of walls, fibrosis, dilatation and nonspecific symptoms such as fever, hypertension and arthralgia. It is a rare disorder with unknown etiology and the worldwide incidence is 0.4 to 2.6 per million.

Objectives: We studied three consanguineous families with consisting of two affected daughters each and their healthy parents in order to identify the disease locus and the causative mutation

Methods: In two of the families, genome-wide single nucleotide polymorphism (SNP) genotyping was performed for available family members using Illumina OmniExpress-24 BeadChip targeting ~700,000 SNP markers. Using genotyping data, we performed multipoint parametric linkage analysis assuming recessive inheritance and complete penetrance. Also exome sequencing was performed for four of the patients to search for rare, homozygous deleterious variants. For TA1 and TA2 families whether the variants were located in a region IBD (identical by descent) in affected sisters or not was investigated.

Results: Whole genome linkage and exome analyses identified homozygous, rare (MAF <0.01) candidate variants shared by the affected sister pairs in the first two families. Candidate variants for the first family were in *ANXA8L1*, *EHBP1L1*, *TULP2*, *MYH14* and *SHANK1* and for the second family in *AP4B1*, *RIMBP3*, *VCX3B* and *NXF2*. In the third family, no candidate homozygous variant was common for the affected sibs, who had different fathers. *In silico* functional predictions of the candidate variants shared by each sister-pair were determined.

Abstract THU0005 – Table 1. *In silico* functional predictions of candidate variants

Family	Gene	Change	SIFT	PolyPhen2	MutationTaster
TA1	<i>ANXA8L1</i>	c.449C>T (p. T150M)	Deleterious	Probably damaging	Disease Causing
	<i>EHBP1L1</i>	c.3595C>T (p.R1199C)	Deleterious	Probably damaging	Polymorphism
	<i>TULP2</i>	c.1300T>C (p.Y434H)	Tolerated	Benign	Polymorphism
	<i>MYH14</i>	c.565C>T (p.R189C)	Deleterious	Probably damaging	Disease Causing
	<i>SHANK1</i>	c.3947G>A (p.G1316D)	Tolerated	Possibly damaging	Disease Causing
TA2	<i>AP4B1</i>	c.263C>T (p.T88I)	Tolerated	Benign	Disease Causing
	<i>RIMBP3</i>	c.3788A>C (p. E1263A)	Tolerated	Benign	Polymorphism
	<i>VCX3B</i>	c.44A>G (p.K15R)	Tolerated	Possibly damaging	Polymorphism
	<i>NXF2</i>	c.1301+1G>A	-	-	Disease Causing

Conclusions: This is the first whole genome linkage analysis and subsequent exome sequencing in TA patients with suggestive recessive inheritance. Possible candidate variants in two out of the three families were determined. However, we could not find any genetic change in terms of genetic mutations, exonic deletions or structural variations shared by these families. We had hoped that the study in these rare families with a pair of TA sibs would unravel a gene responsible for TA. We now question whether the inheritance is dominant with reduced penetrance which requires more familial cases to be studied.

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THU0006

APPLICATION OF MACHINE LEARNING METHODS FOR PREDICTION MODELLING OF PSORIATIC ARTHRITIS IN PATIENTS WITH PSORIASIS

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Background: Approximately 30% of patients with psoriasis develop a chronic inflammatory arthritis referred to as psoriatic arthritis (PsA). The ability to accurately predict which psoriasis patients will develop PsA would enable early intervention and help prevent disability. Both psoriasis and PsA have a substantial genetic risk component, however the utility of using genetic risk factors for the prediction of PsA is currently unknown. Alleles of the human leukocyte antigen (HLA) genes represent the largest genetic effects observed for both psoriasis and PsA (HLA-C*0602 and HLA-B*27 respectively); these genes are highly polymorphic with extensive linkage disequilibrium (LD) which will make variable (feature) selection using statistical models very challenging. Machine learning methods, such as information theoretic criteria, are well suited to this challenge and will find a subset of the original variables that enable more accurate prediction.

Objectives: To apply machine learning methods for feature selection of HLA alleles and evaluate the accuracy of these feature for the prediction of PsA.

Methods: Feature selection was performed using information theoretic criteria methods which are classifier independent methods that provide a ranking of genetic features that differentiate PsA from cutaneous-only psoriasis. Multiple methods were tested; mutual information maximisation (MIM), joint mutual information (JMI), minimal-Redundancy-Maximal-Relevance (mRMR) and conditional mutual information maximisation (CMIM). Two principal components (population stratification) and age of psoriasis onset were included as potential confounders. The Bagged Trees method was used for classification and the performance of the predictive models were assessed using area under the receiver operating characteristic curve. These methods were applied to a dataset of 1462 PsA cases and 1132 cutaneous-only psoriasis cases using 2-digit and 4-digit classical HLA alleles imputed using the SNP2HLA algorithm.

Results: The single most important features based on rank were identified as HLA-B*27 (2-digit) and HLA-B*2705 (4-digit) by the four different feature selection techniques; this is consistent with previous analyses of this data using regression based methods. However, the predictive accuracy of these single features was found to be poor (AUC 0.55 HLA-B*27). Sequentially adding additional HLA features based on rank substantially improved the performance of the classification model where 20 2-digit features selected by JMI demonstrated an average AUC of 0.84 based on 10 cross-fold validation (figure 1).

Conclusions: The results demonstrate that classification models constructed from multiple HLA alleles substantially outperform classification based solely on

the previously reported PsA risk allele (HLA-B*27). Importantly, the study demonstrates that this additional information is efficiently captured using information theoretic criteria methods which capture correlations between markers.

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THU0007 GENETIC VARIANTS IN SLE SUSCEPTIBILITY LOCI, XKR6 AND GLT1D1, ARE ASSOCIATED WITH CHILDHOOD-ONSET SLE IN A KOREAN COHORT

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Background: Systemic lupus erythematosus (SLE) is a polygenic autoimmune disease that occurs in all ages. It has been well documented that younger age of SLE onset is associated with more severe clinical manifestations and worse outcomes. However, impact of genetic variants on age of SLE onset was not fully understood.

Objectives: We investigated a cumulative effect of reported SLE-risk variants on childhood-onset SLE and searched for new risk loci of childhood-onset SLE using a genome-wide SNP analysis.

Methods: We analysed 96 Korean childhood-onset (<16 years old) and 685 adult-onset SLE (≥16 years old) who were previously genotyped by both Immunochip and genome-wide SNP arrays. Individual genetic risk scores (GRS) from well-validated SLE susceptibility loci (45 Asian confirmed non-HLA loci and an HLA-DRB1 amino acid haplotype model) were calculated and tested for their association with childhood-onset SLE. Association of each genetic variant with childhood-onset SLE was analysed using a multivariable logistic regression adjusting for population substructure.

Results: Mean age of SLE onset was 12.5±2.5 years in childhood-onset SLE and 29.0±9.4 in adult-onset SLE. GRS from SLE susceptibility loci was significantly higher in childhood-onset SLE than adult-onset SLE ($p=0.001$). Two SNPs, rs7460469 in *XKR6* and rs7300146 in *GLT1D1*, showed the most significant associations with childhood-onset SLE ($p=1.26 \times 10^{-8}$, OR=0.18, and $p=1.49 \times 10^{-8}$, OR=0.35, respectively). Especially, rs7300146 in *GLT1D1* was the cis expression quantitative trait locus (eQTL) for *SLC15A4*, which has been known an SLE susceptibility gene in a Chinese population. The model consisting of SLE GRS and the two newly identified loci to predict childhood-onset SLE attained an area under curve (AUC) of 0.71 in a receiver operating characteristics (ROC) curve.

Abstract THU0007 – Figure 1. A) association of genetic risk score else. cSLE; childhood-onset, aSLE; adult-onset SLE, GRS; genetic risk score and B) ROC curve for SLE-GRS, GWAS-hitand full model. ROC; receiver operating characteristics, SLE; Systemic lupus erythematosus, GWAS; genome-wide association study

Conclusions: Childhood-onset SLE is associated with a high cumulative SLE-risk effect and two novel SNPs rs7460469 and rs7300146, providing the first predictive model for childhood-onset SLE in Koreans.

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THU0008 LINKING GENETICS TO T-CELL PHENOTYPE IN JIA: RATIONAL FOR IL-2 THERAPY

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Background: Several genetic regions associated with susceptibility to juvenile idiopathic arthritis (JIA), harbour genes involved in the interleukin-2 (IL-2) response which is pivotal in the function of regulatory T cells (T-regs) and their ability to suppress effector T cells. Genetically JIA is similar to type 1 diabetes (T1D) which also demonstrates an enrichment of genes related to IL-2 regulation and response. Early clinical trial data has indicated recombinant IL-2 to be successful in enhancing T-regs in T1D. I hypothesise that IL-2 regulation and response is critical to the development of JIA and therefore IL-2 therapy represents an exciting and viable therapeutic option for JIA.

Objectives: We aim to identify a subset of JIA patients who carry a high burden of genetic risk variants in genes related to IL-2 regulation and response, who could then be targeted for IL-2 therapy. Secondly we will link genetics to cellular phenotypes using CyTOF to identify a subset of cells that are most perturbed in JIA and determine the effects of IL-2 on these cellular subsets.

Methods: A weighted genetic risk score (wGRS) was generated using 9 JIA susceptibility SNPs considered to be within or near to genes involved in interleukin (IL-2) regulation and response.¹ The IL-2 wGRS was tested in an independent set of UK cases (1435) and controls (5181). The risk of developing JIA was assessed by subtype, using logistic regression. A CyTOF panel containing 33 antibodies targeting markers of T cells and T-regulatory cells was developed and tested in CD3 +T cells from two healthy individuals after 12 hour stimulation (anti CD3/CD28 beads plus recombinant IL-2). Cells were stained for all antibodies, iridium and cisplatin and analysed on the CyTOF Helios. Data will be analysed with traditional biaxial gating as well commercially available packages such as cytofkit.

Results: The IL-2 wGRS demonstrated an increased percentage of individuals in the high risk group in the extended oligoarthritis, RF negative and RF positive polyarthritis subtypes suggesting a higher burden of IL-2 related loci. The odds of developing JIA for those in the highest risk group (quintile 5) compared to all others was increased in these subtypes (OR 2.95% CI 1.45–2.76, OR 2.39 95% CI 1.87–3.04, OR 2.14 95% CI 1.49–3.09, respectively). Comparing this to a wGRS generated from JIA susceptibility loci excluding IL-2 related genes shows that this enrichment is specific to the IL-2 wGRS. Biaxial gating of CyTOF data showed increases in activation markers after stimulation (CD25, CD69, CD38 and HLA-DR, decrease CCR7). We demonstrated that our panel can successfully identify traditional CD4 +T cell subsets showing differences between stimulated and unstimulated cells and between individuals.

Conclusions: Our analysis has shown that patients with oligoarthritis and polyarthritis have an increased burden of JIA susceptibility variants in genes related to IL-2 regulation and response suggesting these individuals may benefit from IL-2 therapy. Using the CyTOF panel we can now analyse individuals with high and low GRS allowing us to identify cellular subsets which may be altered by these genetic variants.

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