Supplementary Data: An integrated taxonomy for monogenic inflammatory bowel disease (IBD)

Supplementary Figure Legends

Supplementary Figure 1: Selection for investigating monogenic syndromes and Mendelian disorders associated with IBD

Diagram illustrating the workflow of case appraisal for patients with genetic defects

Supplementary Figure 2: The relationship between the observed/reported penetrance and minimum patient number required to identify monogenic disorders with a 5% penetrance

(**a**) Minimal effect size (observed penetrance) required to detect a >5% penetrance with 90%, 95% or 99% confidence intervals (CI) depending on the size of the case series (number of patients with a gene defect).

(**b**) The minimal number of individuals with IBD phenotype in relation to the total number of patients with gene defects in a case series to confidently detect a >5% penetrance. Nominal penetrance and confidence margins were calculated according to adjusted Wald equation.

Supplementary Figure 3: Nonsense allele frequencies of monogenic IBD genes reveal the relative rarity of nonsense mutations compared to polygenic risk variant NOD2 and excluded genes

(**a**) The LOF or GOF functional effect of gene defects impacts their association with monogenic IBD.

(**b-c**) Monogenic IBD gene examples show reduced allele frequencies of nonsense variants (i.e. LOF, stop gain/stop loss, and frameshift variants) in genes with (**b**) autosomal and (**c**) X-linked inheritance; compared to the benchmark gene *NOD2* or *NOX1* and *DUOX2*. Minor allele frequency of nonsense variants (LOF, i.e. stop gain/stop loss, and frameshift variants) are shown at the respective amino acid position of each gene.

(**d**) Cumulated allele frequency for nonsense variants of monogenic IBD genes is much lower than *NOD2* or other genetic variants. AA= amino acid.

Supplementary Figure 4: Bulk RNA-seq expression of monogenic IBD genes in multiple organs identifies hematopoietic and intestinal-enriched gene clusters

(**a**) Hierarchical clustering and (**b**) principal component analysis of bulk-RNA expression (FPKM) of monogenic-IBD genes in 32 different human tissues[1] shows intestinal and hematopoietic tissue enrichment. (**a**) Heatmaps rows are centered and scaled, rows and columns are clustered using correlation distance and average linkage.

(**c**) Examples of differentially expressed genes from bulk RNA sequencing that are enriched in intestinal (GUCY2, SLC9A3) and lymphoid tissues (IL10RA, PIK3CD).

Supplementary Figure 5: Comparison of representation of monogenic IBD genes in different pathway databases.

(**a**) Presence of genes in database pathways when analyzed together, with an FDR > .05 is shown (blue box). Genes from the validation gene set are shown in bold.

Supplementary Figure 6: Monogenic and polygenic IBD genes are co-expressed in the same cell types and gene modules.

(**a**) For cells from the adult colon or pediatric ileum (x axis), the probability (y axis) that monogenic and polygenic IBD genes are expressed in the same cell type (left) or gene module (right), relative to a background set of genes with matching expression levels (grey bars). Error bars: SEM, P-values: *** $P < .001$.

Supplementary Figure 7: Effects of S3483 treatment on macrophages

a) Live/dead staining on control and S3483 treated macrophages. Monocytes were differentiated in the presence and absence of different concentrations of S3483 over 5 days to optimize experimental conditions. Live/dead staining was performed and analyzed on FACS. Each dot represents an individual donor. Statistical significance was determined using paired t-test *$P < .05$.

b) Short time exposure to S3483 does not affect antimicrobial activity. Gentamicin protection assay of control and S3483 (50mM) treated macrophages shows lack of effect following S3483 exposure for shorter time intervals (24 hours). Each dot represents an individual donor (n=5). CFU = colony-forming unit

Supplementary Figure 8: Hierarchical clustering of the original monogenic IBD genes by phenotype, treatment response, pathway representation and single-cell gene expression provides a scalable data-driven classification

Mean scRNA-seq-expression across cellular compartments from inflamed colonic samples is scaled 0-1, further weighting of inputs is shown (color legend).

Supplementary Figure 9: Treatment response data was aligned to the model taxonomy of monogenic IBD genes.

Treatment responses for different genes and syndromes are based on a previous systematic review[1].

Supplementary Figure 10: Verification of the importance of syndromic phenotypes in classifying monogenic IBD gene defects

(**a**) Monogenic IBD genes with shared syndromic phenotypes show enrichment in shared cell types, based on scRNA-seq expression in inflamed colonic samples.

(**b**) Monogenic IBD genes, particularly those with the same syndromic groups, are co-expressed in the same cell types and gene modules. For gene sets consisting of either: (i) *all* monogenic IBD genes or (ii) monogenic IBD genes *within the same syndromic group* (x axis), the probability (y axis) that two randomly selected genes are co-expressed within a cell type (left, blue bars) or gene module (right, blue bars), relative to a background set of genes with matching expression (grey bars). UC and CD shown. Error bars: SEM. P-values: NS: not significant, * $P < 0.05$, *** $P < .001$.

Supplementary Figure 11: Penetrance and pathway representation of the validation gene set

(**a**) Black dots: number of patients with intestinal inflammation and the gene defect. Dashed lines: penetrance thresholds. Bars: 90% CI. N.B: Penetrance estimates of 100% in this gene set are confounded by small case numbers identified and described.

(**b**) Hierarchical clustering of the validation gene set in Reactome pathways indicating stability of the association between a shared representation in Reactome pathways and overlapping syndromic phenotypes. New genes added are shown in bold.

Supplementary Figure 12: Hierarchical clustering of the validation and original monogenic IBD genes by phenotype, treatment response, pathway representation and single-cell gene expression

(a) Mean scRNA-seq-expression across cellular compartments from inflamed colonic samples is scaled 0-1, further weighting of inputs is shown (color legend).

Supplementary Figure 13: Sub-clusters of monogenic IBD genes from weighted hierarchical clustering are robust to the addition of newly-identified genes

(a) Sub-clusters from the original taxonomy (left) keep their structure following the addition of 25% more genes in the validated taxonomy (right). Arrows and numbering link corresponding clusters. Clusters delineated by clustering distance (indicated in grey).

Supplementary Methods

Literature search approach

A literature search was performed to identify validated Mendelian disorders and syndromes associated with “inflammatory bowel disease”, “Crohn’s disease”, “Ulcerative Colitis” and “colitis” in Pubmed, OMIM, and ClinVar database (*last accessed 31st September 2018*), followed by author correspondence and snowballing of publication references. Poster abstracts were also reviewed from the 2016 Clinical Immunology Society Annual Meeting and the 2014, 2016 and 2017 European Society for Immuno-deficiencies meetings. We did not include Mendelian and syndromal disorders where intestinal inflammation arises de-novo due to a known iatrogenic mechanism, e.g. i) after solid organ transplantation due to treatment with mycophenolate; ii) after treatment with checkpoint inhibitors or iii) after surgery that induces diversion colitis. For inclusion, genes required functional evidence of a deleterious effect from identified variants. We excluded disorders associated with large chromosomal defects or mosaicism, as well as common genetic variants, where the minor allele frequency did not support a causal monogenic relationship.

Case definitions

Definitions and concepts of the monogenic IBD classification were agreed after interdisciplinary expert consensus of pediatric and adult gastroenterologists, clinical and basic immunologists, and geneticists. Case definitions were initially discussed at the international Very Early Onset Inflammatory Bowel Disease (VEOIBD) Workshop in Oxford, held in September 2016 (**Extended Data Table 1**).

It was acknowledged in the case definitions that:

i) Oligo- or polygenic contributions are likely but evidence for a contribution of common IBD loci in addition to the pathogenic variants are lacking for nearly all of the defects currently associated with 'monogenic IBD'. Formal statistical evidence that polygenic IBD risk variant burden contributes to the development of IBD-like inflammation in patients has been described in chronic granulomatous disease supporting the concept of lead pathogenic mutations and oligogenic/polygenic modifiers[3].

ii) Monogenic IBD includes inflammatory enteropathies with increased intestinal cellular infiltrate but does not include non-inflammatory autoimmune enteropathies seen in diseases such as non-inflammatory forms of congenital diarrhea.

iii) In most cases there is no endoscopic and histological difference between the spectrum of classical/polygenic IBD and monogenic IBD. In the literature, the intestinal inflammatory lesions are described interchangeably as IBD and IBD-like, Crohn's disease and CD-like, UC and UC-like. The proportion of patients classified as unclassified IBD is particularly high in patients with infantile IBD and monogenic IBD [4,5].

Gene names were recorded according to Human Gene Organization nomenclature[6].

IBD penetrance estimation

The penetrance of an IBD-like phenotype in patients with validated variants was determined from literature searches for large, recent available cohorts, with details confirmed through author correspondence (>550 correspondence emails sent to study authors) **Extended Data Table 2-3)**). In order to avoid penetrance inflation, we focused on unselected cohorts of patients with the gene defects, not studies that

solely genotyped IBD patients. If studies described less than 10 individuals with a given gene defect (exceptionally rare or newly discovered gene defects), multiple cohorts were summated. IBD penetrance for the most extreme genotype was counted; for example for genes with autosomal recessive inheritance, only patients with biallelic variants were considered. Some genes lacked available unselected cohorts that had sufficient long-term phenotypic data, for example *NOX1* and *RET*. Where no patients with intestinal inflammation were identified in cohorts of less than 100 participants, the estimated penetrance would default to 0 and disorders were classified as low-penetrance, additional cohorts were then summated in this circumstance to better depict the estimated penetrance within these rare monogenic defects.

High-penetrance genes were defined as those with a greatest penetrance than biallelic *NOD2* variants p.Arg702Trp rs2066844; p.Gly908Arg rs2066845 and p.Leu1007fsinsC rs5743293[7–10].

Penentrance Estimation

Penetrance and confidence intervals were based on the modified Wald equation (where m= number of patients with Mendelian IBD; n= number of patients with the pathogenic gene defect; and z= 1.645 (90% CI), z= 1.96 (95% CI), and z= 2.576 for 99% CI, respectively).

We estimated penetrance $p' = \frac{\mathrm{m}+0.5z^2}{\mathrm{n}+z^2}$

and confidence interval $CI = p' \pm z\sqrt{\frac{p'(1-p')}{n+z^2}}$

Identifying candidate genes within IBD loci

To identify credible candidate genes in IBD-associated loci, we gathered data from four sources: three polygenic IBD meta-analyses[11–13] and one fine-mapping study[14] (**Extended Data Table 4)**. The candidate genes were identified by bioinformatic prioritization of candidate genes within IBD loci (using eQTLs and coding SNPs, as well as network prioritization algorithms GRAIL and DAPPLE)[11–13], alongside fine-mapping of IBD loci to localize signals to single genes[11,14]. All candidate genes from those sources were combined to provide a long-list of candidates for each locus. In

total, we combined data on 223 non-MHC loci, with a total of 343 candidate genes prioritized. 167 loci included at least one candidate gene, and 84 had exactly one prioritized gene. In addition, we assigned a subset of loci as having a high-confidence candidate gene, defined according to bioinformatic evidence, fine-mapping and manual annotation.

1. Bioinformatic: Multiple sources of bioinformatic evidence that uniquely implicate a single gene (i.e. there is exactly one gene that is identified by at least two prioritization techniques).
2. Fine-mapping: the fine-mapping localizes the signal to a region that contains exactly one gene.
3. Manual: Several well-established genes (*PTPN22, ATG16L1, NOD2, FUT2, IRF5, ITGAL, IL23R, IL10, IFIH1, IRGM, CAR9* and *TYK2)* were manually assigned to high-confidence, based on existing functional studies. .

By this analysis, a total of 65 loci had exactly one high-confidence candidate gene. One additional locus was removed from the high-confidence list because of a clash between sources: fine-mapping and bioinformatic analysis around the SNP rs10065637 gave conflicting results, with bioinformatic analyses converging on the gene *IL6ST*, but fine-mapping localized the gene to the nearby *ANKRD55*. In all other cases, converging bioinformatic information, fine-mapping and manual annotation agreed. A total of four genes were included in the confidence list to manual annotation only (*FUT2, IFIH1, IL10* and *IRGM*). These genes were all prioritized by bioinformatic analysis, but were not included in the high-confidence list as they were only supported by one source of annotation (*FUT2* by a coding SNP, *IFIH1* and *IRGM* by GRAIL), or because multiple genes in the locus were supported by two or more prioritization sources *(IL10*, which was joined by nearby genes *IL19, IL20* and *IL24*).

For the network analysis of gene set overlap (**Fig. 1e**), the representation factor of two gene sets was calculated based on a total number of 18,000 human genes.

Gene damage intolerance analysis and allele frequency in reference cohorts

The functional outcome of gene defects (loss of function or gain of function (LOF/GOF)) was determined from the reported cases. Nonsense variants analyzed included LOF variants, sum of stop-loss/stop-gain and frameshift variants. The sum of essential LOF variants included not only the relative number of variants normalized to the gene size (pLI score), but also the minor allele frequency in aggregated population data. Genes with GOF or hypomorphic variants were not included in this analysis.

Phenotype assessment

1. The presence of a phenotypic trait in at least one included patient was scored as present.
2. The age of IBD diagnosis was recorded as the time of endoscopic confirmation or the time of intestinal symptom onset if there was >1 year delay prior to endoscopy.
3. Intestinal phenotype (CD, UC or IBDU; disease location; perianal disease (fistulas and/or abscess formation); penetrating disease; strictures, histological features of granuloma or defined epithelial defects such as tufting and apoptosis).
4. For published reports of patients with gene defects and IBD, the effectiveness of allogenic HSCT on IBD was assessed according to the need for further immune-modulating IBD treatment.

Due to lack of standardized study designs and outcomes, effects of biologic or immune-modulatory treatments were not assessed by us.

scRNAseq analysis of colonic and ileal samples

For colonic scRNA-seq analyses, “Epithelial” and “lamina propria” fractions were separated from each sample, with clustering of cells into immune, epithelial and stromal compartments, as previously described[15]. Transcriptionally distinct sub-clusters of cells were identified and organized into subsets with known lineage relationships[15].

For pediatric ileal samples, raw sequence reads in FASTQ format were obtained (described further in Ref.[16]) and re-aligned to the GRCh38-3.0.0 human reference

transcriptome using the CellRanger v3.1.0 pipeline (10x Genomics) with default parameters. The resulting gene expression matrices were analyzed using Scanpy package v1.5.1[17]. After quality control and doublet exclusion by scrublet[18], terminal ileum scRNA-seq data included 58,900 cells from 8 healthy pediatric patients and 7 patients with CD. Healthy and CD cells were clustered and annotated together, and annotations were further refined after integration with fetal and healthy adult samples as described in Ref[16] . Gene expression was normalized according to the mean expression of the gene across all 51 cells.

Cell subsets:

CM= central memory; EEC= enteroendocrine cells; EM= effector memory; EMRA= CD45RA+ effector memory; FDC= follicular DC; GC= germinal centre cells, gd= gamma delta; IEL= intra-epithelial T lymphocytes; ILCs= innate lymphoid cells; LP= lamina propria; M cell 'Microfold' cells; MAIT= mucosal-associated invariant T; NKs= natural killer cells; p/m DC= plasmacytoid/myeloid DCs; SMC= smooth muscle cells; TA= transit amplifying cells; Tfh= T follicular helper cells; WNT...= fibroblast subsets;

Differential expression analysis

Differential expression (DE) tests were performed using MAST[19], which fit a hurdle model to the expression of each gene, consisting of logistic regression for the zero process (i.e. whether the gene is expressed) and linear regression for the continuous process (i.e. the expression level) (**Fig.4e**). To reduce the size of the inference problem, separate models were fit for each annotated cell subset, comparing cells within the given cell subsets to all other cells. The regression model included terms to capture the effects of the cell subset and the disease state on gene expression, while controlling for cell complexity (i.e. the number of genes detected per cell).

Specifically, we used the regression formula, $Y_i \sim X + D + N$, where Y_i was the standardized $\log_2$(TP10K+1) expression vector for gene *i* across all cells, *X* was a binary variable reflecting cell subset membership (e.g. T_{regs} vs. non-T_{regs}), *D* was the disease state associated with each cell, and *N* was the number of genes detected in each cell. To identify genes that were specific to cell subsets in healthy subjects and IBD (*i.e.* UC or CD) patients, we used two disease states: Healthy and IBD. Additionally, a few heuristics were used to increase the speed of the tests: we

required all tested genes to have a minimum fold change of 1.2 and to be expressed by at least 1% of the cells within the group of interest, and cells were evenly down sampled across groups so that a maximum of 2,500 cells were tested for each cell subset. In all cases, the discrete and continuous coefficients of the model were retrieved and p-values were calculated using the likelihood ratio test in MAST. Q-values were separately estimated for each cell subset comparison using the Benjamini-Hochberg FDR. Unless otherwise indicated, all reported DE coefficients and q-values correspond to the discrete component of the model (i.e. the logistic regression).

Gene signature score- mean expression analysis

For scaled mean expression of monogenic and polygenic IBD gene sets (**Fig. 3f**), to prevent highly expressed genes from dominating a gene signature score, we scaled each gene of the $\log_2$(TP10K+1) expression matrix by its root mean squared expression across cells (using the 'scale' function in R with center = FALSE). The signature score for each cell was then computed as the mean scaled expression across all genes in the signature. To identify statistically significant changes in gene signature expression within each subset, we compared the change in gene expression of the gene signature to a null distribution that was estimated from 100 background sets of genes. Each background set was selected to have matching expression levels; using 20 equal-frequency expression bins defined using the healthy cells within the subset.

Reactome pathway analysis

Analysis of monogenic IBD genes in Reactome database pathways was assessed as a entire group. The presence or absence of monogenic IBD genes in included pathways was scored (1 or 0 respectively). Non-specific terms like 'Immune system' were filtered out.

Gene modules of co-expressed genes

We subsampled cells from each cell subset to create a dataset with a more balanced cell subset distribution. For subsets containing fewer than 1,000 cells, we retained all cells belonging to that subset. cNMF was run on a subset of 2,000 variable genes, which were estimated from the linear relationship between the mean and the

coefficient of variation of gene expression[20], but was re-fit to include estimates for all genes.

Statistical analysis of enriched co-expressed gene sets in cellular subsets and gene mocules

To identify cell subsets that were statistically enriched for the expression of monogenic IBD genes, we computed the mean $\log_2$(TP10K+1) expression of each gene across all cell subsets, then discretized these expression levels using an expression cutoff of 0.25, which resulted in ~2,215 expressed genes per cell subset (other cutoffs yield congruent results (**Extended Data Fig. 7c**). We then scored each cell subset according to the number of monogenic IBD genes it expressed. To identify gene modules that were statistically enriched for the expression of monogenic IBD genes, we calculated an enrichment score by the number of genes from the monogenic IBD gene set that were in the top 250 genes of each gene module. To estimate significance, we compared these enrichment scores to a null distribution that was estimated from 100 background sets of genes. Each background gene set was selected to have matching expression levels, using 20 equal-frequency expression bins that were defined across all cells in the dataset. To determine whether monogenic IBD genes were significantly co-expressed within cell subsets and gene modules, we examined all pairs of genes within the monogenic IBD gene set, and compared their frequency of co-expression to a null distribution that was estimated, as previously described.

Human samples and patient recruitment

The study was approved by the institutional review boards (Oxford IBD cohort study and a sub-project to investigate rare diseases). All patients or guardians provided written informed consent. Homozygous pathogenic variants in G6PC3 (n=2; c.911dupC (p.Gln305fs*82)) and SLC37A4 (n=4; c.1105_1106insA (p.Val369AspfsX33); c.1179G>A (p.Trp320Ter); c.1042_1043del/1211delCT (p.Leu348fs); c.1108_1109delCT (p.Leu370Vfs*53)) were reported by clinical centers (CD phenotype n=5, age 9-39 years). Control peripheral blood mononuclear cells (PBMCs) were obtained from healthy volunteers recruited via the Oxford gastrointestinal biobank or supplied from the NHS blood bank as leukocyte cones.

Myeloid dysfunction in congenital neutropenia

Chemicals and reagents

The following reagents were used to perform functional experiments on primary human monocyte derived macrophages: cholinergic acid derivative S4383 (50μM; Sigma), Rapamycin (50μM; Tocris), and 100ng/ml mCSF (R&D Bioscience).

Macrophage Differentation

Monocytes enriched by the adherence method were selected on 10cm culture dish plates in RPMI 1640 medium (Sigma). Differentiation of human monocytes to macrophages were carried out over the period of 5 days in the presence of 100ng/ml Mcsf (R&D Bioscience) in RPMI 1640 medium (Sigma) supplemented with 10% fetal calf serum (Sigma).

Gentamicin protection assay

Monocyte-derived macrophages (MDM) were treated with *Salmonella enterica serovar typhimurium*-expressing GFP strain (NCTC12023) for 1 hour, with a 1:10 multiplicity of infection, followed by gentamicin treatment. The NCTC12023 strain expressing GFP under a pH sensitive promoter was used for a FACS-based gentamicin protection assay, where cells were detached and samples were acquired by FACS.

Sea horse (glycolysis stress and mito-stress)

Primary monocytes differentiated to macrophages were treated with S3483 or were left untreated. For both the glycolysis stress test and mito-stress test, 100,000 MDM were plated in seahorse 96-well cell culture plate and assays were performed as per the manufacturer's protocol and as described previously[21]. For metabolomics analyses, p-values were generated using ANOVA (independent conditions).

Metabolomics

Metabolomics was performed using an ICS5000+ ion-chromatography system coupled to a Q-Exactive Orbitrap mass spectrometer (Thermo, Hermel, UK). Details of the method used can be found in our recent publication[22].

FACS Assays- pS6

Quantification of phosphorylation of S6 ribosomal protein (pS6) was performed by intracellular staining. MDMs were fixed and permeabilised with the Cytofix/Cytoperm Fixation/Permeabilization Solution Kit (BD Biosciences) according to the manufacturer's instructions. MDM were stained intra-cellularly stained with phospho-S6 (ser235, ser236) (clone cupk43k, eBioscience). All the samples were acquired on FACS and analyzed by FlowJo software.

Taxonomy

Weighted hierarchical clustering of monogenic IBD genes on the basis of syndromic phenotype, HSCT outcomes, functional assays, scRNA-seq compartmental expression (inflamed colonic data) and Reactome pathways provides a scalable data-driven taxonomy are as shown (**Extended Data Fig. 8**). As genes enriched in non-hematopoietic cell types were less well represented in Reactome pathways, a manually curated epithelial label was assigned for clearer visualization, based on the phenotype of congenital diarrhea, epithelial non-hematopoietic scRNAseq expression, lack of hematopoietic stem cell transplant (HSCT) response, and lack of detection in PBMC proteomic datasets.

Online resources / URLs

The following online data sources have been accessed:

Online Mendelian Inheritance in Man (OMIM): http://www.omim.org

ExAC browser: https://gnomad.broadinstitute.org/

ClinVar: www.ncbi.nlm.nih.gov/clinvar/

ClinGen: https://clinicalgenome.org

Single cell transcriptomics portal https://portals.broadinstitute.org/single_cell/

Cytoscape version 3.7.2: https://cytoscape.org/

Human Protein Atlas project https://www.proteinatlas.org

Extended Data Table 1: Definitions

IBD Type	Definitions

Polygenic IBD:	Crohn's disease (CD), Ulcerative colitis (UC) and IBD unclassified (IBDu) are well-established according to revised Porto criteria (ESPGHAN)[23] as well as ECCO[24,25]. IBDu refers only to colitis that does not meet UC diagnostic criteria[26]. There are patients with small and large bowel inflammatory enteropathy not fitting CD, a group of patients not classified by the PORTO Criteria.
Monogenic IBD (Mendelian disorder associated IBD):	IBD-like intestinal inflammation (CD-like, UC-like, IBDu, and inflammatory enteropathy) in patients with rare monogenic disorders that follow a Mendelian inheritance pattern. The penetrance of intestinal inflammation is high.

Supplementary Table 2:

Key references of relevant cases of patients with monogenic IBD and references for those who have undergone HSCT. Outcomes of the impact on intestinal inflammation following HSCT is shown.

Gene	Genotype Included	References	HSCT or additional detail references	HSCT resolves intestinal inflammation (yes: > 80% no: < 30%)	Number of reported HSCT cases (A: ≥ 10 B: 5-9 C: < 5)
IL10RB	Biallelic	27–31	27,28,32,33	yes	B
IL10RA	Biallelic	34,35	28,30,31,33,36,37	yes	A
IL10	Biallelic	28,38	30,38	yes	C
RIPK1	Biallelic	39,40	40	yes	C
NCF4	Biallelic	41,42	41,43,44	yes	C
BACH2	Heterozygous	45,46			
TRIM22	Biallelic	47	48		
LRBA	Biallelic	49	50–53	yes	B
TTC7A	Biallelic	54	5,54	no	B
WIPF1	Biallelic	55,56			
POLA1	X linked	57,58			
EPCAM	Biallelic	59–62			
IL2RA	Biallelic	63–65			
ALPI	Biallelic	66			
CYBC1	Biallelic	67			
MALT1	Biallelic	68,69	68,70,71	yes	C
CYBB	X linked	72–77	78,79	yes	A
SLC37A4	Biallelic	80–84			
PIK3CD LOF	Biallelic	85,86			
TGFB1	Biallelic	87			

FOXP3	X linked	[88–90]	[90,91]	yes	A
DKC1	X linked	[92]			
TNFAIP3	Heterozygous	[93]			
NCF1	Biallelic	[78,94,95]	[78,94,95]	yes	A
IL21	Biallelic	[96]			
BCL10	Biallelic	[97]			
NFAT5	Heterozygous	[98]			
IRF2BP2	Heterozygous	[99,100]			
STAT3	Heterozygous	[101–104]	[101]	yes	C
TTC37	Biallelic + heterozygous	[5,105–107]	[105]	no	C
NLRC4	Heterozygous	[108–112]			
LACC1	Biallelic	[113,114]	[115]		
IKBKG	X linked	[116–118]	[119,120]	no	A
GUCY2C	Heterozygous	[121,122]			
XIAP	X linked	[123,124]	[123,125–128]	yes	A
HPS4	Biallelic	[129–132]			
SLC9A3	Biallelic	[133]			
ARPC1B	Biallelic	[134]			
PIK3R1 LOF	Biallelic	[135,136]			
RBCK1	Biallelic	[137]			
ZAP70 HYPOMORPH	Biallelic	[138,139]			
ZAP70	Biallelic	[140]			
ICOS	Biallelic	[60,141,142]	[143]	yes	C
NCF2	Biallelic	[73,78,144–149]	[78,150]	yes	C
CTLA4	Heterozygous	[151,152]	[153]	yes	B
FERMT1	Biallelic	[154,155]			
RELA	Heterozygous	[156]			
ITCH	Biallelic	[157]			
IKBA	Heterozygous	[158]	[159,160]	yes	C
DOCK2	Biallelic	[161,162]	[161]	yes	C
SIRT1	Heterozygous	[163]			
COL7A1	Biallelic/AR	[164]			
RAG1 HYPOMORPH	Biallelic	[165–169]	[168]		
RTEL1	Biallelic	[170–172]			
MVK	Biallelic	[173–175]			
SKIV2L	Biallelic	[105]			
HPS1	Biallelic	[130,176]	(Cavounidis et al, in preparation)		
SLC26A3	Biallelic	[177,178]			
G6PC3	Biallelic	[179–181]	[182,183], this study	yes	C
SLCO2A1	Biallelic	[184–186]			
CD40 LG	X linked	[187–191]			
TRNT1	Biallelic	[192,193]			
STIM1	Biallelic	[194 195]			
TGFBR1	Heterozygous	[196,197]			
NPC1	Biallelic	[128,198]	[128]		
WAS	X linked	[199–203]	[202,204]	yes	C
TGFBR2	Heterozygous	[196,197]			
RAG2 HYPOMORPH	Biallelic	[205,206]			
MASP2	Biallelic	[207–209]			

CD3G HYPOMORPH	Biallelic	210,211	212	yes	C
HPS3	Biallelic	213	214		
PTEN	Heterozygous	215			
ITGB2	Biallelic	216–222	223,224	yes	C
TYMP	Biallelic	225,226			
STAT1	Heterozygous	227,228	229	yes	B
ADA2	Biallelic	230–233	233	yes	C
BTK	X linked	234–238			
DCLRE1C HYPOMORPH	Biallelic	166,239–241	242	yes	C
AICDA	Biallelic	243–245			
STXBP2	Biallelic	246–249			
NEUROG3	Biallelic	60,250			
PIK3R1 GOF	Heterozygous	251,252			
PEPD	Biallelic	253,254			
GATA2	Heterozygous	255–257			
CFTR	'Genotyped'	258,259 unpublished (UK Cystic Fibrosis Trust)			
PIK3CD GOF	Heterozygous	252,260–265	265	yes	C
ZBTB24	Biallelic	266,267			
DOCK8	Biallelic	268–270			
CYBA	Biallelic	75,271–274			
PLCG2	Heterozygous	275,276			
SH2D1A	X linked	277–279			
CMT4C	Biallelic	280,281			
PTCH1	Heterozygous	282,283			
CYLD	Heterozygous	284,285			
GPIHBP1	Biallelic	286,287			
SBDS	Biallelic	288,289			
PCSK1	Biallelic	290–293			
MYO5B	Biallelic	60,294			
AIRE	Biallelic	295–297			
IL2RG HYPOMORPH	X-linked	298–300			
LIG4 HYPOMORPH	Biallelic	300,301			
ADA HYPOMORPH	Biallelic	300			
ANKZF1	Biallelic	302			
CD55	Biallelic	303,304			
POLG1	Biallelic	305,306			
DUOX2	Biallelic	307–312			
MEFV	Biallelic	313–315			

Supplementary Table 3- Excluded Syndrome References:

Gene/Syndrome	Genotype included	Ref	Additional details
Possible syndromal IBD- unknown genetic basis			

Obesity, hypothyroidism, craniosynostosis, cardiac hypertrophy, colitis, and developmental delay	Unknown	[316]	
LACH syndrome	Unknown	[317]	
Melkersson Rosenthal syndrome	Unknown	[318,319]	
Cutaneous photosensitivity and severe colitis	Unknown	[320]	
No Mendelian Inheritance			
KRAS	Heterozygous/lymphoid	[321,322]	
Lack of IBD evidence/unable to exclude infectious cause for colitis			
FCN3	Biallelic	[323]	
EGFR	Biallelic	[324]	
IL21R	Biallelic	[325]	
ADAM17	Biallelic	[326,327]	
CARD9	Biallelic/GWAS	[328–330]	[331–337]
ORAI1	Biallelic	[338,339]	
LYST		[340]	Chediak-Higashi syndrome
Lack of genotyping			
?HPS6		[341–343]	
?G6PDH		[344]	
?OPLAH		[345,346]	Oxoprolinase deficiency
?C2		[347–349]	C2 Deficiency
?C1NH		[349–353]	C1 esterase deficiency
?C6		[354]	C6 deficiency
?WFS1	Biallelic	[355–358]	
?BLM	Biallelic	[359,360]	
?FAS; FAS-LG	'Mutations'	[361–363]	
?RFXANK; RFXAP; CIITA; RFX5	Biallelic	[364–366]	Bare lymphocyte syndrome
Lacking functional validation			
DTNBP1	Biallelic	[367]	Hermansky Pudlak syndrome
GAL3ST2	Biallelic	[113]	
Genetic alteration exceeds a single gene			
XO	Turner syndrome		
Trisomy 21	Downs syndrome		
Unpublished			
STXBP3	Biallelic	[368]	
FERMT3	'Causative'	[191]	
Excluded on cumulative allele frequency			
NOX1	X linked	[310,369]	
RET	Germline	[370]	

Supplementary Table 4: Genes included in the analysis of the intersection of monogenic IBD genes and polygenic IBD loci (**Fig. 1e**)

Confident IBD GWAS genes (n=65)	**Additional IBD GWAS genes (n=214)**	**High penetrance monogenic IBD (n=55*)**	**Moderate penetrance monogenic IBD (n=26)**
TNFRSF14	*TNFRSF18*	*IL10RB*	*SLC26A3*
IL23R	*TNFRSF9*	*IL10RA*	*G6PC3*
PTPN22	*USP1*	*IL10*	*SLCO2A1*
SLAMF8	*BTBD8*	*RIPK1*	*TRNT1*
FCGR2A	*EDG1*	*NCF4*	*ITGB2*
PTGS2	*ADAM30*	*BACH2*	*RAG1*
IL10	*RORC*	*TRIM22*	*STIM1*
THADA	*MSTO1*	*TTC7A*	*IL2RG*
REL	*CD244*	*POLA1*	*LIG4*
SPRED2	*SELP*	*CD55*	*TGFBR1*
IFIH1	*FASLG*	*ANKZF1*	*NPC1*
STAT4	*C1orf53*	*ALPI*	*DCLRE1C*
ATG16L1	*PTPRC*	*CYBC1*	*NCF2*
GPR35	*IRF6*	*MALT1*	*TGFBR2*
MST1	*ADCY3*	*CYBB*	*RAG2*
NFKBIZ	*UCN*	*SLC37A4*	*CD3G*
LPP	*BRE*	*PIK3CD*	*MASP2*
BANK1	*IL18R1*	*TGFB1*	*HPS3*
NFKB1	*CD302*	*FOXP3*	*TYMP*
IL2	*ITGA4*	*DKC1*	*WAS*
DAP	*PLCL1*	*TNFAIP3*	*CYBA*
OSMR	*ICOS*	*IL21*	*CD40LG*
TMEM174	*CXCR1*	*BCL10*	*ADA*
NDFIP1	*CCL20*	*NFAT5*	*STAT1*
IRGM	*SP140*	*IRF2BP2*	*CECR1*
IL12B	*BOK*	*STAT3*	*BTK*
CDKAL1	*PDCD1*	*TTC37*	
BACH2	*FLJ78302*	*LRBA*	
PRDM1	*ITIH4*	*IL2RA*	
TRAF3IP2	*RFT1*	*NLRC4*	
RSPO3	*HGFAC*	*RTEL1*	
TNFAIP3	*SLC10A4*	*LACC1*	
RPS6KA2	*CXCL5*	*IKBKG*	
CARD11	*SLC9A3*	*GUCY2C*	
SKAP2	*PTGER4*	*XIAP*	
JAZF1	*IL6ST*	*SLC9A3*	

EPO	*ERAP1*	*ARPC1B*		
IRF5	*IRF1*	*PIK3R1*		
JAK2	*DUSP1*	*RBCK1*		
CARD9	*CPEB4*	*ICOS*		
MAP3K8	*DOK3*	*ZAP70*		
CREM	*IRF4*	*CTLA4*		
NKX2-3	*PHACTR2*	*FERMT1*		
CD6	*MAP3K7IP2*	*RELA*		
C11orf30	*KDELR2*	*ITCH*		
IFNG	*AHR*	*HPS4*		
LACC1	*ITGB8*	*NCF1*		
UBAC2	*ZPBP*	*NFKBA*		
FOS	*SMURF1*	*DOCK2*		
GPR65	*DLD*	*WIPF1*		
RASGRP1	*CUL1*	*SIRT1*		
SMAD3	*PTK2B*	*MVK*		
SOCS1	*RIPK2*	*SKIV2L*		
ITGAL	*TRIB1*	*COL7A1*		
NOD2	*NFIL3*	*HPS1*		
PLCG2	*TNFSF15*			
KSR1	*IL15RA*			
CCL2	*CISD1*			
STAT3	*C10orf58*			
CD226	*TRIM8*			
NFATC1	*LSP1*			
TYK2	*CNTF*			
FUT2	*C11orf9*			
CD40	*CCDC88B*			
NCF4	*CTSW*			
	JRKL			
	FAM55A			
	CXCR5			
	CD27			
	LOH12CR1			
	MUC19			
	SH2B3			
	PRKAB1			
	TNFSF11			
	ZFP36L1			
	ITPKA			
	CRTC3			
	PRKCB			
	EIF3C			
	ZFP90			
	IRF8			

	GSDMA *RPS6KB1* *CYTH1* *SMAD7* *GPX4* *CEBPG* *CALM3* *KIR2DL1* *DNMT3B* *CEP250* *ADA* *CEBPB* *ZNF831* *LIME1* *IFNGR2* *ICOSLG* *CCDC116* *LIF* *TOM1* *ATF4* *TEF* *TNFRSF4* *DOCK7* *RIT1* *CD48* *SELE* *TNFSF18* *TRAF3IP3* *FOSL2* *IL18RAP* *PLA2R1* *CERKL* *RFTN2* *CD28* *CXCR2* *ATG4B* *LTF* *PRKCD* *SERBP1P3* *TEC* *CXCL1* *ANKRD55* *ERAP2* *CSF2* *DUSP22*			

	CYTH3 *TNFSF8* *IL2RA* *IPMK* *TSPAN14* *NFKB2* *TNNI2* *FADS1* *FLRT1* *FOSL1* *MAML2* *FAM55D* *TNFRSF1A* *NDUFAF1* *IL27* *GSDMB* *TUBD1* *NLRP2* *PROCR* *HNF4A* *SLC2A4RG* *IFNAR1* *MAPK1* *OSM* *TAB1* *NHP2L1* *UBQLN4* *F11R* *SELL* *IL1R1* *LY75* *CTLA4* *SLC11A1* *CCR1* *SFMBT1* *TXK* *CXCL3* *IL31RA* *LNPEP* *IL13* *FADS2* *RPS6KA4* *RELA* *LTBR* *NUPR1*			

	IKZF3 *NLRP7* *UQCC* *TNFRSF6B* *GART* *RIMBP3* *MTMR3* *ITLN1* *IL1R2* *ARPC2* *CCR3* *CXCL2* *IL3* *TRPT1* *SNX32* *RABEP2* *ORMDL3* *ZGPAT* *IFNAR2* *UBE2L3* *SLAMF1* *IL1RL1* *PNKD* *CCR2* *CXCL6* *IL4* *SULT1A1* *ZPBP2* *IL10RB* *YDJC* *USF1* *IL1RL2* *TMBIM1* *CCR5* *IL8* *SLC22A4* *SULT1A2* *TMEM50B* *PF4* *IL5* *PF4V1* *PDLIM4* *SLC22A5*		

Table 5: Recently identified genes for taxonomy validation

Gene	Genotype Included	References	HSCT or additional detail references	HSCT resolves intestinal inflammation (yes: > 80% no: < 30%)	Number of reported HSCT cases (A: ≥ 10 B: 5-9 C: < 5)
CARMIL2	Biallelic	371–376			
IL2RB	Biallelic	377,378			
CARD8	Biallelic	379	380		
CARD11	Heterozygous	381–383			
IKZF1	Heterozygous	384			
SCGN	Biallelic	385			
CDC42	Heterozygous	386,387	388		
NOP10	Mixed	389,390			
CBS	Biallelic	391,392			
CASP8	Biallelic	393,394			
IL37	Biallelic	395			
NLRP3	Heterozygous	396,397			
PI4KA	Biallelic	398,399			
AGR2	Biallelic	400			
ELF4	X-linked	401			
SYK	Heterozygous	402			
STXBP3	Mixed	403		yes	C
HSPA1L	Heterozygous primarily	404,405			
SAMD9	Heterozygous	406–408		unclear	
WNT2B	Biallelic	409,410			
PRKCD	Biallelic	411	412		
PTPN2	Heterozygous	413			
SHARPIN	Biallelic	414			
FMNL2	Heterozygous	415	416		
FCHO1	Biallelic	417			
IARS2	Biallelic	418			
WDR1	Biallelic	419,420			
NR4A1	Heterozygous	421			
JAK1	Mosaicism	422			

Table 6: Phenotypic features of the validation set of genes

Gene	GOF	Syndrome	Colitis resolution with HSCT	DHR assay positive	Perianal abscess formation	Impaired bacterial handling
CARMIL2						
IL2RB		IPEX-like				
CARD8						1
CARD11						

SCGN						
CDC42						1
NOP10		Dyskeratosis congenita				
CASP8					1	
IL37						
PI4KA		IBD, intestinal atresia and combined immunodeficiency				
AGR2		Congenital diarrhea				
ELF4					1	
SYK	1				1	
STXBP3			1			
HSPA1L						
SAMD9	1		unclear			
WNT2B		Congenital diarrhea				
PRKCD		Chronic granulomatous disease		1		1
PTPN2		IPEX-like				
FMNL2	1				1	1
IKZF1						

Supplementary References

1. Uhlen M, Fagerberg L, Hallstrom BM, et al. Tissue-based map of the human proteome. Science (80-) 2015;347:1260419–1260419.
2. Nambu R, Warner N, Mulder DJ, et al. A Systematic Review of Monogenic Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2021:1212.
3. Huang C, Ravin SS De, Paul AR, et al. Genetic Risk for Inflammatory Bowel Disease Is a Determinant of Crohn's Disease Development in Chronic Granulomatous Disease. Inflamm Bowel Dis 2016;22:2794–2801.
4. Prenzel F, Uhlig HH. Frequency of indeterminate colitis in children and adults with IBD — a metaanalysis. J Crohn's Colitis 2009;3:277–281.
5. Kammermeier J, Dziubak R, Pescarin M, et al. Phenotypic and Genotypic Characterisation of Inflammatory Bowel Disease Presenting Before the Age of 2 years. J Crohn's Colitis 2017;11:60–69.
6. Tweedie S, Braschi B, Gray K, et al. Genenames.org: The HGNC and VGNC resources in 2021. Nucleic Acids Res 2021;49:D939–D946.
7. Brant SR, Wang M-H, Rawsthorne P, et al. A Population-Based Case-Control Study of CARD15 and Other Risk Factors in Crohn's Disease and Ulcerative Colitis. Am J Gastroenterol 2007;102:313–323.
8. Silver J. The Importance of Penetration. Inflamm Bowel Dis 2003;9:341.
9. Zhou Z, Lin X, Akolkar PN, et al. Variation at NOD2/CARD15 in familial and sporadic cases of Crohn's disease in the Ashkenazi Jewish population. Am J Gastroenterol 2002;97:3095–3101.

10. Yazdanyar S, Kamstrup PR, Tybjærg-Hansen A, et al. Penetrance of NOD2/CARD15 genetic variants in the general population. 2010;182:661–665.
11. Lange KM de, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat Genet 2017;49:256–261.
12. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119–24.
13. Liu JZ, Sommeren S van, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979–986.
14. Huang H, Fang M, Jostins L, et al. Fine-mapping inflammatory bowel disease loci to single-variant resolution. Nature 2017;547:173–178.
15. Smillie CS, Biton M, Ordovas J, et al. Intra-and Inter-cellular Rewiring of the Human Colon during Ulcerative Colitis.
16. Elmentaite R, Ross ADB, Roberts K, et al. Single-Cell Sequencing of Developing Human Gut Reveals Transcriptional Links to Childhood Crohn's Disease. Dev Cell 2020;55:771-783.e5.
17. Wolf FA, Angerer P, Theis FJ. SCANPY: large-scale single-cell gene expression data analysis. Genome Biol 2018;19:15.
18. Wolock SL, Lopez R, Klein AM, et al. Scrublet: Computational Identification of Cell Doublets in Single-Cell Transcriptomic Data. Cell Syst 2019;8:281-291.e9.
19. Finak G, McDavid A, Yajima M, et al. MAST: A flexible statistical framework for assessing transcriptional changes and characterizing heterogeneity in single-cell RNA sequencing data. Genome Biol 2015;16:278.
20. Smillie CS, Biton M, Ordovas-Montanes J, et al. Intra- and Inter-cellular Rewiring of the Human Colon during Ulcerative Colitis. Cell 2019;178:714-730.e22.
21. Schulthess J, Pandey S, Capitani M. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages. Immunity 2019;50:432-445.e7.
22. Walsby-Tickle J, Gannon J, Hvinden I, et al. Anion-exchange chromatography mass spectrometry provides extensive coverage of primary metabolic pathways revealing altered metabolism in IDH1 mutant cells. Commun Biol 2020;3:1–12.
23. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014;58:795–806.
24. Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohn's Colitis 2017;11:649–670.
25. Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohn's Colitis 2017;11:3–25.
26. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19:5A-36A.

27. Glocker E-O, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med 2009;361:2033–45.
28. Kotlarz D, Beier R, Murugan D, et al. Loss of Interleukin-10 Signaling and Infantile Inflammatory Bowel Disease: Implications for Diagnosis and Therapy. Gastroenterology 2012;143:347–355.
29. Begue B, Verdier J, Rieux-Laucat F, et al. Defective IL10 Signaling Defining a Subgroup of Patients With Inflammatory Bowel Disease. Am J Gastroenterol 2011;106:1544–1555.
30. Engelhardt KR, Shah N, Faizura-Yeop I, et al. Clinical outcome in IL-10– and IL-10 receptor–deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 2013;131:825-830.e9.
31. Pigneur B, Escher J, Elawad M, et al. Phenotypic Characterization of Very Early-onset IBD Due to Mutations in the IL10, IL10 Receptor Alpha or Beta Gene. Inflamm Bowel Dis 2013;19:2820–2828.
32. Karaca NE, Aksu G, Ulusoy E, et al. Early Diagnosis and Hematopoietic Stem Cell Transplantation for IL10R Deficiency Leading to Very Early-Onset Inflammatory Bowel Disease Are Essential in Familial Cases. Case reports Immunol 2016;2016:5459029.
33. Mukhopadhyay S, Heinz E, Porreca I, et al. Loss of IL-10 signaling in macrophages limits bacterial killing driven by prostaglandin E2. J Exp Med 2020;217.
34. Shouval DS, Ouahed J, Biswas A, et al. Interleukin 10 Receptor Signaling. In: *Advances in immunology*.Vol 122.; 2014:177–210.
35. Zhu L, Shi T, Zhong C, et al. IL-10 and IL-10 Receptor Mutations in Very Early Onset Inflammatory Bowel Disease. Gastroenterol Res 2017;10:65–69.
36. Huang Z, Peng K, Li X, et al. Mutations in Interleukin-10 Receptor and Clinical Phenotypes in Patients with Very Early Onset Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:578–590.
37. Murugan D, Albert MH, Langemeier J, et al. Very Early Onset Inflammatory Bowel Disease Associated with Aberrant Trafficking of IL-10R1 and Cure by T Cell Replete Haploidentical Bone Marrow Transplantation. J Clin Immunol 2014;34:331–339.
38. Glocker E-O, Frede N, Perro M, et al. Infant colitis—it's in the genes. Lancet 2010;376:1272.
39. Li Y, Führer M, Bahrami E, et al. Human RIPK1 deficiency causes combined immunodeficiency and inflammatory bowel diseases. Proc Natl Acad Sci 2019;116:970–975.
40. Cuchet-Lourenço D, Eletto D, Wu C, et al. Biallelic RIPK1 mutations in humans cause severe immunodeficiency, arthritis, and intestinal inflammation. Science (80-) 2018;361:810–813.
41. Matute JD, Arias AA, Wright NAM, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40phox and selective defects in neutrophil NADPH oxidase activity. Blood 2009;114:3309–3315.
42. Geer A van de, Nieto-Patlán A, Kuhns DB, et al. Inherited p40phox deficiency differs from classic chronic granulomatous disease. J Clin Invest 2018;128:3957–3975.
43. Wright M, Chandrakasan S, Okou DT, et al. Early Onset Granulomatous Colitis Associated with a Mutation in NCF4 Resolved with Hematopoietic Stem Cell

Transplantation. J Pediatr 2019;210:220–225.
44. Li Y, Lv M, Su C, et al. P40phox-deficient mice exhibit impaired bacterial clearance and enhanced pro-inflammatory responses during Salmonella enterica serovar Typhimurium infection. Front Immunol 2017;8:1270.
45. Afzali B, Grönholm J, Vandrovcova J, et al. BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. Nat Immunol 2017;18:813–823.
46. Rae W, Ward D, Mattocks C, et al. Clinical efficacy of a next-generation sequencing gene panel for primary immunodeficiency diagnostics. Clin Genet 2018;93:647–655.
47. Li Q, Lee CH, Peters LA, et al. Variants in TRIM22 That Affect NOD2 Signaling Are Associated With Very-Early-Onset Inflammatory Bowel Disease. Gastroenterology 2016;150:1196–1207.
48. Lou J, Wang Y, Zheng X, et al. TRIM22 regulates macrophage autophagy and enhances *Mycobacterium tuberculosis* clearance by targeting the nuclear factor–multiplicity κB/beclin 1 pathway. J Cell Biochem 2018;119:8971–8980.
49. Gámez-Díaz L, August D, Stepensky P, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. J Allergy Clin Immunol 2016;137:223–230.
50. Tesi B, Priftakis P, Lindgren F, et al. Successful Hematopoietic Stem Cell Transplantation in a Patient with LPS-Responsive Beige-Like Anchor (LRBA) Gene Mutation. J Clin Immunol 2016;36:480–489.
51. Seidel MG, Hirschmugl T, Gamez-Diaz L, et al. Long-term remission after allogeneic hematopoietic stem cell transplantation in LPS-responsive beige-like anchor (LRBA) deficiency. J Allergy Clin Immunol 2015;135:1384-90.e1–8.
52. Sari S, Dogu F, Hwa V, et al. A Successful HSCT in a Girl with Novel LRBA Mutation with Refractory Celiac Disease. J Clin Immunol 2016;36:8–11.
53. Bakhtiar S, Gámez-Díaz L, Jarisch A, et al. Treatment of Infantile Inflammatory Bowel Disease and Autoimmunity by Allogeneic Stem Cell Transplantation in LPS-Responsive Beige-Like Anchor Deficiency. Front Immunol 2017;8:52.
54. Lien R, Lin Y-F, Lai M-W, et al. Novel Mutations of the Tetratricopeptide Repeat Domain 7A Gene and Phenotype/Genotype Comparison. Front Immunol 2017;8:1066.
55. Pfajfer L, Seidel MG, Houmadi R, et al. WIP deficiency severely affects human lymphocyte architecture during migration and synapse assembly. Blood 2017;130:1949–1953.
56. Al-Mousa H, Hawwari A, Al-Ghonaium A, et al. Hematopoietic stem cell transplantation corrects WIP deficiency. J Allergy Clin Immunol 2017;139:1039-1040.e4.
57. Starokadomskyy P, Gemelli T, Rios JJ, et al. DNA polymerase-α regulates the activation of type I interferons through cytosolic RNA:DNA synthesis. Nat Immunol 2016;17:495–504.
58. Starokadomskyy P, Sifuentes-Dominguez L, Gemelli T, et al. Evolution of the skin manifestations of X-linked pigmentary reticulate disorder. Br J Dermatol 2017;177:e200–e201.
59. Gerada J. Mucosal Inflammation as a Component of Tufting Enteropathy. ImmunoGastroenterology 2013;2:62.
60. Charbit-Henrion F, Parlato M, Hanein S, et al. Diagnostic Yield of Next-generation Sequencing in Very Early-onset Inflammatory Bowel Diseases: A Multicentre Study. J Crohn’s Colitis 2018.

61. Drury S, Thames NE, Drury S, et al. Shortening the diagnostic odyssey of patients with very early onset inflammatory bowel disease; RaPid Peadiatric Sequencing (RaPS) View project Great Ormond Street Hospital for Children NHS Foundation Trust. ASHG 2013 Conf poster 2014.
62. Pathak SJ, Mueller JL, Okamoto K, et al. EPCAM mutation update: Variants associated with congenital tufting enteropathy and Lynch syndrome. Hum Mutat 2019;40:142–161.
63. Caudy AA, Reddy ST, Chatila T, et al. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked–like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol 2007;119:482–487.
64. Goudy K, Aydin D, Barzaghi F, et al. Human IL2RA null mutation mediates immunodeficiency with lymphoproliferation and autoimmunity. Clin Immunol 2013;146:248–261.
65. Joosse M, Charbit-Henrion F, Raatgeep H, et al. P095 Consequences of an IL2RA locus duplication in a very early onset inflammatory bowel disease patient. J Crohn's Colitis 2018;12:S141–S142.
66. Parlato M, Charbit-Henrion F, Pan J, et al. Human ALPI deficiency causes inflammatory bowel disease and highlights a key mechanism of gut homeostasis. EMBO Mol Med 2018;10:e8483.
67. Arnadottir GA, Norddahl GL, Gudmundsdottir S, et al. A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease. Nat Commun 2018;9:4447.
68. Charbit-Henrion F, Jeverica AK, Bègue B, et al. Deficiency in Mucosa-associated Lymphoid Tissue Lymphoma Translocation 1. J Pediatr Gastroenterol Nutr 2017;64:378–384.
69. Blazina Š, Markelj G, Jeverica AK, et al. Autoimmune and Inflammatory Manifestations in 247 Patients with Primary Immunodeficiency—a Report from the Slovenian National Registry. J Clin Immunol 2016;36:764–773.
70. Punwani D, Wang H, Chan AY, et al. Combined Immunodeficiency Due to MALT1 Mutations, Treated by Hematopoietic Cell Transplantation. J Clin Immunol 2015;35:135–146.
71. Rozmus J, McDonald R, Fung S-Y, et al. Successful clinical treatment and functional immunological normalization of human MALT1 deficiency following hematopoietic stem cell transplantation. Clin Immunol 2016;168:1–5.
72. Angelino G, Angelis P De, Faraci S, et al. Inflammatory bowel disease in chronic granulomatous disease: An emerging problem over a twenty years' experience. Pediatr Allergy Immunol 2017;28:801–809.
73. Schäppi MG, Klein NJ, Lindley KJ, et al. The nature of colitis in chronic granulomatous disease. J Pediatr Gastroenterol Nutr 2003;36:623–31.
74. Martire B, Rondelli R, Soresina A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: An Italian multicenter study. Clin Immunol 2008;126:155–164.
75. Köker MY, Camcıoğlu Y, Leeuwen K van, et al. Clinical, functional, and genetic characterization of chronic granulomatous disease in 89 Turkish patients. J Allergy Clin Immunol 2013;132:1156-1163.e5.
76. Kawai T, Nishikomori R, Heike T. Diagnosis and Treatment in Anhidrotic Ectodermal Dysplasia with Immunodeficiency. Allergol Int 2012;61:207–217.
77. Labrosse R, Abou-Diab J, Blincoe A, et al. Very Early-Onset Inflammatory Manifestations of X-Linked Chronic Granulomatous Disease. Front Immunol

2017;8:1167.
78. Güngör T, Teira P, Slatter M, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet 2014;383:436–448.
79. Defendi F, Decleva E, Martel C, et al. A novel point mutation in the CYBB gene promoter leading to a rare X minus chronic granulomatous disease variant - Impact on the microbicidal activity of neutrophils. Biochim Biophys Acta - Mol Basis Dis 2009;1792:201–210.
80. Melis D, Fulceri R, Parenti G, et al. Genotype/phenotype correlation in glycogen storage disease type 1b: a multicentre study and review of the literature. Eur J Pediatr 2005;164:501–508.
81. Yamaguchi T, Ihara K, Matsumoto T, et al. Inflammatory Bowel Disease-Like Colitis in Glycogen Storage Disease Type 1b. Inflamm Bowel Dis 2001;7:128–132.
82. Davis MK, Rufo PA, Polyak SF, et al. Adalimumab for the treatment of Crohn-like colitis and enteritis in glycogen storage disease type Ib. J Inherit Metab Dis 2008;31:505–509.
83. Prada-Arias M, Gómez-Veiras J, Vázquez JL, et al. Iliopsoas abscess as a complication of glycogen storage disease 1b. J Pediatr Surg Case Reports 2017;16:39–42.
84. Volz MS, Nassir M, Treese C, et al. Inflammatory bowel disease (IBD)-like disease in a case of a 33-year old man with glycogenosis 1b. BMC Gastroenterol 2015;15:45.
85. Sogkas G, Fedchenko M, Dhingra A, et al. Primary immunodeficiency disorder caused by phosphoinositide 3–kinase δ deficiency. J Allergy Clin Immunol 2018;142:1650-1653.e2.
86. Zhang KJ, Husami A, Marsh R, et al. Identification of a phosphoinositide 3-kinase (PI-3K) p110δ (PIK3CD) deficient individual. 2013 CIS Annu Meet 2013.
87. Kotlarz D, Marquardt B, Barøy T, et al. Human TGF-β1 deficiency causes severe inflammatory bowel disease and encephalopathy. Nat Genet 2018;50:344–348.
88. Barzaghi F, Amaya Hernandez LC, Neven B, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. J Allergy Clin Immunol 2018;141:1036-1049.e5.
89. Okou DT, Mondal K, Faubion WA, et al. Exome Sequencing Identifies a Novel FOXP3 Mutation in a 2-Generation Family With Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2014;58:561–568.
90. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: A paradigm of immunodeficiency with autoimmunity. Front Immunol 2012;3:1–25.
91. Duclaux-Loras R, Charbit-Henrion F, Neven B, et al. Clinical Heterogeneity of Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome: A French Multicenter Retrospective Study. Clin Transl Gastroenterol 2018;9:201.
92. Jonassaint NL, Guo N, Califano JA, et al. The gastrointestinal manifestations of telomere-mediated disease. Aging Cell 2013;12:319–323.
93. Berteau F, Rouviere B, Delluc A, et al. Autosomic dominant familial Behçet

disease and haploinsufficiency A20: A review of the literature. Autoimmun Rev 2018;17:809–815.
94. Freudenberg F, Wintergerst U, Roesen-Wolff A, et al. Therapeutic strategy in p47-phox deficient chronic granulomatous disease presenting as inflammatory bowel disease. J Allergy Clin Immunol 2010;125:943-946.e1.
95. Wolach B, Gavrieli R, Boer M de, et al. Analysis of Chronic Granulomatous Disease in the Kavkazi Population in Israel Reveals Phenotypic Heterogeneity in Patients with the Same NCF1 mutation (c.579G>A). J Clin Immunol 2018;38:193–203.
96. Salzer E, Kansu A, Sic H, et al. Early-onset inflammatory bowel disease and common variable immunodeficiency–like disease caused by IL-21 deficiency. J Allergy Clin Immunol 2014;133:1651-1659.e12.
97. Torres JM, Martinez-Barricarte R, García-Gómez S, et al. Inherited BCL10 deficiency impairs hematopoietic and nonhematopoietic immunity. J Clin Invest 2014;124:5239–5248.
98. Boland BS, Widjaja CE, Banno A, et al. Immunodeficiency and Autoimmune Enterocolopathy Linked to NFAT5 Haploinsufficiency. J Immunol 2015;194:2551–2560.
99. Hsu A, Keller M, Rae W, et al. Abstract: Heterozygous IRF2BP2 Mutations Associated with Dominant CVID, Granulomata and Colitis. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
100. Keller MD, Pandey R, Li D, et al. Mutation in IRF2BP2 is responsible for a familial form of common variable immunodeficiency disorder. J Allergy Clin Immunol 2016;138:544-550.e4.
101. Milner JD, Vogel TP, Forbes L, et al. Early-onset lymphoproliferation and autoimmunity caused by germline STAT3 gain-of-function mutations. Blood 2015;125:591–599.
102. Slowik V, Dinwiddie DL, Ciaccio CE, et al. A Novel Variant in the STAT3 Gene Associated with Autoimmune Enteropathy in a Father & Son Duo. J Genomes Exomes 2014;3:1–5.
103. Haapaniemi EM, Kaustio M, Rajala HLM, et al. Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in STAT3. Blood 2015;125:639–648.
104. Lee WI, Chen CC, Jaing TH, et al. A Nationwide Study of Severe and Protracted Diarrhoea in Patients with Primary Immunodeficiency Diseases. Sci Rep 2017;7:1–11.
105. Fabre A, Bourgeois P, Coste M-E, et al. Management of syndromic diarrhea/tricho-hepato-enteric syndrome: A review of the literature. Intractable Rare Dis Res 2017;6:152–157.
106. Busoni VB, Lemale J, Dubern B, et al. IBD-Like Features in Syndromic Diarrhea/Trichohepatoenteric Syndrome. J Pediatr Gastroenterol Nutr 2017;64:37–41.
107. Fabre A, Martinez-Vinson C, Goulet O, et al. Syndromic diarrhea/Tricho-hepato-enteric syndrome. Orphanet J Rare Dis 2013;8:5.
108. Rodrigues F, Hentgen V, Bachmeyer C, et al. Les maladies auto-inflammatoires associées aux mutations de NLRC4 : revue systématique de la littérature. La Rev Médecine Interne 2018;39:279–286.
109. Romberg N, Moussawi K Al, Nelson-Williams C, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. Nat Genet 2014;46:1135–1139.

110. Canna SW, Jesus AA de, Gouni S, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet 2014;46:1140–1146.
111. Mendonca L, Caroli F, Grossi A, et al. Abstract: Homozygous NLCR4 P.A160T Associated with Entercolitis and Immune Dysregulation Syndrome. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
112. Canna SW, Girard C, Malle L, et al. Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. J Allergy Clin Immunol 2017;139:1698–1701.
113. Patel N, Mouzan MI El, Al-Mayouf SM, et al. Study of Mendelian forms of Crohn's disease in Saudi Arabia reveals novel risk loci and alleles. Gut 2014;63:1831–1832.
114. KARACAN İ, UĞURLU S, ŞAHIN S, et al. LACC1 Gene Defects in Familial Form of Juvenile Arthritis. J Rheumatol 2018;45:726–728.
115. Huang C, Hedl M, Ranjan K, et al. LACC1 Required for NOD2-Induced, ER Stress-Mediated Innate Immune Outcomes in Human Macrophages and LACC1 Risk Variants Modulate These Outcomes. Cell Rep 2019;29:4525-4539.e4.
116. Cheng LE, Kanwar B, Tcheurekdjian H, et al. Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome. Clin Immunol 2009;132:124–131.
117. Hanson EP, Monaco-Shawver L, Solt LA, et al. Hypomorphic nuclear factor-κB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. J Allergy Clin Immunol 2008;122:1169-1177.e16.
118. Artac H, Emsen A, Ucaryilmaz H, et al. Infliximab Therapy for Steroid-Refractory Inflammatory Colitis in an Infant with X-linked Anhidrotic Ectodermal Dysplasia with Immunodeficiency. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
119. Miot C, Imai K, Imai C, et al. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic IKBKG /NEMO mutations. Blood 2017;130:1456–1467.
120. Hedl M, Yan J, Witt H, et al. IRF5 Is Required for Bacterial Clearance in Human M1-Polarized Macrophages, and IRF5 Immune-Mediated Disease Risk Variants Modulate This Outcome . J Immunol 2019;202:920–930.
121. Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial Diarrhea Syndrome Caused by an Activating GUCY2C Mutation. N Engl J Med 2012;366:1586–1595.
122. Müller T, Rasool I, Heinz-Erian P, et al. Congenital secretory diarrhoea caused by activating germline mutations in GUCY2C. Gut 2016;65:1306–1313.
123. Speckmann C, Lehmberg K, Albert MH, et al. X-linked inhibitor of apoptosis (XIAP) deficiency: The spectrum of presenting manifestations beyond hemophagocytic lymphohistiocytosis. Clin Immunol 2013;149:133–141.
124. Yang X, Kanegane H, Nishida N, et al. Clinical and Genetic Characteristics of XIAP Deficiency in Japan. J Clin Immunol 2012;32:411–420.
125. Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. Genet Med 2011;13:255–262.
126. Aguilar C, Lenoir C, Lambert N, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis–deficient male patients and female symptomatic

carriers. J Allergy Clin Immunol 2014;134:1131-1141.e9.
127. Ono S, Okano T, Hoshino A, et al. Hematopoietic Stem Cell Transplantation for XIAP Deficiency in Japan. J Clin Immunol 2017;37:85–91.
128. Schwerd T, Pandey S, Yang H-T, et al. Impaired antibacterial autophagy links granulomatous intestinal inflammation in Niemann–Pick disease type C1 and XIAP deficiency with NOD2 variants in Crohn's disease. Gut 2017;66:1060–1073.
129. Anderson PD, Huizing M, Claassen DA, et al. Hermansky-Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. Hum Genet 2003;113:10–17.
130. Hussain N, Quezado M, Huizing M, et al. Intestinal Disease in Hermansky-Pudlak Syndrome: Occurrence of Colitis and Relation to Genotype. Clin Gastroenterol Hepatol 2006;4:73–80.
131. Bastida J, Gonzalez-Porras J, Lozano M, et al. ABSTRACT: Five New Cases of Hermansky-Pudlak Syndrome: Identification of Novel Genetic Variants in HPS4 and HPS3 Associated to Relevant Clinical Cases. In: *EHA 2017 Congress Poster*.; 2018.
132. Lozynska LY, Plawski A, Lozynska MR, et al. Variant of rare Hermansky - Pudlak syndrome associated with granulomatous colitis: diagnostics, clinical course and treatment. Exp Oncol 2018;40:73–78.
133. Janecke AR, Heinz-Erian P, Yin J, et al. Reduced sodium/proton exchanger NHE3 activity causes congenital sodium diarrhea. Hum Mol Genet 2015;24:6614–6623.
134. Kahr WHA, Pluthero FG, Elkadri A, et al. Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease. Nat Commun 2017;8:14816.
135. Conley ME, Dobbs AK, Quintana AM, et al. Agammaglobulinemia and absent B lineage cells in a patient lacking the p85α subunit of PI3K. J Exp Med 2012;209:463–470.
136. Tang P, Upton JEM, Barton-Forbes MA, et al. Autosomal Recessive Agammaglobulinemia Due to a Homozygous Mutation in PIK3R1. J Clin Immunol 2018;38:88–95.
137. Boisson B, Laplantine E, Prando C, et al. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat Immunol 2012;13:1178–1186.
138. Liu Q, Wang Y-P, Liu Q, et al. Novel compound heterozygous mutations in ZAP70 in a Chinese patient with leaky severe combined immunodeficiency disorder. Immunogenetics 2017;69:199–209.
139. Gavino C, Landekic M, Zeng J, et al. Morpholino-based correction of hypomorphic ZAP70 mutation in an adult with combined immunodeficiency. J Allergy Clin Immunol 2017;139:1688-1692.e10.
140. Shirkani A, Shahrooei M, Azizi G, et al. Novel Mutation of ZAP-70-related Combined Immunodeficiency: First Case from the National Iranian Registry and Review of the Literature. Immunol Invest 2017;46:70–79.
141. Schepp J, Chou J, Skrabl-Baumgartner A, et al. 14 Years after Discovery: Clinical Follow-up on 15 Patients with Inducible Co-Stimulator Deficiency. Front Immunol 2017;8:964.
142. Takahashi N, Matsumoto K, Saito H, et al. Impaired CD4 and CD8 Effector Function and Decreased Memory T Cell Populations in ICOS-Deficient Patients. J Immunol 2009;182:5515–5527.

143. Chou J, Massaad MJ, Cangemi B, et al. A novel mutation in ICOS presenting as hypogammaglobulinemia with susceptibility to opportunistic pathogens. J Allergy Clin Immunol 2015;136:794-797.e1.
144. Marks DJB, Miyagi K, Rahman FZ, et al. Inflammatory Bowel Disease in CGD Reproduces the Clinicopathological Features of Crohn's Disease. Am J Gastroenterol 2009;104:117–124.
145. Ben-Farhat K, Ben-Mustapha I, Ben-Ali M, et al. A Founder Effect of c.257 + 2T > C Mutation in NCF2 Gene Underlies Severe Chronic Granulomatous Disease in Eleven Patients. J Clin Immunol 2016;36:547–554.
146. Vignesh P, Rawat A, Kumar A, et al. Chronic Granulomatous Disease Due to Neutrophil Cytosolic Factor (NCF2) Gene Mutations in Three Unrelated Families. J Clin Immunol 2017;37:109–112.
147. Kotlarz D, Gurkan OE, Haskologlu ZS, et al. Differential diagnosis in ulcerative colitis in an adolescent: Chronic granulomatous disease needs extra attention. World J Gastrointest Pathophysiol 2017;8:87.
148. Mohammed R. Gastrointestinal Abnormalities among Patients with Chronic Granulomatous Disease. J Clin Cell Immunol 2014;05.
149. Muise AM, Xu W, Guo C-H, et al. NADPH oxidase complex and IBD candidate gene studies: identification of a rare variant in NCF2 that results in reduced binding to RAC2. Gut 2012;61:1028–1035.
150. Merling RK, Sweeney CL, Chu J, et al. An AAVS1-targeted minigene platform for correction of iPSCs from all five types of chronic granulomatous disease. Mol Ther 2015;23:147–157.
151. Schwab C, Gabrysch A, Olbrich P, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4–insufficient subjects. J Allergy Clin Immunol 2018;142:1932–1946.
152. Cienkusz M, Drabko K, Lejman M, et al. CTLA-4 Deficiency in a 6-year Old Child with Multiple Organ Autoimmune Disease- Case Report. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
153. Slatter MA, Engelhardt KR, Burroughs LM, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. J Allergy Clin Immunol 2016;138:615-619.e1.
154. Has C, Castiglia D, Rio M del, et al. Kindler syndrome: Extension of FERMT1 mutational spectrum and natural history. Hum Mutat 2011;32:1204–1212.
155. Youssefian L, Vahidnezhad H, Barzegar M, et al. The Kindler Syndrome: A Spectrum of FERMT1 Mutations in Iranian Families. J Invest Dermatol 2015;135:1447–1450.
156. Badran YR, Dedeoglu F, Leyva Castillo JM, et al. Human RELA haploinsufficiency results in autosomal-dominant chronic mucocutaneous ulceration. J Exp Med 2017;214:1937–1947.
157. Lohr NJ, Molleston JP, Strauss KA, et al. Human ITCH E3 Ubiquitin Ligase Deficiency Causes Syndromic Multisystem Autoimmune Disease. Am J Hum Genet 2010;86:447–453.
158. Boisson B, Puel A, Picard C, et al. Human IκBα Gain of Function: a Severe and Syndromic Immunodeficiency. J Clin Immunol 2017;37:397–412.
159. Nagasawa M, Ohkawa T, Takagi M, et al. A Stable Mixed Chimera After SCT with RIC in an Infant with IκBα Hypermorphic Mutation. J Clin Immunol 2017;37:413–414.
160. Moriya K, Sasahara Y, Ohnishi H, et al. IKBA S32 Mutations Underlie Ectodermal Dysplasia with Immunodeficiency and Severe Noninfectious

Systemic Inflammation. J Clin Immunol 2018;38:543–545.
161. Dobbs K, Domínguez Conde C, Zhang S-Y, et al. Inherited DOCK2 Deficiency in Patients with Early-Onset Invasive Infections. N Engl J Med 2015;372:2409–2422.
162. Osaimi M Al, Shendi H, Geha RS, et al. Abstract: DOCK2 Deficiency Results in Mitochondrial Dysfunction in Activated T Cells. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
163. Biason-Lauber A, Böni-Schnetzler M, Hubbard BP, et al. Identification of a SIRT1 Mutation in a Family with Type 1 Diabetes. Cell Metab 2013;17:448–455.
164. Freeman EB, Köglmeier J, Martinez AE, et al. Gastrointestinal complications of epidermolysis bullosa in children. Br J Dermatol 2008;158:1308–1314.
165. Delmonte OM, Schuetz C, Notarangelo LD. RAG Deficiency: Two Genes, Many Diseases. J Clin Immunol 2018;38:646–655.
166. Al-Herz W, Massaad MJ, Chou J, et al. DNA recombination defects in Kuwait: Clinical, immunologic and genetic profile. Clin Immunol 2018;187:68–75.
167. Hedayat M, Massaad MJ, Lee YN, et al. Lessons in gene hunting: A RAG1 mutation presenting with agammaglobulinemia and absence of B cells. J Allergy Clin Immunol 2014;134:983-985.e1.
168. Sharapova SO, Guryanova IE, Pashchenko OE, et al. Molecular Characteristics, Clinical and Immunologic Manifestations of 11 Children with Omenn Syndrome in East Slavs (Russia, Belarus, Ukraine). J Clin Immunol 2016;36:46–55.
169. Walter JE, Rosen LB, Csomos K, et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. J Clin Invest 2015;125:4135–4148.
170. Speckmann C, Sahoo SS, Rizzi M, et al. Clinical and Molecular Heterogeneity of RTEL1 Deficiency. Front Immunol 2017;8:449.
171. Ballew BJ, Joseph V, De S, et al. A Recessive Founder Mutation in Regulator of Telomere Elongation Helicase 1, RTEL1, Underlies Severe Immunodeficiency and Features of Hoyeraal Hreidarsson Syndrome Scott HS, ed. PLoS Genet 2013;9:e1003695.
172. Touzot F, Kermasson L, Jullien L, et al. Extended clinical and genetic spectrum associated with biallelic RTEL1 mutations. Blood Adv 2016;1:36–46.
173. Bader-Meunier B, Florkin B, Sibilia J, et al. Mevalonate Kinase Deficiency: A Survey of 50 Patients. Pediatrics 2011;128:e152–e159.
174. Levy M, Arion A, Berrebi D, et al. Severe Early-Onset Colitis Revealing Mevalonate Kinase Deficiency. Pediatrics 2013;132:e779–e783.
175. Dunn K, Pasternak B, Kelsen JR, et al. Mevalonate kinase deficiency presenting as recurrent rectal abscesses and perianal fistulae. Ann Allergy, Asthma Immunol 2018;120:214–215.
176. Hermos CR, Huizing M, Kaiser-Kupfer MI, et al. Hermansky-Pudlak syndrome type 1: gene organization, novel mutations, and clinical-molecular review of non-Puerto Rican cases. Hum Mutat 2002;20:482–482.
177. Assche G Van, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. J Crohn's Colitis 2010;4:63–101.
178. Wedenoja S, Ha Glund P, Holmburg C. Review article: the clinical management of congenital chloride diarrhoea. Aliment Pharmacol Ther 2010;31:477–485.

179. Banka S, Newman WG. A clinical and molecular review of ubiquitous glucose-6-phosphatase deficiency caused by G6PC3 mutations. Orphanet J Rare Dis 2013;8:84.
180. Scotet V, Duguépéroux I, Saliou P, et al. Evidence for decline in the incidence of cystic fibrosis: a 35-year observational study in Brittany, France. Orphanet J Rare Dis 2012;7:14.
181. Kaya Z, Eğritaş Ö, Albayrak M, et al. Resolution of Inflammatory Colitis With Pegfilgrastim Treatment in a Case of Severe Congenital Neutropenia Due to Glucose 6 Phosphatase Catalytic Subunit-3 Deficiency. J Pediatr Hematol Oncol 2014;36:e316–e318.
182. Bolton C, Burch N, Morgan J, et al. Remission of Inflammatory Bowel Disease in Glucose-6-Phosphatase 3 Deficiency by Allogeneic Haematopoietic Stem Cell Transplantation. J Crohn's Colitis 2020;14:142–147.
183. Goenka A, Doherty JA, Al-Farsi T, et al. Neutrophil dysfunction triggers inflammatory bowel disease in G6PC3 deficiency. J Leukoc Biol 2020:JLB.5AB1219-699RR.
184. Hou Y, Lin Y, Qi X, et al. Identification of mutations in the prostaglandin transporter gene SLCO2A1 and phenotypic comparison between two subtypes of primary hypertrophic osteoarthropathy (PHO): A single-center study. Bone 2018;106:96–102.
185. Umeno J, Hisamatsu T, Esaki M, et al. A Hereditary Enteropathy Caused by Mutations in the SLCO2A1 Gene, Encoding a Prostaglandin Transporter Copenhaver GP, ed. PLOS Genet 2015;11:e1005581.
186. Uchida K, Nakajima A, Ushijima K, et al. Pediatric-onset Chronic Nonspecific Multiple Ulcers of Small Intestine. J Pediatr Gastroenterol Nutr 2017;64:565–568.
187. Wang L-L, Zhou W, Zhao W, et al. Clinical Features and Genetic Analysis of 20 Chinese Patients with X-Linked Hyper-IgM Syndrome. J Immunol Res 2014;2014:1–12.
188. Levy J, Espanol-Boren T, Thomas C, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 1997;131:47–54.
189. Mitsui-Sekinaka K, Imai K, Sato H, et al. Clinical features and hematopoietic stem cell transplantations for CD40 ligand deficiency in Japan. J Allergy Clin Immunol 2015;136:1018–1024.
190. Qiu K-Y, Liao X-Y, Wu R-H, et al. X-linked Hyper-IgM Syndrome: A Phenotype of Crohn's Disease with Hemophagocytic Lymphohistiocytosis. Pediatr Hematol Oncol 2017;34:428–434.
191. Lega S, Pin A, Arrigo S, et al. Abstract: Genetic Characterization of Very Early Onset IBD with Next Generation Sequencing Technologies. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
192. Giannelou A, Wang H, Zhou Q, et al. Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors. Ann Rheum Dis 2018;77:612–619.
193. Frans G, Moens L, Schaballie H, et al. Homozygous N-terminal missense mutation in TRNT1 leads to progressive B-cell immunodeficiency in adulthood. J Allergy Clin Immunol 2017;139:360-363.e6.
194. Parry DA, Holmes TD, Gamper N, et al. A homozygous STIM1 mutation impairs store-operated calcium entry and natural killer cell effector function without clinical immunodeficiency. J Allergy Clin Immunol 2016;137:955-957.e8.

195. Fuchs S, Rensing-Ehl A, Speckmann C, et al. Antiviral and Regulatory T Cell Immunity in a Patient with Stromal Interaction Molecule 1 Deficiency. J Immunol 2012;188:1523–1533.
196. Guerrerio AL, Frischmeyer-Guerrerio PA, Huang C, et al. Increased Prevalence of Inflammatory Bowel Disease in Patients with Mutations in Genes Encoding the Receptor Subunits for TGFβ. Inflamm Bowel Dis 2016;22:2058–2062.
197. Naviglio S, Arrigo S, Martelossi S, et al. Severe inflammatory bowel disease associated with congenital alteration of transforming growth factor beta signaling. J Crohn's Colitis 2014;8:770–774.
198. Héron B, Valayannopoulos V, Baruteau J, et al. Miglustat therapy in the French cohort of paediatric patients with Niemann-Pick disease type C. Orphanet J Rare Dis 2012;7:36.
199. Dupuis-Girod S, Medioni J, Haddad E, et al. Autoimmunity in Wiskott-Aldrich Syndrome: Risk Factors, Clinical Features, and Outcome in a Single-Center Cohort of 55 Patients. Pediatrics 2003;111:e622–e627.
200. Albert MH, Bittner TC, Nonoyama S, et al. X-linked thrombocytopenia (XLT) due to WAS mutations: clinical characteristics, long-term outcome, and treatment options. Blood 2010;115:3231–3238.
201. Imai K, Morio T, Zhu Y, et al. Clinical course of patients with WASP gene mutations. Blood 2004;103:456–464.
202. Cannioto Z, Berti I, Martelossi S, et al. IBD and IBD mimicking enterocolitis in children younger than 2 years of age. Eur J Pediatr 2009;168:149–155.
203. Ohya T, Yanagimachi M, Iwasawa K, et al. Childhood-onset inflammatory bowel diseases associated with mutation of Wiskott-Aldrich syndrome protein gene. World J Gastroenterol 2017;23:8544–8552.
204. Lee PP, Lobato-Márquez D, Pramanik N, et al. Wiskott-Aldrich syndrome protein regulates autophagy and inflammasome activity in innate immune cells. Nat Commun 2017;8.
205. Tirosh I, Yamazaki Y, Frugoni F, et al. Recombination activity of human recombination-activating gene 2 (RAG2) mutations and correlation with clinical phenotype. J Allergy Clin Immunol 2019;143:726–735.
206. Dalal I, Tasher D, Somech R, et al. Novel mutations in RAG1/2 and ADA genes in Israeli patients presenting with T-B- SCID or Omenn syndrome. Clin Immunol 2011;140:284–290.
207. Sokolowska A, Szala A, St Swierzko A, et al. Mannan-binding lectin-associated serine protease-2 (MASP-2) deficiency in two patients with pulmonary tuberculosis and one healthy control. Cell Mol Immunol 2015;12:119–121.
208. Stengaard-Pedersen K, Thiel S, Gadjeva M, et al. Inherited Deficiency of Mannan-Binding Lectin–Associated Serine Protease 2. N Engl J Med 2003;349:554–560.
209. Hejazi R, Hasosah M. Tuberculosis, onychomycosis and immune deficiency in complicated Crohn's disease Unusual association of diseases/symptoms. BMJ Case Rep 2019;12:228986.
210. Gokturk B, Keles S, Kirac M, et al. CD3G Gene Defects in Familial Autoimmune Thyroiditis. Scand J Immunol 2014;80:354–361.
211. Rowe JH, Delmonte OM, Keles S, et al. Patients with CD3G mutations reveal a role for human CD3γ in T reg diversity and suppressive function. Blood 2018;131:2335–2344.

212. Turul Özgür T, Türkkanı Asal G, Çetinkaya D, et al. Hematopoietic stem cell transplantation in a CD3γ-deficient infant with inflammatory bowel disease. Pediatr Transplant 2008;12:910–913.
213. Santiago Borrero PJ, Rodríguez-Pérez Y, Renta JY, et al. Genetic Testing for Oculocutaneous Albinism Type 1 and 2 and Hermansky–Pudlak Syndrome Type 1 and 3 Mutations in Puerto Rico. J Invest Dermatol 2006;126:85–90.
214. D'Costa VM, Coyaud E, Boddy KC, et al. BioID screen of Salmonella type 3 secreted effectors reveals host factors involved in vacuole positioning and stability during infection. Nat Microbiol 2019;4:2511–2522.
215. Chen HH, Händel N, Ngeow J, et al. Immune dysregulation in patients with PTEN hamartoma tumor syndrome: Analysis of FOXP3 regulatory T cells. J Allergy Clin Immunol 2017;139:607-620.e15.
216. Madkaikar M, Italia K, Gupta M, et al. Molecular characterization of leukocyte adhesion deficiency-I in Indian patients: Identification of 9 novel mutations. Blood Cells, Mol Dis 2015;54:217–223.
217. Parvaneh N, Mamishi S, Rezaei A, et al. Characterization of 11 New Cases of Leukocyte Adhesion Deficiency Type 1 with Seven Novel Mutations in the ITGB2 Gene. J Clin Immunol 2010;30:756–760.
218. Liu J, Zhao S, Jiang Z. [Clinical analysis of a Chinese child with leukocyte adhesion deficiency type 1]. Zhonghua er ke za zhi = Chinese J Pediatr 2013;51:531–4.
219. Rose DU De, Giliani S, Notarangelo LD, et al. Long term outcome of eight patients with type 1 Leukocyte Adhesion Deficiency (LAD-1): Not only infections, but high risk of autoimmune complications. Clin Immunol 2018;191:75–80.
220. Marsili M, Lougaris V, Lucantoni M, et al. Successful Anti-TNF-α Treatment in a Girl with LAD-1 Disease and Autoimmune Manifestations. J Clin Immunol 2014;34:788–791.
221. Uzel G, Tng E, Rosenzweig SD, et al. Reversion mutations in patients with leukocyte adhesion deficiency type-1 (LAD-1). Blood 2008;111:209–218.
222. Levy-Mendelovich S, Rechavi E, Abuzaitoun O, et al. Highlighting the problematic reliance on CD18 for diagnosing leukocyte adhesion deficiency type 1. Immunol Res 2016;64.
223. Wolach B, Gavrieli R, Wolach O, et al. Leucocyte adhesion deficiency-A multicentre national experience. Eur J Clin Invest 2019;49:e13047.
224. Demirdjian S, Hopkins D, Cumbal N, et al. *Distinct Contributions of CD18 Integrins for Binding and Phagocytic Internalization of Pseudomonas aeruginosa*. 2020.
225. Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Brain 2011;134:3326–3332.
226. Patel R, Sathiyalingam N, Coulter L, et al. PWE-060 Azathioprine-induced exacerbation of mitochondrial neurogastrointestinal encephalopathy in a patient misdiagnosed with crohn's disease. In: *Inflammatory Bowel Disease*.Vol 66. BMJ Publishing Group Ltd and British Society of Gastroenterology; 2017:A155.2-A156.
227. Uzel G, Sampaio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. J Allergy Clin Immunol 2013;131:1611-1623.e3.

228. Toubiana J, Okada S, Hiller J, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 2016;127:3154–64.
229. Leiding JW, Okada S, Hagin D, et al. Hematopoietic stem cell transplantation in patients with gain-of-function signal transducer and activator of transcription 1 mutations. J Allergy Clin Immunol 2018;141:704-717.e5.
230. Caorsi R, Penco F, Schena F, et al. Monogenic polyarteritis: the lesson of ADA2 deficiency. Pediatr Rheumatol 2016;14:51.
231. Staples E, Simeoni I, Kumararatne D, et al. Abstract: ANA2 deficiency complicated by EBV-driven lymphoproliferative disease. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
232. Schepp J, Proietti M, Frede N, et al. Screening of 181 Patients With Antibody Deficiency for Deficiency of Adenosine Deaminase 2 Sheds New Light on the Disease in Adulthood. Arthritis Rheumatol 2017;69:1689–1700.
233. Hashem H, Kumar AR, Müller I, et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. Blood 2017;130:2682–2688.
234. Barmettler S, Otani IM, Minhas J, et al. Gastrointestinal Manifestations in X-linked Agammaglobulinemia. J Clin Immunol 2017;37:287–294.
235. Maekawa K, Yamada M, Okura Y, et al. X-linked agammaglobulinemia in a 10-year-old boy with a novel non-invariant splice-site mutation in Btk gene. Blood Cells, Mol Dis 2010;44:300–304.
236. Cellier C, Foray S, Hermine O. Regional Enteritis Associated with Enterovirus in a Patient with X-Linked Agammaglobulinemia. N Engl J Med 2000;342:1611–1612.
237. Pac M, Bernatowska EA, Kierkuś J, et al. Clinical research Gastrointestinal disorders next to respiratory infections as leading symptoms of X-linked agammaglobulinemia in children-34-year experience of a single center. Arch Med Sci 2017;13:412–417.
238. García-García E, Staines-Boone AT, Vargas-Hernández A, et al. Clinical and mutational features of X-linked agammaglobulinemia in Mexico. Clin Immunol 2016;165:38–44.
239. Volk T, Pannicke U, Reisli I, et al. DCLRE1C (ARTEMIS) mutations causing phenotypes ranging from atypical severe combined immunodeficiency to mere antibody deficiency. Hum Mol Genet 2015;24:7361–7372.
240. Lee PP, Woodbine L, Gilmour KC, et al. The many faces of Artemis-deficient combined immunodeficiency — Two patients with DCLRE1C mutations and a systematic literature review of genotype–phenotype correlation. Clin Immunol 2013;149:464–474.
241. Sundin M, Uhlin M, Gaballa A, et al. Late presenting atypical severe combined immunodeficiency (SCID) associated with a novel missense mutation in DCLRE1C. Pediatr Allergy Immunol 2018;29:108–111.
242. Rohr J, Pannicke U, Döring M, et al. Chronic Inflammatory Bowel Disease as Key Manifestation of Atypical ARTEMIS Deficiency. J Clin Immunol 2010;30:314–320.
243. Quartier P, Bustamante J, Sanal O, et al. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 2004;110:22–29.
244. Minegishi Y, Lavoie A, Cunningham-Rundles C, et al. Mutations in Activation-

Induced Cytidine Deaminase in Patients with Hyper IgM Syndrome. Clin Immunol 2000;97:203–210.
245. Trotta L, Hautala T, Hämäläinen S, et al. Enrichment of rare variants in population isolates: single AICDA mutation responsible for hyper-IgM syndrome type 2 in Finland. Eur J Hum Genet 2016;24:1473–1478.
246. Pagel J, Beutel K, Lehmberg K, et al. Distinct mutations in STXBP2 are associated with variable clinical presentations in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL5). Blood 2012;119:6016–6024.
247. Meeths M, Entesarian M, Al-Herz W, et al. Spectrum of clinical presentations in familial hemophagocytic lymphohistiocytosis type 5 patients with mutations in STXBP2. Blood 2010;116:2635–2643.
248. Filion C, Maffucci P, Church J, et al. A Case of B Lymphocytopenia with STXBP2 and PRF1 Variants. 17th Bienn Meet Eur Soc Immunodefic Poster 2016. Available at: https://www.morressier.com/article/57bc1755d462b80290b4d59f [Accessed August 28, 2018].
249. Vogel GF, Rijn JM van, Krainer IM, et al. Disrupted apical exocytosis of cargo vesicles causes enteropathy in FHL5 patients with Munc18-2 mutations. JCI insight 2017;2.
250. Wang J, Cortina G, Wu SV, et al. Mutant Neurogenin-3 in Congenital Malabsorptive Diarrhea. N Engl J Med 2006;355:270–280.
251. Lucas CL, Chandra A, Nejentsev S, et al. PI3Kδ and primary immunodeficiencies. Nat Rev Immunol 2016;16:702–714.
252. Farachi S, Werner L, Konnikova L, et al. DOP010 Activating PIK3CD mutations cause severe intestinal lymphonodular hyperplasia and an IBD-like phenotype. ECCO IBD Conf 2018 Abstr 2018. Available at: https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2018/item/dop010-activating-pik3cd-mutations-cause-severe-intestinal-lymphonodular-hyperplasia-and-an-ibd-like-phenotype.html [Accessed August 10, 2018].
253. Kuloglu Z, Kansu A, Serwas N, et al. Inflammatory Bowel Disease-like Phenotype in a Young Girl with Prolidase Deficiency: a New Spectrum of Clinical Manifestation. Genet Couns 2015;26:205–11.
254. Hintze JP, Kirby A, Torti E, et al. Prolidase Deficiency in a Mexican-American Patient Identified by Array CGH Reveals a Novel and the Largest PEPD Gene Deletion. Mol Syndromol 2016;7:80–6.
255. Farrill PO, Berron L, Segura N, et al. Abstract: Deficiency of GATA-2 an Entity of Multiple Phenotypes. Clinical Case. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
256. Donadieu J, Lamant M, Fieschi C, et al. Natural history of GATA2 deficiency in a survey of 79 French and Belgian patients. Haematologica 2018;103:1278–1287.
257. Hirabayashi S, Strahm B, Urbaniak S, et al. Unexpected High Frequency of GATA2 Mutations in Children with Non-Familial MDS and Monosomy 7. Blood 2012;120.
258. Lloyd-Still JD. Crohn's Disease and Cystic Fibrosis. Dig Dis Sci 1994;39:880–885.
259. Cystic Fibrosis Trust. *UK Cystic Fibrosis Registry Annual Data Report 2016*. 2017.
260. Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of

activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study. J Allergy Clin Immunol 2017;139:597-606.e4.
261. Goyal R. PIK3CD Immunodeficiency with Colitis, Pancreatic Insufficiency and Ascites. CIS Annu Meet POSTER 2016 2016.
262. Elgizouli M, Lowe DM, Speckmann C, et al. Activating PI3Kδ mutations in a cohort of 669 patients with primary immunodeficiency. Clin Exp Immunol 2016;183:221–229.
263. Hartman HN, Niemela J, Hintermeyer MK, et al. Gain of Function Mutations of PIK3CD as a Cause of Primary Sclerosing Cholangitis. J Clin Immunol 2015;35:11–14.
264. Rae W, Ramakrishnan KA, Gao Y, et al. Precision treatment with sirolimus in a case of activated phosphoinositide 3-kinase δ syndrome. Clin Immunol 2016;171:38–40.
265. Okano T, Imai K, Tsujita Y, et al. Hematopoietic stem cell transplantation for progressive combined immunodeficiency and lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase δ syndrome type 1. J Allergy Clin Immunol 2019;143:266–275.
266. Bernuth H von, Ravindran E, Du H, et al. Combined immunodeficiency develops with age in Immunodeficiency-centromeric instability-facial anomalies syndrome 2 (ICF2). Orphanet J Rare Dis 2014;9:116.
267. Conrad MA, Dawany N, Sullivan KE, et al. Novel ZBTB24 Mutation Associated with Immunodeficiency, Centromere Instability, and Facial Anomalies Type-2 Syndrome Identified in a Patient with Very Early Onset Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:2252–2255.
268. Sanal O, Jing H, Ozgur T, et al. Additional diverse findings expand the clinical presentation of DOCK8 deficiency. J Clin Immunol 2012;32:698–708.
269. Engelhardt KR, Gertz ME, Keles S, et al. The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. J Allergy Clin Immunol 2015;136:402–412.
270. Alroqi FJ, Charbonnier L-M, Keles S, et al. DOCK8 Deficiency Presenting as an IPEX-Like Disorder. J Clin Immunol 2017;37:811–819.
271. Al-Bousafy A, Al-Tubuly A, Dawi E, et al. Libyan Boy with Autosomal Recessive Trait (p22-phox defect) of Chronic Granulomatous Disease. Libyan J Med 2006;1:162–171.
272. Rae J, Noack D, Heyworth PG, et al. Molecular analysis of 9 new families with chronic granulomatous disease caused by mutations in CYBA, the gene encoding p22(phox). Blood 2000;96:1106–12.
273. Kim YM, Park JE, Kim JY, et al. Genetic Analysis of 10 Unrelated Korean Families with p22-phox-deficient Chronic Granulomatous Disease: An Unusually Identical Mutation of the CYBA Gene on Jeju Island, Korea. J Korean Med Sci 2009;24:1045.
274. Ladinsky HT, Perez EE, Dorsey MJ. Chronic granulomatous disease associated colitis leading to profound zinc deficiency. J Allergy Clin Immunol Pract 2014;2:217–219.
275. Zhou Q, Lee G-SS, Brady J, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cγ2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. Am J Hum Genet 2012;91:713–720.
276. Ombrello MJ, Remmers EF, Sun G, et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med 2012;366:330–8.

277. Meazza R, Tuberosa C, Cetica V, et al. Diagnosing XLP1 in patients with hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol 2014;134:1381-1387.e7.
278. Kanegane H, Yang X, Zhao M, et al. Clinical features and outcome of X-linked lymphoproliferative syndrome type 1 (SAP deficiency) in Japan identified by the combination of flow cytometric assay and genetic analysis. Pediatr Allergy Immunol 2012;23:488–493.
279. Serra EG, Schwerd T, Moutsianas L, et al. Somatic mosaicism and common genetic variation contribute to the risk of very-early-onset inflammatory bowel disease. Nat Commun 2020;11:995.
280. Azzedine H, Ravise N, Verny C, et al. Spine deformities in Charcot-Marie-Tooth 4C caused by SH3TC2 gene mutations. Neurology 2006;67:602–606.
281. Houlden H, Laura M, Ginsberg L, et al. The phenotype of Charcot–Marie–Tooth disease type 4C due to SH3TC2 mutations and possible predisposition to an inflammatory neuropathy. Neuromuscul Disord 2009;19:264–269.
282. Evans DG, Oudit D, Smith MJ, et al. First evidence of genotype–phenotype correlations in Gorlin syndrome. J Med Genet 2017;54:530–536.
283. Fujii K, Miyashita T, Omata T, et al. Gorlin syndrome with ulcerative colitis in a Japanese girl. Am J Med Genet 2003;121A:65–68.
284. Grossmann P, Vanecek T, Steiner P, et al. Novel and Recurrent Germline and Somatic Mutations in a Cohort of 67 Patients From 48 Families With Brooke–Spiegler Syndrome Including the Phenotypic Variant of Multiple Familial Trichoepitheliomas and Correlation With the Histopathologic Findings in 379. Am J Dermatopathol 2013;35:34–44.
285. Peltonen S, Kankuri-Tammilehto M. Brooke-Spiegler Syndrome Associated with Ulcerative Rectosigmoiditis. Acta Derm Venereol 2013;93:112–113.
286. Patni N, Brothers J, Xing C, et al. Type 1 hyperlipoproteinemia in a child with large homozygous deletion encompassing GPIHBP1. J Clin Lipidol 2016;10:1035-1039.e2.
287. Gonzaga-Jauregui C, Mir S, Penney S, et al. Whole-Exome Sequencing Reveals GPIHBP1 Mutations in Infantile Colitis With Severe Hypertriglyceridemia. J Pediatr Gastroenterol Nutr 2014;59:17–21.
288. Donadieu J, Fenneteau O, Beaupain B, et al. Classification of and risk factors for hematologic complications in a French national cohort of 102 patients with Shwachman-Diamond syndrome. Haematologica 2012;97:1312–1319.
289. Keogh SJ, McKee S, Smithson SF, et al. Shwachman-Diamond syndrome: a complex case demonstrating the potential for misdiagnosis as asphyxiating thoracic dystrophy (Jeune syndrome). BMC Pediatr 2012;12:631.
290. Frank GR, Fox J, Candela N, et al. Brief Communication Severe obesity and diabetes insipidus in a patient with PCSK1 deficiency. Mol Genet Metab 2013;110:191–194.
291. Martín MG, Lindberg I, Solorzano-Vargas RS, et al. Congenital proprotein convertase 1/3 deficiency causes malabsorptive diarrhea and other endocrinopathies in a pediatric cohort. Gastroenterology 2013;145:138–148.
292. Stijnen P, Ramos-Molina B, O'Rahilly S, et al. PCSK1 Mutations and Human Endocrinopathies: From Obesity to Gastrointestinal Disorders. Endocr Rev 2016;37:347–371.
293. Jackson RS, Creemers JWM, Farooqi IS, et al. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. J Clin Invest 2003;112:1550–60.

294. Dhekne HS, Pylypenko O, Overeem AW, et al. MYO5B , STX3 , and STXBP2 mutations reveal a common disease mechanism that unifies a subset of congenital diarrheal disorders: A mutation update. Hum Mutat 2018;39:333–344.
295. Posovszky C, Lahr G, Schnurbein J von, et al. Loss of Enteroendocrine Cells in Autoimmune-Polyendocrine-Candidiasis-Ectodermal-Dystrophy (APECED) Syndrome with Gastrointestinal Dysfunction. J Clin Endocrinol Metab 2012;97:E292–E300.
296. Ferre EMN, Rose SR, Rosenzweig SD, et al. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. JCI insight 2016;1.
297. Perheentupa J. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy. J Clin Endocrinol Metab 2006;91:2843–2850.
298. Kayserova J, Bronsky J, Formankova R, et al. Normal Level of TREC/KREC in a 5-Year-Old Boy Diagnosed Subsequently with IL-2R Gamma Chain Deficiency by Whole-Exome Sequencing. ESID Conf Poster 2016.
299. Pashchenko O, Kondratenko I, Vakhlyarskaya S, et al. Two Family Cases of Late Diagnostic of Atypical X-SCID With NGS. In: *The 18th Biennial Meeting of the European Society for Immunodeficiencies*.; 2018.
300. Felgentreff K, Perez-Becker R, Speckmann C, et al. Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency. Clin Immunol 2011;141 SRC-:73–82.
301. Buck D, Moshous D, de Chasseval R, et al. Severe combined immunodeficiency and microcephaly in siblings with hypomorphic mutations in DNA ligase IV. Eur J Immunol 2006;36:224–235.
302. Haaften-Visser DY van, Harakalova M, Mocholi E, et al. Ankyrin repeat and zinc-finger domain-containing 1 mutations are associated with infantile-onset inflammatory bowel disease. J Biol Chem 2017;292:7904–7920.
303. Ozen A, Comrie WA, Ardy RC, et al. CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis. N Engl J Med 2017;377:52–61.
304. Kurolap A, Eshach-Adiv O, Hershkovitz T, et al. Loss of CD55 in Eculizumab-Responsive Protein-Losing Enteropathy. N Engl J Med 2017;377:87–89.
305. Kollberg G, Moslemi AR, Darin N, et al. POLG1 mutations associated with progressive encephalopathy in childhood. J Neuropathol Exp Neurol 2006;65:758–768.
306. Hikmat O, Tzoulis C, Chong WK, et al. The clinical spectrum and natural history of early-onset diseases due to DNA polymerase gamma mutations. Genet Med 2017 1911 2017;19:1217–1225.
307. Fu C, Xie B, Zhang S, et al. Mutation screening of the TPO gene in a cohort of 192 Chinese patients with congenital hypothyroidism. BMJ Open 2016;6:e010719.
308. Park K-J, Park H-K, Kim Y-J, et al. DUOX2 Mutations Are Frequently Associated With Congenital Hypothyroidism in the Korean Population. Ann Lab Med 2016;36:145–153.
309. Maruo Y, Nagasaki K, Matsui K, et al. Natural course of congenital hypothyroidism by dual oxidase 2 mutations from the neonatal period through puberty. Eur J Endocrinol 2016;174:453–463.
310. Hayes P, Dhillon S, O'neill K, et al. Defects in Nicotinamide-adenine Dinucleotide Phosphate Oxidase Genes NOX1 and DUOX2 in Very Early Onset Inflammatory Bowel Disease. Cell Mol Gastroenterol Hepatol

2015;1:489–502.
311. Parlato M, Charbit-Henrion F, Hayes P, et al. First Identification of Biallelic Inherited DUOX2 Inactivating Mutations as a Cause of Very Early Onset Inflammatory Bowel Disease. Gastroenterology 2017;153:609-611.e3.
312. Levine AP, Pontikos N, Schiff ER, et al. Genetic Complexity of Crohn's Disease in Two Large Ashkenazi Jewish Families. Gastroenterology 2016;151:698–709.
313. Beşer ÖF, Kasapçopur Ö, Çokuğraş FÇ, et al. Association of Inflammatory Bowel Disease With Familial Mediterranean Fever in Turkish Children. J Pediatr Gastroenterol Nutr 2013;56:498–502.
314. Özçakar ZB, Çakar N, Uncu N, et al. Familial Mediterranean fever-associated diseases in children. QJM 2016;110:hcw230.
315. Yildirim ME, Kurtulgan HK, Ozdemir O, et al. Prevalence of MEFV gene mutations in a large cohort of patients with suspected familial Mediterranean fever in Central Anatolia. Ann Saudi Med 2019;39:382–387.
316. Tan TY, Amor DJ. Obesity, hypothyroidism, craniosynostosis, cardiac hypertrophy, colitis, and developmental delay: A novel syndrome. Am J Med Genet Part A 2007;143A:114–118.
317. Bonkowsky JL, Bohnsack JF, Pennington MJ, et al. Leukoencephalopathy, arthritis, colitis, and hypogammaglobulinemia (LACH) in two brothers: A novel syndrome? Am J Med Genet 2004;128A:52–56.
318. Lloyd DA, Payton KB, Guenther L, et al. Melkersson-Rosenthal syndrome and Crohn's disease: one disease or two? Report of a case and discussion of the literature. J Clin Gastroenterol 1994;18:213–7.
319. Ilnyckyj A, Aldor TA, Warrington R, et al. Crohn's disease and the Melkersson-Rosenthal syndrome. Can J Gastroenterol 1999;13:152–4.
320. Labrune P, Huguet P, Alagille D, et al. Familial cutaneous photosensitivity and colitis with lethal outcome. J Med Genet 1991;28:114–6.
321. Addissie YA, Kotecha U, Hart RA, et al. Craniosynostosis and Noonan syndrome with KRAS mutations: Expanding the phenotype with a case report and review of the literature. Am J Med Genet A 2015;167A:2657–63.
322. Moritake H, Takagi M, Kinoshita M, et al. Autoimmunity Including Intestinal Behçet Disease Bearing the KRAS Mutation in Lymphocytes: A Case Report. Pediatrics 2016;137:e20152891.
323. Schlapbach LJ, Thiel S, Kessler U, et al. Congenital H-ficolin deficiency in premature infants with severe necrotising enterocolitis. Gut 2011;60:1438–9.
324. Campbell P, Morton PE, Takeichi T, et al. Epithelial inflammation resulting from an inherited loss-of-function mutation in EGFR. J Invest Dermatol 2014;134:2570–2578.
325. Erman B, Bilic I, Hirschmugl T, et al. Combined immunodeficiency with CD4 lymphopenia and sclerosing cholangitis caused by a novel loss-of-function mutation affecting IL21R. Haematologica 2015;100:e216–e219.
326. Blaydon DC, Biancheri P, Di W-L, et al. Inflammatory Skin and Bowel Disease Linked to *ADAM17* Deletion. N Engl J Med 2011;365:1502–1508.
327. Bandsma RHJ, Goor H van, Yourshaw M, et al. Loss of ADAM17 is associated with severe multiorgan dysfunction. Hum Pathol 2015;46:923–8.
328. Drummond RA, Lionakis MS. Mechanistic Insights into the Role of C-Type Lectin Receptor/CARD9 Signaling in Human Antifungal Immunity. Front Cell Infect Microbiol 2016;6:39.
329. Fairfax BP, Humburg P, Makino S, et al. Innate Immune Activity Conditions the

Effect of Regulatory Variants upon Monocyte Gene Expression Europe PMC Funders Group. Science (80-) 2014;343:1246949.
330. Zhong X, Chen B, Yang L, et al. Molecular and physiological roles of the adaptor protein CARD9 in immunity. Cell Death Dis 2018;9:52.
331. Drummond RA, Collar AL, Swamydas M, et al. CARD9-Dependent Neutrophil Recruitment Protects against Fungal Invasion of the Central Nervous System May RC, ed. PLOS Pathog 2015;11:e1005293.
332. Lanternier F, Mahdaviani SA, Barbati E, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species–induced meningoencephalitis, colitis, or both. J Allergy Clin Immunol 2015;135:1558-1568.e2.
333. Lanternier F, Barbati E, Meinzer U, et al. Inherited CARD9 Deficiency in 2 Unrelated Patients With Invasive Exophiala Infection. J Infect Dis 2015;211:1241–1250.
334. Lanternier F, Pathan S, Vincent QB, et al. Deep Dermatophytosis and Inherited CARD9 Deficiency. N Engl J Med 2013;369:1704–1714.
335. Gavino C, Hamel N, Zeng J Bin, et al. Impaired RASGRF1/ERK–mediated GM-CSF response characterizes CARD9 deficiency in French-Canadians. J Allergy Clin Immunol 2016;137:1178-1188.e7.
336. Grumach AS, Queiroz-Telles F de, Migaud M, et al. A Homozygous CARD9 Mutation in a Brazilian Patient with Deep Dermatophytosis. J Clin Immunol 2015;35:486–490.
337. Drewniak A, Gazendam RP, Tool ATJ, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. Blood 2013;121:2385–2392.
338. McCarl C-A, Picard C, Khalil S, et al. ORAI1 deficiency and lack of store-operated Ca2+ entry cause immunodeficiency, myopathy, and ectodermal dysplasia. J Allergy Clin Immunol 2009;124:1311-1318.e7.
339. Lian J, Cuk M, Kahlfuss S, et al. ORAI1 mutations abolishing store-operated Ca2+ entry cause anhidrotic ectodermal dysplasia with immunodeficiency. J Allergy Clin Immunol 2018;142:1297-1310.e11.
340. Nagai K, Ochi F, Terui K, et al. Clinical characteristics and outcomes of chédiak-Higashi syndrome: A nationwide survey of Japan. Pediatr Blood Cancer 2013;60:1582–1586.
341. Mora AJ, Wolfsohn DM. The management of gastrointestinal disease in hermansky-pudlak syndrome. J Clin Gastroenterol 2011;45:700–702.
342. Huizing M, Pederson B, Hess RA, et al. Clinical and cellular characterisation of Hermansky-Pudlak syndrome type 6. J Med Genet 2009;46:803–10.
343. Miyamichi D, Asahina M, Nakajima J, et al. Novel HPS6 mutations identified by whole-exome sequencing in two Japanese sisters with suspected ocular albinism. J Hum Genet 2016;61:839–842.
344. Sheehan RG, Necheles TF, Lindeman RJ, et al. Regional Enteritis and Granulomatous Colitis Associated with Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency. N Engl J Med 1967;277:1124–1126.
345. Larsson A, Mattsson B, Wauters EA, et al. 5-oxoprolinuria due to hereditary 5-oxoprolinase deficiency in two brothers--a new inborn error of the gamma-glutamyl cycle. Acta Paediatr Scand 1981;70:301–8.
346. Almaghlouth I, Mohamed J, Al-Amoudi M, et al. 5-Oxoprolinase deficiency: report of the first human OPLAH mutation. Clin Genet 2012;82:193–196.
347. SLADE JD, LUSKIN AT, GEWURZ H, et al. Inherited Deficiency of Second

Component of Complement and HLA Haplotype A10,B18 Associated with Inflammatory Bowel Disease. Ann Intern Med 1978;88:796.
348. Matsuura H, Murai M, Hashimoto T, et al. C2 Deficiency Vasculitis: Complication of Enterocolitis, Cutaneous Ulcers, and Neuropsychiatric Disorder. Am J Gastroenterol 1983;Vol 78:p1-5.
349. Marks DJB, Seymour CR, Sewell GW, et al. Inflammatory bowel diseases in patients with adaptive and complement immunodeficiency disorders. Inflamm Bowel Dis 2010;16:1984–1992.
350. Farkas H, Gyeney L, Nemesánszky E, et al. Coincidence of hereditary angioedema (HAE) with Crohn's disease. Immunol Invest 1999;28:43–53.
351. Freeman HJ. Hereditary Angioneurotic Edema and Familial Crohn's Disease. Can J Gastroenterol 2000;14:337–339.
352. Kothari ST, Shah AM, Botu D, et al. Isolated angioedema of the bowel due to C1 esterase inhibitor deficiency: a case report and review of literature. J Med Case Rep 2011;5:62.
353. Koruth JS, Eckardt AJ, Levey JM. Hereditary angioedema involving the colon: endoscopic appearance and review of GI manifestations. Gastrointest Endosc 2005;61:p 907-911.
354. Matsubayashi T, Kaneko S, Shimizu M, et al. Colitis associated with deficiency of the sixth component of complement and congenital chronic neutropenia. Acta Paediatr 2007;90:1211–1212.
355. Hardy C, Khanim F, Torres R, et al. Clinical and Molecular Genetic Analysis of 19 Wolfram Syndrome Kindreds Demonstrating a Wide Spectrum of Mutations in WFS1. Am J Hum Genet 1999;65:1279–1290.
356. Heredia ML de, Clèries R, Nunes V. Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. Genet Med 2013;15:497–506.
357. Ouweland JMW van den, Cryns K, Pennings RJE, et al. Molecular characterization of WFS1 in patients with Wolfram syndrome. J Mol Diagnostics 2003;5:88–95.
358. Giuliano F, Bannwarth S, Monnot S, et al. Wolfram syndrome in French population: Characterization of novel mutations and polymorphisms in theWFS1 gene. Hum Mutat 2005;25:99–100.
359. German J, Sanz MM, Ciocci S, et al. Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. Hum Mutat 2007;28:743–753.
360. Wang J, German J, Ashby K, et al. Ulcerative colitis complicated by dysplasia-adenoma-carcinoma in a man with Bloom's syndrome. J Clin Gastroenterol 1999;28:380–2.
361. Shah S, Wu E, Rao VK, et al. Autoimmune Lymphoproliferative Syndrome: an Update and Review of the Literature. Curr Allergy Asthma Rep 2014;14:462.
362. Teachey DT, Greiner R, Seif A, et al. Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome. Br J Haematol 2009;145:101.
363. Bi LL, Pan G, Atkinson TP, et al. Dominant inhibition of Fas ligand-mediated apoptosis due to a heterozygous mutation associated with autoimmune lymphoproliferative syndrome (ALPS) Type Ib. BMC Med Genet 2007;8:41.
364. Ouederni M, Vincent QB, Frange P, et al. Major histocompatibility complex class II expression deficiency caused by a RFXANK founder mutation: a survey of 35 patients. Blood 2011;118:5108–5118.

365. Krawczyk M, Reith W. Regulation of MHC class II expression, a unique regulatory system identified by the study of a primary immunodeficiency disease. Tissue Antigens 2006;67:183–197.
366. Klein C, Lisowska-Grospierre B, LeDeist F, et al. Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. J Pediatr 1993;123:921–8.
367. Lowe GC, Guiu IS, Chapman O, et al. Microsatellite markers as a rapid approach for autozygosity mapping in Hermansky-Pudlak syndrome: Identification of the second HPS7 mutation in a patient presenting late in life. Thromb Haemost 2013;109:766.
368. Kelsen JR, Ouahed J, Spessott WA, et al. 25 Mutations in STXBP3 Contribute to Very Early Onset of IBD, Immunodeficiency and Hearing Loss. Gastroenterology 2018;154:S40–S41.
369. Schwerd T, Bryant R V., Pandey S, et al. NOX1 loss-of-function genetic variants in patients with inflammatory bowel disease. Mucosal Immunol 2018;11:562–574.
370. Lacher M, Fitze G, Helmbrecht J, et al. Hirschsprung-associated enterocolitis develops independently of NOD2 variants. J Pediatr Surg 2010;45:1826–1831.
371. Alazami AM, Al-Helale M, Alhissi S, et al. Novel CARMIL2 Mutations in Patients with Variable Clinical Dermatitis, Infections, and Combined Immunodeficiency. Front Immunol 2018;0:203.
372. Sorte HS, Osnes LT, Fevang B, et al. A potential founder variant in CARMIL2/RLTPR in three Norwegian families with warts, molluscum contagiosum, and T-cell dysfunction. Mol Genet Genomic Med 2016;4:604–616.
373. Magg T, Shcherbina A, Arslan D, et al. CARMIL2 Deficiency Presenting as Very Early Onset Inflammatory Bowel Disease. Inflamm Bowel Dis 2019;25:1788–1795.
374. Shamriz O, Simon AJ, Lev A, et al. Exogenous interleukin-2 can rescue in-vitro T cell activation and proliferation in patients with a novel capping protein regulator and myosin 1 linker 2 mutation. Clin Exp Immunol 2020;200:215–227.
375. Kolukisa B, Baser D, Akcam B, et al. Evolution and long-term outcomes of combined immunodeficiency due to CARMIL2 deficiency. Allergy 2021;00:12.
376. Bosa L, Batura V, Colavito D, et al. Novel CARMIL2 loss-of-function variants are associated with pediatric inflammatory bowel disease. Sci Rep 2021;11:5945.
377. Zhang Z, Gothe F, Pennamen P, et al. Human interleukin-2 receptor b mutations associated with defects in immunity and peripheral tolerance. J Exp Med 2019;216:1311–1327.
378. Fernandez IZ, Baxter RM, Garcia-Perez JE, et al. A novel human IL2RB mutation results in T and NK cell-driven immune dysregulation. 2019.
379. Mao L, Kitani A, Similuk M, et al. Loss-of-function CARD8 mutation causes NLRP3 inflammasome activation and Crohn's disease. J Clin Invest 2018;128:1793–1806.
380. Ko DC, Shukla KP, Fong C, et al. A Genome-wide In Vitro Bacterial-Infection Screen Reveals Human Variation in the Host Response Associated with Inflammatory Disease. Am J Hum Genet 2009;85:214.
381. Ma CA, Stinson JR, Zhang Y, et al. Germline hypomorphic CARD11 mutations in severe atopic disease. Nat Genet 2017;49:1192.

382. Dadi H, Jones TA, Merico D, et al. Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11). J Allergy Clin Immunol 2018;141:1818-1830.e2.
383. Dorjbal B, Stinson JR, Ma CA, et al. Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease. J Allergy Clin Immunol 2019;143:1482–1495.
384. Brodie SA, Khincha PP, Giri N, et al. Pathogenic germline IKZF1 variant alters hematopoietic gene expression profiles. Cold Spring Harb Mol Case Stud 2021;7.
385. Sifuentes-Dominguez L, Li H, Llano E, et al. SCGN deficiency results in colitis susceptibility. Elife 2019;8.
386. Lam MT, Coppola S, Krumbach OHF, et al. A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function. J Exp Med 2019;216:2778–2799.
387. Su HC, Orange JS. The Growing Spectrum of Human Diseases Caused by InheritedCDC42 Mutations. J Clin Immunol 2020;40:551–553.
388. Tackenberg H, Möller S, Filippi M-D, et al. The Small GTPase Cdc42 Is a Major Regulator of Neutrophil Effector Functions. Front Immunol 2020;0:1197.
389. Balogh E, Chandler JC, Varga M, et al. Pseudouridylation defect due to DKC1 and NOP10 mutations causes nephrotic syndrome with cataracts, hearing impairment, and enterocolitis. Proc Natl Acad Sci U S A 2020;117:15137–15147.
390. Walne AJ, Vulliamy T, Marrone A, et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Hum Mol Genet 2007;16:1619–1629.
391. Gaustadnes M, Wilcken B, Oliveriusova J, et al. The molecular basis of cystathionine β-synthase deficiency in Australian patients: Genotype-phenotype correlations and response to treatment. Hum Mutat 2002;20:117–126.
392. Alsahli S, Anazi A Al, Hatlani MM Al, et al. Severe Crohn's Disease Manifestations in a Child with Cystathionine b-Synthase Deficiency. 2018.
393. Lehle AS, Farin HF, Marquardt B, et al. Intestinal Inflammation and Dysregulated Immunity in Patients With Inherited Caspase-8 Deficiency. Gastroenterology 2019;156:275–278.
394. Kanderova V, Grombirikova H, Zentsova I, et al. Lymphoproliferation, immunodeficiency and early-onset inflammatory bowel disease associated with a novel mutation in Caspase 8. Haematologica 2019;104:e32.
395. Zhang ZZ, Zhang Y, He T, et al. Homozygous IL37 mutation associated with infantile inflammatory bowel disease. Proc Natl Acad Sci 2021;118.
396. Louvrier C, Assrawi E, Khouri E El, et al. NLRP3-associated autoinflammatory diseases: Phenotypic and molecular characteristics of germline versus somatic mutations. J Allergy Clin Immunol 2020;145:1254–1261.
397. Zhou L, Liu T, Huang B, et al. Excessive deubiquitination of NLRP3-R779C variant contributes to very-early-onset inflammatory bowel disease development. J Allergy Clin Immunol 2021;147:267–279.
398. Salter CG, Cai Y, Lo B, et al. Biallelic PI4KA variants cause neurological, intestinal and immunological disease. Brain 2021.
399. Verdura E, Rodríguez-Palmero A, Vélez-Santamaria V, et al. Biallelic PI4KA

variants cause a novel neurodevelopmental syndrome with hypomyelinating leukodystrophy. Brain 2021.
400. Al-Shaibi AA, Abdel-Motal UM, Hubrack SZ, et al. Human AGR2 Deficiency Causes Mucus Barrier Dysfunction and Infantile Inflammatory Bowel Disease. Cell Mol Gastroenterol Hepatol 2021.
401. Tyler PM, Bucklin ML, Zhao M, et al. Human autoinflammatory disease reveals ELF4 as a transcriptional regulator of inflammation. Nat Immunol 2021 229 2021;22:1118–1126.
402. Wang L, Aschenbrenner D, Zeng Z, et al. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. Nat Genet 2021 534 2021;53:500–510.
403. Ouahed J, Kelsen JR, Spessott WA, et al. Variants in STXBP3 are Associated with Very Early Onset Inflammatory Bowel Disease, Bilateral Sensorineural Hearing Loss and Immune Dysregulation. J Crohn's Colitis 2021;2021:1–12.
404. Takahashi S, Andreoletti G, Chen R, et al. De novo and rare mutations in the HSPA1L heat shock gene associated with inflammatory bowel disease. Genome Med 2017 91 2017;9:1–11.
405. Crowley E, Warner N, Pan J, et al. Prevalence and Clinical Features of Inflammatory Bowel Diseases Associated With Monogenic Variants, Identified by Whole-Exome Sequencing in 1000 Children at a Single Center. Gastroenterology 2020;158:2208–2220.
406. Narumi S, Amano N, Ishii T, et al. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet 2016 487 2016;48:792–797.
407. Formankova R, Kanderova V, Rackova M, et al. Novel SAMD9 Mutation in a Patient With Immunodeficiency, Neutropenia, Impaired Anti-CMV Response, and Severe Gastrointestinal Involvement. Front Immunol 2019;0:2194.
408. Ishige T, Guo C, Warner N, et al. *Functional analysis implicating SAMD9 mutation for intestinal inflammation in patients with MIRAGE syndrome and inflammatory bowel disease*.
409. O'Connell AE, Zhou F, Shah MS, et al. Neonatal-Onset Chronic Diarrhea Caused by Homozygous Nonsense WNT2B Mutations. Am J Hum Genet 2018;103:131–137.
410. Zhang YJ, Jimenez L, Azova S, et al. Novel variants in the stem cell niche factor WNT2B define the disease phenotype as a congenital enteropathy with ocular dysgenesis. Eur J Hum Genet 2021;29:998.
411. Neehus A-L, Moriya K, Nieto-Patlán A, et al. Impaired respiratory burst contributes to infections in PKCδ-deficient patients. J Exp Med 2021;218.
412. Ochs HD, Thrasher A;, Dupuis-Girod S, et al. Impaired microbial killing by neutrophils from patients with protein kinase C delta deficiency. J Allergy Clin Immunol 2015;136:1404-1407.e10.
413. Parlato M, Nian Q, Charbit-Henrion F, et al. Loss-of-Function Mutation in PTPN2 Causes Aberrant Activation of JAK Signaling Via STAT and Very Early Onset Intestinal Inflammation. Gastroenterology 2020;159:1968-1971.e4.
414. Oda H, Beck D, Manthiram K, et al. O33 Biallelic loss of functions in sharpin cause autoinflammation. In: *10th Congress of International Society of Systemic Auto-Inflammatory Diseases (ISSAID)*.Vol 17. Genoa, Italy: BioMed Central; 2019:18.
415. Trefzer R, Elpeleg O, Gabrusskaya T, et al. Characterization of a L136P mutation in Formin-like 2 (FMNL2) from a patient with chronic inflammatory

bowel disease Komarova Y, ed. PLoS One 2021;16:e0252428.
416. Naj X, Hoffmann A-K, Himmel M, et al. The Formins FMNL1 and mDia1 Regulate Coiling Phagocytosis of Borrelia burgdorferi by Primary Human Macrophages. 2013.
417. Aydemir S, Islek A, Nepesov S, et al. Inflammatory Bowel Disease and Guillain Barre Syndrome in FCHO1 Deficiency. J Clin Immunol 2021 416 2021;41:1406–1410.
418. Fagbemi A, Newman WG, Tangye SG, et al. Refractory very early-onset inflammatory bowel disease associated with cytosolic isoleucyl-tRNA synthetase deficiency: A case report. World J Gastroenterol 2020;26:1841.
419. Cotter C, Keeley M, Hashemi I, et al. Multidisciplinary Approach to Evaluation and Treatment of Infantile Onset Inflammatory Bowel Disease. J Allergy Clin Immunol 2021;147:AB62.
420. Millstead J, Kamat A, Duffner U, et al. WD Repeat Domain 1 (WDR1) Deficiency Presenting as a Cause of Infantile Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2020;71:e113–e117.
421. Masago K, Fujita S. Novel NR4A1 Arg293Ser Mutation in Patients With Familial Crohn's Disease. In Vivo (Brooklyn) 2021;35:2135–2140.
422. Gruber CN, Calis JJA, Buta S, et al. Complex Autoinflammatory Syndrome Unveils Fundamental Principles of JAK1 Kinase Transcriptional and Biochemical Function. Immunity 2020;53:672.