allele, was detected in 12 heterozygous patients with. The p.Q141K variant, detected in the homozygous stage in three patients and in 31 patients as heterozygous variant. Heterozygous rare variants p.R45Q, p. G354R, p.A607V, and novel variant p.E344D were detected in one heterozygous patient each; heterozygous p.M131I and p.R236X in two patients.

Conclusion: In this study, significantly higher frequency of dysfunctional ABCG2 variants, common and rare, in comparison with common European population, were identified. On the other hand, the frequency of probably protective allele variant p.V12M was significantly lower in CKD cohort (MAF in our cohort = 0,036/ MAF in the European population = 0,061). Further analysis of ABCG2 association with CKD events *via* ABCG2 inflammation role is necessary. In conclusions, our finding of one novel, five rare and two common non-synonymous ABCG2 allelic variants in a sample of 167 CKD patients suggests that the ABCG2 variants should be considered a risk factor for CKD.

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POS0355 ASSOCIATIONS BETWEEN HLA-DRB1 SHARED EPITOPES ALLELES AND ANTI-RA33 ANTIBODIES IN DIFFERENT SUBSETS OF RHEUMATOID ARTHRITIS IN MALAYSIAN POPULATION

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Background: The mechanisms affecting anti-RA33 antibody's involvement in RA pathogenesis is still unclear. Refining our understanding of anti-RA33's role in RA in relation to known RA-associated genes and serological elements is needed.

Objectives: We investigated the relationship between RA-associated HLA-DRB1 epitope (SE) allele and presence of anti-RA33 antibodies in different serological subsets of rheumatoid arthritis in a Malaysian population.

Methods: Serum samples from 550 RA cases comprising seronegative (negative for anti-CCP2, IgG and IgM, n=250), seropositive (triple-autoantibody positive, n=150), singular anti-CCP2 positive (n=100), and double RF positive RA (n=50) were chosen from the Malaysian Epidemiological Investigations of RA (MyEIRA) case-control study. Three hundred MyEIRA population controls were used for comparison. All serum samples were assayed using a commercial anti-RA33 ELISA kit. All genetic samples were genotyped for four-digit HLA-DRB1 alleles using the PCR-SSO method on Luminex platform.

Results: The proportions of anti-RA33 positive was 20.9% in all RA cases (i.e. 34% in RF only positive RA; 25% in seropositive RA; 18% in seronegative RA and 18% in anti-CCP2 only positive RA). The HLA-DRB1 shared epitope alleles were significantly associated with anti-RA33 positive in the seropositive RA subgroup (OR=6.9, 95% CI 1.4-34.8; p=0.02). We observed significant association between anti-RA33 negative and HLA-DRB1 SE alleles among the seropositive RA patients (OR=4.5, 95% CI 2.8-7.2; p<0.001) and among CCP only positive RA (OR=4.4; 95% CI 2.6-7.4; p<0.01). No association was observed between anti-RA33 status and HLA-DRB1 SE alleles in seronegative RA and RF only positive RA.

Conclusion: The HLA-DRB1 SE alleles increased the risk of seropositive and CCP only positive RA independent of anti-RA33 positivity.

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POS0356 THE RELATIONSHIP OF GENETICS AND CLINICALLY SUSPECT ARTHRALGIA IN RA DEVELOPMENT ASSESSED USING HC, CSA AND RA PATIENTS

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Background: The identification of a pre-RA stage of patients with clinically suspect arthralgia (CSA) has proven to be beneficial in the early detection of Rheumatoid disease. Similarly, genetic susceptibility studies have identified important genetic risk factors for the development of (CCP positive) RA.[1] The question that arises is whether these findings represent independent etiological pathways and could therefore be complimentary in the early diagnosis of RA.

Objectives: To corroborate the knowledge of genetic differences between HC and RA patients and extend it to include the CSA stage of disease.

Methods: We used three datasets sampled from the same region in the Netherlands: 1,085 healthy controls (HC), 530 CSA and 1,277 RA patients. CSA patients were monitored for a median of 2 years for conversion into clinically apparent inflammatory arthritis (CSAc) or not (CSAnc).[2] We assessed the association between HLA SE and disease stage using logistic regression. The analysis was repeated in the CCP positive and CCP negative strata of both the CSA and the RA populations.

Results: Consistent with previous studies, HLA SE was significantly enriched in RA patients compared to HC (OR 2.28) (Figure 1). HLA SE also differentiated HC vs CSAc (OR 1.69), CSAnc vs CSAc (OR 1.74), and CSAnc vs RA (0R 2.35). No difference was found in HC vs CSAnc and CSAc vs RA.

Conclusion: HLA SE is more prevalent in patients who developed (rheumatoid) arthritis than in both healthy controls and CSA patients who do not progress to arthritis. The results presented here seem to indicate a clear distinction between CSA patients who develop arthritis and those who do not. We therefore believe that known RA genetics play a role in the development of arthritis rather than the CSA symptoms. While this relationship varies by CCP status, an independent effect remains. Studies into the broader role of genetics beyond HLA SE are currently underway.

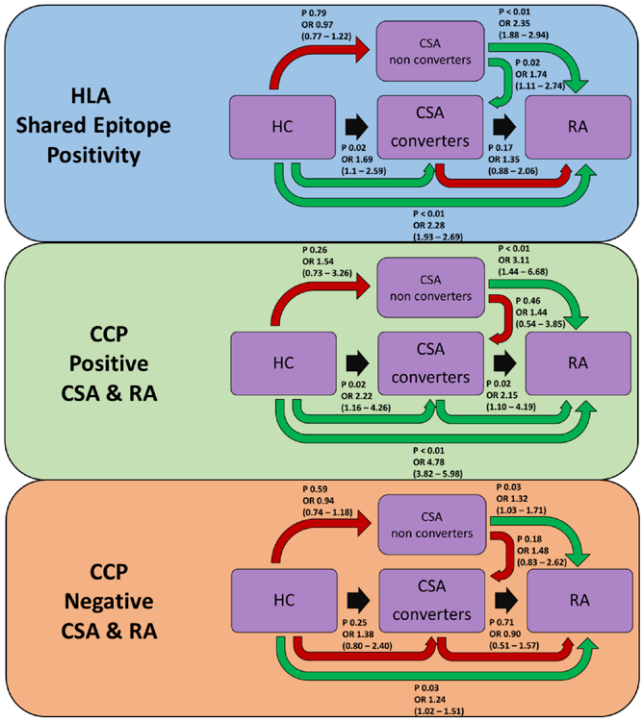

Figure 1. Distinguishing ability of HLA SE across HC, CSAc, CSAnc and RA in the full populations as well as in the CCP positive and negative stratifications. The arrowhead indicates the "case" status in each logistic regression. OR's (95% CI) derived from regression coefficients indicate the change in odds ratio attributable to HLA SE positivity.

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POS0357 MiRNAs CORRELATE WITH IMPROVEMENT IN DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS ON TUMOUR NECROSIS FACTOR INHIBITORS

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Background: Tumour necrosis factor inhibitors (TNFi) although effective in the treatment of rheumatoid arthritis (RA), show a variable response rate. Therefore, there is a need to identify treatment response predictors to inform therapy selection in order to practise precision medicine. MicroRNAs (miRNAs) are endogenous, single-stranded, non-coding RNAs that can alter gene expression by regulating messenger RNA translation. There is evidence for miRNA involvement in RA pathogenesis and they may serve as a useful biomarker of treatment response.
Objectives: To identify miRNAs associated with response to TNFi in RA.
Methods: Biologic naïve patients were selected from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS), a prospective multi-center UK study investigating treatment response biomarkers to TNFi with a primary outcome measure of change in DAS28 scores. Patients were stratified into European League Against Rheumatism (EULAR) good or non-responders based on their 3 or 6-month DAS28-CRP score.
Pre-treatment and 3-month post-treatment serum samples were substrates for miRNA profiling, which was conducted by FIRALIS using the HTG EdgeSeq miRNA whole transcriptome V2 targeted sequencing assay. Linear modelling using R package limma compared miRNA expression at (i) pre-treatment and at three-months, in EULAR good-responders and non-responders (ii) longitudinal change in expression from pre-treatment to three-months in EULAR good and non-responders.
A literature search was conducted to identify miRNAs associated with RA as a diagnostic and/or treatment response predictor. Data on these miRNAs were extracted from the miRNAs identified in the serum samples. A correction for multiple testing was applied to statistical tests.
Results: A total of 54 patients were analysed; of these, 35 (65%) were female, median disease duration [inter-quartile range] was 6 years [2 – 14] (n=51), and 44/51 (86%) patients were on a concomitant disease modifying anti-rheumatic drug. Of the 54 patients, 39 (72%) were classified as EULAR good-responders and 15 (28%) as non-responders. 1880 miRNAs were detected in the serum samples. 64 miRNAs were identified to be associated with RA from the literature, of which, 26 were identified in the serum samples tested.
No difference in pre-treatment or three-month miRNA levels was seen comparing EULAR good-responders and non-responders **(FDR p<0.05)**. There was a significant differential expression of four miRNAs at 3-months in good-responders compared with pre-treatment levels; miR-125a-3p (downregulated, p-value 0.002), miR-149-3p (upregulated, p-value 0.004), miR-766-3p (downregulated, p-value 0.008), miR-146b-5p (upregulated, p-value 0.006). No significant differences were observed between 3-months and baseline in non-responders.
Conclusion: Although no pre-treatment miRNAs were associated with TNFi response, changes in the levels of four miRNAs were detected at 3-months compared to baseline in EULAR good-responders. Future work involves validation of these samples in a larger patient cohort and analysing miRNA levels at 6 and 12 months. Replication and validation of these results in larger studies are required to analyse the role of miRNAs in stratifying EULAR good-responders from non-responders at three-months, and as treatment response predictors to TNFi in RA.
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POS0358 EVALUATION OF THE EFFECT OF mTOR EXPRESSION ON THE CLINICAL MANIFESTATIONS OF KNEE OSTEOARTHRITIS IN OBESE AND NORMAL WEIGHT PATIENTS

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Background: Currently, a large number of molecular biological and genetic markers are known to be involved in the development of osteoarthritis (OA). The mammalian target of rapamycin (mTOR) signaling pathway is responsible for chondrocyte proliferation, cartilage matrix production, and cell growth. OA is characterized by increased mTOR synthesis, which is accompanied by an increase in proliferative activity and destruction of chondrocytes. Obesity is an important factor in the progression of knee OA. The study of mTOR expression in patients with OA and obesity is an urgent task in the development of personalized OA therapy.
Objectives: To determine the expression of mTOR in patients with knee OA in combination with obesity and normal body weight. To evaluate the effect of mTOR on the clinical manifestations of OA in patients with different body mass index (BMI).
Methods: The study included 73 female patients aged 45-65 y.o. with Kellgren-Lawrence stage II-III knee OA. The patients were divided into 2 groups: group 1 (n=50) with obesity (BMI > 30 kg / cm2) and group 2 (n=23) with normal or increased body weight (BMI < 30 kg/cm2). The average age of patients with obesity is 56.5 ± 5.87 years, without obesity - 58.7 ± 5.43 years. Clinical manifestations were evaluated by a WOMAC. RNA was isolated from the patients ' blood samples, which was used to determine the expression of mTOR.
Results: Patients with knee OA with and without obesity did not differ in age. OA develops at an earlier age in obese patients, than in non-obese patients (p < 0.001). Patients from 1 group had a high BMI > 30 kg/m2 at the onset of OA. Obese patients had more severe knee OA is significantly more often detected: Kellgren-Lawrence stage III was determined in 10% of obese patients and in 4.35% - without obesity (p < 0.001). Significantly higher values of the WOMAC index pain, stiffness, joint functional failure, and total WOMAC were observed in obese patients (p = 0.006, p = 0.039, p = 0.037, and p = 0.014, respectively). Obese patients had higher VAS pain scores (p < 0.05) compared to patients with a lower BMI. Obese patients had a higher mTOR expression (p < 0.05) of 8.02±8.62, compared to non-obese patients. High mTOR expression was associated with VAS knee pain (r=0.78; p < 0.05) and WOMAC pain (r=0.89; p<0.05) in obese patients (Table 1).

Table 1. Correlation of m-TOR

Parameters	mTOR (1 group, n=50)	mTOR (2 group, n=23)
Body weight	p > 0,05	p > 0,05
Pain (VAS)	r=0,78; p<0,05	p = 0,07; r = 0,45
Pain (WOMAC)	r=0,89; p<0,05	p > 0,05
Total WOMAC	p > 0,05	p > 0,05

Conclusion: Our study showed that patients with obesity and knee OA have higher rates of mTOR expression, compared to patients with normal body weight. High mTOR expression correlates with the severity of knee pain in obese patients. Thus, the evaluation of mTOR expression in obese patients and knee OA plays an important role in predicting the severity of clinical manifestations of OA, and may influence the choice of personalized therapy tactics for such patients.
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