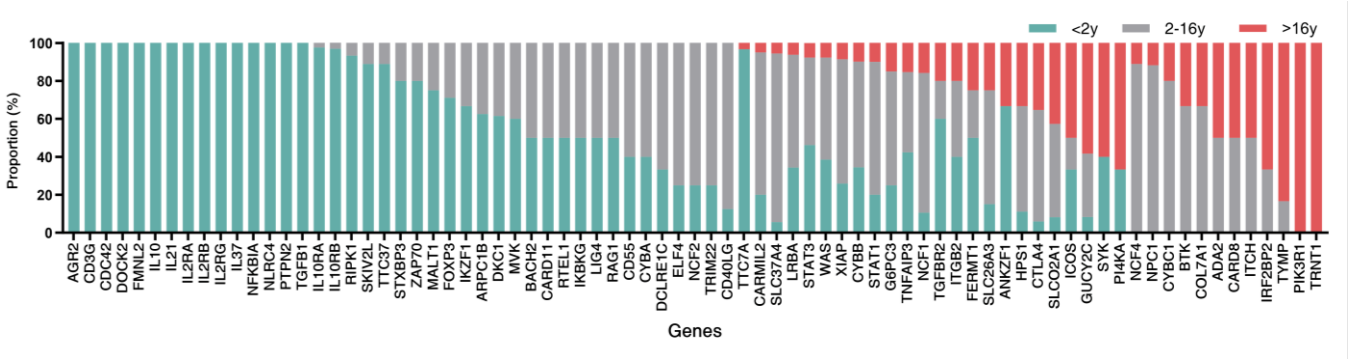
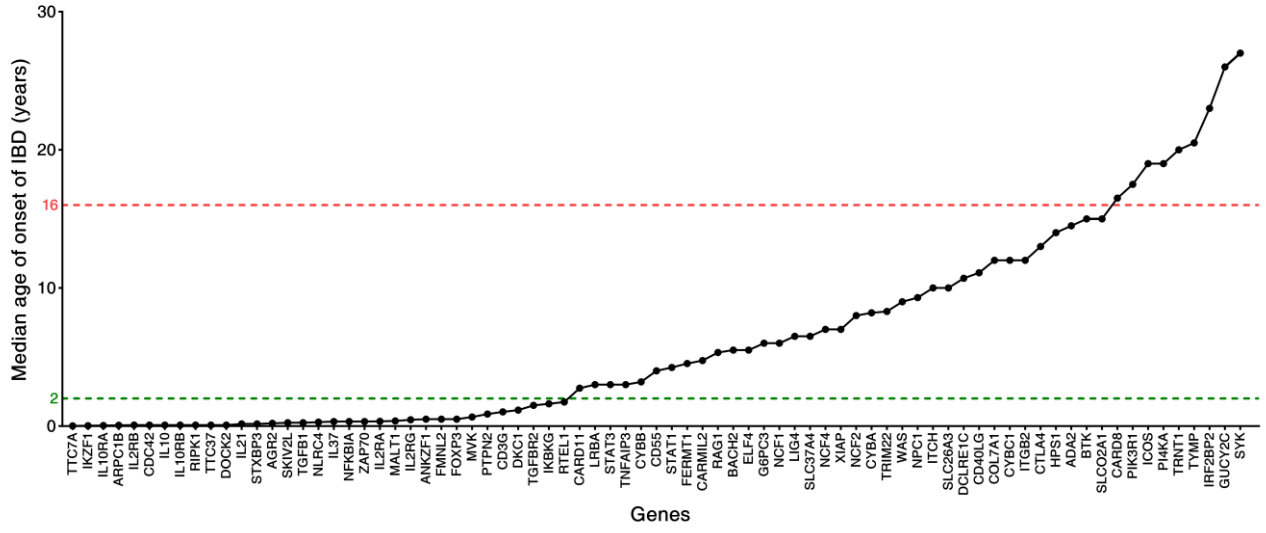
Supporting information



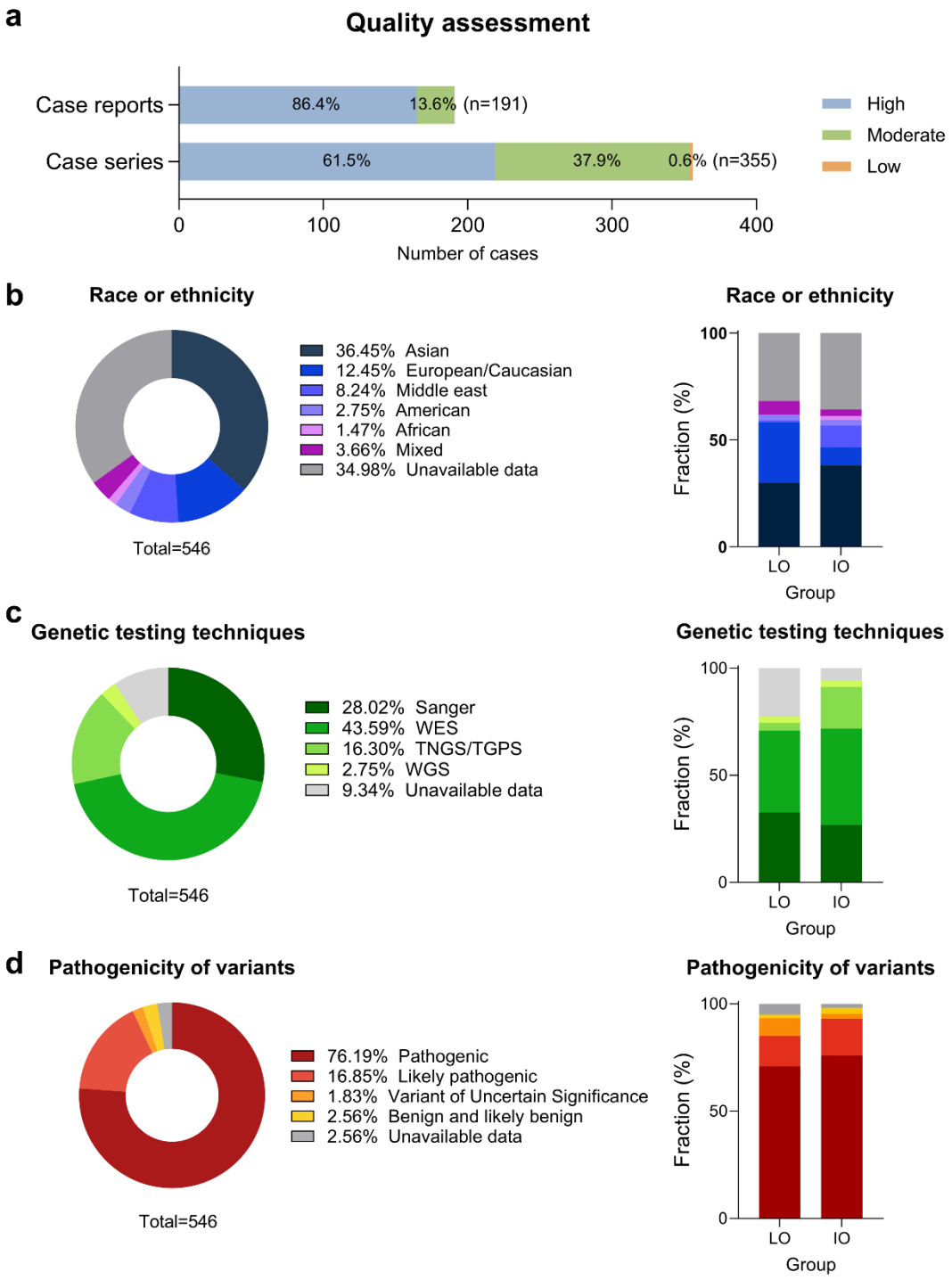
Supplementary Figure 1. Pathogenic genes and case distribution in infantile-onset and late-onset mIBD

A total of 77 pathogenic genes were identified in infantile-onset and late-onset mIBD cases, and the case proportion associated with each gene was analyzed. Green bars represent the proportion of patients with the onset of IBD-like phenotypes before age 2, while red bars indicate those with onset after age 16, respectively. Gray bars denote the remaining patients with onset between ages 2 and 16.



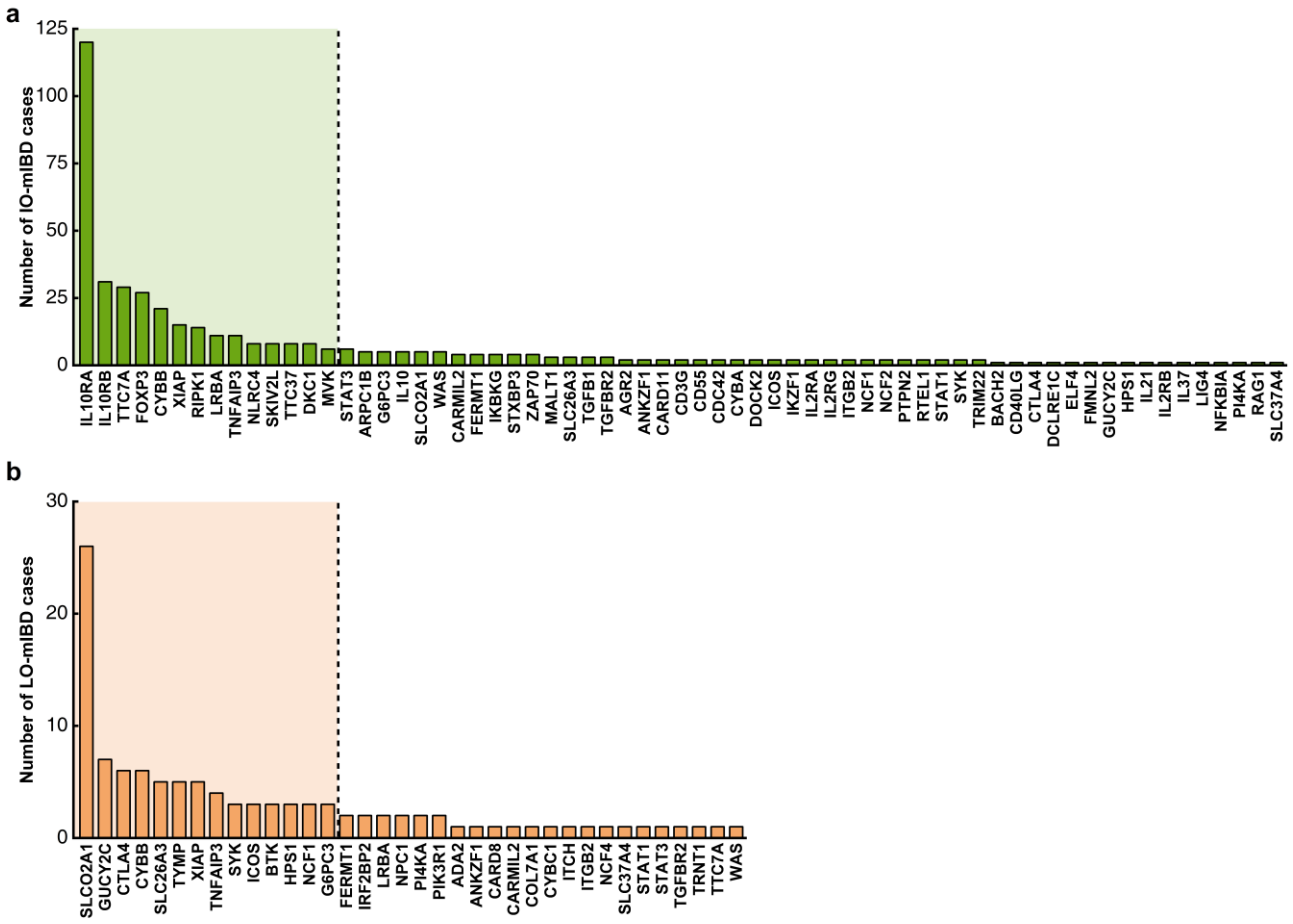
Supplementary Figure 2. Median age at onset of IBD-like phenotypes for each gene

The median age of onset of IBD-like manifestations for each gene was denoted by solid dots, calculated from all cases of mIBD screened in this (88 genes in total). The green and red lines represent the age thresholds of 2 years and 16 years, respectively.



Supplementary figure 3. Additional information on the included cases.

(a) Quality assessment of 546 cases included in this study, based on the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series, respectively. Studies were categorized as high (≥7), moderate (4–6), and low quality (0–3). (b) Race or ethnicity distribution of the cases included in this study. (c) Genetic testing technologies employed in the cases included in this study. (d) Variant pathogenicity assessment of the cases, evaluated according to the American College of Medical Genetics and Genomics (ACMG) criteria. Abbreviations: WES, whole exome sequencing; TNGS, targeted next-generation sequencing; TGPS: targeted gene panel sequencing; WGS, whole genome sequencing.



Supplementary Figure 4. Stratification and ranking of cases based on pathogenic genes in infantile-onset and late-onset mIBD

A total of 65 pathogenic genes were found in patients with infantile-onset mIBD (a) and 36 in late-onset mIBD (b). The case number for each gene defect is represented by the bars. The top 14 common genes in each group (highlighted) were chosen for further stratified analysis of features.

Supplementary Table1A. Categories and definitions of variant zygosity, referring to Klein, C. et al.[1]

Zygosity	Definition
Homozygotes	Both alleles of the gene are affected by the same variant
Compound heterozygotes (CH)	Two alleles of the gene are affected by different variants
Hemizygotes	One allele of the gene is affected while the other allele is absent or non-functional, observed in x-linked genes
Heterozygotes	Only one allele of the gene is affected

Supplementary Table1B. Categories and definitions of gastrointestinal phenotypes

GI phenotypes	Definition
CD	Crohn's disease (-like)
UC	Ulcerative colitis (-like)
IBDU/IC	IBD-unclassified or indeterminate colitis (-like)
IBD	IBD (-like) without delineating specific subtypes
Others	Other chronic intestinal inflammation resembling IBD, including intestinal Behçet's disease (iBD), chronic non-specific enterocolitis (CNE), autoimmune enteropathy, granulomatous colitis, chronic granulomatous disease (CGD) colitis, cryptogenic multifocal ulcerous stenosing enteritis (CMUSE), chronic enteropathy associated with the SLCO2A1 gene (CEAS), chronic non-specific multiple ulcers of the small intestine (CNSU), common variable immunodeficiency-associated enteropathy

Supplementary Table1C. Definition and criteria of gastrointestinal histopathological patterns, referring to Wilkins, B. J. et al.[2]

Intestinal pathologic patterns	Definition
Chronic active enteritis	Active inflammation (neutrophilic cryptitis and crypt abscesses) and chronic mucosal changes (crypt branching, crypt dropout, increased lymphoplasmacytic mucosal inflammation causing crypt liftoff)
Apoptosis or epithelial injury	Dilated with attenuated epithelial layers, loss of goblet or Paneth cells, crypt abscesses containing sloughed epithelial cells or apoptotic debris
Eosinophil-rich pattern	Lamina propria clustering and eosinophilic infiltration of surface and crypt epithelium
Lymphocytic pattern	Diffuse crypt and surface intraepithelial infiltration by lymphocytes, nodular lymphoid hyperplasia, lymphocyte or plasma cell depletion
Granulomatous pattern	Large and confluent sarcoid-like granulomas with multinucleated giant cells

Supplementary Table1D. Details for comorbidities assessed in this study

Category	Criteria or definition
Autoimmune disease	Autoimmune arthritis, thyroiditis, hepatitis, or pancreatitis; type 1 diabetes mellitus; psoriasis; systemic lupus erythematosus; Sjogren's syndrome; autoimmune hemolytic anemia, autoimmune neutropenia; immune thrombocytopenic purpura; glomerular nephropathy; nephrotic syndrome and autoimmune
Autoinflammation	Periodic fever of unknown origin; unexplained systemic inflammation of the skin, mucosa, serosa, or other organs; and persistent elevated inflammatory markers
Recurrent infections, fevers	Recurrent, severe, or opportunistic infections and fevers reported by authors based on clinical, laboratory, and other examing information
HLH/MAS	Hemophagocytic lymphohistiocytosis or macrophage activation syndrome reported by authors based on clinical, laboratory, and other examing information
Ectodermal dysplasia	Skin, hair, dental, or nail abnormalities
Dysmorphism	Dysmorphism in the face, limbs, or organs

Supplementary Table2A. JBI Critical Appraisal Checklist for Case Reports.

		Yes = 1	No/unclear = 0
1	Were patient's demographic characteristics clearly described?	□	□
2	Was the patient's history clearly described and presented as a timeline?	□	□
3	Was the current clinical condition of the patient on presentation clearly described?	□	□
4	Were diagnostic tests or assessment methods and the results clearly described?	□	□
5	Was the intervention(s) or treatment procedure(s) clearly described?	□	□
6	Was the post-intervention clinical condition clearly described?	□	□
7	Were adverse events (harms) or unanticipated events identified and described?	□	□
8	Does the case report provide takeaway lessons?	□	□
Score (0~3; low, 4~6:moderate; 7~8:high)			

Supplementary Table 2B. JBI Critical appraisal checklists for case series.

		Yes = 1	No/unclear = 0
1	Were there clear criteria for inclusion in the case series?	□	□
2	Was the condition measured in a standard, reliable way for all participants included in the case series?	□	□
3	Were valid methods used for identification of the condition for all participants included in the case series?	□	□
4	Did the case series have consecutive inclusion of participants?	□	□
5	Did the case series have complete inclusion of participants?	□	□
6	Was there clear reporting of the demographics of each participant in the study?	□	□
7	Was there clear reporting of clinical information of each participant?	□	□
8	Were the outcomes or follow up results of each case clearly reported?	□	□
9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	□	□
10	Was statistical analysis appropriate?	□	□
Score (0~3; low, 4~6:moderate; 7~10:high)			

Supplementary Table 3. Univariate logistic regression of the variant zygosity in patients with late-onset and infantile onset mIBD

	OR (95% CI)	P value
Homozygotes (Ref)		
Heterozygotes	**2.564 (1.453, 4.523)**	**0.001**
Compound heterozygotes	0.683 (0.388, 1.203)	0.187
Hemizygotes	0.744 (0.392, 1.410)	0.365
Compound heterozygotes (Ref)		
Heterozygotes	**3.753 (1.948, 7.228)**	**<0.001**
Homozygotes	1.464 (0.831, 2.577)	0.187
Hemizygotes	1.089 (0.531, 2.234)	0.816
Hemizygotes (Ref)		
Heterozygotes	**3.446 (1.677, 7.083)**	**0.001**
Compound heterozygotes	0.918 (0.448, 1.884)	0.816
Homozygotes	1.344 (0.709, 2.549)	0.365
Heterozygotes (Ref)		
Compound heterozygotes	**0.266 (0.138, 0.513)**	**<0.001**
Hemizygotes	**0.290 (0.141, 0.596)**	**0.001**
Homozygotes	**0.390 (0.221, 0.688)**	**0.001**

Supplementary Table 4. Multivariate logistic regression analysis of demographic and clinical characteristics between LO-mIBD and IO-mIBD, adjusted for sex, consanguinity, and genotypes.

	Model 1		Model 2 (adjusted for sex)		Model 3 (adjusted for sex and consanguinity)		Model 4 (adjusted for genotypes)	
	OR (95% CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Sex (male)	0.57 (0.38, 0.88)	**0.011**	-	-	-	-	0.60 (0.34, 1.03)	0.063
Parental consanguinity	0.49 (0.27, 0.88)	**0.015**	0.45 (0.25, 0.82)	**0.009**	-	-	0.57 (0.27, 1.21)	0.143
Family history of similar monogenic disorders	1.46 (0.92, 2.32)	0.108	1.45 (0.91, 2.31)	0.122	1.58 (0.96, 2.56)	0.063	1.03 (0.56, 1.86)	1.000
Family history of IBD-like manifestations	0.86 (0.52, 1.42)	0.553	0.84 (0.50, 1.40)	0.496	0.86 (0.51, 1.46)	0.570	0.75 (0.39, 1.42)	0.372
Zygosity								
Homozygotes (Ref)	-	-	-	-	-	-	-	-
Compound heterozygotes	0.68 (0.39, 1.20)	0.187	0.67 (0.37, 1.19)	0.167	0.519(0.249, 1.080)	0.079	0.91 (0.42, 1.95)	0.803
Heterozygotes	2.56 (1.45, 4.52)	**0.001**	2.51 (1.41, 4.45)	**0.002**	2.313(1.114, 4.802)	**0.024**	1.31 (0.65, 2.63)	0.45
Hemizygotes	0.74 (0.39, 1.41)	0.365	1.00 (0.50, 2.00)	0.989	0.982(0.426, 2.263)	0.966	0.41 (0.19, 0.89)	**0.024**
Intestinal phenotypes								
IBD‡ (Ref)	-	-	-	-	-	-	-	-
UC	6.22 (1.99, 19.49)	**0.002**	6.97 (2.16, 22.55)	**0.001**	10.37 (2.46, 43.79)	**0.001**	4.29 (1.16, 15.79)	**0.029**
CD	8.53 (4.02, 18.11)	**<0.001**	10.12 (4.58, 22.39)	**<0.001**	12.37 (4.99, 30.64)	**<0.001**	11.57 (4.41, 30.40)	**<0.001**
IBDU/IC	1.10 (0.13, 9.20)	0.931	1.78 (0.21, 15.49)	0.601	-	-	-	-
Others§	6.71 (3.17, 14.21)	**<0.001**	7.72 (3.50, 17.03)	**<0.001**	8.89 (3.62, 21.83)	**<0.001**	4.51 (1.85, 11.02)	**0.001**
GI symptoms								
Abdominal pain	4.62 (2.80, 7.62)	**<0.001**	4.50 (2.71, 7.45)	**<0.001**	6.35 (3.58, 11.27)	**<0.001**	3.04 (1.56, 5.93)	**0.001**
Diarrhea	0.16 (0.09, 0.29)	**<0.001**	0.17 (0.09, 0.31)	**<0.001**	0.12 (0.06, 0.24)	**<0.001**	0.45 (0.23, 0.89)	**0.021**
Hematochezia	0.29 (0.18, 0.48)	**<0.001**	0.30 (0.18, 0.49)	**<0.001**	0.25 (0.14, 0.45)	**<0.001**	0.40 (0.21, 0.74)	**0.003**

	Model 1		Model 2 (adjusted for sex)		Model 3 (adjusted for sex and consanguinity)		Model 4 (adjusted for genotypes)	
	OR (95% CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Perianal disease	0.10 (0.05, 0.20)	**<0.001**	0.10 (0.05, 0.19)	**<0.001**	0.09 (0.04, 0.19)	**<0.001**	0.31 (0.14, 0.70)	**0.003**
GI complications								
Intestinal fistula	0.38 (0.09, 1.67)	0.294	0.37 (0.08, 1.62)	0.187	0.46 (0.10, 2.07)	0.313	-	0.506
Perforation	0.58 (0.20, 1.72)	0.324	0.58 (0.20, 1.72)	0.326	0.19 (0.03, 1.43)	0.106	0.78 (0.18, 3.38)	1.000
Stricture	2.24 (1.32, 3.81)	**0.002**	2.31 (1.35, 3.94)	**0.002**	2.13 (1.17, 3.88)	**0.013**	1.64 (0.78, 3.43)	0.191
Lesion sites								
Esophagus/Stomach	1.32 (0.76, 2.31)	0.328	1.34 (0.76, 2.38)	0.318	1.49 (0.79, 2.82)	0.221	0.86 (0.44, 1.69)	0.669
Duodenum	0.76 (0.43, 1.34)	0.340	0.79 (0.44, 1.40)	0.410	0.73 (0.39, 1.39)	0.340	0.49 (0.24, 0.98)	**0.041**
Small intestine	3.37 (2.08, 5.45)	**<0.001**	3.50 (2.15, 5.70)	**<0.001**	4.18 (2.41, 7.28)	**<0.001**	2.97 (1.61, 5.51)	**<0.001**
Colon	0.25 (0.15, 0.43)	**<0.001**	0.25 (0.15, 0.43)	**<0.001**	0.21 (0.12, 0.38)	**<0.001**	0.30 (0.15, 0.60)	**0.001**
Rectum	0.45 (0.22, 0.90)	**0.021**	0.42 (0.21, 0.86)	**0.018**	0.40 (0.19, 0.83)	**0.015**	0.49 (0.20, 1.16)	0.100
Upper GI involvement[¶]	1.01 (0.61, 1.67)	0.962	1.00 (0.60, 1.66)	0.983	1.02 (0.58, 1.80)	0.934	0.68 (0.37, 1.26)	0.221
Endoscopic findings								
Ulcer	3.21 (1.31, 7.86)	**0.008**	3.99 (1.50, 10.56)	**0.005**	5.16 (1.73, 15.34)	**0.003**	7.91 (2.58, 24.26)	**<0.001**
Erosion	0.75 (0.37, 1.52)	0.422	0.72 (0.35, 1.50)	0.381	0.69 (0.29, 1.46)	0.296	0.35 (0.14, 0.85)	**0.017**
Pseudopolyps	0.21 (0.06,0.70)	**0.006**	0.22 (0.07, 0.74)	**0.014**	0.15 (0.03, 0.63)	**0.010**	0.47 (0.12, 1.85)	0.269
Pathological features								
Villous atrophy	0.20 (0.06, 0.68)	**0.005**	0.20 (0.06, 0.68)	**0.009**	0.14 (0.03, 0.62)	**0.009**	0.39 (0.11, 1.44)	0.146
Chronic active enteritis	0.71 (0.38, 1.31)	0.272	0.74 (0.40, 1.39)	0.352	0.72 (0.35, 1.46)	0.362	1.46 (0.68, 3.12)	0.334
Apoptosis or epithelial injury	0.50 (0.17, 1.48)	0.202	0.50 (0.17, 1.49)	0.216	0.71 (0.23, 2.20)	0.550	0.49 (0.15, 1.59)	0.227
Eosinophil-rich	0.90 (0.29, 2.75)	1.000	0.97 (0.32, 3.00)	0.961	1.03 (0.32, 3.34)	0.963	0.43 (0.11, 1.59)	0.193
Lymphocytic	2.43 (1.10, 5.38)	**0.025**	2.39 (1.04, 5.46)	**0.039**	3.10 (1.21, 7.93)	**0.018**	1.84 (0.69, 4.85)	0.217
Granulomatous	2.36 (1.10, 5.05)	**0.024**	2.47 (1.14, 5.33)	**0.022**	2.63 (1.09, 6.35)	**0.032**	1.66 (0.64, 4.32)	0.297
Extraintestinal manifestations								

	Model 1		Model 2 (adjusted for sex)		Model 3 (adjusted for sex and consanguinity)		Model 4 (adjusted for genotypes)	
	OR (95% CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
> 1 EIMs	0.92 (0.60, 1.39)	0.680	0.85 (0.55, 1.30)	0.450	0.91 (0.57, 1.45)	0.692	1.02 (0.76, 1.37)	0.889
> 2 EIMs	1.14 (0.72, 1.81)	0.582	1.06 (0.66, 1.71)	0.813	1.15 (0.69, 1.91)	0.605	0.94 (0.59, 1.49)	0.790
Anemia	1.98 (1.23, 3.18)	**0.004**	1.84 (1.14, 2.98)	**0.013**	1.73 (1.02, 2.92)	**0.041**	1.55 (1.00, 2.39)	**0.049**
Growth retardation	0.16 (0.09, 0.30)	**<0.001**	0.15 (0.08, 0.29)	**<0.001**	0.14 (0.07, 0.28)	**<0.001**	0.17 (0.07, 0.42)	**<0.001**
Oral lesions	0.39 (0.20, 0.77)	**0.005**	0.39 (0.20, 0.76)	**0.006**	0.42 (0.21, 0.85)	**0.016**	0.57 (0.26, 1.23)	0.141
Skin lesions	0.70 (0.45, 1.11)	0.128	0.69 (0.43, 1.10)	0.115	0.64 (0.38, 1.07)	0.089	1.13 (0.73, 1.77)	0.586
Musculoskeletal abnormality	3.45 (2.06, 5.77)	**<0.001**	3.17 (1.88, 5.35)	**<0.001**	3.67 (2.06, 6.56)	**<0.001**	2.15 (1.20, 3.83)	**0.008**
Hepato-splenic-biliary abnormality	0.97 (0.53, 1.79)	0.933	1.01 (0.54, 1.86)	0.983	1.22 (0.63, 2.35)	0.577	0.68 (0.35, 1.33)	0.255
Chronic renal disease	0.96 (0.20, 4.59)	1.000	1.10 (0.23, 5.30)	0.908	1.02 (0.21, 4.98)	0.984	1.49 (0.09, 23.81)	1.000
Chronic pulmonary disease	2.29 (0.94, 5.61)	0.111	2.18 (0.88, 5.37)	0.091	2.73 (1.01, 7.42)	**0.049**	2.09 (0.69, 6.37)	0.306
Cardiovascular abnormality	0.85 (0.28, 2.56)	0.983	0.84 (0.28, 2.54)	0.751	0.77 (0.22, 2.75)	0.668	1.00 (0.29, 13.70)	1.000
Endocrine abnormality	1.38 (0.53, 3.58)	0.692	1.32 (0.47, 3.72)	0.595	1.18 (0.37, 3.78)	0.781	1.12 (0.40, 3.13)	0.827
Hematological abnormality	1.50 (0.74, 3.01)	0.256	1.57 (0.77, 3.18)	0.212	1.57 (0.72, 3.45)	0.259	1.35 (0.60, 3.07)	0.459
Neurological abnormality	1.74 (0.80, 3.77)	0.157	1.62 (0.74, 3.54)	0.228	1.85 (0.83, 4.12)	0.132	1.00 (0.29, 13.70)	1.000
Ocular and auditory abnormality	0.63 (0.14, 2.88)	0.794	0.66 (0.14, 3.00)	0.589	0.72, (0.15, 3.33)	0.669	0.37 (0.04, 3.29)	0.641
Lymphadenopathy	1.87 (0.79, 4.46)	0.150	2.03 (0.84, 4.91)	0.116	2.53 (0.99, 6.44)	0.052	1.33 (0.53, 3.31)	0.542
Comorbidities								
Recurrent infections	0.60 (0.38, 0.94)	**0.024**	0.59 (0.36, 0.93)	**0.024**	0.69 (0.42, 1.14)	0.143	0.57 (0.38, 0.85)	**0.004**
Relapsing fever	0.31 (0.15, 0.63)	**0.001**	0.30 (0.15, 0.63)	**0.001**	0.26 (0.11, 0.62)	**0.002**	0.42 (0.19, 0.93)	**0.023**
Autoimmune disease	1.24 (0.63, 2.46)	0.537	1.12 (0.57, 2.36)	0.668	1.21 (0.57, 2.58)	0.623	0.67 (0.32, 1.41)	0.286
Autoinflammation	0.73 (0.35, 1.54)	0.408	0.72 (0.34, 1.52)	0.385	0.80 (0.35, 1.82)	0.600	1.00 (0.42, 2.34)	0.993
HLH/MAS	0.27 (0.04, 2.06)	0.302	0.29 (0.04, 2.25)	0.237	0.36 (0.05, 2.89)	0.336	0.21 (0.03, 1.71)	0.210

	Model 1		Model 2 (adjusted for sex)		Model 3 (adjusted for sex and consanguinity)		Model 4 (adjusted for genotypes)	
	OR (95% CI)	P value	OR (95%CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Allergy	0.38 (0.05, 2.99)	0.562	0.48 (0.06, 3.84)	0.488	0.58 (0.07, 4.89)	0.618	0.75 (0.07, 8.13)	1.000
Ectodermal dysplasia	0.63 (0.21, 1.85)	0.394	0.61 (0.21, 1.81)	0.375	0.53 (0.15, 1.82)	0.311	0.66 (0.21, 2.09)	0.480
Dysmorphism	0.55 (0.19, 1.62)	0.273	0.55 (0.19, 1.62)	0.277	0.67 (0.22, 2.02)	0.478	0.37 (0.08, 1.72)	0.319
Malignancy	1.47 (0.56, 3.84)	0.606	1.53 (0.58, 4.05)	0.388	1.29 (0.40, 4.10)	0.672	2.99 (0.77, 11.63)	0.189

CD, Crohn's disease; UC, ulcerative colitis; IBDU, IBD-unclassified; IC, indeterminate colitis; GI, gastrointestinal tract.

‡. Gastrointestinal phenotypes labeled as IBD without specifying the exact subtype.

§. Other chronic intestinal inflammation resembling IBD, see detailed definitions in Supplementary Table 1B.

¶. The upper gastrointestinal tract includes the esophagus, stomach, and duodenum.

Supplementary Table 5. Multivariate logistic regression analysis of surgical rates of intestinal resection between LO-mIBD and IO-mIBD, adjusted for gastrointestinal complications and genotypes.

	Model 1		Model 2 (adjusted for intestinal fistula)		Model 3 (adjusted for perforation)		Model 4 (adjusted for stricture)		Model 4 (adjusted by genotypes)	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Intestinal resection	4.08 (2.42, 6.87)	**<0.001**	4.89 (2.75, 8.68)	**<0.001**	5.13 (2.85, 9.21)	**<0.001**	3.70 (2.07, 6.62)	**<0.001**	3.43 (1.68, 7.00)	**0.001**

Supplementary Table 6. Sensitivity analysis of demographic and clinical characteristics in patients with late-onset and infantile-onset mIBD

	Original analysis			Sensitivity analysis				
	LO-mIBD	IO-mIBD	P value	LO-mIBD		IO-mIBD		P value
	% (N†)	% (N†)		n‡	%	n‡	%	
Parental consanguinity	17.4 (92)	30.1 (356)	**0.015**	19	17.3	119	27.3	**0.031**
Family history of similar monogenic disorders	45.7 (92)	36.5 (356)	0.108	46	41.8	159	36.5	0.300
Family history of IBD-like manifestations	28.3 (92)	31.5 (356)	0.553	31	28.2	125	28.7	0.919
GI symptoms								
Abdominal pain	46.2 (93)	15.7 (344)	**<0.001**	47	42.7	68	15.6	**<0.001**
Diarrhea	66.7 (93)	92.4 (344)	**<0.001**	73	66.4	362	83.0	**<0.001**
Hematochezia	31.2 (93)	60.8 (344)	**<0.001**	34	30.9	238	54.6	**<0.001**
Perianal disease	10.6 (94)	53.7 (376)	**<0.001**	12	10.9	218	50.0	**<0.001**
GI complications								
Intestinal fistula	2.2 (89)	5.7 (335)	0.294	2	1.8	22	5.0	0.224
Perforation	4.5 (89)	7.5 (335)	0.324	5	4.5	29	6.7	0.414
Stricture	31.5 (89)	17.0 (335)	**0.002**	31	28.2	74	17.0	**0.008**
Lesion sites								
Esophagus/Stomach	23.6 (89)	19.0 (343)	0.328	23	20.9	83	19.0	0.657
Duodenum	20.2 (89)	25.1 (343)	0.340	22	20.0	98	22.5	0.575
Small intestine	58.4 (89)	29.4 (343)	**<0.001**	58	52.7	128	29.4	**<0.001**
Colon	62.9 (89)	87.2 (343)	**<0.001**	69	62.7	340	78.0	**0.001**
Rectum	11.2 (89)	22.2 (343)	**0.021**	12	10.9	86	19.7	**0.031**
Upper GI involvement	31.5 (89)	31.2 (343)	0.962	31	28.2	136	31.2	0.540
Endoscopic findings								
Ulcer	90.9 (66)	75.7 (210)	**0.008**	80	72.7	330	75.7	0.521
Erosion	18.2 (66)	22.9 (210)	0.422	20	18.2	74	17.0	0.764
Pseudopolyps	4.5 (66)	18.6 (210)	**0.006**	5	4.5	60	13.8	**0.008**
Pathological features								
Villous atrophy	5.5 (55)	22.9 (236)	**0.005**	6	5.5	75	17.2	**0.002**
Chronic active enteritis	63.6 (55)	71.2 (236)	0.272	70	63.6	239	54.8	0.095
Apoptosis or epithelial injury	7.3 (55)	13.6 (236)	0.202	8	7.3	46	10.6	0.303
Eosinophil-rich	7.3 (55)	8.1 (236)	1.000	8	7.3	27	6.2	0.679
Lymphocytic	20.0 (55)	9.3 (236)	**0.025**	17	15.5	41	9.4	0.066
Granulomatous	21.8 (55)	10.6 (236)	**0.024**	18	16.4	46	10.6	0.090
Extraintestinal manifestations								
> 1 EIMs	49.1 (110)	51.3 (423)	0.680	54	49.1	220	50.5	0.798
> 2 EIMs	29.1 (110)	26.5 (423)	0.582	32	29.1	116	26.6	0.600
Anemia	30.9 (110)	18.4 (423)	**0.004**	34	30.9	80	18.3	**0.004**

	Original analysis			Sensitivity analysis				
	LO-mIBD	IO-mIBD	P value	LO-mIBD		IO-mIBD		P value
	% (N†)	% (N†)		n‡	%	n‡	%	
Growth retardation	11.8 (110)	44.9 (423)	**<0.001**	13	11.8	193	44.3	**<0.001**
Oral lesions	10.0 (110)	22.0 (423)	**0.005**	11	10.0	94	21.6	**0.006**
Skin lesions	29.1 (110)	36.9 (423)	0.128	32	29.1	158	36.2	0.160
Musculoskeletal abnormality	29.1 (110)	10.6 (423)	**<0.001**	32	29.1	46	10.6	**<0.001**
Hepato-splenic-biliary abnormality	13.6 (110)	13.9 (423)	0.933	15	13.6	60	13.8	0.973
Chronic renal disease	1.8 (110)	1.9 (423)	1.000	2	1.8	8	1.8	1.000
Chronic pulmonary disease	7.3 (110)	3.3 (423)	0.111	8	7.3	14	3.2	0.096
Cardiovascular abnormality	3.6 (110)	4.3 (423)	0.983	4	3.6	18	4.1	1.000
Endocrine abnormality	5.5 (110)	4.0 (423)	0.692	6	5.5	17	3.9	0.645
Hematological abnormality	10.9 (110)	7.6 (423)	0.256	12	10.9	33	7.6	0.255
Neurological abnormality	9.1 (110)	5.4 (423)	0.157	10	9.1	24	5.5	0.164
Ocular and auditory abnormality	1.8 (110)	2.8 (423)	0.794	2	1.8	12	2.8	0.829
Lymphadenopathy	7.3 (110)	4.0 (423)	0.150	8	7.3	17	3.9	0.130
Comorbidities								
Recurrent infections	30.0 (110)	41.8 (423)	**0.024**	33	30.0	179	41.1	**0.034**
Relapsing fever	8.2 (110)	22.5 (423)	**0.001**	9	8.2	96	22.0	**0.001**
Autoimmune disease	10.9 (110)	9.0 (423)	0.537	12	10.9	39	8.9	0.527
Autoinflammation	8.2 (110)	10.9 (423)	0.408	9	8.2	46	10.6	0.461
HLH/MAS	0.9 (110)	3.3 (423)	0.302	1	0.9	14	3.2	0.320
Allergy	0.9 (110)	2.4 (423)	0.562	1	0.9	10	2.3	0.587
Ectodermal dysplasia	3.6 (110)	5.7 (423)	0.394	4	3.6	24	5.5	0.427
Dysmorphism	3.6 (110)	6.4 (423)	0.273	4	3.6	27	6.2	0.301
Malignancy	5.5 (110)	3.8 (423)	0.606	6	5.5	16	3.7	0.562

†. N = number of cases with available information about the features in the reports.

‡. n = the expected number of cases based on the assumed $RI_{LTFU/FU}$.

Supplementary Table 7. Treatment interventions in patients with late-onset and infantile-onset mIBD

	LO-mIBD		IO-mIBD		P value
	n/N†	%	n/N†	%	
Conventional Treatment					
5-ASA	27/90	30.0	108/378	28.6	0.797
GCS	44/90	48.9	218/378	57.7	0.156
IS	21/90	23.3	208/378	55.0	**<0.001**
Biologics/small molecules					
Anti-TNFα	22/90	24.4	114/378	30.2	0.304
Anti-IL12/23	4/90	4.4	1/378	0.3	**0.006**
Anti-integrin	3/90	3.3	6/378	1.6	0.384
Anti-JAK/STAT	0/90	0.0	4/378	1.1	1.000
Anti-IL1β/1R	0/90	0.0	17/378	4.5	0.053
Anti-CD20 (Rituximab)	1/90	1.1	2/378	0.5	0.474
Anti-IL6R (Tocilizumab)	0/90	0.0	1/378	0.3	1.000
CTLA4-Ig (Abatacept)	2/90	2.2	2/378	0.5	0.168
Anti-TNFα plus IS	7/90	7.8	96/378	25.4	**<0.001**
Anti-IL12/23 plus IS	1/90	1.1	1/378	0.3	0.348
Anti-integrin plus IS	1/90	1.1	6/378	1.6	1.000
Others					
Antibiotics	15/90	16.7	91/378	24.1	0.161
Enteral nutrition	3/90	3.3	31/378	8.2	0.120
Parenteral nutrition	2/90	2.2	104/378	27.5	**<0.001**
IVIG	19/90	21.1	60/378	15.9	0.273
Surgery					
Intestinal resection	34/90	37.8	50/378	13.2	**<0.001**
Perianal surgery‡	1/10	10.0	26/194	13.4	1.000
HSCT	3/90	3.3	100/378	26.5	**<0.001**

5-ASA, 5-aminosalicylic acid; GCS, Glucocorticoids; IS, immune suppressant and modulators, including azathioprine, methotrexate, cyclosporine, thalidomide, tacrolimus, and sirolimus; TNFα, tumor necrosis factor alpha; IVIG, Intravenous immunoglobulin; HSCT, hematopoietic stem cell transplantation.

†. n = number of cases presenting the corresponding features; N = number of cases with available information about the features in the reports.

‡. Calculated based on cases presenting with perianal lesions.

Supplementary Table 8. Genetic features and mechanisms of the top 14 pathogenic genes in patients with late-onset and infantile-onset mIBD

Gene	Inher-itance	Disease syndrome	Pathways	Mechanisms related to intestinal inflammation	Ref
LO-mIBD					
SLCO2A1	AR	primary hypertrophic osteoarthropathy (PHO)	Lipid and prostaglandin transport	Defective prostaglandin transport, mucosal barrier damage	3, 4
GUCY2C	AD	Congenital diarrhea	cGMP biosynthesis and guanylyl cyclase (GC) signaling	Disrupted intraluminal electrolyte milleu & dysbiosis	5, 6
CTLA4	AD	IPEX (-like)	Treg transcription, CD28 co-stimulation, TCR	dysregulation of Treg and hyperactivation of effector T cells	7, 8
SLC26A3	AR	Congenital diarrhea	Bicarbonate and chloride transport	Disrupted intraluminal electrolyte milleu & dysbiosis	9-11
TYMP	AR	Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Mitochondrial DNA, apoptosis	Dysmotility and/or linked to the mitochondrial dysfunction of intestinal cells	12, 13
SYK	AD	Immunodeficiency and systemic inflammatory disease	AKT, NF-κB, BCR signaling, FCγR-phagocytosis	Hyperinflammatory response to dectin ligands	14, 15
ICOS	AR	Common variable immunodeficiency (CVID)	AKT, NF-κB, CD28 signaling	Insufficient IL-10 production by T cells and impaired co-stimulation	16, 17
BTK	XLR	X-linked agammaglobulinemia (XLA)	NF-κB, TLR, FCγR-phagocytosis,	Impaired B cell function and heightened Th1 response	18, 19
HPS1	AR	Hermansky-pudlak syndrome (HPS)	Vesicle-mediated transport	Impaired antimicrobial activity due to defective vesicle transport	20, 21
NCF1	AR	Chronic granulomatous disease (CGD)	ROS production, RHO GTPase	Impaired antimicrobial activity due to NADPH oxidase defect	22-24
G6PC3	AR	Congenital neutropenia	AKT, gluconeogenesis, carbohydrate biosynthesis	Impaired neutrophil function and antimicrobial activity	14, 25, 26
Overlapping in LO-mIBD and IO-mIBD					
CYBB	XLR	Chronic granulomatous disease (CGD)	ROS production, RHO, RAC1 & 2 GTPase	Impaired antimicrobial activity due to NADPH oxidase defect	22-24
XIAP	XLR	X-linked lymphoproliferative disease	RIPK1 necrosis, TNFα, apoptosis,	Dysregulation of cell apoptosis and impaired pathogen recognition	14, 27-29

Gene	Inher-itance	Disease syndrome	Pathways	Mechanisms related to intestinal inflammation	Ref
		(XLP)	NOD2 signaling		
TNFAIP3	AD	A20 haploinsufficiency (HA20)	NF-KB, TNFα	Increased expression of NF- κB- mediated proinflammatory cytokines	30, 31
IO-mIBD					
IL10RA	AR	Infantile enterocolitis and fistulizing disease	IL10 signaling	Impaired IL-10 mediated control of inflammatory responses with IL-1 and IL-23	14, 32-35
IL10RB	AR	Infantile enterocolitis and fistulizing disease	IL10 signaling	Impaired IL-10 mediated control of inflammatory responses with IL-1 and IL-23	14, 32-35
TTC7A	AR	Intestinal atresia and immunodeficiency	Cell cycle, protein transport	Defective epithelial polarization/apoptosis and lymphocyte selection defect	36-39
FOXP3	XLR	IPEX (-like)	Treg transcription	Defective in regulatory T cell differentiation and activity with impaired effector cell control	40-42
RIPK1	AR	Immunodeficiency with autoinflammation	NF-KB and TLR signaling, RIPK1 necrosis, TNFα	Aberrant TNF-induced cell death with epithelial barrier erosion	43-45
LRBA	AR	IPEX (-like)	Mitophagy, protein localization	Defective in regulatory T cell differentiation and activity with impaired effector cell control	46, 47
SKIV2L	AR	Trichohepatoenteric syndrome (THES)	mRNA processing, RIG- I- like receptor (RLR)	Likely dominant epithelial defect in combination with a lymphocyte selection defect	48-50
NLRC4	AD	Macrophage activation syndrome (MAS)-like	NOD2 signaling, inflammasome, apoptosis	NLRC4 inflammasome activation, IL-1 and IL-18 secretion	51, 52
TTC37	AR	Trichohepatoenteric syndrome (THES)	mRNA processing	Likely dominant epithelial defect in combination with a lymphocyte selection defect	53, 54
DKC1	XLR	Dyskeratosis congenita	Telomere extension	T-cell deficiency and defective epithelial barrier function	55-57
MVK	AR	Hyper IgD syndrome (HIDS)	Cholesterol biosynthetic	Hyperinflammation due to defective mevalonate metabolism, inflammasome and IL-1 activation	58-60

Data are referred to the On-line Mendelian Inheritance in Man (OMIM)

AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive.

Supplementary Table 9. Gene ontology (GO) enrichment analysis for the most common pathogenic genes in patients with late-onset and infantile-onset mIBD (top 11 gene defects after excluding 3 overlapping genes, CYBB, XIAP, and TNFAIP3)

LO-mIBD				IO-mIBD			
GO ID	**GO Term**	**-Log10(*p*)**	**Gene fraction (%)**	**GOID**	**GO Term**	**-Log10(*p*)**	**Gene fraction (%)**
GO:0071226	Cellular response to molecule of fungal origin	7.17×10^{-7}	45.45	GO:0004920	Interleukin-10 receptor activity	1.20×10^{-7}	36.36
hsa04380	Osteoclast differentiation	1.61×10^{-5}	27.27	GO:0050727	Regulation of inflammatory response	2.49×10^{-7}	54.54
GO:0030139	Endocytic vesicle	2.38×10^{-4}	27.27	GO:0055087	Ski complex	3.59×10^{-7}	36.36
GO:0050863	Regulation of T cell activation	3.20×10^{-4}	27.27	GO:0004496	Mevalonate kinase activity	3.63×10^{-4}	18.18
GO:0015711	Organic anion transport	3.47×10^{-4}	27.27	GO:0070926	Regulation of ATP:ADP antiporter activity	3.63×10^{-4}	27.27
GO:0016170	Interleukin-15 receptor binding	3.63×10^{-4}	18.18	GO:0000495	Box H/ACA sno(s)RNA 3'-end processing	7.25×10^{-4}	18.18
GO:0031085	BLOC-3 complex	7.25×10^{-4}	27.27	GO:0032002	Interleukin-28 receptor complex	1.09×10^{-3}	27.27
GO:0009032	Thymidine phosphorylase activity	7.25×10^{-4}	27.27	GO:0072557	IPAF inflammasome complex	1.45×10^{-3}	27.27
GO:0004346	Glucose-6-phosphatase activity	1.09×10^{-3}	18.18	GO:0034497	Protein localization to phagophore assembly site	5.79×10^{-3}	9.09
GO:0048469	Cell maturation	2.00×10^{-3}	27.27	GO:0046854	Phosphatidylinositol phosphate biosynthetic process	2.37×10^{-2}	18.18
GO:0004383	Guanylate cyclase activity	2.90×10^{-3}	2/11				

GO annotation and enrichment analysis were conducted using Metascape (https://metascape.org/gp/index.html#/).

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