ABCG2. Thus, to estimate the risk of genetic variants of *ABCG2* more comprehensively, we analysed the association between all exonic variants and gout susceptibility.
Objectives: The main purpose of this study was to perform comprehensive *in silico* evaluation of the effects of all types of rare and common exonic *ABCG2* variants on gout susceptibility in Japanese population.
Methods: We previously sequenced all the exons of *ABCG2* in 480 patients with gout and 480 healthy controls (Japanese males) and performed functional analyses of non-synonymous variants. In this present study, we analysed the correlation between urate transport function and scaled C-score of CADDv1.3 (CADD score) of non-synonymous variants. We additionally performed Receiver Operating Characteristic (ROC) curve analysis and selected variants with altered function of more than 50% compared to wild-type ABCG2. Stratified association analyses and multivariate logistic regression analysis were performed to evaluate the effects of selected rare and common *ABCG2* variants on gout susceptibility.
Results: We identified 4 common and 26 rare exonic or closely situated intronic variants of *ABCG2*. CADD scores showed significant correlation with the results of functional analyses on urate transport (p=0.014, r=−0.539). ROC curve analysis showed an area under the curve (AUC) of 0.775. The optimal cutoff value of CADD score was 15 for classifying variants with altered function of more than 50% compared to wild-type ABCG2 (sensitivity=0.88, specificity=0.67). Therefore, we selected variants with a CADD score greater than 15 for downstream analyses. All intronic or synonymous variants had low CADD scores and thus were removed. Multivariate logistic regression analysis showed that the rare variants of *ABCG2* were associated with a significantly increased risk of gout and the size effect of these rare variants (odds ratio [OR]=2.7, p=0.012) was similar to that of the common variants, Q126X (OR=3.3, p=4.8×10–6) and Q141K (OR=2.3, p=8.6×10–1^6).
Conclusions: This study confirmed that both common and rare variants in *ABCG2* increase gout susceptibility. Furthermore, our *in silico* analyses suggest that synonymous and splice-site variants of *ABCG2* may not play a key role in the pathogenesis of gout.

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Acknowledgements: We would like to thank all the participants and the members of Japan Multi-Institutional Collaborative Cohort Study Shizuoka Field for their contribution.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.1030

THU0004 A DE NOVO NON-SENSE ERAP1 POLYMORPHISM IN TWO HLA-B*27-NEGATIVE TWINS WITH AXIAL SPONDYLOARTHRITIS

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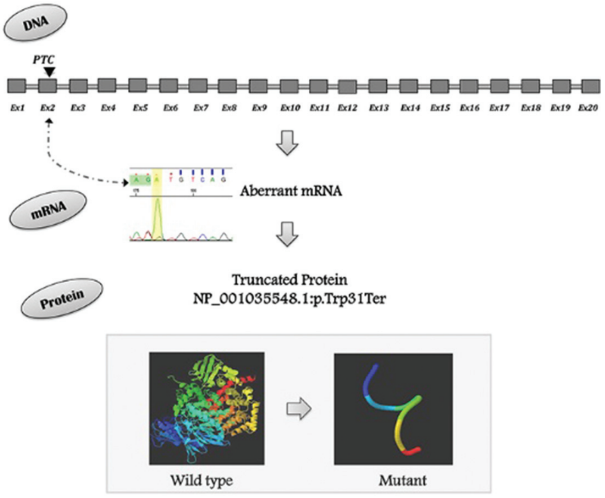
Background: Axial spondyloarthritis (axSpA) is a group of inflammatory disorders primarily affecting the spine that includes ankylosing spondylitis (AS) and non-radiographic axSpA. AS is strongly associated with HLA-B*27. A small percentage of HLA-B*27-positive subjects develop AS, suggesting the role of other genes in AS susceptibility.[1,2] Among these genes, *ERAP1* acts as "molecular ruler". It encodes the endoplasmic reticulum aminopeptidase 1 protein, responsible for the peptides trimming for the efficient binding to class I major histocompatibility complex (MHC). Several common gene SNPs (single nucleotide polymorphisms) were associated with the susceptibility to AS, but the presence of other *ERAP1* polymorphisms was supposed to explain the genotype-phenotype correlation.[1,3,4]
Objectives: The aim of this study is to genotype the *ERAP1* gene whole structure searching for common and additional polymorphisms in two HLA-B*27-negative twins.
Methods: We integrated a bioinformatics and a second level molecular approach in order to characterise *ERAP1* gene. Specific primer pairs were designed for the coverage of all gene regions. Genomic DNA was isolated from the whole blood of two 36 years-old axSpA male twins. They are HLA-B*27-negative (HLA-A*02, HLA-A*32; HLA-B*07; HLA-CW*07). The coexistence of Crohn's disease (CD) was documented in both patients after the initial diagnosis of axSpA.
Primer-specific polymerase chain reaction (PCR) was carried out. PCR products were sequenced and bioinformatics tools (BlastN and Mutation Surveyor) were queried for the mutational analysis. Phyre2 on line software was used for predicting the protein tertiary structure.
Results: Molecular characterisation of *ERAP1* gene identified a *de novo* homozygous guanine to adenine substitution at 15 132 position of exon 2 nucleotide sequence (NG_027839.1:g.15312G>A). This substitution is a stop-codon variation that directly generates an early premature termination codons (PTC). The 3D model of the protein showed a significant difference of the folding when wild-type and mutant protein were compared. The non-sense transcript could result in the production of a truncated protein, formed by 30 amino acids (NP_001035548.1:p.Trp31Ter) (figure 1).



Abstract THU0004 – Figure 1. The effect of the novel stop-codon variant at DNA, RNA and protein level. The novel substitution generates a PTC in *ERAP1* exon 2, that could be responsible for the production of an aberrant mRNA and of the truncated protein. The protein tertiary structure prediction by Phyre2 software is shown.

Conclusions: A *de novo* stop-codon *ERAP1* variant was identified for the first time in axSpA. We suggest that the PTC-related ERAP1 protein could contribute to AS risk by affecting the protein role.

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Acknowledgements: Thanks to Professor Ignazio Olivieri to have conveyed us the importance of honesty and humility, to teach us the enthusiasm of knowing and doing.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.5405

THU0005 WHOLE GENOME LINKAGE AND EXOME SEQUENCING ANALYSES IN TAKAYASU ARTERITIS FAMILIES

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Background: Takayasu arteritis (TA) is an inflammatory large vessel vasculitis affecting mainly aorta and its branches. Inflammation in vessels causes thickening

Ann Rheum Dis: first published as 10.1136/annrheumdis-2018-eular.6749 on 12 June 2018. Downloaded from http://ard.bmj.com/ on November 10, 2024 by guest. Protected by copyright.

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.

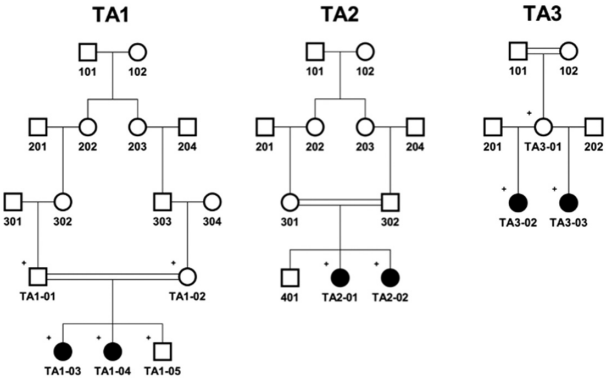
Objectives: We studied three consanguineous families with consisting of two affected daughters each and their healthy parents in order to identify the disease locus and the causative mutation

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	*ANXA8L1*	c.449C>T (p. T150M)	Deleterious	Probably damaging	Disease Causing
	EHBP1L1	c.3595C>T (p.R1199C)	Deleterious	Probably damaging	Polymorphism
	TULP2	c.1300T>C (p.Y434H)	Tolerated	Benign	Polymorphism
	MYH14	c.565C>T (p.R189C)	Deleterious	Probably damaging	Disease Causing
	SHANK1	c.3947G>A (p.G1316D)	Tolerated	Possibly damaging	Disease Causing
TA2	*AP4B1*	c.263C>T (p.T88I)	Tolerated	Benign	Disease Causing
	RIMBP3	c.3788A>C (p. E1263A)	Tolerated	Benign	Polymorphism
	VCX3B	c.44A>G (p.K15R)	Tolerated	Possibly damaging	Polymorphism
	NXF2	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.

Acknowledgements: This study was supported by TÜBITAK (Grant No 114Z829).

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.6749

THU0006

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

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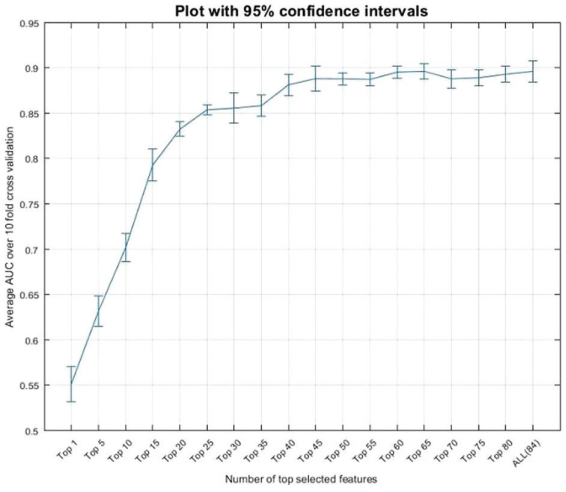
Background: Approximately 30% of patients with psoriasis develop a chronic inflammatory arthritis referred to as psoriatic arthritis (PsA). The ability to accurately predict which psoriasis patients will develop PsA would enable early intervention and help prevent disability. Both psoriasis and PsA have 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

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