis                                 |
| GO:0043233 | 0.16   | 0.18   | Ibex  | binding                                                   |
| GO:0042221 | 0.16   | 0.18   | Ibex  | non-membrane-bounded organelle                            |
| GO:0032561 | 0.16   | 0.30   | Ibex  | transition metal ion binding                              |
| GO:0007154 | 0.16   | 0.17   | Ibex  | negative regulation of cellular protein metabolic process |
| GO:0002831 | 0.20   | 0.32   | Ibex  | nucleoside phosphate binding                              |
| GO:0001816 | 0.20   | 0.27   | Ibex  | positive regulation of apoptotic process                  |
| GO:0022402 | 0.13   | 0.20   | Ibex  | detection of chemical stimulus                            |
| GO:0044706 | 0.12   | 0.29   | Ibex  | channel activity                                          |
| GO:0008643 | 0.18   | 0.41   | Ibex  | embryo development ending in birth or egg hatching        |

**Supplementary Table S8** Top 20 enrichment results for allele-specific expression genes in Reactome

| Terms         | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------|----------|--------------|--------------|-------------------|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immune System | Reactome | R-HSA-168256 | 144          | 2096              | 1.24E-32 | 9.59E-29          | TNFRSF25 LOC102168547 AP1M1 AGA C5AR2 SERPINB1 B2M CALM1 ACA A1 MIB2 PYGB C7H1orf35 IRAK3 STK11IP UNKL LTA4H HK3 CTSD SIGLEC10 LY96 CTSS SOS2 IKBKB CRCP AKT1 CXCL8 KIF5B FCER2 FBXL5 VIM PTGES2 TLR9 ELMO2 CD300E RASGRP1 CCL5 NFKBIA MX2 NCSTN IRS2 TRIB3 ICOSLG IFIT3 TIRAP DGAT1 ZBP1 TRAF7 FBXL12 OSM LOC102186356 PJA2 RAB7A CSK TICAM2 HERC1 HERC6 ANAPC1 ITPR3 RHOA RPS6KA5 IRF5 LOC102171703 TNFAIP6 HMOX2 TCIRG1 CD14 FBXO30 PPIA SIGIRR PPP2R5D BAIAP2 CD3G LOC102184087 NCF2 NCF1 PTX3 LOC102183941 AMPD3 ARRB1 DCTN2 AREG IL9R STAT1 ACTR10 PGLYRP1 FBXW8 LOC102170640 MARK3 PML DUSP4 MAPK8 DUSP6 BOLA2B ATP6V0B LOC102179713 SH3RF1 LTB FBXW2 LOC102188986 NUP50 CDA RBSN MAP2K1 GLB1 AGPAT2 PRKACB NBEAL2 MVP NCKAP1L CD55 CD |

| Terms                      | Database | ID           | Input<br>number | Background<br>number | P-Value  | Corrected<br>P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------|----------|--------------|-----------------|----------------------|----------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |          |              |                 |                      |          |                      | 58 CD59 BIRC3 NLRC4 PLCG1 RIPK2 ATP11B PGLYRP4 P2RX1 BTN2A2 LOC102190927 ARHGAP45 PPL CXCR1 NOD2 ITGAL DPP7 RAC1 PRKCD PLAU LOC108633263 LOC102180421 LOC102178567 DUSP16 EIF4E3 LOC102176695 SAMHD1 LOC102176691 CFD LOC102189932 MAP3K14 PLAC8 LNPEP CM6                                                                                                                                                                                                                          |
| Innate<br>Immune<br>System | Reactome | R-HSA-168249 | 89              | 1043                 | 4.40E-26 | 1.70E-22             | LOC102168547 AP1M1 AGA C5AR2 SERPINB1 B2M CALM1 CXCR1 PYGB C7H1orf35 IRAK3 STK11IP LTA4H HK3 CTSD LY96 CTSS IKBKB CRCP PTGES2 TLR9 ELMO2 CD300E RASGRP1 NFKBIA NCSTN TIRAP DGAT1 ZBP1 RAB7A ITPR3 RHOA ACTR10 RPS6KA5 TNFAIP6 HMOX2 TCIRG1 CD14 ITGAL PPIA SIGIRR PPP2R5D BAIAP2 CD3G NCF2 NCF1 LOC102183941 AMPD3 MAP2K1 TICAM2 PTX3 DUSP4 MAPK8 DUSP6 ATP6V0B CDA RBSN PGLYRP1 GLB1 AGPAT2 PRKACB NBEAL2 MVP NCKA P1L CD55 CD58 CD59 BIRC3 NLRC4 PLCG1 RIPK2 ATP11B PGLYRP4 P2RX1 |

| Terms                    | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                 |
|--------------------------|----------|---------------|--------------|-------------------|----------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |          |               |              |                   |          |                   | ARHGAP45 ACAA1 NOD2 DPP7 RAC1<br> PRKCD PLAU LOC108633263 LOC102180421 LOC102178567 LOC102176691<br> CFD MAP3K14 PLAC8 CMTM6                                                                                                                                                                                                          |
| Neutrophil degranulation | Reactome | R-HSA-6798695 | 51           | 478               | 4.79E-19 | 5.30E-16          | NCKAP1L LOC102168547 ACTR10 AMPD3 CD58 AP1M1 AGA NCSTN LTA4H B2M NBEAL2 P2RX1 ARHGAP45 TICAM2 DGAT1 PLAC8 PTX3 ACAA1 CXCR1 C7H1orf35 STK11IP DPP7 MVP RAB7A CD59 RAC1 HK3 CTSD PRKCD PLAU PYGB CD55 LOC102180421 SERPINB1 RHOA CTSS CDA LOC102176691 PTGES2 CFD TNFAIP6 PGLYRP1 GLB1 HMOX2 TCIRG1 CD14 ITGAL AGPAT2 CMTM6 PPIA ATP11B |
| Metabolism               | Reactome | R-HSA-1430728 | 113          | 2075              | 4.44E-18 | 3.61E-15          | NQO2 AKT1 PYCR2 ASS1 CALM1 TIAM2 PYGB NDUFA10 PYGM FMO2 HAL TBXAS1 HMGCL HK3 TNFRSF21 GNPAT CNDP2 INPP5A INPP5B INPP5E ADCY3 PTGES2 MMAB LOC102189950 TNFAIP8L2 SLC7A5 SERINC3 TRIB3 URO1 DGAT1 LOC102169935 LOC102186759 RIDA PNPLA2 TKT PNPLA7 HNMT SLC46A1 PARP4 NAXD ITPR3 BLVR                                                   |

| Terms                  | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------|----------|---------------|--------------|-------------------|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adaptive Immune System | Reactome | R-HSA-1280218 | 59           | 748               | 3.76E-16 | 2.64E-13          | A CSGALNACT2 UBE2I GALK1 LOC106503208 HMOX2 NUBP2 BTD HS6ST1 PPP2R5D LOC102183750 AMPD3 MBOAT7 HAAO NCOR2 TMEM86B SLC52A2 SACM1L GPCPD1 NDUFA3 RPS29 ARSG PRKAR1A CHST15 IDUA NUP50 CDA ACOX3 LOC102181832 GSTM3 GSTZ1 SLC22A13 GLB1 PITPNM1 AGPAT2 PRKACB DECR2 SLC35D1 SPHK1 RPS10 BPGM RPS19 NFYC PLCG1 LOC102189751 ADPGK GPD2 LTA4H OPLAH SLC37A1 PFKP CRYL1 ACAA1 PDK2 NARFL ST3GAL2 ST3GAL1 ESRRA LOC102190167 CHST11 UPP1 INPP1 SAMHD1 LOC102176691 SLC16A3 PFKFB2 OAZ2 PFKFB4 GNA15 LOC102189835 NDUFS6 SDHB |
|                        |          |               |              |                   |          |                   | UNKL NCF1 LOC102189932 LOC102168547 ACTR10 AP1M1 IKBKB ANAPC1 PLCG1 RIPK2 TRAF7 TRIB3 DCTN2 BTN2A2 ICOSLG ITGAL TIRAP ITPR3 SH3RF1 MIB2 PPL FBXW8 FBXL12 LOC102186356 MAP3K14 FBXW2 PJA2 LOC102183941 RAB7A NFKBIA CSK RAC1                                                                                                                                                                                                                                                                                           |

| Terms               | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------|----------|--------------|--------------|-------------------|----------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Signal Transduction | Reactome | R-HSA-162582 | 122          | 2689              | 7.24E-14 | 3.11E-11          | CTSD HERC1 LNPEP LOC108633263 SIGLEC10 HERC6 LY96 LOC102178567 CTSS NCF2 LOC102188986 LOC102176695 RASGRP1 AKT1 KIF5B CALM1 FBXL5 B2M LOC102190927 CD14 FBXO30 PRKACB PPP2R5D CD3G LOC102171703 PPIA CD300E                                                                                                                                                                                                                                                                                                                              |
|                     |          |              |              |                   |          |                   | AHCTF1 WLS C5AR2 AKT1 EEF2K CALM1 GRK6 ARHGEF7 RBPJ GRK5 GRK3 MIB2 ARHGAP22 DOK1 ARHGAP27 PLXND1 IGF1R LOC108638461 CTSD STK4 LOC102179758 IKBKB INPP5B ADCY3 CXCL8 KIF5B FCER2 F2R GRB7 GRB10 TLR9 ELMO2 LOC102189950 RASGRP1 CCL5 ITGA2 NFKBIA KAT2B NCSTN TRIB3 KREMEN1 SERPINE1 CKBR ADORA2B MAML2 MKL1 TIAM2 ACVRL1 SIRT6 CSK ITPR3 RHOA RPS6KA5 TAGAP TCIRG1 PPP2R5D BAIAP2 CCNK TFDP2 NCF2 NCF1 RXFP4 CCR3 LOC102180576 CTNND1 ARRB1 CBX6 NCOR2 AREG STAT1 ADAP1 MARK3 PML DUSP4 MAPK8 DUSP6 ATP6V0B FGD4 DAGLB LOC102185066 OTUL |

| Terms                  | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------|----------|--------------|--------------|-------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Metabolism of proteins | Reactome | R-HSA-392499 | 96           | 2012              | 3.25E-12 | 8.67E-10          | IN PRKAR1A GHSR TJP1 SOS2 TACC3 MAP2K1 IRS2 RGS19 PRKACB LPAR6 SPHK1 NCKAP1L CD55 ADGRE1 LOC102176598 PLCG1 RIPK2 ECE1 NOXA1 ADCYAP1R1 OPRL1 LOC102179713 ARHGAP45 FAS LOC102184572 UHMK1 CXCR1 PDK2 PXN ARHGDIA RGS9 PRKCH RAC1 PRKCD NUMB BIRC3 DUSP16 GNA15 MBD3 GPR132 FES                                                                                                                                                                                                 |
|                        |          |              |              |                   |          |                   | RPN1 CPM LOC102168547 B2M USP24 USP22 CALM1 EIF3E CUL9 COG2 WIP1 CTSD LOC102173518 LOC102179758 RNF185 CXCL8 KIF5B FBXL5 KDELR2 FOXK1 NFKBIA KAT2B NCSTN ARFGAP2 ADORA2B MKL1 TULP4 DERL1 FBXL12 TOP2B RAB7A TARS2 RHOA UBE2I LOC102184009 ITM2B FBXO30 ST8SIA4 LOC102182048 UBE2T MTRF1L EIF2B2 CARS2 ARRB1 DCTN2 POFUT2 NCOR2 AREG RAB8A PNPLA2 ACTR10 FBXW8 PML RAB13 CD59 OTULIN MRPS18A YKT6 LOC102169730 ST3GAL1 GOLM1 FBXW2 NUP50 GALNT10 ERO1B GLB1 RNF144A SPHK1 RPS1 |

| Terms                                  | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------|----------|---------------|--------------|-------------------|----------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        |          |               |              |                   |          |                   | 0 CD55 RPS19 USP3 BIRC3 NFYC MRPS15 RIPK2 OTUB1 LOC102184572 TGOLN2 NOD2 MGAT4A FEM1B RGS9 FEM1A ST3GAL2 PIGB TTLL1 ST3GAL5 RPS29 ARSG DPH7 MBD1 CREB3L4 DCAF4 TARS ATF3                                                                                                                                                   |
| Signaling by Receptor Tyrosine Kinases | Reactome | R-HSA-9006934 | 37           | 458               | 6.99E-11 | 1.13E-08          | NCF2 NCF1 NCKAP1L ITGA2 SPHK1 NCSTN AKT1 PLCG1 CTNND1 TRIB3 ADCYAP1R1 AREG STAT1 CALM1 ARHGEF7 ADAP1 PXN DUSP4 DUSP6 ATP6V0B IGF1R CSK RAC1 PRKCD FES ITPR3 RHOA RPS6KA5 GRB10 IRS2 TCIRG1 GRB7 PRKACB PPP2R5D BAIAP2 TLR9 ELMO2                                                                                           |
| Cytokine Signaling in Immune system    | Reactome | R-HSA-1280215 | 52           | 836               | 9.56E-11 | 1.45E-08          | RASGRP1 LOC102168547 CCL5 TRIB3 BIRC3 IKBKB AKT1 PLCG1 RIPK2 ARRB1 TLR9 IFIT3 AREG B2M STAT1 CALM1 LOC102170640 OSM MARK3 PML IRAK3 MAPK8 DUSP6 BOLA2B NFKBIA LOC102179713 CSK MX2 NOD2 PRKCD LTB TNFRSF25 DUSP4 DUSP16 SOCS2 EIF4E3 NUP50 SAMHD1 RPS6KA5 IRF5 FCER2 CXCL8 LOC102171703 MAP2K1 IRS2 VIM MAP3K14 SIGIRR PPP |

| Terms                       | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                 |
|-----------------------------|----------|---------------|--------------|-------------------|----------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |          |               |              |                   |          |                   | 2R5D IL9R LOC102184087 PPIA                                                                                                                                                                                                                                                           |
| Hemostasis                  | Reactome | R-HSA-109582  | 43           | 617               | 1.63E-10 | 2.25E-08          | RASGRP1 EHD1 CD58 SLC7A5 ITGA6 AKT1 PLCG1 DOCK9 KIF5B CD2 ARRB1 P2RX1 P2RX5 SERPINE1 CALM1 SLC8A1 CABLES2 ITGA2 PRKCH DAGLB CSK RAC1 PRKCD PLAU LOC102180421 LOC102169725 ITPR3 RHOA PLEK ATP2B4 AKAP1 RBSN CFD F2R GNA15 ITGAL GRB7 PRKACB PPP2R5D LOC102189950 SLC16A3 PPIA PRKAR1A |
| Toll-like Receptor Cascades | Reactome | R-HSA-168898  | 21           | 154               | 2.23E-10 | 2.97E-08          | TICAM2 CTSS NFKBIA RPS6KA5 TLR9 TIRAP RBSN BIRC3 MAP2K1 IKKBK LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4                                                                                                                                                |
| VEGFA-VEGFR2 Pathway        | Reactome | R-HSA-4420097 | 17           | 97                | 3.84E-10 | 4.50E-08          | NCF2 NCF1 NCKAP1L CALM1 ITPR3 RAC1 PRKCD SPHK1 AKT1 PLCG1 PRKACB PXN CTNND1 TRIB3 BAIAP2 RHOA ELMO2                                                                                                                                                                                   |
| Signaling by VEGF           | Reactome | R-HSA-194138  | 17           | 106               | 1.28E-09 | 1.31E-07          | NCF2 NCF1 NCKAP1L CALM1 ITPR3 RAC1 PRKCD SPHK1 AKT1 PLCG1 PRKACB PXN CTNND1 TRIB3 BAIAP2 RHOA ELMO2                                                                                                                                                                                   |
| Disease                     | Reactome | R-HSA-16      | 57           | 1049              | 1.43E-09 | 1.44E-07          | RPS10 LOC102168547 TRAK1 AP1M1                                                                                                                                                                                                                                                        |

| Terms                                   | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------|----------|--------------|--------------|-------------------|----------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         |          | 43685        |              |                   |          |                   | KAT2B NCSTN IKBKB AKT1 PLCG1 IRS2 CTNND1 ARRB1 KREMEN1 OPLAH AREG UBAP1 MAML2 STAT1 TIRAP RBPJ MIB2 NCOR2 DERL1 FAM114A2 MARK3 B2M RPS19 NFKBIA TBXAS1 CSK RAC1 CLCN6 RPS29 LOC108633263 GTF2E2 LY96 LOC102190167 IDUA FGFR1 VAMP1 NUP50 GALK1 RNF185 LOC106503208 SYT2 CALM1 MAP2K1 GLB1 CTDP1 BTD CD14 PPP2R5D SLC35D1 MMAB LOC102182048 PPIA CCNK                                                          |
| Post-translational protein modification | Reactome | R-HSA-597592 | 69           | 1412              | 1.79E-09 | 1.71E-07          | RPN1 ST8SIA4 RAB7A CPM FOXK1 CD55 USP3 BIRC3 KAT2B OTULIN RIPK2 ARFGAP2 ARRB1 DCTN2 DERL1 USP24 OTUB1 NCOR2 AREG RAB8A FBXO30 CALM1 POFUT2 ACTR10 LOC102184572 MKL1 TULP4 USP22 TGOLN2 PNPLA2 FBXL12 CUL9 NOD2 PML MBD1 RAB13 FEM1B FEM1A ST3GAL2 PIGB CD59 TTLL1 ST3GAL5 FBXW8 RHOA COG2 DCAF4 YKT6 ST3GAL1 LOC102173518 ARSG GOLM1 LOC102179758 FBXW2 UBE2I NUP50 GALNT10 DPH7 RNF185 TOP2B LOC102184009 FB |

| Terms                                           | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                   |
|-------------------------------------------------|----------|--------------|--------------|-------------------|----------|-------------------|-------------------------------------------------------------------------------------------------------------------------|
|                                                 |          |              |              |                   |          |                   | XL5 GLB1 MGAT4A NFKBIA RNF144A KDEL2 LOC102182048 UBE2T                                                                 |
| Toll Like Receptor TLR6:TLR2 Cascade            | Reactome | R-HSA-168188 | 16           | 95                | 2.09E-09 | 1.96E-07          | RPS6KA5 TIRAP NFKBIA MAP2K1 IKBKB LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4              |
| MyD88:MAPK cascade initiated on plasma membrane | Reactome | R-HSA-166058 | 16           | 95                | 2.09E-09 | 1.96E-07          | RPS6KA5 TIRAP NFKBIA MAP2K1 IKBKB LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4              |
| Toll Like Receptor 4 (TLR4) Cascade             | Reactome | R-HSA-166016 | 18           | 128               | 2.76E-09 | 2.46E-07          | TICAM2 RPS6KA5 TIRAP NFKBIA BIRC3 MAP2K1 IKBKB LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4 |
| Toll Like Receptor 2 (TLR2) Cascade             | Reactome | R-HSA-181438 | 16           | 98                | 3.12E-09 | 2.72E-07          | RPS6KA5 TIRAP NFKBIA MAP2K1 IKBKB LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4              |
| Toll Like Receptor TLR1:TLR2 Cascade            | Reactome | R-HSA-168179 | 16           | 98                | 3.12E-09 | 2.72E-07          | RPS6KA5 TIRAP NFKBIA MAP2K1 IKBKB LY96 CD14 RIPK2 LOC108633263 SIGIRR NOD2 PPP2R5D IRAK3 MAPK8 DUSP6 DUSP4              |



**Supplementary Table S9** Top 20 enrichment results for alternative splicing genes in Reactome

| Terms         | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------|----------|--------------|--------------|-------------------|----------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immune System | Reactome | R-HSA-168256 | 91           | 2096              | 9.91E-19 | 6.28E-15          | UBE2Q2 TNFRSF25 IKBKB PTK2B IKBKE LOC102186637 PECAM1 DYNLT1 MIB2 CUL7 IRAK4 HK3 SEC24D SIGLEC10 PLD4 CXCL8 KIF5B TARM1 ADAM8 CYLD LOC102175896 LOC102189890 RNF213 EVL UBE2D4 CD209 LAIR1 TIRAP MGAM PIK3R2 LOC102186356 SURF4 GHDC PKM IL4R ASB3 UBA7 HERC5 ITPR2 ANAPC2 RHO ITGAX IRF1 ABCE1 ZNR1 UBE2O IRF4 UBE2F ITGAM RNF125 CD19 LOC102169209 RAF1 STAT6 PELI1 STAT1 RACGAP1 ITGA2B MAPK9 RAB14 AREL1 IRF3 SH3RF1 UNC13D LOC102178529 FLT3LG UBE2V1 CLEC6A NBEAL2 LOC102175938 TOM1 BIRC3 PLCG2 MAP2K1 BIN2 FYB FYN ACAA1 NRG1 LOC102188617 CRACR2A CD44 TPP2 GALNS LOC102180421 LOC102186814 LOC102176695 RAB24 HVCN1 CASP9 ADAR |
| Innate Immune | Reactome | R-HSA-168249 | 55           | 1043              | 8.13E-15 | 6.43E-12          | LOC102169209 RAB14 HK3 FYN BIRC3 IKBKB CD209 TARM1 LAIR1 IKBK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| Terms      | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                            |
|------------|----------|---------------|--------------|-------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| System     |          |               |              |                   |          |                   | E RAF1 IRF3 BIN2 STAT6 PELI1 LOC102175938 TIRAP MGAM DYNLT1 ACAA1 PIK3R2 TOM1 MAPK9 LOC102188617 SURF4 IRAK4 CRACR2A ITGAX PECAM1 CD44 GALNS GHDC UBA7 UNC13D HERC5 LOC102180421 LOC102189890 ITPR2 UBE2V1 RHOF PLD4 LOC102178529 RAB24 PLCG2 HVCN1 MAP2K1 ADAM8 CASP9 CYLD ITGAM CLEC6A RNF125 PKM NBEAL2 CD19                                                                                  |
| Metabolism | Reactome | R-HSA-1430728 | 80           | 2075              | 7.94E-14 | 5.59E-11          | PNPLA7 BPGM PGS1 NADSYN1 ACOX3 MOCS2 LOC102183750 LOC102189751 SGMS1 SCAP SUOX NR1H3 MLX ST3GAL6 LOC102170668 PCYT2 LHPP OGDH LOC102169935 CIAPIN1 LOC102186759 OPLAH ALAS1 ACAA1 RPE PIK3R2 HK3 MED14 MTHFD1 CAD MTMR3 RAB14 PNPLA6 GALT ST3GAL1 TPMT RAB5A MIGA2 PIKFYVE GNB5 CD44 MED31 GALNS KDSR GYS1 SEC24D CPTP GUK1 PUDP ECI1 PIK3R5 ITPR2 TBL1X CHST3 RTEL1 TSPO HSD17B4 PHYH PLD4 PLA2 |

| Terms                    | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                       |
|--------------------------|----------|---------------|--------------|-------------------|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |          |               |              |                   |          |                   | G15 CA9 ARSG SDSL INPP5E NAXD UCKL1 ACAD8 LOC106503208 OSBP L5 PLCG2 ACSL5 NUBP2 MTF1 PDK3 DTYMK PITPNM2 INPP5B MMAB OSBP SLC19A1                                                                                                                                           |
| Adaptive Immune System   | Reactome | R-HSA-1280218 | 38           | 748               | 3.65E-10 | 1.16E-07          | UBE2Q2 EVL LOC102175938 UBE2D4 IKBKB CD209 LAIR1 RAF1 FYB ASB3 TIRAP RACGAP1 FYN MIB2 PIK3R2 LOC102186356 CUL7 LOC102188617 AREL1 LOC102186637 SH3RF1 TPP2 PLCG2 SEC24D HERC5 SIGLEC10 TPR2 UBE2V1 ANAPC2 LOC102176695 ZNR1 UBE2O UBA7 KIF5B UBE2F LOC102175896 RNF213 CD19 |
| Metabolism of lipids     | Reactome | R-HSA-556833  | 37           | 728               | 6.19E-10 | 1.70E-07          | SGMS1 PGS1 SCAP PNPLA6 LOC102186759 ACAA1 ALAS1 PIK3R5 PNPLA7 PIK3R2 MED14 OSBPL5 MTMR3 RAB14 NR1H3 MED31 RAB5A MIGA2 PIKFYVE CPTP PCYT2 SEC24D HSD17B4 TSPO PHYH PLD4 PLA2G15 KDSR ARSG TBL1X INPP5E MTF1 ACOX3 ACSL5 ECI1 PITPNM2 OSBP                                    |
| Neutrophil degranulation | Reactome | R-HSA-6798695 | 29           | 478               | 1.11E-09 | 2.61E-07          | LOC102175938 TOM1 TARM1 LAIR1 BIN2 PECAM1 MGAM DYNLT1 ACAA                                                                                                                                                                                                                  |

| Terms                                                  | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                              |
|--------------------------------------------------------|----------|---------------|--------------|-------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| on                                                     |          |               |              |                   |          |                   | 1 CD44 LOC102188617 SURF4 GHDC PKM HK3 GALNS UNC13D LOC102180421 LOC102189890 RHOF ITGAX LOC102178529 RAB24 HVCN1 ADAM8 RAB14 ITGAM CRACR2A NBEAL2                                                                                                                 |
| Disease                                                | Reactome | R-HSA-1643685 | 42           | 1049              | 3.39E-08 | 4.57E-06          | HDAC9 IKBKB MPRIP MAP2K1 SLC29A3 ADAMTS14 MPDU1 PMM2 RAF1 OPLAH EPS15 GTF2E2 STAT1 TIRAP ITGA2B FYN MIB2 THBS1 PIK3R2 SV2A IRAK4 GALT TGFB1 APH1B TPMT GALNS GYS1 NRG1 TSC2 CHST3 LOC102175896 TBL1X MYO18A TBP AKAP9 CASP9 LOC106503208 POMT1 APC NTHL1 MMAB CD19 |
| Class I MHC mediated antigen processing & presentation | Reactome | R-HSA-983169  | 22           | 370               | 1.58E-07 | 1.77E-05          | UBE2Q2 LOC102175938 UBE2D4 IKBKB LOC102186637 ASB3 TIRAP MIB2 CUL7 LOC102188617 AREL1 SH3RF1 TPP2 SEC24D HERC5 UBE2V1 ANAPC2 ZNR1 UBE2O UBA7 UBE2F RN213                                                                                                           |
| Metabolism of proteins                                 | Reactome | R-HSA-392499  | 62           | 2012              | 2.15E-07 | 2.18E-05          | ERCC8 UBE2Q2 MTRF1L BIRC3 ST3GAL1 CALU PMM2 TRAM1 ADAMTS1                                                                                                                                                                                                          |

| Terms                          | Database | ID                | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------|----------|-------------------|--------------|-------------------|----------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                |          |                   |              |                   |          |                   | 4 MPDU1 IKBKE SEC16A EXOSC3 U<br>SP25 LOC102186637 APH1B ST6GAL<br>NAC4 ZBTB17 PIAS3 COMMD7 THBS<br>1 MRPL55 AMDHD2 CUL9 DDB2 AAR<br>S2 CUL7 RAB14 TTLL5 DCP2 TGFB<br>R1 RAB5A ST3GAL6 ASB3 GNB5 COG<br>2 LARGE2 LOC102186814 GGA1 SEC<br>24D GGA3 PCGF2 MYSM1 USP19 NF<br>RKB USP37 EXOC2 PTRH2 ARSG RA<br>B24 B3GALNT2 CXCL8 KIF5B DAP3 <br>UBE2F RABGGTB METTL22 CYLD R<br>NF144A POMT1 APC HLTF |
| Hemostasi<br>s                 | Reactome | R-HSA-109<br>582  | 29           | 617               | 2.17E-07 | 2.18E-05          | ATP2A3 ZFPM1 PHF21A ECM1 PLCG<br>2 RAF1 DGKZ PECAM1 RACGAP1 IT<br>GA2B FYN CD84 THBS1 DOK2 PIK3R<br>5 PIK3R2 DAGLB RAB5A GNB5 CD44<br> FERMT3 LOC102180421 TMX3 ITPR<br>2 ITGAX IRF1 KIF5B CALU ITGAM                                                                                                                                                                                               |
| Phospholip<br>id<br>metabolism | Reactome | R-HSA-148<br>3257 | 16           | 212               | 4.19E-07 | 3.64E-05          | PLD4 PLA2G15 RAB5A MIGA2 PIKFY<br>VE PCYT2 PGS1 INPP5E PIK3R5 PN<br>PLA7 PNPLA6 PITPNM2 OSBPL5 MT<br>MR3 RAB14 PIK3R2                                                                                                                                                                                                                                                                               |
| Post-transl<br>ational         | Reactome | R-HSA-597<br>592  | 47           | 1412              | 9.28E-07 | 6.83E-05          | ERCC8 UBE2Q2 BIRC3 ST3GAL1 AD<br>AMTS14 MPDU1 IKBKE PMM2 SEC16                                                                                                                                                                                                                                                                                                                                      |

| Terms                               | Database | ID           | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                                                                                                                                                        |
|-------------------------------------|----------|--------------|--------------|-------------------|----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| protein modification                |          |              |              |                   |          |                   | A USP25 LOC102186637 ASB3 ST6GALNAC4 PIAS3 COMMD7 THBS1 AMDHD2 CUL9 DDB2 CUL7 RAB14 TTLL5 TGFBF1 RAB5A ST3GAL6 COG2 LARGE2 LOC102186814 SEC24D PCGF2 MYSM1 USP19 NFRKB USP37 PTRH2 ARSG RAB24 B3GALNT2 CALU UBE2F RABGGTB METTL22 CYLD RN144A POMT1 APC HLTF |
| Toll Like Receptor 4 (TLR4) Cascade | Reactome | R-HSA-166016 | 12           | 128               | 1.46E-06 | 9.42E-05          | IRF3 PELI1 TIRAP BIRC3 IKBKB PLCG2 MAP2K1 ITGAM IKBKE UBE2V1 MAPK9 IRAK4                                                                                                                                                                                     |
| DNA Repair                          | Reactome | R-HSA-73894  | 19           | 331               | 1.80E-06 | 0.000109636       | ERCC8 SPIDR RTEL1 SIRT6 SPRTN ACD PNKP ERCC5 TERF2 UBA7 PIAS3 DDB2 ATR NTHL1 POLL NFRKB POLM LOC102186637 UVSSA                                                                                                                                              |
| Gene expression (Transcription)     | Reactome | R-HSA-74160  | 47           | 1448              | 1.80E-06 | 0.000109636       | HDAC9 MTERF1 LOC102189751 GTF3C5 LOC102180305 TSC2 SAP130 CDC7 LOC102170668 GTF2E2 INTS10 STAT1 POLDIP3 ITGA2B LOC102170775 THBS1 BRPF1 CNOT8 MED14 ZFP69 ZNF263 DDB2 PRELID3A ZNF664 KMT2C TCF7 ZFP1 TFAM BANP T                                            |

| Terms                                          | Database | ID            | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                                                                      |
|------------------------------------------------|----------|---------------|--------------|-------------------|----------|-------------------|----------------------------------------------------------------------------------------------------------------------------|
|                                                |          |               |              |                   |          |                   | CF3 MED31 ZNF446 SNAPC4 PHF20 MGA PCGF2 TBL1X TBP RABGGTB ATR HTT PRDM1 FAS ZNF500 PLAGL1 ZNF394 PHF1                      |
| Diseases of signal transduction                | Reactome | R-HSA-5663202 | 20           | 374               | 2.69E-06 | 0.000153335       | APH1B TGFB1 TBL1X STAT1 MYO18A HDAC9 ITGA2B FYN AKAP9 MIB2 CASP9 MPRIIP MAP2K1 PIK3R2 RAF1 NRG1 APC LOC102175896 TSC2 CD19 |
| Platelet activation, signaling and aggregation | Reactome | R-HSA-76002   | 16           | 260               | 5.08E-06 | 0.000259451       | DGKZ PECAM1 DAGLB PLCG2 GNB5 ITGA2B FYN CALU ECM1 THBS1 FERMT3 PIK3R5 PIK3R2 TMX3 ITPR2 RAF1                               |
| Toll-like Receptor Cascades                    | Reactome | R-HSA-168898  | 12           | 154               | 8.57E-06 | 0.000388544       | IRF3 PELI1 TIRAP BIRC3 IKBKB PLCG2 MAP2K1 ITGAM IKBKE UBE2V1 MAPK9 IRAK4                                                   |
| Centrosome maturation                          | Reactome | R-HSA-380287  | 9            | 81                | 8.57E-06 | 0.000388544       | CEP164 SFI1 AKAP9 CEP192 HAUS3 LOC102188159 PCNT CDK5RAP2 TUBGCP2                                                          |
| Recruitment of mitotic centrosome              | Reactome | R-HSA-380270  | 9            | 81                | 8.57E-06 | 0.000388544       | CEP164 SFI1 AKAP9 CEP192 HAUS3 LOC102188159 PCNT CDK5RAP2 TUBGCP2                                                          |

| Terms                          | Database | ID | Input<br>number | Background<br>number | P-Value | Corrected<br>P-Value | Input |
|--------------------------------|----------|----|-----------------|----------------------|---------|----------------------|-------|
| e proteins<br>and<br>complexes |          |    |                 |                      |         |                      |       |

**Supplementary Table S10** Overlap between TLR-cascade (map04620) and ASEGs/ASSGs

| Types | Genes                                                                                                |
|-------|------------------------------------------------------------------------------------------------------|
| ASEGs | <i>CXCL8, MAP2K1, IKBKB, MAPK8, IRF5, NFKBIA, CD14, RAC1, LY96, TIRAP, CCL5, STAT1, TICAM2, TLR9</i> |
| ASSGs | <i>TIRAP, IRAK4, IKBKB, IRF3, IKBKE, STAT1, CD40, CXCL8, MAP2K1</i>                                  |

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