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 reed buck (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 Ka and Ks and the Ka/Ks ratio for each orthologous gene, while lineage-specific Ka/Ks 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® UltraTM 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 \( F_\text{ST} \) 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 $\text{FDR}\leq0.05\%$.

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 1487 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 (PRR) pathways and other receptor pathways are marked in green and orange, respectively, while others are in gray.
**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 S13 Comparison of STAT1 isoforms in different species. STAT1 splicing isoform in goat first appeared in Bovidae, but not in pig or other mammals.
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:ENSBTAG000000013693.5 | transcript:ENSBTAT00000018202.4 | pep:ENSBTAP000000018202 | na          |
| gene:ENSBTAG000000043561.1 | transcript:ENSBTAT00000065069.1 | pep:ENSBTAP000000053147 | COX1        |
| gene:ENSBTAG000000014158.5 | transcript:ENSBTAT00000018816.4 | pep:ENSBTAP000000018816 | CCNT2       |
| gene:ENSBTAG000000023918.4 | transcript:ENSBTAT00000055181.2 | pep:ENSBTAP000000050989 | na          |
| gene:ENSBTAG000000046915.1 | transcript:ENSBTAT00000066040.1 | pep:ENSBTAP000000053954 | na          |
| gene:ENSBTAG000000047426.1 | transcript:ENSBTAT00000064259.1 | pep:ENSBTAP000000055421 | LYPD6       |
| gene:ENSBTAG000000021883.4 | transcript:ENSBTAT00000029169.4 | pep:ENSBTAP00000029169 | AP3M1       |
| gene:ENSBTAG000000021706.5 | transcript:ENSBTAT00000028930.5 | pep:ENSBTAP00000028930 | TBX3        |
| gene:ENSBTAG00000007441.4 | transcript:ENSBTAT0000009785.4 | pep:ENSBTAP0000009785 | SEC23IP     |
| gene:ENSBTAG000000008013.4 | transcript:ENSBTAT00000044459.1 | pep:ENSBTAP00000041953 | LRR2C       |
| gene:ENSBTAG00000006921.5 | transcript:ENSBTAT0000009089.5 | pep:ENSBTAP0000009089 | ABCA6       |
| gene:ENSBTAG000000013556.5 | transcript:ENSBTAT00000018027.5 | pep:ENSBTAP00000018027 | UNC13D      |
| gene:ENSBTAG000000044151.2 | transcript:ENSBTAT00000061288.2 | pep:ENSBTAP00000053262 | ANKDD1B     |
| gene:ENSBTAG000000046421.1 | transcript:ENSBTAT0000008579.5 | pep:ENSBTAP0000008579 | na          |
| gene:ENSBTAG000000045860.1 | transcript:ENSBTAT0000002951.5 | pep:ENSBTAP0000002951 | na          |
| gene:ENSBTAG000000013364.5 | transcript:ENSBTAT0000017778.5 | pep:ENSBTAP0000017778 | LIPM        |
| gene:ENSBTAG000000019007.3 | transcript:ENSBTAT0000025298.3 | pep:ENSBTAP0000025298 | na          |
| gene:ENSBTAG000000021337.5 | transcript:ENSBTAT0000028448.5 | pep:ENSBTAP0000028448 | SBF1        |
| gene:ENSBTAG000000035777.3 | transcript:ENSBTAT0000050265.3 | pep:ENSBTAP0000046998 | na          |
| gene:ENSBTAG00000002138.5 | transcript:ENSBTAT0000015977.5 | pep:ENSBTAP0000015977 | PADI1       |
| gene:ENSBTAG000000019555.4 | transcript:ENSBTAT0000026057.4 | pep:ENSBTAP0000026057 | ZSCAN20     |
| gene:ENSBTAG000000047862.1 | transcript:ENSBTAT0000063587.1 | pep:ENSBTAP0000055397 | na          |
| gene:ENSBTAG000000040323.2 | transcript:ENSBTAT0000057166.2 | pep:ENSBTAP0000052542 | na          |
| gene:ENSBTAG000000045731.1 | transcript:ENSBTAT0000063972.1 | pep:ENSBTAP0000054874 | 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:ENSBTAG0000002937.5  | transcript:ENSBTAT00000003821.5  | pep:ENSBTAP00000003821  | ADGRE3      |
| gene:ENSBTAG000000030714.3 | 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:ENSBTAT0000009973.1  | pep:ENSBTAP0000009973  | ZSWIM2      |
| gene:ENSBTAG00000021414.5  | transcript:ENSBTAT00000028547.4  | pep:ENSBTAP00000028547  | na          |
| gene:ENSBTAG0000002331.5  | transcript:ENSBTAT0000003008.5  | pep:ENSBTAP0000003008  | 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 | MUC13       |
| gene:ENSBTAG00000010382.5 | transcript:ENSBTAT00000013702.5 | pep:ENSBTAP00000013702 | RECK        |
| gene:ENSBTAG0000000076.4 | transcript:ENSBTAT0000000084.4 | pep:ENSBTAP0000000084 | TP53RK      |
| gene:ENSBTAG00000027326.4 | transcript:ENSBTAT00000039179.4 | pep:ENSBTAP00000038979 | CSMD2       |
| gene:ENSBTAG00000046729.1 | transcript:ENSBTAT00000065674.1 | pep:ENSBTAP00000055770 | KHK         |
| gene:ENSBTAG00000005784.5 | transcript:ENSBTAT0000007609.5 | pep:ENSBTAP0000007609 | na          |
| gene:ENSBTAG00000011325.5 | transcript:ENSBTAT00000015052.5 | pep:ENSBTAP00000015052 | na          |
| gene:ENSBTAG00000022227.4 | transcript:ENSBTAT00000030005.4 | pep:ENSBTAP00000029993 | na          |
| gene:ENSBTAG00000008943.4 | transcript:ENSBTAT0000011774.4 | pep:ENSBTAP0000011774 | ZSCAN12     |
| gene:ENSBTAG00000040459.1 | transcript:ENSBTAT0000052426.1 | pep:ENSBTAP0000048758 | na          |
| gene:ENSBTAG00000011403.4 | transcript:ENSBTAT0000015156.4 | pep:ENSBTAP0000015156 | na          |
| gene:ENSBTAG00000015810.5 | transcript:ENSBTAT0000020999.5 | pep:ENSBTAP0000020999 | PLET1       |
| gene:ENSBTAG00000002773.5 | transcript:ENSBTAT000003593.5 | pep:ENSBTAP000003593 | na          |
| gene:ENSBTAG00000040392.2 | transcript:ENSBTAT0000010394.5 | pep:ENSBTAP0000010394 | na          |
| gene:ENSBTAG00000038368.2 | transcript:ENSBTAT0000056122.2 | pep:ENSBTAP0000051461 | SNRPG       |
| gene:ENSBTAG00000001810.4 | transcript:ENSBTAT000002366.4 | pep:ENSBTAP000002366 | SCAF11      |
| gene:ENSBTAG00000031355.1 | transcript:ENSBTAT0000044432.1 | pep:ENSBTAP0000041928 | na          |
| gene:ENSBTAG000000038286.1 | transcript:ENSBTAT0000055170.1 | pep:ENSBTAP0000048663 | na          |
| gene:ENSBTAG00000018290.4 | transcript:ENSBTAT0000024340.4 | pep:ENSBTAP0000024340 | IL9         |
| gene:ENSBTAG00000040367.1 | transcript:ENSBTAT0000044482.2 | pep:ENSBTAP0000048506 | RRP8        |
| gene:ENSBTAG00000000697.5 | transcript:ENSBTAT0000039795.4 | pep:ENSBTAP0000039583 | LAMB4       |
| gene:ENSBTAG00000033169.3 | transcript:ENSBTAT0000047111.2 | pep:ENSBTAP0000044341 | LAMB4       |
| Gene ID | Transcript ID | Peptide ID | Gene Symbol |
|---------|---------------|------------|-------------|
| gene:ENSBTAG000000015868.4 transcript:ENSBTAT00000021092.4 pep:ENSBTAP00000021092 | LIG4 |
| gene:ENSBTAG000000043990.2 transcript:ENSBTAT00000061105.2 pep:ENSBTAP00000053440 | KHDRBS2 |
| gene:ENSBTAG000000038794.2 transcript:ENSBTAT00000053653.1 pep:ENSBTAP00000047510 | TMEM245 |
| gene:ENSBTAG00000007823.4 transcript:ENSBTAT00000010295.4 pep:ENSBTAP00000010295 | TG |
| gene:ENSBTAG00000001034.4 transcript:ENSBTAT0000001371.4 pep:ENSBTAP0000001371 | IL1B1R |
| gene:ENSBTAG00000012577.4 transcript:ENSBTAT00000016697.4 pep:ENSBTAP00000016697 | UVSSA |
| gene:ENSBTAG000000015517.5 transcript:ENSBTAT00000020621.4 pep:ENSBTAP00000020621 | na |
| gene:ENSBTAG000000045664.1 transcript:ENSBTAT00000064452.1 pep:ENSBTAP00000056252 | LRRC41 |
| gene:ENSBTAG000000015729.5 transcript:ENSBTAT00000020879.5 pep:ENSBTAP00000020879 | ADH7 |
| gene:ENSBTAG000000035710.4 transcript:ENSBTAT00000061334.2 pep:ENSBTAP00000053687 | ZBBX |
| gene:ENSBTAG00000015839.5 transcript:ENSBTAT00000021045.5 pep:ENSBTAP00000021045 | MAP4 |
| gene:ENSBTAG000000019919.4 transcript:ENSBTAT00000026536.4 pep:ENSBTAP00000026536 | na |
| gene:ENSBTAG00000002501.5 transcript:ENSBTAT0000003250.5 pep:ENSBTAP0000003250 | CUEDC2 |
| gene:ENSBTAG00000004585.5 transcript:ENSBTAT0000006021.4 pep:ENSBTAP0000006021 | CCDC30 |
| gene:ENSBTAG00000011481.5 transcript:ENSBTAT00000065322.1 pep:ENSBTAP00000056128 | IL12RB1 |
| gene:ENSBTAG00000011036.5 transcript:ENSBTAT00000014658.5 pep:ENSBTAP00000014658 | CEACAM20 |
| gene:ENSBTAG000000024891.4 transcript:ENSBTAT00000034665.4 pep:ENSBTAP00000034552 | na |
| gene:ENSBTAG00000007955.5 transcript:ENSBTAT00000010460.3 pep:ENSBTAP00000010460 | SEZ6L2 |
| gene:ENSBTAG000000046727.1 transcript:ENSBTAT00000062985.1 pep:ENSBTAP00000055309 | na |
| gene:ENSBTAG000000036297.3 transcript:ENSBTAT00000050795.3 pep:ENSBTAP00000047450 | RBFA |
| gene:ENSBTAG00000019686.5 transcript:ENSBTAT00000047448.3 pep:ENSBTAP00000044656 | NCKAP1L |
| gene:ENSBTAG00000005190.4 transcript:ENSBTAT0000006842.4 pep:ENSBTAP0000006842 | 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:ENSBTAT0000021815.5 | pep:ENSBTAP0000021815 | IRX6        |
| gene:ENSBTAG00000014762.5 | transcript:ENSBTAT0000065058.1 | pep:ENSBTAP0000056176 | ISG20       |
| gene:ENSBTAG00000020155.5 | transcript:ENSBTAT0000064867.1 | pep:ENSBTAP0000054813 | RP1L1       |
| gene:ENSBTAG00000044195.2 | transcript:ENSBTAT0000061463.2 | pep:ENSBTAP0000053549 | SDK2        |
| gene:ENSBTAG00000011349.5 | transcript:ENSBTAT0000015083.5 | pep:ENSBTAP0000015083 | CDH24       |
| gene:ENSBTAG00000021791.4 | transcript:ENSBTAT0000029045.4 | pep:ENSBTAP0000029045 | PARP9       |
| gene:ENSBTAG00000019231.4 | transcript:ENSBTAT0000025606.4 | pep:ENSBTAP0000025606 | MAIP1       |
| gene:ENSBTAG00000045606.1 | transcript:ENSBTAT0000066010.1 | pep:ENSBTAP0000054961 | na          |
| gene:ENSBTAG0000002539.4 | transcript:ENSBTAT0000042716.3 | pep:ENSBTAP0000040347 | TRIOBP      |
| gene:ENSBTAG00000021557.2 | transcript:ENSBTAT0000028720.2 | pep:ENSBTAP0000028720 | FUT2        |
| gene:ENSBTAG0000000799.4 | transcript:ENSBTAT000001057.4 | pep:ENSBTAP000001057 | ICA1        |
| gene:ENSBTAG00000005183.5 | transcript:ENSBTAT000006828.5 | pep:ENSBTAP000006828 | MVK         |
| gene:ENSBTAG00000040305.2 | transcript:ENSBTAT0000057213.2 | pep:ENSBTAP0000050373 | na          |
| gene:ENSBTAG00000023933.4 | transcript:ENSBTAT0000042743.3 | pep:ENSBTAP0000040372 | SEC16A      |
| gene:ENSBTAG00000014599.5 | transcript:ENSBTAT0000019433.5 | pep:ENSBTAP0000019433 | LRR2C66     |
| gene:ENSBTAG00000012837.5 | transcript:ENSBTAT0000017057.5 | pep:ENSBTAP0000017057 | COL6A6      |
| gene:ENSBTAG00000037803.1 | transcript:ENSBTAT0000055475.1 | pep:ENSBTAP0000051224 | ZNF197      |
| gene:ENSBTAG00000009907.5 | transcript:ENSBTAT0000013073.5 | pep:ENSBTAP0000013073 | MAPK4       |
| gene:ENSBTAG00000026825.1 | transcript:ENSBTAT0000038349.1 | pep:ENSBTAP0000038164 | TMEM37      |
| gene:ENSBTAG00000006721.5 | transcript:ENSBTAT0000047621.3 | pep:ENSBTAP0000044811 | TWISTNB     |
| gene:ENSBTAG00000008253.5 | transcript:ENSBTAT0000010864.5 | pep:ENSBTAP0000010864 | EXPH5       |
| Gene ID     | Transcript ID                  | Peptide ID            | Gene Symbol |
|------------|--------------------------------|-----------------------|-------------|
| gene:ENSBTAG000000038267.2 | transcript:ENSBTAT000000052988.2 | pep:ENSBTAP000000050887 | 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:ENSBTAG000000047943.1 | transcript:ENSBTAT000000064919.1 | pep:ENSBTAP000000054477 | na          |
| gene:ENSBTAG00000004423.5  | transcript:ENSBTAT00000005797.5   | pep:ENSBTAP00000005797  | ARHGAP42    |
| gene:ENSBTAG00000013245.5  | transcript:ENSBTAT00000053490.2   | pep:ENSBTAP00000047648  | ITPR3       |
| gene:ENSBTAG00000012682.5  | transcript:ENSBTAT00000047528.3   | pep:ENSBTAP00000044729  | UNC13A      |
| gene:ENSBTAG00000005753.5  | transcript:ENSBTAT00000007566.5   | pep:ENSBTAP00000007566  | PARP6       |
| gene:ENSBTAG000000047174.1 | transcript:ENSBTAT000000064843.1 | pep:ENSBTAP00000047648  | ARHGAP42    |
| gene:ENSBTAG00000004464.5  | transcript:ENSBTAT00000005861.5   | pep:ENSBTAP00000005861  | C17orf53    |
| gene:ENSBTAG000000046101.1 | transcript:ENSBTAT000000064558.1 | pep:ENSBTAP00000005450  | na          |
| gene:ENSBTAG000000032224.3 | transcript:ENSBTAT00000023466.5   | pep:ENSBTAP00000023466  | na          |
| gene:ENSBTAG000000021150.5 | transcript:ENSBTAT00000032152.4   | pep:ENSBTAP00000032090  | na          |
| gene:ENSBTAG000000032429.3 | transcript:ENSBTAT00000046004.3   | pep:ENSBTAP00000043341  | OR10AD1     |
| gene:ENSBTAG000000038327.2 | transcript:ENSBTAT00000052094.2   | pep:ENSBTAP00000050462  | na          |
| gene:ENSBTAG000000047078.1 | transcript:ENSBTAT00000064859.1   | pep:ENSBTAP00000054706  | NTF4        |
| gene:ENSBTAG00000000712.5  | transcript:ENSBTAT0000000956.5    | pep:ENSBTAP0000000956   | FBXW2       |
| gene:ENSBTAG00000011922.5  | transcript:ENSBTAT0000015828.4    | pep:ENSBTAP0000015828   | PLEC        |
| gene:ENSBTAG00000006240.3  | transcript:ENSBTAT0000008190.2    | pep:ENSBTAP0000008190   | TLR4        |
| gene:ENSBTAG00000017426.5  | transcript:ENSBTAT0000023165.5    | pep:ENSBTAP0000023165   | PDCD6IP     |
| gene:ENSBTAG00000007062.5  | transcript:ENSBTAT0000009285.5    | pep:ENSBTAP0000009285   | IGFBP5      |
| gene:ENSBTAG000000047569.1 | transcript:ENSBTAT00000065958.1   | pep:ENSBTAP00000055893  | na          |
| gene:ENSBTAG000000048135.1 | transcript:ENSBTAT00000066155.1   | pep:ENSBTAP00000055469  | na          |
| Gene ID          | Transcript ID          | Peptide ID          | Gene Symbol |
|------------------|------------------------|---------------------|-------------|
| gene:ENSBTAG00000000237.4 transcript:ENSBTAT00000000291.4 pep:ENSBTAP000000042520 | na                        |
| gene:ENSBTAG0000000039615.2 transcript:ENSBTAT0000000054186.2 pep:ENSBTAP000000049857 | na                        |
| gene:ENSBTAG0000000020532.5 transcript:ENSBTAT0000000027356.5 pep:ENSBTAP000000048750 | na                        |
| gene:ENSBTAG0000000018872.4 transcript:ENSBTAT0000000025122.4 pep:ENSBTAP000000025122 | F12                        |
| gene:ENSBTAG0000000018134.5 transcript:ENSBTAT0000000024140.4 pep:ENSBTAP000000024140 | AREG                       |
| gene:ENSBTAG0000000003937.4 transcript:ENSBTAT000000005143.4 pep:ENSBTAP00000005143 | na                        |
| gene:ENSBTAG0000000021310.5 transcript:ENSBTAT0000000018302.5 pep:ENSBTAP000000018302 | COL4A4                     |
| gene:ENSBTAG0000000005154.4 transcript:ENSBTAT000000006789.4 pep:ENSBTAP00000006789 | APCDD1                     |
| gene:ENSBTAG0000000040153.2 transcript:ENSBTAT0000000053199.2 pep:ENSBTAP000000050564 | na                        |
| gene:ENSBTAG0000000030564.3 transcript:ENSBTAT0000000043163.3 pep:ENSBTAP000000040753 | na                        |
| gene:ENSBTAG0000000014768.5 transcript:ENSBTAT000000019646.5 pep:ENSBTAP000000019646 | ZNF786                     |
| gene:ENSBTAG0000000046228.1 transcript:ENSBTAT000000064530.1 pep:ENSBTAP000000056226 | na                        |
| gene:ENSBTAG0000000046321.1 transcript:ENSBTAT000000015433.5 pep:ENSBTAP000000015433 | TSPOAP1                    |
| gene:ENSBTAG0000000006933.5 transcript:ENSBTAT000000009104.5 pep:ENSBTAP000000009104 | PPP1R10                    |
| gene:ENSBTAG0000000024545.4 transcript:ENSBTAT000000017605.5 pep:ENSBTAP000000017605 | DCHS2                      |
| gene:ENSBTAG0000000046313.1 transcript:ENSBTAT0000000063186.1 pep:ENSBTAP00000005319 | CCDC54                     |
| gene:ENSBTAG0000000040232.5 transcript:ENSBTAT000000005544.5 pep:ENSBTAP000000005544 | TMIE                       |
| gene:ENSBTAG000000002853.5 transcript:ENSBTAT000000043065.2 pep:ENSBTAP000000040660 | HRC                        |
| gene:ENSBTAG0000000027629.4 transcript:ENSBTAT000000004244.5 pep:ENSBTAP000000004244 | na                        |
| gene:ENSBTAG0000000025320.4 transcript:ENSBTAT000000049153.3 pep:ENSBTAP000000046086 | AKAP1                      |
| gene:ENSBTAG0000000012721.4 transcript:ENSBTAT000000016909.4 pep:ENSBTAP000000016909 | HOGA1                      |
| gene:ENSBTAG0000000048115.1 transcript:ENSBTAT0000000063444.1 pep:ENSBTAP000000056282 | na                        |
| gene:ENSBTAG0000000025526.4 transcript:ENSBTAT000000035900.4 pep:ENSBTAP000000035767 | MDC1                       |
| gene:ENSBTAG000000002962.5 transcript:ENSBTAT000000003860.5 pep:ENSBTAP000000003860 | na                        |
| gene:ENSBTAG0000000046138.1 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-381| 6            | 393               | 0.0003839 | 0.02617453       | ENSBTAP00000055309|ENSBTAP0000003455|2|ENSBTAP00000048758|ENSBTAP000000041000|ENSBTAP00000038888|ENSBTAP00000020621 |
| Immune System                 | Reactome | R-HSA-168| 14           | 2096              | 0.0004358 | 0.02617453       | ENSBTAP000000013702|ENSBTAP00000003593|ENSBTAP000000044656|ENSBTAP00000003821|ENSBTAP00000041928|ENSBTAP00000010969|ENSBTAP00000018027|ENSBTAP000000002951|ENSBTAP000000052286|ENSBTAP000000034373|ENSBTAP00000024340|ENSBTAP000000056252|ENSBTAP000000056128|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|ENSBTA P00000022355|ENSBTAP00000056315                              |
| negative regulation of cell cycle arrest | Gene Ontology      | GO:0071157        | 2            | 5                 | 0.000116    | 0.024096          | ENSBTAP000000055397|ENSBTA P00000055770                           |
| L-amino acid transmembrane transporter activity | Gene Ontology      | GO:0015179        | 2            | 5                 | 0.000116    | 0.024096          | ENSBTAP000000023823|ENSBTA P00000010394                             |
| cellular anatomical entity         | Gene Ontology      | GO:0110165        | 18           | 2864              | 0.000128    | 0.024096          | ENSBTAP00000015977|ENSBTA P00000016173|ENSBTAP00000038979|ENSBTAP00000013702|ENSBTAP00000047510|ENSBTAP0000029169|ENSBTAP000000003084|ENSBTAP00000010969|ENSBTAP00000056315|ENSBTAP00000005989|ENSBTAP000000003437|ENSBTAP000000038888|ENSBTAP00000056252|ENSBTAP00000053954|ENSBTAP00000005612|ENSBTAP00000020621|ENSBT
| Terms                                      | Database       | ID                  | Input number | Background number | P-Value  | Corrected P-Value | Input                        |
|-------------------------------------------|----------------|---------------------|--------------|-------------------|----------|------------------|------------------------------|
| membrane                                  | Gene Ontology  | GO:0016020          | 12           | 1443              | 0.000167 | 0.024096         | AP000000055421|ENSBTAP00000017800 |
| histone-lysine N-methyltransferase activity| Gene Ontology  | GO:0018024          | 2            | 7                 | 0.000198 | 0.024096         | ENSBTAP000000055397|ENSBTAP00000055770 |
| alpha-beta T cell differentiation involved in immune response | Gene Ontology  | GO:0002293          | 2            | 7                 | 0.000198 | 0.024096         | ENSBTAP00000056128|ENSBTAP0000001371 |
| 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 | P0000000023823| 2            | 9                 | 0.000301    | 0.025515          | P000000055770                               |
| L-alpha-amin o acid transport | Gene Ontology | GO:1902475 | 2            | 9                 | 0.000301    | 0.025515          | ENSBTAP00000010394                         |
| nitrogen compound metabolic process | Gene Ontology | GO:0006807 | 12           | 1541              | 0.000302    | 0.025515          | ENSBTAP00000016697|ENSBTA P00000009973|ENSBTAP00000048506|ENSBTAP000000048421|ENSBTAP00000010295|ENSBTAP0000009631|ENSBTAP00000009810|ENSBTAP000000018816|ENSBTAP00000002951|ENSBTAP00000039583|ENSBTAP000000052174|ENSBTAP00000028448                                      |
| single-stranded DNA binding   | Gene Ontology | GO:0003697  | 2            | 10                | 0.000361    | 0.026175          | ENSBTAP000000055397|ENSBTA P000000055770                                      |
| positive regulation of ATPase activity | Gene Ontology | GO:0032781  | 2            | 10                | 0.000361    | 0.026175          | ENSBTAP000000055397|ENSBTA P000000055770                                      |
| DNA catabolic process         | Gene Ontology | GO:0006308  | 2            | 11                | 0.000426    | 0.026175          | ENSBTAP000000055397|ENSBTA P000000055770                                      |
| 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         | ENSBTAP000000055397|ENSBTA000000055770|ENSBTAP00000018816 |
| TOR signaling                             | Gene Ontology    | GO:0031929| 2            | 12                | 0.000496  | 0.026175         | ENSBTAP000000023823|ENSBTA00000010394  |
| ion binding                               | Gene Ontology    | GO:0043167| 9            | 962               | 0.000501  | 0.026175         | ENSBTAP00000020580|ENSBTA000000038979|ENSBTAP00000010295|ENSBTAP00000009810|ENSBTAP0000015052|ENSBTAP000000052286|ENSBTAP00000015977|ENSBTAP00000024275 |
| olfactory receptor activity               | Gene Ontology    | GO:0004984| 3            | 67                | 0.000628  | 0.028604         | ENSBTAP000000048758|ENSBTA000000041000|ENSBTAP000000034552 |
| binding                                   | Gene Ontology    | GO:0005488| 14           | 2247              | 0.00086   | 0.034926         | ENSBTAP00000020580|ENSBTA00000003008|ENSBTAP000000022355|ENSBTAP000000052542|ENSBTAP000000015052|ENSBTAP000000056315|ENSBTAP00000005397|ENSBTAP000000024340|ENSBTAP000000055770|ENSBTAP00000023743|ENSBTAP0000000020621|ENSBTAP00000015977|ENSBTAP00000024275 |
| Terms                                      | Database       | ID          | Input number | Background number | P-Value  | Corrected P-Value | Input                                                                 |
|-------------------------------------------|----------------|-------------|--------------|-------------------|----------|-------------------|------------------------------------------------------------------------|
| molecular function regulator              | Gene Ontology  | GO:0098772  | 5            | 307               | 0.000901 | 0.035291          | BTAP00000024275|ENSBTAP00000021092                                                     |
| sensory perception of chemical stimulus   | Gene Ontology  | GO:0007606  | 3            | 78                | 0.00096  | 0.036324          | ENSBTAP00000010295|ENSBTAP00000000084|ENSBTAP00000009631|ENSBTAP000000044656|ENSBTAP00000028448 |
| embryonic appendage morphogenesis         | Gene Ontology  | GO:0035113  | 2            | 18                | 0.001026 | 0.036577          | ENSBTAP000000026607|ENSBTAP00000000084 |
| metal ion binding                         | Gene Ontology  | GO:0046872  | 7            | 657               | 0.001034 | 0.036577          | ENSBTAP00000021092|ENSBTAP0000003821|ENSBTAP00000009636|ENSBTAP00000055397|ENSBTAP00000054874|ENSBTAP0000005770|ENSBTAP0000000698 |
| 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|ENSBTAP00000000084 |
| Terms                                      | Database               | ID          | Input number | Background number | P-Value  | Corrected P-Value | Input                          |
|--------------------------------------------|------------------------|-------------|--------------|-------------------|----------|------------------|--------------------------------|
| stem cell population maintenance          | Gene Ontology          | GO:0019827  | 2            | 22                | 0.001481 | 0.045127         | ENSBTAP00000021092|ENSBTA P000000028930 |
| immune receptor activity                   | Gene Ontology          | GO:0140375  | 2            | 22                | 0.001481 | 0.045127         | ENSBTAP00000056128|ENSBTA P00000001371 |
| histone methylation                        | Gene Ontology          | GO:0016571  | 2            | 23                | 0.001607 | 0.047652         | ENSBTAP00000055397|ENSBTA P00000055770 |
## 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-162 | 16           | 2689              | 4.67E-06 | 0.00474170       | ENSBTAP00000049857|ENSBTAP00000018302|ENSBTAP00000023466|ENSBTAP000000050887|ENSBTAP000000043341|ENSBTAP000000027416|ENSBTAP00000005797|ENSBTAP000000055893|ENSBTAP000000054961|ENSBTAP000000054706|ENSBTAP000000017057|ENSBTAP000000056282|ENSBTAP0000000547648|ENSBTAP00000024140 |
| G alpha (s) signalling events | Reactome | R-HSA-418 | 7            | 536               | 2.84E-05 | 0.00982455       | ENSBTAP00000049857|ENSBTAP00000023466|ENSBTAP000000050887|ENSBTAP000000043341|ENSBTAP000000050373|ENSBTAP000000054961|ENSBTAP0000000547648|ENSBTAP000000056282 |
| Olfactory Signaling Pathway  | Reactome | R-HSA-381 | 6            | 393               | 4.71E-05 | 0.01223478       | ENSBTAP00000023466|ENSBTAP000000050887|ENSBTAP000000043341|ENSBTAP000000050373|ENSBTAP000000054961|ENSBTAP000000056282 |
| Terms                                           | Database | ID         | Input number | Background number | P-Value | Corrected P-Value | Input                                                                 |
|-------------------------------------------------|----------|------------|--------------|-------------------|---------|------------------|----------------------------------------------------------------------|
| Signaling by Receptor Tyrosine Kinases          | Reactome | R-HSA-900  | 6            | 458               | 0.00010803 | 0.01868955 | ENSBTAP00000018302|ENSBTA P00000054706|ENSBTAP00000055893|ENSBTAP000000017057|ENSBTAP 00000024140 |
| ER to Golgi Anterograde Transport               | Reactome | R-HSA-199  | 4            | 154               | 0.00013068 | 0.01937873 | ENSBTAP00000040753|ENSBTA P00000004244|ENSBTAP00000054961|ENSBTAP 00000024140 |
| Assembly of collagen fibrils and other multimeric structures | Reactome | R-HSA-202  | 3            | 60                | 0.00015104 | 0.01959741 | ENSBTAP00000015828|ENSBTA P00000018302|ENSBTAP00000017057 |
| Transport to the Golgi and subsequent modification | Reactome | R-HSA-948  | 4            | 185               | 0.00025935 | 0.02278378 | ENSBTAP00000040753|ENSBTA P00000004244|ENSBTAP00000024140 |
| GPCR downstream signalling                       | Reactome | R-HSA-388  | 8            | 1108              | 0.00043532 | 0.03092901 | ENSBTAP00000049857|ENSBTA P00000023466|ENSBTAP00000054961|ENSBTAP 000000054961 |
| Terms                          | Database  | ID        | Input number | Background number | P-Value   | Corrected P-Value | Input                                      |
|-------------------------------|-----------|-----------|--------------|-------------------|-----------|------------------|--------------------------------------------|
| Collagen formation Reactome   | R-HSA-147 | 4290      | 3            | 89                | 0.00046190| 0.03092901       | ENSBTAP00000015828|ENSBTA P000000018302|ENSBTAP00000017057   |
| Cell junction organization    | R-HSA-446 | 728       | 3            | 90                | 0.00047674| 0.03092901       | ENSBTAP00000015083|ENSBTA P00000053549|ENSBTAP00000015828   |
| Nicotinamide salvaging Reactome | R-HSA-197 | 264       | 2            | 19                | 0.00053394| 0.03260226       | ENSBTAP00000007566|ENSBTA P00000029045   |
| Signaling by GPCR Reactome    | R-HSA-372 | 790       | 8            | 1170              | 0.00062101| 0.03392724       | ENSBTAP00000049857|ENSBTA P00000023466|ENSBTAP00000050887   |
| Mitochondrial calcium ion transport | R-HSA-894 | 9215      | 2            | 23                | 0.00075959| 0.03892686       | ENSBTAP00000046086|ENSBTA P00000025606   |
**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:000760| 4            | 145               | 0.000104244| 0.018689559     | ENSBTAP00000056282|ENSBTAP00000005544|ENSBTAP00000054961|ENSBTAP00000050887 |
| DNA catabolic process               | Gene Ontology    | GO:000630| 2            | 11                | 0.000199992| 0.022783787     | ENSBTAP00000056176|ENSBTAP00000054477 |
| regulation of blood coagulation     | Gene Ontology    | GO:003019| 3            | 12                | 0.000233079| 0.022783787     | ENSBTAP00000008190|ENSBTAP00000025122 |
| detection of chemical stimulus      | Gene Ontology    | GO:0005090| 7            | 73                | 0.000263396| 0.022783787     | ENSBTAP00000043341|ENSBTAP00000054961|ENSBTAP00000050887 |
| involved in sensory perception      | Gene Ontology    | GO:005078| 9            | 1778              | 0.000576837| 0.033264293     | ENSBTAP00000040660|ENSBTAP0000021815|ENSBTAP00000010864|ENSBTAP00000029045|ENSBTAP00000023165|ENSBTAP00000050373|ENSBTAP00000055450|ENSBTAP00000050564 |
| I band                              | Gene             | GO:003167| 2            | 24                | 0.000822030| 0.0389268552    | ENSBTAP00000040660|ENSBTAP00000050564 |


| Ontology                      | Gene          | GO:004322 | 4 | 8 | 63 | 0.00000004244 |
|-------------------------------|---------------|-----------|---|---|----|---------------|
| intracellular organelle       | Ontology      | 9         | 10| 1863| 0.00082503 | 0.0389268 |
|                               | ENSBTAP00000040660| ENSBTAP00000027497| ENSBTAP000000512 | ENSBTAP000000016909 | ENSBTAP00000025606 | ENSBTAP0000000000000054706 |
| collagen metabolic process    | Gene          | GO:003296 | 3 | 2 | 27 | 0.001023697 | 0.0461999 |
|                               | Ontology      | 9         | 9 | 84 | 84 | 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: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:0001775  | 0.26   | 0.20   | Goat   | receptor-mediated endocytosis                                                |
| GO:0003006  | 0.25   | 0.18   | 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:0030997  | 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 |
|------------------|----------|---------|--------------|-------------------|-----------|-------------------|
| Immune System    | Reactome | R-HSA-16| 8256         | 144               | 2096      | 1.24E-32          | 9.59E-29          |

Input:
- TNFRSF25
- LOC102168547
- AP1M1
- A1
- C5AR2
- SERPINB1
- B2M
- CALM1
- ACA1
- MIB2
- PYGB
- C7H1orf35
- IRAK3
- STK11
- UNKL
- LTA4H
- HK3
- CTSD
- SIGLEC10
- LY96
- CTSS
- SOS2
- IKBKB
- CRCP
- AKT1
- CXCL8
- KIF5B
- FCER2
- FBXL5
- VIM
- PTGES2
- TLR9
- ELMO2
- CD300E
- RASGRP1
- CL5
- NFKBIA
- MX2
- NCSTN
- IRS2
- TRIB3
- COSLG
- IFIT3
- TIRAP
- DGAT1
- ZBP1
- TRAF7
- FBXL12
- OSM
- LOC102186356
- PJA2
- RAB7A
- CSK
- TICAM2
- HERC1
- HERC6
- ANAPC1
- TPR3
- RHOA
- RPS6KA5
- IRF5
- LOC102171703
- TNFAIP6
- HMOX2
- TCIRG1
- CD14
- FXO30
- PPIA
- SIGIRR
- PPP2R5D
- BAIAP2
- CD3G
- LOC102184087
- NCF2
- NCF1
- PTX3
- LOC102183941
- AMPD3
- AR RB1
- DCTN2
- AREG
- IL9R
- STAT1
- ACTR10
- PGLYRP1
- FBXW8
- LOC102170640
- MARK3
- PML
- DUSP4
- MAPK8
- DUSP6
- BOL2
- ATP6V0B
- LOC102179713
- SH3RF1
- LTB
- FBXW2
- LOC102188986
- NUP500
- CDC42
- RBSN
- MAP2K1
- GLB1
- AGPAT2
- PRKACB
- NBEAL2
- MVP
- NCKAP1L
- CD55
- CD
| Terms                  | Database | ID       | Input number | Backgroun d number | P-Value    | Corrected P-Value | Input                                                                 |
|-----------------------|----------|----------|--------------|-------------------|------------|-------------------|----------------------------------------------------------------------|
| Innate Immune System  | Reactome | R-HSA-16 | 89           | 1043              | 4.40E-26   | 1.70E-22          | LOC102168547|AP1M1|AGA|C5AR2|SE RPINB1|B2M|CALM1|CXCR1|PYGB|C7 H1orf35|IRAK3|STK11IP|LTA4H|HK3|CT SD|LY96|CTSS|KBK|CRCP|PTGES2|TLR9|ELMO2|CD300E|RASGRP1|NFkB IA|NCSTN|TIRAP|DGAT1|ZBP1|RA7A|ITPR3|RHOA|ACTR10|RPS6KA5|TNFA P6|HMOX2|TCIRG1|CD14|ITGAL|PPIA|SIGIRR|PPP2R5D|BAIAP2|CD3G|NCF2 |NCF1|LOC102183941|AMPD3|MAP2K1 |TICAM2|PTX3|DUSP4|MAPK8|DUSP6|ATP6V0B|CA|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                        |
|------------------------------|----------|-----------|--------------|-------------------|------------|-------------------|------------------------------|
| Neutrophil degranulation     | Reactome | R-HSA-67 98695 | 51           | 478               | 4.79E-19   | 5.30E-16          | [ARHGAP45|ACAA1|NOD2|DPP7|RAC1|PRKCD|PLAU|LOC108633263|LOC102180421|LOC102178567|LOC102176691|CFD|MAP3K14|PLAC8|CMTM6 |
| Neutrophil degranulation     | Reactome | R-HSA-14 30728 | 113          | 2075              | 4.44E-18   | 3.61E-15          | NQO2|AKT1|PYCR2|ASS1|CALM1|TIA2|M2|PYGB|NDUFA10|PYGM|FM02|HAL|TBXAS1|HMGCL|H3|TNFRSF21|GNP2|AT|CNDP2|INPP5A|INPP5B|INPP5E|AD|CY3|PTGES2|MMA8|LOC102189950|TNFAIP8L2|SLC7A5|SERINC3|TRIB3|URTCT1|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 |
|-------|----------|----------|--------------|-------------------|---------|------------------|-------|
|       |          |          | A|CSGALNACT2|UBE2I|GALK1|LOC106503208|HMOX2|NUBP2|BTLD|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|AGPA2|PRKACB|DECR2|SLC35D1|SPHK1|RPS10|BPGM|RPS19|NFYC|PLCG1|LOC102189751|ADPGK|GPD2|LTA4H|OPLAH|SLC37A1|PFKP|CRYL1|ACAA1|PDK2|NARFL|ST3GAL2|ST3GAL1|ESISRA|LOC102190167|CHST11|UPP1|INPP1|SAMHD1|LOC102176691|SLC16A3|PFKFB2|OA2Z2|PFKFB4|GNA15|LOC102189835|NDUFS6|SDHB | UNKL|NCF1|LOC102189932|LOC102168547|ACTR10|AP1M1|IKKB|ANAPC1|PLCG1|RIPK2|TRAFA7|TRIB3|DCTN2|BTN2A2|ICOSLG|ITGAL|TIRAP|TIPAR3|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                                                                 |
|------------------|----------|----|--------------|-------------------|---------|-------------------|-----------------------------------------------------------------------|
| CTSD|HERC1|LNPEP|LOC108633263 | SIGLEC10|HERC6|LY96|LOC10217856 | 7|CTSS|NCF2|LOC102188986|LOC10217695 | RASGRP1|AKT1|KIF5B|CALM1 | FBXL5|B2M|LOC102190927|CD14|FBXO30|PRKACB|PPP2R5D|CD3G|LOC1021703 | PPIA|CD300E |
| AHCTF1|WLS|C5AR2|AKT1|EEF2K|CA LM1|GRK6|ARHGEF7|RBPJ|GRK5|GRK3|MIB2|ARHGAP22|DOK1|ARHGAP27 | PLXND1|IGF1R|LOC108638461|CTSD|STK4|LOC102179758|IKKB|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|TPR3|RHOA|RPS6KA5|TAGAP|TCIRG1|PPP2R5D|BAIAP2|CCNK|TFDP2|NCF2|NCF1|RFXP4|CC R3|LOC102180576|CTNND1|ARRB1|CBX6|NCOR2|AREG|STAT1|ADAP1|MAR K3|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-39 2499 | 96 | 2012 | 3.25E-12 | 8.67E-10 | RPN1|CPM|LOC102168547|B2M|USP2 4|USP22|CALM1|EIF3E|CUL9|COG2|WIP1|CTSD|LOC102173518|LOC1021797 58| RNF185|CXCL8|KIF5B|FBXL5|KDEL R2|FOXK1|NFKBIA|KAT2B|NCSTN|ARF GAP2|ADORA2B|MKL1|TULP4|DERL1|FBXL12|TOP2B|RA B7A|TARS2|ROHA|UBE2I|LOC102184009|ITM2B|FBXO30|ST8SIA4|LOC102182048|UBE2T|MTRF 1L|EIF2B2|CARS2|ARRB1|DCTN2|POF UT2|NCOR2|AREG|RAB8A|PNPLA2|AC TR10|FBXW8|PML|RAB13|CD59|OTTULI N|MRPS18A|YKT6|LOC102169730|ST3 GAL1|GOLM1|FBXW2|NUP50|GALNT1 0|ERO1B|GLB1|RNF144A|SPHK1|RPS1 |
| Terms                                | Database | ID          | Input number | Background number | P-Value        | Corrected P-Value | Input                                       |
|--------------------------------------|----------|-------------|--------------|-------------------|----------------|-------------------|---------------------------------------------|
| Signaling by Receptor Tyrosine Kinases | Reactome | R-HSA-90    | 37           | 458               | 6.99E-11       | 1.13E-08          | NCF2|NCF1|NCKAP1L|ITGA2|SPHK1|NSTN|AKT1|PLCG1|CTNN1|TRIB3|AD|CYAP1R1|AREG|STAT1|CALM1|ARHG|EF7|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-12    | 52           | 836               | 9.56E-11       | 1.45E-08          | RASGRP1|LOC102168547|CCL5|TRIB3|BIRC3|IKBKB|AKT1|PLCG1|RIPK2|ARB1|TLR9|IFIT3|AREG|B2M|STAT1|CALM1|ARHG|EF7|ADAP1|PXN|DUSP4|DUSP6|ATP6V0B|IGF1R|CSK|RAC1|PRKCD|FES|ITPR3|RHOA|RPS6KA5|GRB10|IRS2|TCIRG1|GRB7|PRKACB|PPP2R5D|BAIAP2|TLR9|ELMO2 |
| Terms                        | Database | ID          | Input number | Background number | P-Value   | Corrected P-Value | Input                          |
|------------------------------|----------|-------------|--------------|-------------------|-----------|------------------|--------------------------------|
| Hemostasis                   | Reactome | R-HSA-10    | 43           | 617               | 1.63E-10  | 2.25E-08          | 2R5D|IL9R|LOC102184087|PPIA                          |
|                              |          | 9582        |              |                   |           |                  | RASGRP1|EHDP|CD58|SLC7A5|ITGA6|AKT1|PLCG1|DOCK9|KIF5B|CD2|ARRB1|P2RX1|P2RX5|SERPINE1|CALM1|SLC8A1|CABLES2|ITGA2|PRKCH|DAGLB|CSK|RAC1|PRKCD|PLAU|LOC102180421|LOC102169725|RHOA|PLEK|ATP2B4|AKAP1|RBSN|CFD|F2R|GNA15|ITGAL|GRB7|PRKAC|PPP2R5D|LOC102189950|SLC16A3|PPIA|PRKAR1A|                                            |
| Toll-like Receptor Cascades  | Reactome | R-HSA-16    | 21           | 154               | 2.23E-10  | 2.97E-08          | TICAM2|CTSS|NFKBIA|RPS6KA5|TLR9|TIRAP|RBSN|BIRC3|MAP2K1|IKBKB|LY96|CD14|RIPK2|LOC108633263|SIGIR|NOD2|PPP2R5D|IRAK3|MAPK8|DUSP6|DUSP4|                                              |
| VEGFA-VEGFR2 Pathway         | Reactome | R-HSA-44    | 17           | 97                | 3.84E-10  | 4.50E-08          | NCF2|NCF1|NCKAP1L|CALM1|ITPR3|RAC1|PRKCD|SPHK1|AKT1|PLCG1|PRKAC|PXN|CTNND1|TRIB3|BAIAP2|RHOA|ELMO2|                                            |
| Signaling by VEGF            | Reactome | R-HSA-19    | 17           | 106               | 1.28E-09  | 1.31E-07          | NCF2|NCF1|NCKAP1L|CALM1|ITPR3|RAC1|PRKCD|SPHK1|AKT1|PLCG1|PRKAC|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                                                                 |
|--------------------------|----------|-----|--------------|-------------------|----------|-------------------|------------------------------------------------------------------------|
| KAT2B|NCSTN|IKBKB|AKT1|PLCG1|IR S2|CTNND1|ARRB1|KREMEM1|OPLAH|AREG|UBAP1|MAML2|STAT1|TIRAP|R BPJ|MIB2|NCOR2|DERL1|FAM114A2|M ARK3|B2M|RPS19|NFKBIA|TBXAS1|CSK|RAC1|CLCN6|RPS29|LOC108633263|GTF2E2|LY96|LOC102190167|IDUA|FG FR1|VAMP1|NUP50|GALK1|RNF185|LOC106503208|SYT2|CALM1|MAP2K1|GL B1|CTDP1|BDT|CD14|PPP2R5D|SLC35 D1|MMAB|LOC102182048|PPIA|CCNK |
| Post-translational protein modification | Reactome | R-HSA-59 7592 | 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|LOC102 184572|MKL1|TULP4|USP22|TGOLN2|PNPLA2|FBXL12|CUL9|NOD2|PML|MBD1|RAB13|FEM1B|FEM1A|ST3GAL2|PIGB|CD59|TTLL1|ST3GAL5|FBXW8|RH OA|COG2|DCAF4|YKT6|ST3GAL1|LOC102173518|ARSG|GOLM1|LOC102179758|FBXW2|UBE2|NUP50|GALNT1|DPH7|RNF185|TOP2B|LOC102184009|FB |
| Terms | Database | ID       | Input number | Background number | P-Value  | Corrected P-Value | Input |
|-------|----------|----------|--------------|-------------------|----------|-------------------|-------|
| Toll Like Receptor TLR6:TLR2 Cascade | Reactome | R-HSA-16 8188 | 16            | 95                | 2.09E-09 | 1.96E-07          | XL5|GLB1|MGAT4A|NFKBIA|RNF144A|KDEL2|LOC102182048|UBE2T |
| MyD88:MAP L(TIRAP) cascade initiated on plasma membrane | Reactome | R-HSA-16 6058 | 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-16 6016 | 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-18 1438 | 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-16 8179 | 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-168 256 | 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|EV|UBE2D4|CD209|LAIR1|TIRAP|MGAM|PIK3R2|LOC102186356|SURF4|GHDC|PKM|IL4R|ASB3|UBA7|HERC5|ITPR2|ANAPC2|RHO F|ITGAX|IRF1|ABCE1|ZNRF1|UBE2O|IRF4|UBE2F|ITGAM|RNF125|CD19|LOC102169209|RAF1|STAT6|PELI1|STAT1|RACGAP1|TIGAT2B|MAPK9|RAB14|AREL1|IRF3|SH3RF1|UNC13D|LOC102178529|FLT3LG|UBE2V1|CLEC6A|NEAL2|LOC102175938|TOM1|BIRC3|PLCG2|MAP2K1|BIN2|FYB|FYN|ACAA1|NRG1|LOC102188617|CRACR2A|CD44|TPP2|GALNS|LOC102180421|LOC102186814|LOC102176695|RAB24|VCN1|CASP9|ADAR |
| **Innate Immune**      | Reactome | R-HSA-168 249 | 55          | 1043              | 8.13E-15    | 6.43E-12          | LOC102169209|RAB14|HK3|FYN|BIRC3|IKBKB|CD209|TARM1|LAIR1|IKBKE |
| Terms       | Database | ID          | Input number | Background number | P-Value   | Corrected P-Value | Input                                                                 |
|------------|----------|-------------|--------------|-------------------|-----------|------------------|------------------------------------------------------------------------|
| System     |          |             |              |                   |           |                  | E|RAF1|IRF3|BIN2|STAT6|PELI1|LOC102175938|TIRAP|MGAM|DYNLT1|AC AA1|PIK3R2|TOM1|MAPK9|LOC102188617|SURF4|IRAK4|CRACR2A|TGAX|PECAM1|CD44|GALNS|GHDC|UBA7|UNC13D|HERC5|LOC102180421|LOC102189890|ITPR2|UBE2V1|RHOF|PL D4|LOC102178529|RAB24|PLCG2|HV CN1|MAP2K1|ADAM8|CASP9|CYLD|ITGAM|CLEC6A|RNF125|PKM|NBEAL2|CD19 |
| Metabolism | Reactome | R-HSA-143 0728 | 80           | 2075              | 7.94E-14  | 5.59E-11        | PNPLA7|BPGM|PGS1|NADSYN1|ACO X3|MOC5S2|LOC102183750|LOC102189751|SGMS1|SCAP|SUOX|NR1H3|ML X|ST3GAL6|LOC102170668|PCYT2|L HPP|OGDH|LOC102169935|CIAPlN1|LOC102186759|OPLAH|ALAS1|ACA A1|RPE|PIK3R2|HK3|MED14|MTHFD1|CAD|MTM3R3|RAB14|PNPLA6|GALT|S T3GAL1|TPMT|RAB5A|MIGA2|PIKFYVE|GNB5|CD44|MED31|GALNS|KDSR|GYS1|SEC24D|CPTP|GU K1|PUDP|EC I1|PIK3R5|ITPR2|TBL1X|CHST3|RTEL1|TSPO|HSD17B4|PHYH|PLD4|PLA2 |
| Terms                        | Database   | ID       | Input number | Background number | P-Value   | Corrected P-Value | Input                                                                 |
|------------------------------|------------|----------|--------------|-------------------|-----------|-------------------|-----------------------------------------------------------------------|
| Adaptive Immune System       | Reactome   | R-HSA-128 0218 | 38           | 748               | 3.65E-10  | 1.16E-07          | G15|CA9|ARSG|SDSL|INPP5E|NAXD|UCKL1|ACAD8|LOC106503208|OSBP L5|PLCG2|ACSL5|NUBP2|MTF1|PDK3 |DTYMK|PITPNM2|INPP5B|MMAB|OSBP|SLC19A1 |
| Metabolism of lipids         | Reactome   | R-HSA-556 833 | 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|PKFNYE|CPTP|PCYT2|SEC24D|HSD17B4|TSPO|PHYH|PLD4|PLA2G15|KDS R|ARSG|TBL1X|INPP5E|MTF1|ACOX3|ACSL5|EC1|PITPNM2|OSBP |
| Neutrophil degranulation     | Reactome   | R-HSA-679 8695 | 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|LOC102189890|RHOF|ITGAX|LOC102178529|RAB24|HVCN1|ADAM8 |RAB14|ITGAM|CRACR2A|NBEAL2 |
| Disease               | Reactome | R-HSA-164   | 42           | 1049              | 3.39E-08  | 4.57E-06          | HDAC9|IKK|MPRIP|MAP2K1|SLC29A3|ADAMTS14|MPDU1|PMM2|RAF1|OPLAH|EPS15|GTF2E2|STAT1|TIRAP |ITGA2B|FYN|MIB2|THBS1|PIK3R2|SV2A|IRAK4|GALT|TGFB1|APH1B|TPM2|GALNS|GYS1|NRG1|TSC2|CHST3|LOC102175896|TBL1X|MYO18A|TPBA|KAP9|CASP9|LOC106503208|POMT1|APC|NTHL1|MMAB|CD19 |
| Class I MHC mediated antigen processing & presentation | Reactome | R-HSA-983   | 22           | 370               | 1.58E-07  | 1.77E-05          | UBE2Q2|LOC102175938|UBE2D4|IKKB|LOC102186637|ASB3|TIRAP|MIB2 |CUL7|LOC102188617|AREL1|SH3RF1|TPP2|SEC24D|HERC5|UBE2V1|ANAPC2|ZNRF1|UBE2O|UBA7|UBE2F|RFN213 |
| Metabolism of proteins| Reactome | R-HSA-392   | 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                                                                 |
|-----------------------|----------|--------|--------------|-------------------|-------------|-------------------|----------------------------------------------------------------------|
| Hemostasis            | Reactome | R-HSA-109 | 29           | 617               | 2.17E-07    | 2.18E-05          | MPDU1|IKBKE|SEC16A|EXOSC3|U SP25|LOC102186637|APH1B|ST6GAL NAC4|ZBTB17|PIAS3|COMMD7|THBS1|MRPL55|AMHD2|CUL9|DDB2|AAR S2|CUL7|RAB14|TTL5|DGP2|TGFBR 1|RAB5A|ST3GAL6|ASB3|GNB5|COG 2|LARGE2|LOC102186814|GGA1|SEC 24D|GGA3|PCGF2|MYSM1|USP19|NF RKB|USP37|EXOC2|PTRH2|ARSG|RA B24|B3GALNT2|CXCL8|KIF5B|DAP3|UBE2F|RABGGTB|METTL22|CYLD|RF NF144A|POMT1|APC|HLTF |
| Phospholipid metabolism | Reactome | R-HSA-148 | 16           | 212               | 4.19E-07    | 3.64E-05          | ATP2A3|ZFP21|ECM1|PLCG2|RAF1|DGKZ|PECAM1|RACGAP1|IT GA2B|FYN|CD84|THBS1|DOK2|PIK3R 5|PIK3R2|DAGLB|RAB5A|GNB5|CD44 |FERMT3|LOC102184021|TMX3|ITPR 2|ITGAX|IRF1|KIF5B|CALU|ITGAM |
| Post-translational    | Reactome | R-HSA-597 | 47           | 1412              | 9.28E-07    | 6.83E-05          | ERCC8|UBE2Q2|BIRC3|ST3GAL1|AD AMTS14|MPDU1|IKBKE|PMM2|SEC16 |
| Terms                        | Database | ID       | Input number | Background number | P-Value       | Corrected P-Value | Input                                                                 |
|-----------------------------|----------|----------|--------------|-------------------|---------------|------------------|-----------------------------------------------------------------------|
| protein modification        |          |          |              |                   |               |                  | A|USP25|LOC102186637|ASB3|ST6G ALNAC4|PIAS3|COMMD7|THBS1|AM DHD2|CUL9|DDB2|CUL7|RAB14|TTLL 5|TGFB1|RAB5A|ST3GAL6|COG2|LARGE2|LOC102186814|SEC24D|PCG F2|MYSM1|USP19|NFRKB|USP37|PT RH2|ARSG|RAB24|B3GALNT2|CALU|UBE2F|RABGGTB|METTL22|CYLD|R NF144A|POMT1|APC|HLTF |
| Toll Like Receptor 4 (TLR4) | Reactome | R-HSA-166 016 | 12          | 128               | 1.46E-06      | 9.42E-05        | IRF3|PELI1|TIRAP|BIRC3|IKBK|PLCG2|M APK9|IRAK4 |
| DNA Repair                  | Reactome | R-HSA-738 94 | 19          | 331               | 1.80E-06      | 0.0001096       | ERCC8|SPIDR|RTEL1|SIRT6|SPRTN|ACD|PNKP|ERCC5|TERF2|UBA7|PAS3|DDB2|ATR|NTHL1|POLL|NFRKB|P OLM|LOC102186637|UVSSA |
| Gene expression (Transcript    | Reactome | R-HSA-741 60 | 47          | 1448              | 1.80E-06      | 0.0001096       | HDAC9|MTERF1|LOC102189751|GTF 3C5|LOC102180305|TSC2|SAP130|C DC7|LOC102170668|GTF2E2|INTS10|STAT1|POLDIP3|TGA2B|LOC102170 775|THBS1|BRPF1|CNOT8|MED14|ZF P69|ZNF263|DDB2|PRELID3A|ZNF66 4|KMT2C|TCF7|ZFP1|M1|TFAM|BANP|T |
| Terms                                      | Database  | ID       | Input number | Background number | P-Value     | Corrected P-Value | Input                                      |
|--------------------------------------------|-----------|----------|--------------|-------------------|-------------|-------------------|--------------------------------------------|
| Diseases of signal transduction            | Reactome  | R-HSA-566| 20           | 374               | 2.69E-06    | 0.0001533         | CF3|MED31|ZNF446|SNAPC4|PHF20|MGA|PCGF2|TBL1X|TBP|RABGGTB|ATR|HTT|PRDM1|FAS|ZN500|PLAGL1|ZNF394|PHF1 |
| Platelet activation, signaling and aggregation | Reactome  | R-HSA-760| 16           | 260               | 5.08E-06    | 0.0002594         | APH1B|TGFBR1|TBL1X|STAT1|M1O1|8A|HDAC9|ITGA2B|FYN|AKAP9|MIB2|CASP9|MPRIP|MAP2K1|PIK3R2|RAF1|NRG1|APC|LOC102175896|TSC2|CD19 |
| Toll-like Receptor Cascades                | Reactome  | R-HSA-168| 12           | 154               | 8.57E-06    | 0.0003885         | IRF3|PELI1|TIRAP|BIRC3|IKKB|PLCG2|M2K1|ITGAM|IKBKE|UBE2V1|MAP9|RAK4 |
| Centrosome maturation                     | Reactome  | R-HSA-380| 9            | 81                | 8.57E-06    | 0.0003885         | CEP164|SF11|AKAP9|CEP192|HAUS3|LOC102188159|PCNT|CDK5RAP2|TUBGCP2 |
| Recruitment of mitotic centrosome          | Reactome  | R-HSA-380| 9            | 81                | 8.57E-06    | 0.0003885         | CEP164|SF11|AKAP9|CEP192|HAUS3|LOC102188159|PCNT|CDK5RAP2|TUBGCP2 |
| Terms                      | Database | ID | Input number | Background number | P-Value | Corrected P-Value | Input |
|---------------------------|----------|----|--------------|--------------------|---------|-------------------|-------|
| e proteins and complexes  |          |    |              |                    |         |                   |       |

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

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