Supplementary Information

Supplement to: Saper VE, Ombrello MJ, Tremoulet AH et al. Severe hypersensitivity reactions to IL-1 and IL-6 inhibitors link to common HLA-DRB1*15 alleles

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Supplementary Methods

Approvals

This study was approved by the Institutional Review Board (IRB), Stanford University, (#13932 and #34679). Local IRB from contributing institutions were obtained as needed, based on local practice. Informed consent was obtained, as required, for HLA genotyping or sharing genetic data. Subjects evaluated at the National Institutes of Health (NIH) were enrolled in a study of the natural history, genetics and pathophysiology of systemic arthritis (NCT03510442) and were evaluated with family-based whole exome sequencing (WES). The study was approved by the IRB of the NIH, and parents and subjects provided written informed consent/assent, as appropriate. Subjects with Kawasaki disease (KD) were enrolled at Rady Children's Hospital San Diego in a Phase I/IIa, dose-escalation trial of anakinra for intensification of initial therapy in patients with coronary artery aneurysms on the first echocardiogram (NCT 02179853). The study was approved by the IRB at the University of California San Diego, and parents and subjects signed written consent/assent as appropriate.

Subjects and clinical data collection

Given that sJIA and AOSD are considered a continuum of the same illness[3], Still's is the collective term we used to describe sJIA, AOSD and sJIA-like illness. 131 Still's subjects with either probable drug-reaction or possible drug-tolerance were enrolled. (Figure 1) Still's subjects include sJIA patients meeting an operational case definition, developed by expert consensus as a modification of the ILAR (International League of Associations for Rheumatology) sJIA classification criteria.[1] sJIA-like patients were those managed clinically like sJIA, but not meeting modified ILAR criteria. AOSD patients met Yamaguchi criteria[2] and had onset of disease at ≥ 16 yrs. See tables S3a-b for distribution of patient subtypes. Onset age at Still's diagnosis was evaluated by age group (<2.5yrs, 2.5-10, 10-16, ≥ 16 yrs). KD subjects (n=19) met inclusion criteria for a Phase I/IIa trial of brief anakinra treatment[4]; these criteria included American Heart Association criteria for KD[5] and evidence coronary artery abnormalities. Anakinra doses ranged from 2-8 mg/kg/day. After 2 weeks of anakinra, if abnormalities were persistent, treatment continued for 4 weeks.[4] In the 19 KD subjects studied, treatment duration ranged from 9 to 46 days. For some analyses, comparator populations were Still's (sJIA) cases and healthy control subjects from the International Childhood Arthritis Genetics Consortium (INCHARGE) genome-wide association study.[6] Their drug tolerance status was unknown.

Clinical information was collected using REDCap electronic capture tools[7], hosted at Stanford University. Subjects who scored as drug reaction with eosinophilia and systemic symptoms (DRESS)[8] implicating IL-1 or IL-6 inhibitors included cases with or without diffuse parenchymal lung disease (DLD). We previously reported on Still's cases with parenchymal lung disease, which we called "LD". In that study, we enrolled any Still's subject with parenchymal lung disease.[9] Here we have used a new term, DLD, which refers to a specific type of parenchymal lung disease that occurs in the context of DRESS to IL-1/IL-6 inhibitors. When biopsied, lung tissue shows variant PAP/ELP (see lung histopathology below). Of 46 previously reported Still's cases with LD after drug exposure[9], 20 had genetic information; each classified as DRESS and were included in this analysis. Two further cases with unavailable genetic information had clinical information and classified as DRESS. All DRESS cases occurred between 2006 and March 2021.

RegiSCAR scoring

Registry for serious cutaneous adverse reactions (RegiSCAR) for drug related eosinophilia and systemic symptoms (DRESS), a validated scoring system, was utilized to classify subjects as drug-reactive Still's-DRESS cases vs drug-tolerant Still's controls. The scoring system, developed by expert consensus, intentionally sought to differentiate DRESS from underlying inflammatory illnesses.[10] Initially, elements were determined by the expert panel's review of defined clinical features of DRESS cases collected from 2002 to 2007 covering an area of approximately 170 million inhabitants in Europe and Israel. This was followed by a prospective validation cohort including both probable and definite cases in the analyses (n=117) which verified the scoring system, published in 2013.[8]

RegiSCAR for DRESS uses discrete domains, summarized in the table below, per Kardaun et al 2007 and 2013[8,10], and further explained in 2014, e.g., herpes virus reactivation has no impact on scoring.[11] Classifications are defined as definite case (6-9), probable case 4-5), possible case (2-3), and no case (1 to negative 4). The use of definite and probable classes recognizes the clinical variability of DRESS.[8] Known variability includes transient or absent DRESS features, including lack of eosinophilia or rash, or availability or timing of laboratory assessments including, as was common in our cohort, lack of determination of atypical lymphocytes.[8] Scoring is not altered based on concomitant steroid use, the primary treatment for DRESS[12,13], which can diminish the score. DRESS-related liver involvement is defined as elevation of

aspartate aminotransferase (AST) or alanine aminotransferase (ALT) measuring >2x the upper limit of normal more than once without infection or other documented non-DRESS causes.[8,10,11] We intentionally required absence of macrophage activation syndrome (MAS), a cytokine storm syndrome known to complicate Still's[14], when scoring liver involvement. Features of DRESS often occur sequentially rather than simultaneously, and score diminishes if resolution occurs in < 15 days.[10]

DRESS validation score, as published in Kardaun et al[9-11]

SCORE	**-1**	**0**	**1**	**2**	**min**	**max**
Fever ≥ 38.5 ^{0} C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia Eosinophils Eosinophils, if leukocytes <4000		No/U	 700-1499/µl 10-19.9%	 ≥1500/µl ≥20%	0	2
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement Skin rash extent (% BSA) Skin rash suggesting DRESS Biopsy suggesting DRESS	 No No	 No/U U Yes/U	 >50% Yes		-2	2
Organ involvement * Liver Kidney Lung Muscle/heart Pancreas Other organ(s)		 No/U No/U No/U No/U No/U No/U	 Yes Yes Yes Yes Yes Yes		0	2
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes: ANA Blood culture Serology for HVA/ HVB/ HVC Chlamydia-/ Mycoplasma pneumoniae Other serology/PCR If none are positive and ≥ 3 of above negative			 Yes		0	1
TOTAL SCORE					-4	9

U, Unknown/unclassifiable; BSA, body surface area
* After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs

Skin biopsy reports were available for 12 cases [Still's-DRESS with DLD (6), Still's-DRESS only (6)], and a representative skin biopsy was examined by a pathologist (ST). DLD diagnosis required biopsy or autopsy showing variant pulmonary alveolar proteinosis/endogenous lipoid pneumonia (vPAP/ELP) or chest CT with diffuse bilateral interstitial abnormalities.[8] Histopathologic analysis by a pediatric pulmonary pathologist (GD) is described below. Peripheral eosinophilia during inhibitor treatment was defined as an absolute eosinophil count (AEC) ≥500. To qualify as MAS during inhibitor treatment, drug exposure >4 weeks was required (Table S2).

Ancestry data collection

Ancestry was determined by self-identification. A subset of subjects also underwent ancestry-matching analysis for comparison with INCHARGE subjects (Figure S1). Ancestry data were provided by case reporters based on parents' response and then selection from a list of categories (White, Black, Hispanic, Asian, South Asian, Middle Eastern, noting mixed parentage).

Ancestry groups	
Group	**Definition**
White	Self-identification as White or White European
Middle Eastern	Egypt, Oman, Yemen, Qatar, United Arab Emirates, Iran, Bahrain, Syria, Jordan, Turkey, Lebanon, Saudi Arabia, Kuwait, Iraq, Israel
Hispanic	Self-identification as Hispanic, Latinx, Central or South American
South Asian	Afghanistan, India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan, Maldives
Asian	Central, Northern, Eastern, Western and Southeastern Asia
Black	Self-identification as Black or Black-African

Lung histopathology

Hematoxylin and eosin (H&E) slides of lung tissue from 17 Still's-DRESS with DLD subjects were reviewed (GD); 7 others had pathology reports from treating institutions with similar findings (table S3a). All cases, except for one biopsied in the first month of drug exposure, demonstrated vPAP/ELP, characterized by alveolar filling with eosinophilic proteinaceous material admixed with a variable degree of cholesterol clefts and foamy macrophages, as described. Some degree of inflammation (neutrophils, lymphocytes, plasma cells, eosinophils) was frequently present, as was wall thickening of pulmonary arteries, as described.[8] Increased lung eosinophils are seen in DHR[12] and various inflammatory diseases, including rheumatologic conditions.[15] Grading of eosinophils on biopsy used a semi-quantitative grading scale to assess the number of eosinophils on H&E stain at X20 magnification; at least 10 fields assessed. 0=no eosinophils, 1=scattered eosinophils in few fields, 2=scattered eosinophils in many fields with rare aggregates, 3=scattered eosinophils in most fields with several aggregates, 4=numerous aggregates of eosinophils. 3 cases were graded 0; 5 cases at 1; 8 cases at 2-3; 0 cases at 4. All subjects with tissue graded 0 were on high dose (1-2mg/kg/day) steroids (not shown).

DNA extraction methods

Different DNA extraction methods were used, as follows. Genomic DNA (gDNA) was extracted from peripheral blood samples of subjects recruited at Stanford University using the QIAsymphony DNA Mini Kit (based on silica matrix solid-phase purification) automated protocol, per manufacturer's instructions (Qiagen, Hilden, Germany). For subjects recruited at the NIH, gDNA was extracted from peripheral blood samples using the Maxwell 16 DNA Purification Kits and the automated Maxwell 16 instrument, per manufacturer's instructions (Promega, Madison, WI, United States). For the patients with KD, gDNA was extracted from peripheral blood samples using the Wizard Genomic DNA purification kit, per manufacturer's instructions (Promega, Madison, WI, USA). In the case of formalin-fixed paraffin-embedded (FFPE) samples, gDNA was extracted using the QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany), following the standard protocol of Stanford Molecular Pathology. Quantity and quality of extracted DNA samples were measured by spectrophotometry using the NanoDrop 2000 instrument (Thermo Fisher Scientific, Waltham, MA, USA) or by fluorometric quantification of double-stranded DNA using a Qubit 3 instrument (Thermo-Fisher Scientific, Waltham, MA, USA).

HLA genotyping

HLA genotyping via next-generation sequencing (NGS)

DNA samples were typed for HLA class I (*HLA-A*, *HLA-B* and *HLA-C*) and class II (*HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRB1*, *HLA-DRB3*, *HLA-DRB4*, and *HLA-DRB5*) loci using the MIA FORA NGS FLEX high-throughput semi-automated typing protocol (Immucor, Inc., Norcross, GA, USA) per manufacturer's instructions, as initially reported in Wang, C. et al.[16] This NGS method allowed full-length coverage for HLA class I genes and extensive coverage for class II genes amplified by long range PCR.[17] After DNA library preparation steps, pooled sample libraries were sequenced at a final concentration of 1.3 pM spiked with 20pM PhiX on the Illumina MiniSeq instrument using 150 cycle paired-end kits (Illumina, Inc., San Diego, CA). NGS sequencing reads stored as fastq files were uploaded into the MIA FORA NGS FLEX v4.5 HLA genotyping software (Immucor, Inc.) for: building phased consensus sequences; establishing their respective alignment to reference sequences (according to IPD-IMGT/HLA v3.36.0 database, https://www.ebi.ac.uk/ipd/imgt/hla/ and to MIA FORA FLEX internal reference database of cloned and in-silico HLA allele sequences, https://www.immucor.com/en-us/Products/Pages/MIA-FORA-NGS.aspx).

HLA genotyping via reverse sequence-specific oligonucleotide (rSSO) method

Some extracted DNA samples were tested for *HLA-DQA1*, *HLA-DQB1*, *HLA-DRB1*, *HLA-DRB3*, *HLA-DRB4*, and *HLA-DRB5* loci via reverse sequence-specific oligonucleotide (rSSO) DNA typing method using the LABType SSO HLA semi-automated typing protocol (One Lambda, Inc., Canoga Park, CA) per manufacturer's instructions (https://www.onelambda.com/en/product/labtype-sso.html). HLA genotyping data obtained by rSSO was analyzed according to IPD-IMGT/HLA v3.37.0 release database (https://www.ebi.ac.uk/ipd/imgt/hla/).

HLA genotyping from WES data

36 subjects had whole exome sequencing (WES) data from which HLA genotype was extracted. WES data from 14 subjects were analyzed at Stanford using HLAreporter.[18] In brief, a preliminary high-efficiency mapping of the reads was achieved using Burrows-Wheeler Aligner[19] against a comprehensive reference panel generated from all known HLA alleles in the IMGT/HLA database, followed by a *de novo* assembly of gene-specific mapped reads to contigs using Targeted Assembly of Short Sequence Reads.[20] Typically, contigs with an average coverage-depth of ≥5-fold were picked for HLA allele

assignment. Subsequently, these contigs were matched stepwise against reference databases of HLA alleles, followed by HLA allele calling for HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPB1. WES data from 24 subjects were analyzed at the NIH using HLA:LA[21], a highly accurate graph-based method for extracting HLA alleles from exome and low-coverage whole genome sequencing data. Briefly, input reads were linearly aligned to Population Reference Graph (PRG) reference haplotypes, which include eight GRCh38 MHC haplotypes and all IMGT exonic and genomic sequences, using BWA-MEM.[22] Linear alignments were projected onto the PRG, and the alignments were optimized in a stepwise process. Contigs overlapping the MHC were identified using nucmer[23], and each contig was annotated according to the HLA haplotype with the highest alignment score. HLA sequences were extracted according to genomic position, and HLA typing was performed by minimum edit distance-based matching with the IMGT database. Three subjects were analyzed at Stanford and the NIH, with identical results. For subjects from the INCHARGE sJIA GWAS cohort, HLA alleles at the 8 classical HLA loci (*HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DPA1, HLA-DRB1, HLA-DQA1, HLA-DQB1*) were determined by HLA imputation with SNP2HLA software, as previously described.[24] WES data from 1 subject and both parents were analyzed at The Children's Hospital of Philadelphia (DM) using Explore (Omixon, Budapest, Hungary). Briefly, the fastq files were filtered in Explore for reads deriving from 35 HLA genes/pseudogenes within the MHC (*HLA-A, HLA-B, HLA-C, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPA1, HLA-DPA2, HLA-DPB1, HLA-DPB2, HLA-DQA1, HLA-DQB1, HLA-DRA, HLA-DRB1, HLA-DRB2, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DRB6, HLA-DRB7, HLA-DRB8, HLA-DRB9, HLA-E, HLA-F, HLA-G, HLA-H, HLA-J, HLA-K, HLA-L, HLA-T, HLA-U, HLA-V, HLA-W, HLA-Y*). The filtered reads were analyzed using Explore, targeting the same panel of MHC genes using both an exon-only and full gene analysis modes. Genotype data were reported for classical HLA loci (*HLA-A, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRB1, HLA-DRB3, HLA-DRB4,* and *HLA-DRB5*). Discrepancies between the two methods were resolved manually. Haplotype analysis of the trio confirmed the genotype of the patient. All analysis was conducted using the IMGT/HLA database version 3.38.0.

Data analysis

Six major groups of subjects were used for case/control comparisons:

Group	description (n)	Group	description (n)
1	Still's-DRESS cases (66)	2	Still's controls (65)
3	INCHARGE Still's controls (550)	4	INCHARGE healthy controls (3279)
5	KD suspected anakinra reaction (4)	6	KD no suspected anakinra reaction (15)

Still's-DRESS cases and Still's controls (groups 1 and 2) were compared for clinical and demographic variables. HLA alleles in Still's-DRESS, including cases with and without DLD (group 1), were compared to the INCHARGE datasets of European descent Still's (sJIA) subjects and controls (groups 3 and 4).[6] For ancestry matching of Still's-DRESS and INCHARGE collection (groups 1 and 3 and 4), principal component analysis (PCA) was performed with SNP & Variation Suite 8 (SVS8; Golden Helix, Bozeman, MT, USA), as previously described.[24] Association testing with the INCHARGE collection was performed with SVS8, using logistic regression under the dominant model and including sex as a covariate (table S4).

Analyses to test DRB1*15:01 association in self-identified White Still's-DRESS cases and self-identified ancestry-matched Still's controls (groups 1 and 2) assumed the dominant model and were conducted in the R environment for statistical computing,[25] and p-values and odds ratios with 95% confidence intervals were obtained by Fisher's exact test, using the 'oddsratio.fisher' function in the 'epitools' package.[26]

To generate ancestry-matched cohorts of Still's-DRESS cases and Still's controls (groups 1 and 2) for figure 4, in the absence of ancestry-informative markers, self-identified ancestries were used. Nine cases with ancestry that could not be matched to controls were eliminated from the analysis. All controls (n=30) were used.

Clinical, demographic and HLA allele frequencies were compared between KD-sAR subjects and KD controls (groups 5 and 6).

Supplementary Tables

Notes regarding the tables:

In tables S1-7, sections with data on *cases* are shaded in blue and those with data on *controls* are shaded in green. 

Individual subject IDs are maintained throughout supplementary tables S1a-e and S3a-b.
Individual subject IDs are maintained within and between supplementary tables S7a-b.
For Supplementary tables S1a and S3a, footnotes are provided on the page following the table.
All references are provided at the end of the Supplementary Material.

Table S1a: HLA-DQ and -DR in Still's-DRESS cases

Subject	Ancestry[1]	DQA1	DQB1	DRB1	DRB3/4/5/Absent[2]	DRESS[3,4]
Still's-DRESS cases and diffuse lung disease (DLD) developing during treatment (Still's-DRESS/DLD)						
1	White	*01:02/*01:02	*06:02/*06:04	*15:01/*13:02	DRB5*01:01/DRB3*03:01	A
2	White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:04	DRB5*01:01/DRB3*02:02	A T
3	White	*05:01/*05:01	*02:01/*03:01	*03:01/*11:01	nd	A
4	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	A
5	White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:01	DRB5*01:01/DRB3*03:02	A
6	White	*01:02/*05:01	*06:02/*03:01	*15:01/*12:01	DRB5*01:01/DRB3*02:11	A
7	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	A C
8	White	*01:01/*05:05	*03:01/*05:01	*01:02/*11:06	nd	A
9	White	*01:02/*05:05	*06:02/*03:01	*15:01/*13:03	nd[5]	A
10	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	nd[5]	A C
11	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	T
12	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	A (probable)
13	White	*01:02/*05:01	*06:02/*03:01	*15:01/*13:03	DRB5*01:01/DRB3*01:01	T
14	White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:01	nd[5]	A
15	White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:01	nd[5]	C
16	White	*03:03/*05:05	*03:01/*03:01	*04:07/*11:01	DRB4*01:03/DRB3*02:02	A (probable)
17	White	*01:02/*03:01	*06:02/*03:02	*15:01/*04:04	nd[5]	A
18	White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:01	nd[5]	A
19	White	nd	*06:02/*03:01	*15:01/*11:01	nd[5]	C T A
20	White	*01:02/*05:05	*06:02/*03:01	*15:01/*11:04	DRB5*01:01/DRB3*02:02	A
21	White	*01:02/*01:04	*06:02/*05:03	*15:01/*14:54	DRB5*01:01/DRB3*02:02	C
22	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	A (probable)
23	White	nd	nd	*15:01/*11:04	nd[5]	A
24	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	C
25	White	nd	*06:02/*06:02	*15:01/*15:01	nd[5]	A C
26	White	*01:02/nd	*06:02/nd	*15:01/nd	DRB5*01:01/nd	A C T
27	Native American/White	*01:04/*05:03	*05:03/*03:01	*14:54/*14:02	nd[5]	A
28	Middle Eastern/White	*01:02/*05:01	*06:02/*03:01	*15:01/*11:01	DRB5*01:01/DRB3*02:02	A
29	Middle Eastern	*01:02/*03:01	*06:02/*03:02	*15:01/*04:02	DRB5*01:01/DRB4*01:03	A C T
30	Middle Eastern	*01:02/*05:01	*03:01/*03:01	*11:04/*13:03	nd	C T A
31	Hispanic/White	*05:05/*05:03	*03:01/*03:01	*13:03/*14:02	nd	A
32	Hispanic	*01:02/*05:01	*06:02/*03:01	*13:03/*11:01	DRB3*02:02/DRB3*01:01	C T
33	Hispanic	*01:02/*04:01	*06:02/*04:02	*15:01/*08:02	DRB5*01:01/Absent	A
34	Hispanic	nd	*06:02/*04:02	*15:01/*08:02	DRB5*01:01/Absent	A
35	Hispanic	*01:02/*05:03	*06:02/*03:01	*15:01/*14:02	DRB5*01:01/DRB3*03:01	A T
36	South Asian/White	*01:02/*06:01	*06:02/*03:01	*15:01/*12:02	DRB5*01:01/DRB3*03:01	A T
37	South Asian	*01:02/*05:05	*05:02/*03:01	*15:06/*11:04	DRB5*01:01/DRB3*pos[6]	A C
38	South Asian	*01:02/*01:03	*06:01/*06:01	*15:01/*15:01	nd[5]	A C R T
39	South Asian/Asian	*01:02/*06:01	*05:02/*03:01	*15:01/*12:02	DRB5*01:01/DRB3*03:01	C
40	Black/White	*01:02/nd[7]	*06:02/nd[7]	*15:01/nd[7]	DRB5*01:01/nd[7]	A
41	Black/White	*01:02/*01:02	*06:02/*06:02	*15:01/*11:01	DRB5*01:01/DRB3*02:02	A T
42	Black	*01:02/*05:01	*06:02/*03:01	*15:03/*13:03	DRB5*01:01/DRB3*01:01	A
43	Black	*01:02/*04:01	*06:02/*04:02	*15:03/*03:02	nd[5]	A T
44	Black	*01:02/*01:02	*06:02/*05:01	*15:01/*15:03	DRB5*01:01/DRB5*01:01	A
45	Black	*04:01/*05:05	*03:19/*03:01	*08:04/*08:06	Absent/Absent	C R
46	Hispanic	nd	nd	nd	nd	A T
47	Black/Hispanic	nd	nd	nd	nd	A C
Still's-DRESS cases without DLD (Still's-DRESS only)						**DRESS[3,4]**
1	White	*01:02/*05:05	*06:02/*03:01	*15:01/*11:04	nd[5]	A
2	White	*01:03/*02:01	*06:01/*02:02	*07:01/*08:03	DRB4*01:03/Absent	A
3	White	*01:02/*01:02	*06:02/*06:02	*15:01/*15:01	DRB5*01:01/DRB5*01:01	A
4	White	*01:01/*03:01	*03:02/*05:01	*01:01/*04:02	nd	A R T
5	White	*01:02/*05:01	*06:02/*03:01	*15:01/*13:03	nd[5]	A C R
6	White	*01:02/*03:01	*06:02/*03:02	*15:01/*04:01	nd[5]	A C (probable)
7	White	*01:02/*04:01	*06:02/*04:02	*15:01/*08:04	DRB5*01:01/Absent	A
8	White	*01:02/*01:01	*06:02/*05:01	*15:01/*01:01	DRB5*01:01/Absent	C (probable)
9	White	nd	nd	*15:01/*03:02	nd[5]	A C
10	White	*01/01/*01:01	*05:01/*05:01	*01:01/*01:01	Absent/Absent	C
11	Middle Eastern	*01:02/*05:05	*03:01/*05:02	*15:06/*13:03	DRB5*01:01/DRB3*01:01	A
12	Hispanic	*01:02/*05:05	*06:02/*03:01	*15:01/*13:03	DRB5*01:01/DRB3*01:01	A
13	Hispanic	nd	*06:02/*06:03	*11:01/*13:01	nd	A C T
14	Asian	*01:02/*05:01	*06:02/*02:01	*15:01/*03:01	nd[5]	T A C
15	Asian	*01:02/*01:02	*05:02/*05:02	*15:01/*15:01	nd[5]	A C
16	South Asian	*01:03/*05:05	*06:01/*03:01	*15:01/*11:01	DRB5*01:01/DRB3*02:02	A
17	South Asian	*01:03/*06:01	*06:01/*03:01	*15:01/*12:02	DRB5*01:01/DRB3*03:01	A C R T (probable)
18	Black	*01:02/*01:05	*06:02/*05:01	*12:01/*11:01	DRB3*01:01/DRB3*02:02	T (probable)
Still's cases with suspected anakinra reaction (Still's-sAR)						**sAR**
1	Black	*01:02/*04:01	*06:02/*04:02	*15:03/*03:02	DRB5*01:01/DRB3*01:01	A

Red indicates DRESS/sAR risk allele; nd, not determined; DRESS, drug reaction with eosinophilia and systemic symptoms; sAR, suspected (delayed type) anakinra reaction. Presence of HLA-DRB1*15 in DRESS/DLD vs DRESS-only is similar: 82% vs 72%, p=0.5. Co-occurrence of HLA-DRB1*15:01 and DRB1*11:01 in Still's-DRESS cases does not differ from occurrence of HLA-DRB1*11:01 in Still's controls [18% vs 10%, respectively (p=0.5)]. Four cases have Still's plus Trisomy 21; three carry HLA-DRB1*15:01.

Footnotes for Table S1a

[1]Ancestry self-identification as White, Hispanic, South Asian, Asian or Black, with mixed parentage noted.
[2]Absent: Absence of HLA-DRB3/4/5 when HLA-DRB1*01/*08/*10 are present[27]
[3]DRESS by clinical diagnosis and/or 'definite' by RegiSCAR[11]; (probable): 'probable' by RegiSCAR
[4]Implicated drug for DRESS: A, anakinra C, canakinumab R, rilonacept, T, tocilizumab
[5]Per http://17ihiw.org/17th-ihiw-ngs-hla-data/ and references.[28,29] DRB5*01:01 is tightly linked to DRB1*15:01, 15:03, *15:06.
[6]Does not genotype due to cross mapping.
[7]Imputed as one DRB1*15:01 haplotype by single nucleotide polymorphism (SNP)[30]

Table S1b: HLA-DQ and -DR in Still's controls[1]

Subject	Ancestry[2]	DQA1	DQB1	DRB1	DRB3/4/5/Absent[3]	Drug exposure[4]
Still's controls with uneventful exposure to IL-1/IL-6 inhibitors (drug-tolerant Still's)						
1	White	*01:01/*02:01	*05:01/*03:03	*01:01/*07:01	Absent/DRB4*01:03	A C T
2	White	*01:02/*03:03	*04:02/*06:04	*13:02/*04:04	DRB3*03:01/DRB4*01:03	A C
3	White	*03:03/*04:02	*03:01/*04:02	*04:01/*08:01	DRB4*01:03/Absent	A T
4	White	*01:01/*05:05	*03:01/*05:01	*01:01/*11:04	Absent/DRB3*02:02	A
5	White	*01:01/*03:01	*03:05/*05:01	*01:01/*04:03	Absent/DRB4*01:03	A C
6	White	*05:01/*05:01	*02:01/*03:01	*03:01/*11:04	nd	C
7	White	*01:02/*05:01	*02:01/*06:01	*03:01/*13:02	nd	C
8	White	*01:02/*05:01	*02:01/*06:04	*03:01/*13:02	nd	C
9	White	*03:01/*03:01	*03:02/*06:11	*04:04/*04:05	nd	A C
10	White	*01:01/*03:01	*03:02/*05:01	*01:01/*04:04	nd	C
11	White	*03:01/*05:01	*03:01/*03:01	*04:01/*11:01	nd	T
12	White	*02:01/*02:01	*02:02/*03:03	*07:01/*07:01	DRB3*01:01/DRB4*01:03	A
13	White	*03:01/*05:01	*02:01/*03:02	*03:01/*04:04	DRB4*01:01/DRB3*01:01	A C T
14	White	*05:05/*01:04	*03:01/*05:03	*11:04/*14:54	DRB3*02:02/DRB3*02:02	A C T
15	White	*02:01/*03:03	*03:02/*03:03	*04:01/*07:01	DRB4*01:03N/DRB4*01:03	A
16	White	*01:03/*05:01	*02:01/*06:03	*03:01/*13:01	DRB3*01:01/DRB3*02:02	T
17	White	*01:03/*03:03	*03:01/*06:03	*04:01/*13:01	DRB3*02:02/DRB4*01:03	A
18	White	*05:01/*05:05	*02:01/*03:01	*03:01/*11:01	DRB3*02:02/DRB3*02:02	AT
19	White	*01:02/*02:01	*03:03/*06:04	*07:01/*13:02	DRB4*01:03/DRB3*03:01	T
20	Hispanic	*02:01/*03:01	*02:02/*03:02	*04:01/*07:01	DRB4*01:03/DRB4*01:01	C
21	Hispanic	*01:02/*01:01	*05:01/*05:01	*13:02/*13:02	DRB3*03:01/DRB3*03:01	A C R T
22	Hispanic	*04:01/*04:01	*04:02/*04:02	*08:02/*08:02	Absent/Absent	AT
23	Hispanic	*03:03/*04:01	*03:02/*04:02	*08:02/*04:01	Absent/DRB4*01:03	A
24	South Asian	*03:01/*03:03	*03:01/*03:02	*04:01/*04:04	DRB4*01:03/DRB4*01:03	A C
25	Asian	*02:01/*06:01	*02:02/*03:01	*07:01/*12:02	DRB4*01:03/DRB3*03:01	A C R T
26	Asian	*01:02/*05:01	*02:01/*06:04	*03:01/*13:02	DRB3*02:02/DRB3*03:01	A
27	Black	*03:01/*03:03	*02:02/*03:02	*04:03/*09:01	DRB4*01:03/DRB4*01:03	T
28	Black	*01:02/*02:01	*06:02/*02:02	*15:03/*13:03	DRB5*01:01/DRB3*02:02	A
29	Black	*01:02/*01:01	*05:01/*06:04	*15:03/*13:02	DRB5*01:01/DRB3*03:01	A
30	Black	*01:02/*03:03	*06:02/*02:02	*09:01/*11:01	DRB4*01:01/DRB3*02:02	A

Red indicates DRESS risk alleles; nd, not determined.
[1]Treated uneventfully for ≥1 yr. Definition of drug tolerant is provided in methods.
[2]Ancestry self-identification as White, Hispanic, South Asian, Asian or Black, with mixed parentage noted. [3]Absent: Absence of HLA-DRB3/4/5 when HLA-DRB1*01/*08/*10 are present.[31] [4]A, anakinra C, canakinumab R, rilonacept, T, tocilizumab

Table S1c: Per-drug analyses in Still's subjects

A. Still's-DRESS cases compared to Still's controls				
	Still's-DRESS cases	Still's controls	*P* value	OR (95%CI)
IL-1 inhibitor				
Anakinra	86% (57/66)[1]	70% (21/30)	0.088	
Canakinumab	38% (25/66)	47% (14/30)	0.50	
Rilonacept	8% (5/66)	7% (2/30)	1	
Any anti-IL-1	95% (63/66)	87% (26/30)	0.20	
IL-6 inhibitor				
Tocilizumab	29% (19/66)	40% (12/30)	0.35	
B. Risk associated with HLA-DRB1*15:01 in White/Europeans[2]				
	Carriers of HLA-DRB1*15:01		*P*	OR (95%CI)
	Still's-DRESS cases (White)	INCHARGE-sJIA (European)		
Anakinra	83% (24/29)	24% (130/550)	$2.1x10^{-10}$	14.9 (5.5, 39.8)
Canakinumab	92% (12/13)		$5.3x10^{-7}$	41.3 (5.3, 321.6)
Any anti-IL-1	83% (29/34)		$9.8x10^{-12}$	14.5 (5.9, 35.9)
IL-6 inhibitor (tocilizumab)	80% (4/5)		$3x10^{-2}$	12.7 (1.4, 115.4)
IL-1 inhibitor or tocilizumab	83% (30/36)		$7.5x10^{-13}$	15.5 (6.3, 38.1)
C. Risk associated with HLA-DRB1*15:XX in all ancestries[3]				
	Still's-DRESS cases	Still's controls		
Anakinra	82% (45/55)[1]	9% (2/21)[3]		
Canakinumab	79% (19/24)	0% (0/14)		
Rilonacept	40% (2/5)	0% (0/2)		
Tocilizumab	74% (14/19)	0% (0/12)		

All cases and controls were exposed to 1 to 4 inhibitors. Any anti-IL-1, exposure to one or more of anakinra, canakinumab, or rilonacept; DRESS, drug reaction with eosinophilia and systemic symptoms; *P* value, by Fisher exact test (Part A); *P* value, by logistic regression, with sex as covariate (Part B); OR (95%CI), odds ratio with 95% confidence interval; interval by Fisher exact test (Part A) and logistic regression adjusting with sex as covariate (Part B); CI shown when $P < 0.05$.
[1]Includes one subject with Still's-suspected anakinra reaction (see methods). Data per subject are provided in tables S1a-b.
[2] Part B. Still's-DRESS are self-identified White, INCHARGE-sJIA are European descent. [3] Part C. Full (all ancestries) cohort was used for comparison of Still's-DRESS cases and Still's controls, limiting statistical analysis. Two controls have DRB1*15:03, Black ancestry.

Table S1d: HLA-A, B, C in Still's-DRESS cases

Subject	Ancestry	HLA-A_1	HLA-A_2	HLA-B_1	HLA-B_2	HLA-C_1	HLA-C_2
Still'-DRESS cases and diffuse lung disease (DLD) developing during treatment							
1	White	A*24:138	nd	B*07:02	B*51:08	C*07:02:09	C*16:02
2	White	A*30	nd	B*18:01	B*35:32:02	C*04	C*05
3	White	A*01:01:01G	A*11:50Q	B*08:01:01G	B*37:01:01G	C*06:02:01G	C*07:01:01G
4	White	A*03:01	A*02:01	B*07:02	B*27:05	C*07:02	
5	White	A*11:88	A*24:50	B*51:01	B*44:62	C*15:02	C*06
6	White	A*32:01	A*02:01	B*07:02	B*44:02	C*05:01	C*07:02
7	White	A*02:01	A*02:01	B*15:01	B*07:02	C*03:03	C*07:02
8	White	nd	nd	nd	nd	nd	nd
9	White	nd	nd	nd	nd	nd	nd
10	White	A*02:01:01G	A*02:01:01G	B*07:02:01G	B*15:01:01G	C*03:03:01G	C*07:02:01G
11	White	A*02:01:01:01	A*03:01:01:01	B*07:02:01:01	B*40:01:02:01	C*03:04:01:01	C*07:02:01:03
12	White	A*03	A*29	B*07:02		C*07:02	
13	White	A*02:05	A*24:02	B*07:02	B*38:01:01	C*12:03	C*07:02
14	White	A*03:01:01G	A*26:01:01G	B*39:01:01G	B*44:04	C*04:68	C*01:04
15	White	A*02:05:01G	A*32:01:01G	B*27:08	B*49:01:01G	C*06:02:01G	C*07:01:01G
16	White	A*02:01:01:01	A*68:01:01:02	B*27:02:01:04	B*39:01:01:03	C*02:02:02:01	C*17:03:01:03
17	White	A*02:01:01G	A*31:01:02G	B*40:01:01G	B*53:01:01G	C*03:04:01G	C*12:03:01G
18	White	A*26:01:01G	A*24:02:01G	B*07:02:01G	B*35:01:01G	C*07:02:01G	C*04:01:01G
19	White	A*01:01:01	A*24:02:01	B*35:08:01	B*55:01:01	C*03:03:01	C*04:01:01
20	White	A*02:01:01:01	A*24:02:01:01	B*44:02:01:01	B*44:02:01:03	C*05:01:01:02	C*07:04:01:03
21	White	A*11:01:01:01	A*24:02:01:01	B*35:01:01:05	B*38:01:01:01	C*04:01:01:05	C*12:03:01:01
22-26	White	nd	nd	nd	nd	nd	nd
27	Native American/White	A*11:01:01:01	A*31:01:02:01	B*35:01:01:01	B*48:01:01:01	C*04:01:01:01	C*08:01:01:01
28	Middle Eastern/White	A*30:01:01G	A*68:01:02G	B*44:02:01G	B*51:01:01G	C*07:04:01G	C*14:28:02
29	Middle Eastern	A*24:02:01G	A*66:01:01G	B*18:01:01G	B*41:02:01G	C*12:03:01G	C*17:01:01G
30	Middle Eastern	nd	nd	nd	nd	nd	nd
31	Hispanic/White	nd	nd	nd	nd	nd	nd
32	Hispanic	A*23:01		B*15:03	B*15:274	C*02:14	C*14:02
33	Hispanic	A*02:01:01:01	A*02:06:01:01	B*07:02:01:01	B*51:02:01:01	C*07:02:01:03	C*08:01:01:01
34	Hispanic	A*29:02:01:01	A*31:01:02:01	B*44:03:01:01	B*51:02:01:01	C*16:01:01:01	C*08:01:01:01
35	Hispanic	A*11:01:01:01	A*68:03:01	B*07:02:01:01	B*35:01:01:05	C*07:02:01:01	C*07:74
36	South Asian/White	A*01:01	A*24:02	B*15:02	B*44:02	C*08:02	C*08:10
37	South Asian	A*33:03	A*11:01	B*15:02	B*27:02	C*08:01:	C*15:02
38	South Asian	A*29:01:01G	A*11:88	B*07[1]	B*40:06:01G	C*15:05:01G	C*15:16
39	South Asian/Asian	A*11:01	A*24:02	B*15:02	B*51:06	C*14:02	C*08:01
40	Black/White	nd	nd	nd	nd	nd	nd
41	Black/White	A*31:01	A*02:02	B*07:02	B*15:47:01	C*07:02	C*02:10
42	Black	A*03	A*23	B*44	B*07	C*07:02	C*04:01
43	Black	A*30:02:01G	A*30:01:01G	B*42:01:01G	B*44:03:01G	C*04:01:01G	C*17:01:01G
44	Black	A*01:01:01:01	A*68:02:01:01	B*08:01:01:01	B*53:01:01:01	C*04:01:01:01	C*07:01:01:01
45	Black	A*02:01:01:01	A*33:01:01:01	B*45:01:01:01	B*50:01:01:01	C*06:02:03	C*16:01:01:01
Still's-DRESS cases without DLD							
1	White	nd	nd	nd	nd	nd	nd
2	White	A*02:07:01	A*33:03:01:01	B*44:03:02	B*46:01:01	C*01:02:01:01	C*07:06:01:01
3	White	A*02:01:01:01	A*68:01:02:02	B*44:02:01:01	B*44:02:01:01	C*05:01:01:02	C*05:01:01:02
4	White	nd	nd	nd	nd	nd	nd
5	White	A*03:01:01G	A*01:01:01G	B*41:02:01G	B*08:01:01G	C*17:01:01G	C*07:01:01G
6	White	A*03:01:01G	A*01:01:01G	B*07:02:01G	B*40:01:01G	C*03:04:01G	C*07:02:01G
7	White	A*02:01:01:01	A*02:01:01:01	B*07:02:01:01	B*40:01:02:01	C*03:04:01:01	C*07:02:01:03
8	White	A*24:02:01:01	A*31:01:02:01	B*07:02:01:01	B*15:01:01:01	C*03:03:01:01	C*07:02:01:03
9-10	White	nd	nd	nd	nd	nd	nd
12	Middle Eastern	A*24:02:01:01	A*26:01:01:01	B*35:03:01:01	B*38:01:01:01	C*12:03:01:01	C*12:03:01:01
13	Hispanic	A*01:01:01:01	A*29:02:01:01	B*08:01:01:01	B*47:01:01:03	C*07:01:01:01	C*07:18:01:01
14	Hispanic	A*02:01	A*66:01	B*44:02	B*58:02	C*05: ambiguous 164v09	C*06:02
15	Asian	nd	nd	nd	nd	nd	nd
16	Asian	A*11:XX	A*24:XX	B*15:XX	B*15:XX	C*04:CXX	C*04:XX
17	South Asian	A*11:01:01:01	A*31:01:02:01	B*07:06:01	B*35:03:01:01	C*04:01:01:01	C*07:02:01:01
18	South Asian	A*24:07:01	A*33:03:01:01	B*35:05:01:01	B*40:06:01:02	C*04:01:01:01	C*15:02:01:01
19	Black	A*33:01:01:01	A*36:01	B*45:01:01:01	B*53:01:01:01	C*04:01:01:01	C*06:02:01:01
Still's cases with suspected anakinra reaction (Still's-sAR)							
1	Black	A*02:01:01:01	A*74:01:01:01	B*42:01:01	B*45:01:01:03	C*16:01:01:01	C*17:01:01:02

nd, not determined; G, code for reporting ambiguous allele typing http://hla.alleles.org/alleles/g_groups.html.

[1] Ambiguous HLA-B*07 allele: HLA-B*07:05:01 or HLA-B*07:06.

HLA B7:02 is in linkage disequilibrium with the HLA-DRB1*15:01 haplotype[32] and does not confer an independent association.

Table S1e: HLA-A, B, C in Still's controls

Subject	Ancestry	HLA_A/1	HLA_A/2	HLA_B/1	HLA_B/2	HLA_C/1	HLA_C/2
1	White	A*02:01:01:01	A*02:01:01:01	B*27:05:02:01	B*57:01:01:01	C*02:02:02:01	C*06:02:01:01
2	White	A*02:01:01:01	A*11:01:01:01	B*35:08:01:01	B*40:01:02:01	C*03:04:01:01	C*04:01:01:06
3	White	A*01:01:01:01	A*02:01:01:01	B*37:01:01:01	B*44:02:01:01	C*05:01:01:02	C*06:02:01:01
4	White	A*02:01:01:01	A*24:02:01:01	B*15:01:01:01	B*35:02:01:02	C*03:04:01:01	C*04:01:01:06
5	White	A*30:01:01:01	A*32:01:01:01	B*13:02:01:01	B*44:02:01:01	C*05:01:01:02	C*06:02:01:01
6	White	A*01:01:01G	A*01:83:01	B*08:01:01G	B*35:02:01G	C*04:01:01G	C*07:01:01G
7	White	A*01:01:01G	A*02:01:01G	B*08:01:01G	B*40:01:01G	C*03:04:01G	C*07:01:01G
8	White	A*03:01:01G	A*66:01:01G	B*08:01:01G	B*58:01:01G	C*07:01:01G	C*07:01:01G
9	White	A*01:01:01G	A*02:01:01G	B*08:01:01G	B*49:01:01G	C*07:01:01G	C*07:01:01G
10	White	A*23:01:01G	A*68:01:02G	B*27:05:02G	B*51:01:01G	C*03:04:01G	C*15:02:01G
11	White	A*02:01:01G	A*31:01:02G	B*39:06:02	B*44:02:01G	C*05:01:01G	C*07:02:01G
12	White	A*11:01:01:01	A*30:01:01:01	B*13:02:01:01	B*35:01:01:05	C*04:01:01:01	C*06:02:01:01
13	White	A*01:01:01:01	A*11:01:01:01	nd	nd	nd	nd
14	White	A*02:01:01:01	A*24:02:01:01	B*15:01:01:01	B*35:02:01:02	C*03:03:01:01	C*04:01:01:06
15	White	A*26:01:01:01	A*31:01:02:01	B*27:05:02:09	B*57:01:01:01	C*02:02:02:01	C*06:02:01:01
16	White	A*32:01:01:01	A*68:01:01:02	B*18:01:01:01	B*51:01:01:02	C*03:03:01:01	C*05:01:01:02
17	White	A*02:01:01:01	A*02:01:01:01	B*44:02:01:01	B*55:01:01:01	C*03:03:01:01	C*05:01:01:02
18	White	A*02:01:01:01	A*24:02:01:01	B*18:01:01:06	B*51:01:01:02	C*01:02:01:01	C*05:01:01:01
19	White	A*01:01:01:01	A*24:02:01:01	B*08:01:01:01	B*55:01:01:01	C*03:03:01:01	C*07:01:01:01
20	Hispanic	A*01:01:01:01	A*31:01:02:01	B*07:02:01:01	B*39:02:02:01	C*07:02:01:01	C*07:02:01:03
21	Hispanic	A*23:01:01:01	A*32:01:01:01	B*45:01:01:01	B*51:01:01:03	C*12:03:01:01	C*16:01:01:01
22	Hispanic	A*24:03:01:01	A*68:01:02:01	B*15:01:01:01	B*48:01:01:01	C*01:151	C*08:01:01:01
23	Hispanic	A*02:01:01:01	A*11:01:01:01	B*35:12:01	B*49:01:01:01	C*04:01:01:01	C*07:01:01:01
24	South Asian	A*02:01:01:01	A*11:01:01:01	B*15:01:01:01	B*27:05:02:05	C*02:02:02:01	C*03:04:01:01
25	Asian	A*11:01:01:07	A*33:03:01:01	B*35:05:01:01	B*44:03:02	C*04:01:01:01	C*07:06:01:01
26	Asian	A*33:03:01:01	A*33:03:01:02	B*44:03:01:10	B*58:01:01:03	C*03:02:02:01	C*14:03:01
27	Black	A*03:01:01:05	A*24:02:01:01	B*07:02:01:01	B*15:01:01:01	C*03:03:01:01	C*15:22
28	Black	A*02:02:01:02	A*80:01:01:02	B*45:01:01:03	B*57:03:01:02	C*02:02:02:01	C*16:01:01:01
29	Black	A*02:01:01:01	A*68:02:01:01	B*07:02:01:14	B*45:01:01:01	C*07:02:01:01	C*16:01:01:01
30	Black	A*03:01:01:05	A*36:01	B*49:01:01:01	B*53:01:01:01	C*04:01:01:01	C*07:01:02

nd, not determined; G, code for reporting ambiguous allele typing http://hla.alleles.org/alleles/g_groups.html.

Table S2: Demographics of Still's-DRESS cases and Still's controls

	Still's DRESS cases	Still's controls	*P* value	OR (95%CI)		Still's - DRESS/DLD	Still's - DRESS only	*P* value	OR (95%CI)
Male	21/66 (32%)	33/65 (51%)	**0.03**	0.45 (0.2-0.92)		12/43 (28%)	8/23 (35%)	0.58	0.73 (0.22-2.53)
White	38/66 (53%)	37/65 (57%)	1			25/43 (58%)	14/23 (53%)	1	
Age of Still's disease onset (years)									
<2.5[1]	30/66 (45%)	15/65 (23%)	0.137	0.62 (0.33-1.17)		25/44 (58%)	5/23 (22%)	**0.009**	0.28 (0.11-0.73)
2.5-10	17/66 (26%)	32/65 (49%)				10/44 (23%)	7/23 (30%)		
>10-16	13/66[2] (20%)	15/65 (23%)				5/44 (12%)	9/23[2] (39%)		
>16	6/66 (9%)	3/65 (5%)				4/44 (9%)	2/23 (9%)		

DRESS, drug reaction with eosinophilia and systemic symptoms; *P* value, by Fisher exact test, for sex comparisons and proportional odds regression for age of onset; significant values <0.05 in **bold**; OR (95%CI), odds ratio with 95% confidence interval by Fisher's exact test for sex comparisons and proportional odds regression for age of onset; DRESS/DLD, DRESS with diffuse lung disease; DRESS only, DRESS without DLD; sJIA, systemic onset juvenile idiopathic arthritis (Still's onset <16yrs); AOSD, adult-onset Still's disease (Still's onset ≥16yrs)

[1]Previously reported median age at Still's onset in cases developing DLD was 2.8 y vs. 5.2y in non-DLD Still's.[8]

[2]Includes one case of Still's-suspected anakinra reaction

Table S3a: Clinical features in Still's-DRESS cases[1]

Subject	Illness	Sex	HLA-DRB1*15[2]	Tocilizumab anaphylaxis[3]	MAS[4]	Fatal[5]	Eosinophilia[6]	AST or ALT elevation[7]	Atypical rash[8]	Face or neck rash[9]	PAP/ELP[10]	PH[11]
Still'-DRESS cases and diffuse lung disease (DLD) developing during treatment (Still's-DRESS/DLD)[12]												
1	sJIA	F	1	1	1	0	1	1	1	0	no biopsy	0
2	sJIA	F	1	0	1	0	2	1	1	1	no biopsy	1
3	sJIA	F	0	1	1	1	2	1	1	0	1	1
4	sJIA	M	1	1	1	1	2	1	1	1	1	0
5	sJIA	F	1	1	0	0	2	1	1	na	1	0
6	sJIA-like	F	1	not exposed	1	0	1	1	1	na	1	0
7	sJIA	F	1	not exposed	1	0	2	1	1	1	1	0
8	AOSD	F	0	1	1	1	2	1	1	1	no biopsy	1
9	sJIA	F	1	not exposed	0	1	2	1	1	1	no biopsy	0
10	sJIA	M	1	0	1	0	2	0	1	1	no biopsy	0
11	sJIA	F	1	1	1	0	1	0	1	1	1	0
12	sJIA	M	1	0	1	0	na	1	1	na	no biopsy	0
13	sJIA	F	1	0	0	0	1	1	1	1	1	1
14	sJIA	F	1	0	1	0	2	1	1	0	no biopsy	0
15	sJIA	F	1	not exposed	0	0	1	0	1	na	1	0
16	sJIA	F	0	0	0	0	1	0	no atypical rash[13]		no biopsy	0
17	sJIA	F	1	1	0	0	0	1	1	na	no biopsy	0
18	sJIA	F	1	0	1	0	0	1	1	1	no biopsy	0
19	sJIA	F	1	0	1	0	1	1	1	1	no biopsy	0
20	sJIA	M	1	0	1	0	2	0	1	na	no biopsy	0
21	sJIA	M	1	not exposed	0	0	2	1	1	1	no biopsy	0
22	sJIA	F	1	not exposed	1	0	0	1	1	1	1	0
23	sJIA-like	F	1	not exposed	0	0	1	1	1	1	0	0
24	sJIA	M	1	0	0	0	1	na	1	na	1	0
25	sJIA	M	1	not exposed	1	0	2	1	1	na	no biopsy	0
26	sJIA	M	1	0	1	0	1	1	1	1	1	0
27	sJIA-like	F	0	not exposed	1	0	2	1	1	1	no biopsy	0
28	sJIA-like	F	1	not exposed	0	0	na	1	1	1	1	0
29	sJIA	F	0	1	1	0	2	1	1	1	1	1
30	sJIA	F	0	1	1	0	1	1	1	1	1	0
31	sJIA-like	F	0	0	1	1	2	1	1	na	1	0
32	sJIA	F	1	0	1	0	2	0	1	1	1	0
33	AOSD	M	1	0	1	1	0	1	1	na	1	0
34	sJIA	F	1	not exposed	1	0	2	0	1	1	no biopsy	0
35	sJIA-like	F	1	0	1	0	1	1	1	1	no biopsy	0
36	sJIA	M	1	0	1	0	1	1	1	1	1	0
37	sJIA	M	1	not exposed	1	0	1	0	1	na	1	0
38	sJIA	M	1	1	0	0	2	1	1	1	1	0
39	sJIA	F	1	1	0	0	1	1	1	na	1	0
40	sJIA-like	F	1	0	1	1	2	1	1	1	1	0
41	sJIA	F	1	0	1	0	2	1	1	na	1	0
42	sJIA	M	1	0	0	1	2	1	1	1	1	0
43	AOSD	F	1	0	1	0	2	1	1	na	no biopsy	0
44	AOSD	F	1	0	1	0	2	1	1	0	no biopsy	1
45	sJIA	F	0	1	1	1	2	1	1	1	no biopsy	1
46	AOSD	F	not done	0	0	0	2	1	1	1	no biopsy	1
47	sJIA-like	M	not done	0	0	1	1	1	1	1	1	1
Still's-DRESS cases without DLD (Still's-DRESS only)[14]												
1	sJIA	F	1	0	0	0	2	0	1	1		
2	AOSD	F	0	0	0	0	2	1	1	1		
3	sJIA	F	1	not exposed	1	0	1	1	1	1		
4	sJIA-like	F	0	0	1	0	1	1	1	1		
5	sJIA	M	1	1	0	0	2	0	1	1		
6	sJIA	M	1	not exposed	1	0	2	0	1	1		
7	sJIA	M	1	0	1	0	1	0	1	1		
8	sJIA	F	1	0	1	0	0	0	no atypical rash[13]			
9	sJIA-like	F	0	not exposed	0	0	0	1	1	1		
10	sJIA-like	F	1	not exposed	0	0	2	1	1	1		
11	sJIA	F	1	not exposed	1	0	2	2	1	na		
12	sJIA	M	1	not exposed	0	0	1	0	1	0		
13	sJIA	F	0	0	1	0	1	1	1	1		
14	sJIA	M	1	0	0	0	1	1	1	1		
15	sJIA	F	1	0	1	0	2	1	1	1		
16	sJIA	F	1	not exposed	1	0	1	1	1	1		
17	sJIA	M	1	0	1	0	1	1	1	1		
18	sJIA	F	0	0	0	0	2	0	1	na		
Still's case with suspected anakinra reaction (Still's-sAR)												
1	sJIA	M	1	not exposed	0	0	1	0	no atypical rash			

na, not available; 0=absent 1=present, except for eosinophilia, which is coded as per footnote 6; MAS, macrophage activation syndrome; PH, pulmonary hypertension; sJIA, systemic onset juvenile arthritis (Still's onset <16yrs); sJIA-like, does not fulfill sJIA classification criteria and treated as sJIA; AOSD, adult-onset Still's disease sJIA, (Still's onset ≥16yrs)

Footnotes for Table S3a

[1]Clinical features during treatment with the drug implicated in DRESS.

[2]Presence of HLA-DRB1*15:01, *15:03 or *15:06 (see table S1a).

[3]Immediate anaphylactic reaction (not a delayed hypersensitivity reaction) during tocilizumab administration; all subjects discontinued drug. This reaction was not associated with HLA-DRB1*15:01 in White subjects. HLA-DRB1*15:01 6/19 (31%) vs 2/5 (40%) without HLA-DRB1*15:01, p=0.7 OR 0.7 (0.09, 5.29). Other ancestries show the same pattern.

[4]MAS during inhibitor treatment occurred in cases continuing drug after initial DRESS features. Omitted are 4 cases with brief exposure, as indicated (each drug: 4 days-4 weeks); Drug was stopped after DHR DRESS features began, none had MAS.

[5]Fatalities (8/9) occurred during continuation or restart of implicated drug and only in DRESS/DLD cases. Time from DLD to data close ≥7 months. Fatalities occurred with and without the identified risk allele.

[6]1= peak absolute eosinophil count (AEC) > normal limit <1500/ul (eosinophilic); 2= AEC ≥ 1500/ul (hyper-eosinophilic).[33] For Still's-DRESS/DLD and Still's-DRESS/sAR, respectively, median (IQR) peak AEC = 2000/ul (1075,3438) and 1320/ul (955, 2382) and % eosinophils =20% (13,37) and 14% (11,26), despite concurrent steroids in >60% of subjects. Still's-sAR peak AEC 1042 and 15.5% peak eosinophils.

[7]In the absence of MAS, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal on > 1 occasion during inhibitor treatment.

[8]Non-evanescent rash, often intensely pruritic, variably including hyperpigmentation, eczema, angioedema, confluent erythema, serpiginous, vesicular, and flagellate dermatologic patterns. Skin biopsy reports, provided for 12 cases, were all consistent with drug reaction (interface dermatitis, dyskeratosis, eosinophilia (see fig. 2).

[9]Rash involving the face or neck is highly prevalent (in ~80%) in DRESS-type drug reactions.[10,34]

[10]Variant pulmonary alveolar proteinosis/endogenous lipoid pneumonia with notable presence of lymphocytoplasmic infiltrate and vascular changes.[8]

[11]Pulmonary hypertension by echocardiogram or cardiac catheterization.

[12]Time from first feature of DRESS until recognition of DLD: 1 mo-2.3 yrs.

[13]Subjects without atypical rash had uninterrupted high dose steroid treatment.

[14]Median follow-up from first DRESS feature to data close was 3.9 yrs (range 0.2, 8.7).

Table S3b: Clinical features in Still's controls[1]

Subject	Illness	Sex	HLA-DRB1*15	Tocilizumab anaphylaxis[2]	MAS[3]	Fatal	Eosinophilia[4]	AST-ALT elevation[5]	Atypical rash
1	sJIA	M	0	not exposed	0	0	0	0	0
2	sJIA	M	0	not exposed	1	0	0	0	0
3	sJIA	F	0	0	0	0	0	0	0
4	sJIA	M	0	not exposed	0	0	0	0	0
5	sJIA	F	0	not exposed	0	0	0	0	0
6	sJIA	M	0	not exposed	0	0	0	0	0
7	AOSD	F	0	not exposed	0	0	0	0	0
8	sJIA	F	0	not exposed	0	0	0	0	0
9	sJIA	M	0	not exposed	0	0	0	0	0
10	sJIA	F	0	not exposed	0	0	0	0	0
11	sJIA	F	0	not exposed	0	0	0	0	0
12	sJIA	F	0	not exposed	0	0	0	0	0
13	sJIA	F	0	0	0	0	0	1	0
14	sJIA	M	0	0	0	0	0	1	0
15	sJIA	F	0	not exposed	0	0	0	0	0
16	sJIA	F	0	0	0	0	0	0	0
17	sJIA	M	0	not exposed	0	0	0	0	0
18	sJIA	M	0	not exposed	0	0	0	0	0
19	AOSD	F	0	0	0	0	0	0	0
20	sJIA	M	0	0	0	0	0	0	0
21	sJIA	F	0	0	0	0	0	0	0
22	sJIA	F	0	0	0	0	0	0	0
23	sJIA	F	0	0	0	0	0	0	0
24	sJIA	M	0	not exposed	0	0	0	0	0
25	sJIA	F	0	not exposed	0	0	0	0	0
26	sJIA	F	0	0	0	0	0	0	0
27	sJIA	M	0	0	0	0	0	1	0
28	sJIA	F	1	not exposed	0	0	0	0	0
29	sJIA	F	1	not exposed	0	0	0	0	0
30	sJIA	F	0	not exposed	0	0	0	0	0

0=absent 1=present; sJIA, systemic onset juvenile arthritis (Still's onset <16yrs); AOSD, adult-onset Still's disease (Still's onset ≥16yrs); MAS, macrophage activation syndrome

[1]Treated uneventfully for ≥1 yr. Details of definition provided in methods.

[2]Immediate anaphylactic reaction during tocilizumab administration.

[3]Cytokine storm (macrophage activation syndrome) during treatment with inhibitors.

[4]Peak absolute eosinophil count (AEC) > normal limit occurring during treatment with inhibitors.

[5]In the absence of MAS, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the upper limit of normal on >1 occasion during inhibitor treatment.

Table S4a: HLA class II association analysis by logistic regression in Still's-DRESS cases vs. INCHARGE collection

Ancestry-matched by PCA		Subjects with HLA allele of interest			Still's-DRESS cases vs. INCHARGE Still's (sJIA)		Still's-DRESS cases vs. INCHARGE healthy controls	
	Allele	Still's-DRESS	INCHARGE Still's (sJIA)	INCHARGE controls	*P* value	OR (95% CI)	*P* value	OR (95% CI)
European Still's-DRESS vs. European INCHARGE subjects	HLA-DRB1*15:01[1]	13/14 (93%)	130/550 (24%)	822/3279 (25%)	$2.72x10^{-7}$	40.8 (5.3, 316)	$2.77x10^{-7}$	39.2 (5.1, 300.5)
	HLA-DRB1*15:XX	13/14 (93%)	136/550 (25%)	861/3279 (26%)	$4.51x10^{-7}$	38.5 (5.0, 297.7)	$5.08x10^{-7}$	36.8 (4.8, 281.6)
	HLA-DQB1*06:02	13/14 (93%)	128/550 (23%)	806/3279 (25%)	$2.27x10^{-7}$	41.7 (5.4, 322.4)	$2.13x10^{-7}$	40.4 (5.3, 309.1)
	HLA-DQA1*01:02	13/14 (93%)	188/550 (34%)	1148/3279 (35%)	$1.96x10^{-5}$	24.5 (3.2, 189.1)	$1.78x10^{-5}$	24.4 (3.2, 187.1)
	HLA-DRB1*11:01	4/14 (29%)	103/550 (19%)	313/3279 (10%)	0.43		0.095	3.7 (1.1, 11.9)
	HLA-DQB1*03:01	8/14 (57%)	240/550 (44%)	1072/3279 (33%)	0.40		0.12	
Self-reported "White"		**Subjects with HLA allele of interest**			**Still's-DRESS cases vs. INCHARGE Still's (sJIA)**		**Still's-DRESS cases vs. INCHARGE healthy controls**	
"White" Still's-DRESS vs. European INCHARGE subjects	HLA-DRB1*15:01[1]	30/36 (83%)	130/550 (24%)	822/3279 (25%)	$7.46x10^{-13}$	15.5 (6.3, 38.1)	$2.26x10^{-13}$	15.2 (6.3, 36.6)
	HLA-DRB1*15:XX	30/36 (83%)	136/550 (25%)	861/3279 (26%)	$2.00x10^{-12}$	14.7 (6.0, 36.0)	$8.65x10^{-13}$	14.2 (5.9, 34.3)
	HLA-DQB1*06:02	26/33 (79%)	128/550 (23%)	806/3279 (25%)	$1.61x10^{-10}$	11.7 (5.0, 27.7)	$6.27x10^{-11}$	11.6 (5.0, 26.9)
	HLA-DQA1*01:02	24/31 (77%)	188/550 (34%)	1148/3279 (35%)	$1.25x10^{-6}$	6.4 (2.7, 15.3)	$8.14x10^{-7}$	6.5 (2.8, 15.1)
	HLA-DRB1*11:01	7/35 (20%)	103/550 (19%)	313/3279 (10%)	0.051		$1.48x10^{-2}$	2.3 (1.0, 5.2)

HLA, human leukocyte antigen; sJIA, systemic juvenile idiopathic arthritis; DRESS, drug reaction with eosinophilia and systemic symptoms; INCHARGE, International Childhood Arthritis Genetics Consortium[6]; Still's-DRESS, Still's with DRESS; *P* value and OR (95% CI), odds ratio with 95% confidence interval by logistic regression with sex as a covariate; HLA-DRB1*15:XX, all HLA-DRB1*15 alleles.

[1]HLA-DRB1*15:01~DQA1*01:02~DQB1*06:02 haplotype is in near-complete linkage disequilibrium in European populations.[32]

Table S4b: HLA class II association analysis by logistic regression in European Still's-DRESS subjects vs. European INCHARGE Still's (sJIA) cohort

		Still's-DRESS cases (n=14)		INCHARGE Still's (sJIA) (n=550)	
HLA allele[1]	***P*-value[2]**	**Count**	**Frequency**	**Count**	**Frequency**
HLA-DQB1*06:02	2.27E-07	13/14	0.93	128/550	0.23
HLA-DRB1*15:01	2.72E-07	13/14	0.93	130/550	0.24
HLA-DRB1*15	4.51E-07	13/14	0.93	136/550	0.25
HLA-DQA1*01:02	1.96E-05	13/14	0.93	188/550	0.34
HLA-DQB1*06	0.000106	13/14	0.93	219/550	0.4
HLA-DRB1*13:03	0.0893	2/14	0.14	14/550	0.03
HLA-DQB1*02:01	0.14	1/14	0.07	141/550	0.26
HLA-DQA1*03:01	0.20	2/14	0.14	173/550	0.31
HLA-DRB1*04:01	0.28	1/14	0.07	101/550	0.18
HLA-DRB1*11	0.36	6/14	0.43	159/550	0.29
HLA-DRB1*03:01	0.37	2/14	0.14	141/550	0.26
HLA-DQB1*03:01	0.40	8/14	0.57	240/550	0.44
HLA-DRB1*11:01	0.43	4/14	0.29	103/550	0.19
HLA-DRB1*12:01	0.51	1/14	0.07	22/550	0.04
HLA-DQB1*03:02	0.53	2/14	0.14	108/550	0.2
HLA-DRB1*11:04	0.59	1/14	0.07	43/550	0.08
HLA-DRB1*13:02	0.59	1/14	0.07	47/550	0.09
HLA-DRB1*04:04	0.59	1/14	0.07	45/550	0.08
HLA-DQA1*05:01	0.59	8/14	0.57	303/550	0.55
HLA-DQB1*06:04	0.59	1/14	0.07	43/550	0.08

HLA, human leukocyte antigen; sJIA, systemic juvenile idiopathic arthritis; DRESS, drug reaction with eosinophilia and systemic symptoms; INCHARGE, International Childhood Arthritis Genetics Consortium[6]; *P*-value, by logistic regression with sex as a covariate

[1]Class II alleles not observed in European Still's-DRESS subjects or those present in INCHARGE Still's (sJIA) cases at a frequency below 0.01 are not shown.

[2]Significance threshold was defined by Bonferroni correction ($p<2.0 \times 10^{-4}$).

Table S4c:
HLA class I association analysis by logistic regression in European Still's-DRESS cases vs. European INCHARGE Still's (sJIA) cohort

		Still's-DRESS (n=14)		INCHARGE Still's (sJIA) (n=550)	
HLA allele[1]	***P*-value[2]**	**Count**	**Frequency**	**Count**	**Frequency**
HLA-B*07:02	0.0535	7/14	0.50	123/550	0.22
HLA-B*07	0.0550	7/14	0.50	124/550	0.23
HLA-C*07:02	0.0734	7/14	0.50	132/550	0.24
HLA-A*02:01	0.15	4/14	0.29	281/550	0.51
HLA-C*07:01	0.17	2/14	0.14	183/550	0.33
HLA-B*44:02	0.29	1/14	0.07	100/550	0.18
HLA-C*05:01	0.30	1/14	0.07	97/550	0.18
HLA-B*35	0.32	1/14	0.07	91/550	0.17
HLA-A*32	0.354	2/14	0.14	36/550	0.07
HLA-A*32:01	0.35	2/14	0.14	36/550	0.07
HLA-A*24:02	0.37	1/14	0.07	86/550	0.16
HLA-B*35:02	0.38	1/14	0.07	11/550	0.02
HLA-B*08	0.40	2/14	0.14	135/550	0.25
HLA-B*08:01	0.40	2/14	0.14	135/550	0.25
HLA-A*01	0.41	3/14	0.21	177/550	0.32
HLA-A*01:01	0.41	3/14	0.21	177/550	0.32
HLA-A*03	0.42	5/14	0.36	138/550	0.25
HLA-A*02	0.46	6/14	0.43	289/550	0.53
HLA-B*49	0.47	1/14	0.07	18/550	0.03
HLA-B*49:01	0.47	1/14	0.07	18/550	0.03
HLA-B*39:01	0.47	1/14	0.07	18/550	0.03
HLA-C*07	0.49	9/14	0.64	311/550	0.57
HLA-B*15	0.49	1/14	0.07	70/550	0.13
HLA-C*03:03	0.50	2/14	0.14	54/550	0.10
HLA-B*38	0.50	1/14	0.07	21/550	0.04
HLA-B*38:01	0.50	1/14	0.07	21/550	0.04
HLA-A*24	0.51	3/14	0.21	86/550	0.16
HLA-B*51:01	0.52	1/14	0.07	60/550	0.11
HLA-B*18	0.52	1/14	0.07	62/550	0.11
HLA-B*18:01	0.52	1/14	0.07	62/550	0.11
HLA-C*03	0.52	4/14	0.29	130/550	0.24
HLA-A*26	0.52	1/14	0.07	24/550	0.04
HLA-A*26:01	0.52	1/14	0.07	24/550	0.04
HLA-B*27	0.53	2/14	0.14	54/550	0.10
HLA-B*40:01	0.53	2/14	0.14	59/550	0.11
HLA-C*12:03	0.53	2/14	0.14	55/550	0.10
HLA-C*15:02	0.53	1/14	0.07	25/550	0.05
HLA-B*15:01	0.54	1/14	0.07	62/550	0.11
HLA-A*30	0.54	1/14	0.07	24/550	0.04
HLA-B*39	0.54	1/14	0.07	24/550	0.04
HLA-B*44	0.54	3/14	0.21	145/550	0.26
HLA-B*37	0.55	1/14	0.07	26/550	0.05
HLA-B*37:01	0.55	1/14	0.07	26/550	0.05
HLA-C*06	0.55	2/14	0.14	100/550	0.18
HLA-C*06:02	0.55	2/14	0.14	100/550	0.18
HLA-C*05	0.56	2/14	0.14	97/550	0.18
HLA-C*15	0.56	1/14	0.07	28/550	0.05
HLA-B*27:05	0.56	1/14	0.07	53/550	0.10
HLA-B*51	0.56	2/14	0.14	60/550	0.11
HLA-A*31:01	0.56	1/14	0.07	29/550	0.05
HLA-C*12	0.57	2/14	0.14	63/550	0.11
HLA-A*31	0.57	1/14	0.07	30/550	0.05
HLA-A*11	0.57	2/14	0.14	66/550	0.12
HLA-A*03:01	0.57	4/14	0.29	137/550	0.25
HLA-C*04	0.58	3/14	0.21	101/550	0.18
HLA-C*01	0.58	1/14	0.07	46/550	0.08
HLA-A*29	0.59	1/14	0.07	35/550	0.06
HLA-C*16	0.59	1/14	0.07	44/550	0.08
HLA-B*40	0.59	2/14	0.14	78/550	0.14
HLA-C*03:04	0.59	2/14	0.14	79/550	0.14

HLA, human leukocyte antigen; sJIA, systemic juvenile idiopathic arthritis; DRESS, drug reaction with eosinophilia and systemic symptoms; INCHARGE, International Childhood Arthritis Genetics Consortium[6]; *P*-value, by logistic regression with sex as a covariate

[1]Class I alleles not observed in European Still's-DRESS subjects or those present in INCHARGE Still's (sJIA) cases at a frequency below 0.01 are not shown. [2]Significance threshold was defined by Bonferroni correction ($p<2.0 \times 10^{-4}$).

Table S5: Still's (sJIA)-DRESS cases versus Still's (sJIA) controls (Still's (sJIA) = onset <age 16y) [1]

	Still's (sJIA)-DRESS cases	Still's (sJIA) controls	*P* value	OR (95%CI)
HLA-DRB1*15:01[2]	88% (30/34)	0% (0/17)	4×10^{-10}	Lower bound 18.9
During drug treatment				
eosinophilia[3]	91% (52/57)[4]	0% (0/28)	1×10^{-17}	Lower bound 48.8
elevated LFTs[3]	71% (42/59)	7% (2/28)	9×10^{-9}	30.7 (6.5-293.0)
MAS[3]	56% (35/54)[5]	4% (1/28)	2×10^{-8}	47.5 (6.8-2068)

[1]Subjects are those with HLA data and Still's onset <16 years of age). 8 AOSD subjects (6 Still's-DRESS cases and 2 Still's controls) are removed. [2]Only White Still's (sJIA) subjects are analyzed for association with DRB1*15:01; [3]All ancestry; [4]Cases (n=5) without eosinophilia were on uninterrupted corticosteroid treatment. Data were unavailable for 2 cases. [5]Three drug-reactive cases were unevaluable because treatment was stopped in <4 weeks. *P* values and odds ratio (95% CI) were obtained from Fisher's exact test.

Table S6: HLA-DRB1 allele groups in White Still's-DRESS cases versus White Still's controls

Allele	**DRB1*01:**		**DRB1*03:**		**DRB1*04:**		**DRB1*07:**		**DRB1*08:**			
Present	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**		
Cases (n=36)	4	32	2	34	4	32	1	35	2	34		
Controls (n=19)	4	15	6	13	9	10	4	15	1	18		
***P*, uncorrected**	0.426		0.0156		0.0058		0.0435		1.00			
OR (95%CI)	0.476 [0.08, 2.92]		0.133 [0.01, 0.86]		0.145 [0.03, 0.65]		0.112 [0.002, 1.25]		1.058 [0.05, 65.87]			
Allele	**DRB1*09:**		**DRB1*11:[1]**		**DRB1*12:**		**DRB1*13:**		**DRB1*14:**		**DRB1*15: DRESS risk**	
Present	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**No**	**yes**	**no**
Cases (n=36)	0	36	12	24	1	35	4	32	1	35	30	6
Controls (n=19)	0	19	5	14	0	19	6	13	1	18	0	19
***P*, uncorrected**	1.00		0.761		1.00		0.0774		1.00		6.312×10^{-10}	
OR (95%CI)	NA [0, +∞]		1.392 [0.36, 6.14]		+∞ [0.01, +∞]		0.278 [0.05, 1.39]		0.521 [0.006, 42.59]		+∞ [16.05, +∞]	
***P*, corrected[2]**											6.943×10^{-9}	

OR (95% CI), odds ratio and 95% confidence interval by Fisher's exact test*; P*, uncorrected, p value by Fisher exact test prior to correction for multiple comparisons; *P*, corrected, p value after Bonferroni correction.

[1]HLA-DRB1*11 is sJIA disease-associated in subjects of European descent.[24]

[2]The Bonferroni corrected *P*-value (adjusting for 11 tests) is highly significant for DRB1*15. All other HLA-DR lack significant association with DRESS after correction.

Table S7a: HLA-DQ, HLA-DR and clinical features in Kawasaki disease cases and controls

Subject	Ancestry[1]	DQA1	DQB1	DRB1	DRB3/4/5/Absent
Kawasaki disease cases with features of suspected anakinra reaction (KD-sAR)[2]					
1	White	*01:02/*03:01	*06:02/*03:02	*15:01/*04:02	DRB5*01:01/DRB4*01:03
2	White	*01:01/*05:05	*03:01/*05:01	*01:01/*12:01	Absent/DRB3*02:02
3	Hispanic	*01:02/*01:01	*06:02/*05:01	*15:03/*01:01	DRB5*01:01/Absent
4	White/Asian	*01:02/*05:05	*06:02/*03:01	*15:01/*13:03	DRB5*01:01/DRB3*01:01
Kawasaki disease controls-anakinra tolerant					
1	White	*03:01/*03:01	*03:02/*03:02	*04:01/*04:01	DRB4*01:03/DRB4*01:03
2	Hispanic	*03:01/*05:05	*03:01/*03:02	*01:03/*04:02	DRB4*01:03/Absent
3	Hispanic	*01:01/*05:01	*02:01/*05:01	*01:03/*03:01	Absent/DRB3*02:02
4	Hispanic	*03:03/*04:01	*03:02/*04:02	*04:05/*08:02	DRB4*01:03/Absent
5	Hispanic	*02:01/*05:05	*02:02/*03:01	*07:01/*16:02	DRB4*01:03/DRB5*02:02
6	Hispanic	*01:03/*03:01	*03:02/*06:02	*04:07/*13:01	DRB3*02:02/DRB4*01:03
7	Hispanic	*04:01/*05:05	*03:01/*04:02	*08:02/*16:02	Absent/DRB5*02:02
8	Hispanic	*03:01/*04:01	*03:02/*04:02	*03:02/*04:04	DRB3*01:62/DRB4*01:03
9	Hispanic/White	*05:01/*05:05	*02:01/*03:01	*03:01/*16:02	DRB3*01:01/DRB5*02:02
10	Asian	*01:03/*01:03	*06:01/*06:03	*08:03/*13:01	Absent/DRB3*01:01
11	Asian	*01:02/*05:01	*02:01/*05:02	*03:01/*15:02	DRB5*01:01/DRB3*02:02
12	Asian	*01:03/*06:01	*03:01/*06:01	*12:02/*15:02	DRB5*01:02/DRB3*03:01
13	Asian/White	*03:01/*05:01	*02:01/*03:02	*03:01/*04:03	DRB3*02:02/DRB4*01:03
14	Black	*03:01/*03:03	*03:01/*03:02	*04:01/*04:04	DRB4*01:03/DRB4*01:03
15	Black	*01:02/*02:01	*02:02/*05:02	*13:03/*16:02	DRB3*02:02/DRB5*02:21

Subject	Sex[3]	HLA-DRB1*15[4]	Anakinra duration (days)	Atypical lymphocytes[5]	Eosinophilia[6]	Atypical rash[7]	Face or neck rash[8]
Kawasaki disease cases developing features of DHR during anakinra treatment (KD-sAR)[2]							
1	M	1	39	1	1	0	0
2	M	0	41	1	1	0	0
3	M	1	42	1	1	1	1
4	M	1	13	0	1	0	0
Kawasaki disease controls-anakinra tolerant							
1	M	0	9	0	0	0	
2	M	0	41	0	0	0	
3	M	0	41	0	0	0	
4	M	0	17	0	0	0	
5	M	0	37	0	0	0	
6	M	0	10	0	0	0	
7	M	0	39	0	0	0	
8	M	0	11	1	0	0	
9	M	0	13	0	0	0	
10	M	0	46	0	0	0	
11	F	1	28	0	0	0	
12	F	1	12	0	0	0	
13	F	0	41	0	0	0	
14	M	0	43	0	0	0	
15	M	0	16	0	0	0	

0=absent, 1=present, except for eosinophilia, coded as per footnote 6; KD-sAR, Kawasaki disease with suspected anakinra reaction

[1]Ancestry self-identification as White, Hispanic, South Asian, Asian or Black, with mixed parentage noted.

[2]Data were incomplete for scoring by RegiSCAR for DRESS. Definition for suspected anakinra reaction is in methods.

[3]No significant difference in sex frequency between KD-sAR and KD-anakinra tolerant [M vs F OR 0.5 (95% CI 0.02,11.4), p=0.66]

[4]Presence of HLA-DRB1*15:01, *15:02, *15:03 or *15:06.

[5]Atypical lymphocytes were >2% of WBC and increase >2% from value prior to anakinra.

[6]1=AEC ≥ 500 and elevated over baseline study value (eosinophilic); 2=AEC ≥ 1500/ul and elevated over baseline study value (hyper-eosinophilic).[31] AEC ranged from 630/ul to 1071/ul.

[7]Non-evanescent rash began during anakinra treatment, described as intensely pruritic with erythema and localized swelling.

[8]Rash involving the face or neck is highly prevalent (noted in ~80%) in DRESS type drug reactions.[10,34]

Table S7b: HLA-A, HLA-B, HLA-C Kawasaki disease cases and controls

Subject	Ancestry	HLA-A_1	HLA-A_2	HLA-B_1	HLA-B_2	HLA-C_1	HLA-C_2
Kawasaki disease cases with features of suspected anakinra reaction (KD-sAR)							
1	White	A*03:01:01:01	A*11:01:01:01	B*07:02:01:01	B*35:01:01:05	C*04:01:01:06	C*07:02:01:03
2	White	A*02:01:01:01	A*11:01:01:01	B*27:05:02:05	B*35:03:01:03	C*01:02:01:01	C*04:01:01:01
3	Hispanic	A*11:01:01:01	A*68:02:01:01	B*27:05:02:05	B*49:01:01:01	C*01:02:01:01	C*03:04:02
4	White/Asian	A*01:01:01:01	A*24:02:01:01	B*07:02:01:01	B*44:03:02	C*07:02:01:03	C*07:06:01:01
Kawasaki disease controls-anakinra tolerant							
1	White	A*24:02:01:01	A*24:02:01:01	B*15:01:01:01	B*18:01:01:02	C*03:03:01:01	C*05:01:01:02
2	Hispanic	A*01:01:01:01	A*03:01:01:01	B*18:01:01:02	B*44:02:01:01	C*05:01:01:02	C*07:01:01:01
3	Hispanic	A*02:01:01:01	A*26:01:01:01	B*07:02:01:01	B*58:01:01:03	C*03:02:02:05	C*07:02:01:03
4	Hispanic	A*02:01:01:01	A*02:01:01:01	B*35:08:01:01	B*35:12:01	C*04:01:01:01	C*04:01:01:14
5	Hispanic	A*02:06:01:01	A*23:01:01:01	B*08:01:01:01	B*35:14:01	C*03:04:01:12	C*04:01:01:01
6	Hispanic	A*03:01:01:01	A*31:02:01	B*35:01:01:07	B*52:01:02:01	C*03:03:01:01	C*06:02:01:01
7	Hispanic	A*02:06:01:01	A*24:02:01:01	B*15:01:01:01	B*35:16	C*01:02:01:01	C*04:01:01:01
8	Hispanic	A*30:01:01:01	A*31:01:02:01	B*42:01:01	B*51:01:01:05	C*15:09	C*17:01:01:02
9	Hispanic/White	A*01:01:01:01	A*31:01:02:01	B*08:01:01:01	B*35:49	C*04:01:01:01	C*07:01:01:01
10	Asian	A*03:01:01:01	A*24:02:01:01	B*44:02:01:01	B*54:01:01	C*01:02:01:05	C*05:01:01:02
11	Asian	A*24:07:01	A*33:03:01:01	B*38:02:01	B*58:01:01:03	C*03:02:02:05	C*07:02:01:01
12	Asian	A*11:01:01:01	A*24:02:01:01	B*15:02:01:01	B*52:01:01:02	C*08:01:01:01	C*12:02:02:01
13	Asian/White	A*11:01:01:01	A*24:02:01:01	B*40:01:02:01	B*50:01:01:01	C*04:82	C*06:02:01:02
14	Black	A*02:01:01:01	A*02:01:01:01	B*07:02:01:01	B*44:02:01:01	C*05:01:01:02	C*07:02:01:03
15	Black	A*02:05:01:01	A*30:02:01:02	B*15:16:01:02	B*57:03:01:01	C*14:02:01:02	C*18:02:01

Table S8: Published case reports of delayed drug reactions implicating IL-1 or IL-6 inhibitors

Age /Sex	Ancestry	Condition (inciting drug)	Eosinophilia	Rash	SCAR	other organs	Outcome[1]	Ref
48M	White	rheumatoid arthritis (A)	1	1	0	liver	resolved	35
adult F	NA	rheumatoid arthritis (T)	1	1	DRESS	GI, liver	resolved	36
52F	NA	rheumatoid arthritis (T)	1	1	0	GI	resolved	37
69F	NA	rheumatoid arthritis (T)	1	1	0	none	resolved	38[2]
53F	NA	rheumatoid arthritis (A)	skin biopsy	1	0	none	resolved	38[2]
38F	NA	rheumatoid arthritis (A)	skin biopsy	1	dDHRs	Respiratory, GI	resolved	39
69F	NA	polyarthritis (T)	1	1	DRESS	HLH	fatal	40
55F	NA	adult-onset Still's disease (T)	1	1	DRESS	liver	resolved	41
70M	White	COVID-19 cytokine storm (T)	1	1	0	none	resolved	42
82F	Black	giant cell arteritis (T)	na	1	SJS	oral pharynx	resolved	43
12F	NA	polyarticular arthritis (T)	1	1	0	fascia	sclerotic skin lesions	44
2F	White	autoinflammatory disorder (A)	1	1	DRESS	liver, HHV6+	resolved	45
2F	Black	autoinflammatory disorder (C)	1	1	DRESS	lymph nodes	resolved	45
2F	White	autoinflammatory disorder (C)	1	1	DRESS	lung, MAS	improved lung disease	46
15F	White	autoimmune disorder (C)	0	1	DRESS	lymph nodes	resolved	na[3]

1= present, 0= absent; na, not available

Age, in years; Ancestry, self-identified; A, anakinra; T, tocilizumab; C, canakinumab; SCAR, severe cutaneous adverse reaction; DRESS, Drug reaction with eosinophilia and systemic symptoms: dDHRs, drug-related delayed hypersensitivity reaction with systemic involvement; SJS, Stevens-Johnson Syndrome; HLH hemophagocytic lymphohistiocytosis; HHV6+, human herpes virus 6 reactivation; MAS, macrophage activation syndrome

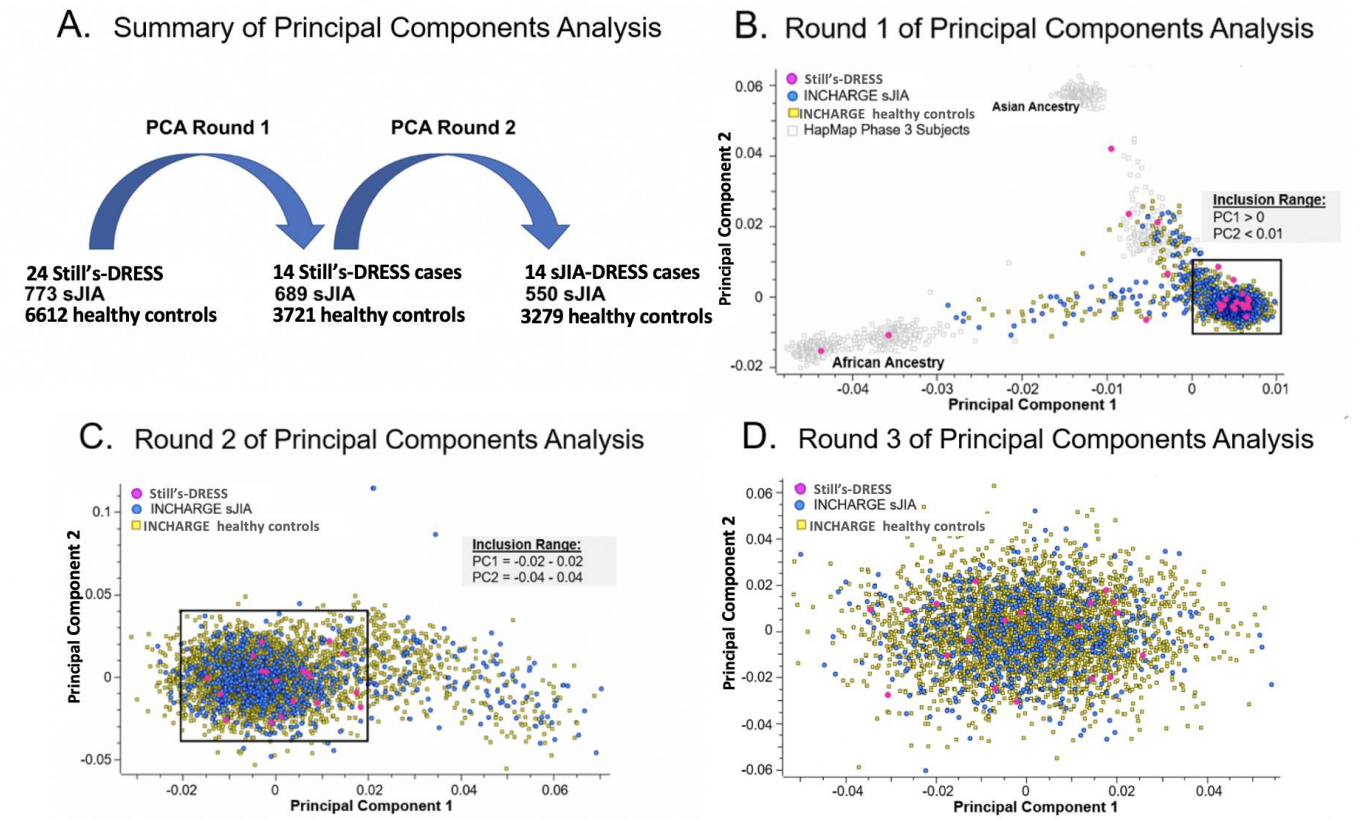
[1]Drug was withdrawn in all cases shown; outcome reported ≥ 1 month after drug withdrawal.

[2]Report of five cases with anakinra rash, each with skin biopsy showing prominent eosinophilia. Included here are cases stopping drug due to reaction.

[3] This is a new case in our collection with an undifferentiated autoimmune disorder associated with multiple auto-antibodies who developed a diffuse pruritic, erythrodermic rash with clusters of non-herpetic vesicles, facial swelling, fever, gastrointestinal symptoms, diffuse lymphadenopathy and negative evaluation for infection, occurring 2 weeks after initial dose of canakinumab. HLA typing found HLA-DRB1*15:01.

Supplementary Figures

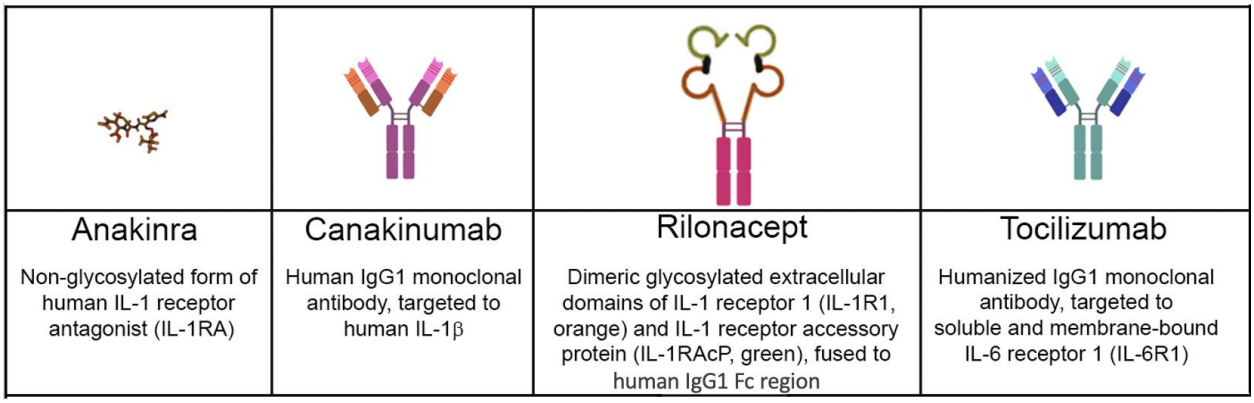
Figure S1



PCA, principal components analysis; sJIA, systemic onset juvenile idiopathic arthritis; DRESS, drug reaction with eosinophilia and systemic symptoms; INCHARGE, International Childhood Arthritis Genetics Consortium[6]; GWAS, genome wide association study.

Supplementary Figure 1. Ancestral matching of INCHARGE Still's (sJIA) GWAS cases and healthy controls with Still's-DRESS cases by principal component analysis. Panel **(A)** shows sample accounting through the principal component analysis**. (B)** Principal components (PCs) were calculated using a linkage disequilibrium reduced set of intersecting SNPs between Still's-DRESS subjects (pink circles), INCHARGE Still's (sJIA) cases (blue circles) and healthy controls (yellow circles), and subjects from the HapMap3[47] populations (grey boxes). PCs were plotted to identify subjects of European ancestry, marked by the black box, which were carried forward into round 2. **(C)** The second round of PCs were calculated for this reduced set of subjects and were plotted to exclude additional ancestrally dissimilar subjects**. (D)** The third round of PCs were calculated for the subset of subjects defined by round 2, and round 3 PCs were plotted to examine the structure of the final study population. Genomic control inflation factors were calculated for Still's-DRESS vs. Still's (sJIA) GWAS (λ_{GC}=1·0142) and Still's-DRESS vs. GWAS healthy controls (λ_{GC}=1·048) and indicated robust matching.

Figure S2



Supplementary Figure 2. Chemical structures of cytokine inhibitors implicated in HLA-DRB1*15 associated DRESS. Shown are diagrams of the structures of IL-1 inhibitors (anakinra, canakinumab, rilonacept) and an IL-6 inhibitor (tocilizumab), as described in references[48-51] respectively. The diagrams reflect the relative sizes of the molecules, with the anakinra structure shown at 3X magnification to be visible. Anakinra blocks the biologic activity of IL-1α and IL-1β by competitive inhibition of their binding to IL-1R1. Rilonacept acts as a decoy receptor ("trap") for IL-1β and, with lesser affinity, binds endogenous IL-1RA and IL-1α. Canakinumab binds IL-1β only, and tocilizumab inhibits IL-6 activity by blocking its binding to IL-6R1.

References for supplementary information

1. DeWitt EM, Kimura Y, Beukelman T, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2012;64(7):1001-10. doi: 10.1002/acr.21625
2. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992;19(3):424-30.
3. Inoue N, Shimizu M, Tsunoda S, et al. Cytokine profile in adult-onset Still's disease: Comparison with systemic juvenile idiopathic arthritis. *Clinical Immunology* 2016;169:8-13. doi: https://doi.org/10.1016/j.clim.2016.05.010
4. Tremoulet AH, Jain S, Kim S, et al. Rationale and study design for a phase I/IIa trial of anakinra in children with Kawasaki disease and early coronary artery abnormalities (the ANAKID trial). *Contemp Clin Trials* 2016;48:70-5. doi: 10.1016/j.cct.2016.04.002
5. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;135(17):e927-e99. doi: 10.1161/CIR.0000000000000484
6. Ombrello MJ, Arthur VL, Remmers EF, et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. *Ann Rheum Dis* 2017;76(5):906-13. doi: 10.1136/annrheumdis-2016-210324
7. The Stanford REDCap platform (http://redcap.stanford.edu) is developed and operated by Stanford Medicine Research IT team. The REDCap platform services at Stanford are subsidized by a) Stanford School of Medicine Research Office, and b) the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TR001085.
8. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol* 2013;169(5):1071-80. doi: 10.1111/bjd.12501
9. Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis* 2019;78(12):1722-31. doi: 10.1136/annrheumdis-2019-216040
10. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156(3):609-11. doi: 10.1111/j.1365-2133.2006.07704.x

11. Kardaun SH, Mockenhaupt M, Roujeau JC. Comments on: DRESS syndrome. *J Am Acad Dermatol* 2014;71(5):1000-00.e2. doi: 10.1016/j.jaad.2013.11.053
12. Taweesedt PT, Nordstrom CW, Stoeckel J, et al. Pulmonary Manifestations of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Systematic Review. *Biomed Res Int* 2019;2019:7863815. doi: 10.1155/2019/7863815
13. Kim GY, Anderson KR, Davis DMR, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) in the pediatric population: A systematic review of the literature. *J Am Acad Dermatol* 2020 doi: 10.1016/j.jaad.2020.03.081
14. Gurion R, Lehman TJ, Moorthy LN. Systemic arthritis in children: a review of clinical presentation and treatment. *Int J Inflam* 2012;2012:271569. doi: 10.1155/2012/271569
15. Tamaki H, Chatterjee S, Langford CA. Eosinophilia in Rheumatologic/Vascular Disorders. *Immunol Allergy Clin North Am* 2015;35(3):453-76. doi: 10.1016/j.iac.2015.05.001
16. Wang C, Krishnakumar S, Wilhelmy J, et al. High-throughput, high-fidelity HLA genotyping with deep sequencing. *Proc Natl Acad Sci U S A* 2012;109(22):8676-81. doi: 10.1073/pnas.1206614109
17. Thorstenson YR, Creary LE, Huang H, et al. Allelic resolution NGS HLA typing of Class I and Class II loci and haplotypes in Cape Town, South Africa. *Hum Immunol* 2018;79(12):839-47. doi: 10.1016/j.humimm.2018.09.004
18. Huang Y, Yang J, Ying D, et al. HLAreporter: a tool for HLA typing from next generation sequencing data. *Genome Med* 2015;7(1):25. doi: 10.1186/s13073-015-0145-3
19. Li H, Durbin R. Fast and accurate long-read alignment with Burrows-Wheeler transform. *Bioinformatics* 2010;26(5):589-95. doi: 10.1093/bioinformatics/btp698
20. Warren RL, Holt RA. Targeted assembly of short sequence reads. *PLoS One* 2011;6(5):e19816. doi: 10.1371/journal.pone.0019816
21. Dilthey AT, Mentzer AJ, Carapito R, et al. HLA*LA-HLA typing from linearly projected graph alignments. *Bioinformatics* 2019;35(21):4394-96. doi: 10.1093/bioinformatics/btz235
22. Li H. Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM. *ArXiv e-prints* 2013. https://ui.adsabs.harvard.edu/#abs/2013arXiv1303.3997L (accessed March 01, 2013).
23. Delcher AL, Phillippy A, Carlton J, et al. Fast algorithms for large-scale genome alignment and comparison. *Nucleic Acids Res* 2002;30(11):2478-83. doi: 10.1093/nar/30.11.2478
24. Ombrello MJ, Remmers EF, Tachmazidou I, et al. HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. *Proc Natl Acad Sci U S A* 2015;112(52):15970-5. doi: 10.1073/pnas.1520779112
25. R: A language and environment for statistical computing [program]. Vienna, Austria: R Foundation for Statistical Computing, 2018.
26. Aragon T. epitools: Epidemiology Tools. R package version 0.5-7. 2012 ed.
27. Degenhardt F, Wendorff M, Wittig M, et al. Construction and benchmarking of a multi-ethnic reference panel for the imputation of HLA class I and II alleles. *Hum Mol Genet* 2019;28(12):2078-92. doi: 10.1093/hmg/ddy443
28. Creary LE, Gangavarapu S, Mallempati KC, et al. Next-generation sequencing reveals new information about HLA allele and haplotype diversity in a large European American population. *Hum Immunol* 2019;80(10):807-22. doi: 10.1016/j.humimm.2019.07.275
29. Creary LE, Mallempati KC, Gangavarapu S, et al. Deconstruction of HLA-DRB1*04:01:01 and HLA-DRB1*15:01:01 class II haplotypes using next-generation sequencing in European-Americans with multiple sclerosis. *Mult Scler* 2019;25(6):772-82. doi: 10.1177/1352458518770019
30. de Bakker PI, McVean G, Sabeti PC, et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. *Nat Genet* 2006;38(10):1166-72. doi: 10.1038/ng1885
31. Abou Taam R, Jaubert F, Emond S, et al. Familial interstitial disease with I73T mutation: A mid- and long-term study. *Pediatr Pulmonol* 2009;44(2):167-75. doi: 10.1002/ppul.20970
32. Maiers M, Gragert L, Klitz W. High-resolution HLA alleles and haplotypes in the United States population. *Hum Immunol* 2007;68(9):779-88. doi: 10.1016/j.humimm.2007.04.005
33. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol* 2019;94(10):1149-67. doi: 10.1002/ajh.25617
34. Cho YT, Yang CW, Chu CY. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System. *Int J Mol Sci* 2017;18(6) doi: 10.3390/ijms18061243
35. Lungoci ER, Hacard F, Nicolas JF, et al. Anakinra delayed skin allergy expressing as both injection site reactions and generalized exanthema. *Eur J Dermatol* 2015;25(5):503-4. doi: 10.1684/ejd.2015.2624
36. Massolino RI, Hissaria P, Lee A, et al. Tocilizumab-induced drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient with rheumatoid arthritis. *Rheumatol Adv Pract* 2018;2(2):rky029. doi: 10.1093/rap/rky029
37. Morrisroe K, Wong M. Drug-induced hypereosinophilia related to tocilizumab therapy for rheumatoid arthritis. *Rheumatology (Oxford)* 2015;54(11):2113-4. doi: 10.1093/rheumatology/kev275
38. Vila AT, Puig L, Fernández-Figueras MT, et al. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005;153(2):417-23. doi: 10.1111/j.1365-2133.2005.06635.x
39. Mori T, Yamamoto T. Tocilizumab-induced pustular drug eruption. *Int J Rheum Dis* 2017;20(11):1776-77. doi: 10.1111/1756-185X.12658
40. Ben Said B, Gerfaud-Valentin M, Seve P. Fatal DRESS syndrome under tocilizumab treatment for seronegative polyarthritis. *J Allergy Clin Immunol Pract* 2018;6(3):1048-49. doi: 10.1016/j.jaip.2017.08.041

41. Zuelgaray E, Domont F, Peiffer-Smadja N, et al. Tocilizumab-Induced Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome in Adult-Onset Still Disease. *Ann Intern Med* 2017;167(2):141-42. doi: 10.7326/L16-0592
42. Sernicola A, Carnicelli G, Di Fraia M, et al. 'Toxic erythema' and eosinophilia associated with tocilizumab therapy in a COVID-19 patient. *Journal of the European Academy of Dermatology and Venereology* 2020;34(8):e368-e70. doi: https://doi.org/10.1111/jdv.16620
43. Venkateswaran N, Khianey R, Generoso A. Stevens Johnson Syndrome in a Patient with Giant Cell Arteritis During Short Term Tocilizumab Therapy. *Cureus* 2020;12(4):e7662-e62. doi: 10.7759/cureus.7662
44. Aeschlimann FA, Dumaine C, Wörner A, et al. Serious adverse events in children with juvenile idiopathic arthritis and other rheumatic diseases on tocilizumab - a real-world experience. *Semin Arthritis Rheum* 2020;50(4):744-48. doi: 10.1016/j.semarthrit.2020.05.013
45. Polivka L, Diana JS, Soria A, et al. Probable DRESS syndrome induced by IL-1 inhibitors. *Orphanet J Rare Dis* 2017;12(1):87. doi: 10.1186/s13023-017-0645-x s
46. Bader-Meunier B, Hadchouel A, Berteloot L, et al. Effectiveness and safety of ruxolitinib for the treatment of refractory systemic idiopathic juvenile arthritis like associated with interstitial lung disease : a case report. *Ann Rheum Dis* 2020 doi: 10.1136/annrheumdis-2020-216983
47. Altshuler DM, Gibbs RA, Peltonen L, et al. Integrating common and rare genetic variation in diverse human populations. *Nature* 2010;467(7311):52-8. doi: 10.1038/nature09298
48. Kopf M, Bachmann MF, Marsland BJ. Averting inflammation by targeting the cytokine environment. *Nat Rev Drug Discov* 2010;9(9):703-18. doi: 10.1038/nrd2805
49. Dhimolea E. Canakinumab. *MAbs* 2010;2(1):3-13. doi: 10.4161/mabs.2.1.10328 [published Online First: 2010/01/15]
50. Hoffman HM, Yasothan U, Kirkpatrick P. Rilonacept. *Nature Reviews Drug Discovery* 2008;7(5):385-86. doi: 10.1038/nrd2579
51. Oldfield V, Dhillon S, Plosker GL. Tocilizumab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2009;69(5):609-32. doi: 10.2165/00003495-200969050-00007