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Diagram 1.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.747

POS0347

SPECIFIC MITO-NUCLEAR INTERACTIONS AND mt16519C VARIANT AS PREDICTIVE BIOMARKERS FOR THE RAPIDLY PROGRESSIVE OSTEOARTHRITIS OF THE KNEE. DATA FROM THE OSTEOARTHRITIS INITIATIVE

A. Durán-Sotuela¹, M. Fernandez-Moreno¹, M. E. Vazquez Mosquera¹, P. Ramos-Louro¹, A. Dalmao-Fernandez¹, S. Relaño-Fernandez¹, V. Suárez-Ulloa², V. Balboa-Barreiro³, N. Oreiro¹, J. Vázquez García¹, F. J. Blanco¹, I. Rego-Perez¹ on behalf of Grupo de investigación en Reumatología (GIR). ¹Instituto de Investigación Biomédica de A Coruña (INIBIC). Complejo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña., Servicio de Reumatología, A Coruña, Spain; ²Instituto de Investigación Biomédica de A Coruña (INIBIC). Complejo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña., Plataforma de Bioinformática, A Coruña, Spain; ³Instituto de Investigación Biomédica de A Coruña (INIBIC). Complejo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña., Unidad de apoyo a la investigación, A Coruña, Spain

Background: The early identification of patients with rapid progressive osteoarthritis (RPOA) could allow the implementation of prevention strategies and their inclusion in clinical trials. Polymorphisms in nuclear and mitochondrial DNA (mtDNA) have been associated with OA. Preliminary analyses by our group showed nuclear single nucleotide polymorphism (nSNP) rs12107036 of TP63 as a potential risk factor for RPOA of the knee.

Objectives: i) To analyze interactions between mtDNA haplogroups and rs12107036 ii) To apply Next Generation Sequencing (NGS) to discover novel mitochondrial variants to construct predictive models of RPOA of the knee.

Methods: 1102 Caucasian subjects from the OAI were classified as follows: i) Rapid progressors (N=255), baseline KL grade 0-1 or 2 in at least one knee, that increases up to KL≥ 3 or 4 respectively during 48-month follow-up. ii) Non-rapid progressors (N=847), with the same baseline characteristics as rapid progressors, but with slower or no evolution over time.

mtDNA haplogroups and rs12107036 were assigned by mini-sequencing techniques. Novel mtDNA variants were studied by NGS. Statistical analyses included chi-square tests and generalized estimating equations. Relative excess risk due to interaction (RERI) and attributable proportion (AP) were evaluated for the additive interaction between mtDNA clusters and nSNP rs12107036. A nomogram for the estimation of the risk of RPOA was also developed. Analyses were performed using SPSS Statistics v24 and epi.R package included in R software v3.6.3.

Results: Chi-square analyses revealed an increased risk of RPOA in patients with the allele G of rs12107036 and mtDNA cluster UK (OR 2,013; p=0,001). An excess of 70,3% of RERI between nSNP rs12107036 and mtDNA clusters was detected, indicating that 47,1% (AP) of the risk is attributable to this interaction, therefore harboring both genetic factors increase the risk of RPOA up to 4,7 times compared to harboring just one. mtDNA sequencing revealed the variant mt16519C overrepresented in rapid-progressors (OR 1,620; p=0,002).

Table 1 shows the predictive model for the risk of RPOA. The interaction between the allele G of rs12107036 and mtDNA cluster KU (OR 1,727; p=0,036), in addition to the variant mt16519C (OR 1,690; p=0,003), showed a significant association with the RPOA phenotype regardless of age, BMI, contralateral knee OA, previous injury and WOMAC pain. Image 1 displays the nomogram for predicting risk of RPOA; as an example, a 70 year old male, with a BMI of 28, WOMAC pain score of 10, contralateral OA and presence of both mito-nuclear interaction and mt16519C, has a risk of RPOA of 0,7.

Conclusion: mtDNA genetic variants are useful, not only as modulators of the influence of specific nuclear polymorphisms on the risk of developing RPOA, but also as candidate genetic biomarkers of this phenotype.

Table 1. Predictive model for the risk of RPOA phenotype

Variable	p-value	OR	min 95% CI	MAX 95% CI
Clinical and genetic variables				
Age	<0,001 [#]	1,056	1,038	1,074
Female	0,143	1,260	0,925	1,718
BMI	<0,001 [#]	1,065	1,030	1,101
Contralateral OA	<0,001 [#]	1,927	1,413	2,626
Previous Injury	<0,001 [#]	1,770	1,293	2,422
WOMAC pain	0,001 [#]	1,097	1,039	1,159
rs12107036 G	0,172	1,226	0,915	1,643
mt16519 C	0,003 [#]	1,690	1,202	2,375
mtDNA Clusters^s				
Others	0,803	0,921	0,482	1,760
TJ	0,482	1,209	0,712	2,052
UK	0,136	0,698	0,435	1,120
HV				Reference
rs12107036 G*mtDNA Cluster				
G * Others	0,502	0,789	0,395	1,576
G * TJ	0,158	0,647	0,353	1,185
G * UK	0,036 [#]	1,727	1,036	2,881
G * HV			Reference	

^smtDNA Clusters: haplogroups with a common phylogenetic origin BMI: Body Mass Index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; OR: Odds Ratio; CI: confidence interval; #: statistical significance declared at P ≤ 0.05, in bold.

Image 1. Nomogram for the estimation of the risk of RPOA phenotype. Circles represent the values for the example. Clusters: haplogroups with a common phylogenetic origin BMI: Body Mass Index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.750

POS0348

GENETIC SUSCEPTIBILITY VARIANTS FOR RHEUMATOID ARTHRITIS ARE NOT ASSOCIATED WITH EARLY REMISSION; A MULTI-COHORT STUDY

S. Jurado Zapata¹, M. Maurits¹, Y. Abraham², E. Van den Akker³, A. Barton⁴, P. Brown⁵, A. Cope⁶, I. González-Álvarez⁷, C. Goodyear⁸, A. van der Helm - van Mil¹, X. Hu⁹, T. Huizinga¹, M. Johannesson¹⁰, L. Klareskog¹⁰, D. Lendrem¹¹, I. McInnes¹², F. Morton¹², C. Paterson¹², D. Porter¹², A. Pratt¹¹, L. Rodríguez Rodríguez¹³, D. Sieghart¹⁴, P. Studenic¹⁴, S. Verstappen¹⁴, L. Padyukov¹⁰, A. Winkler⁹, J. D. Isaacs⁵,

R. Knevel¹, ¹Leiden University Medical Center, Rheumatology, Leiden, Netherlands; ²Janssen Pharmaceutical Companies of Johnson & Johnson, Discovery Science/ Computational Biology, Beerse, Belgium; ³Leiden University Medical Center, Leiden Computational Biology Center, Leiden, United Kingdom; ⁴University of Manchester, Division of Musculoskeletal & Dermatological Sciences, Manchester, United Kingdom; ⁵Newcastle University, Institute of Cellular Medicine, Newcastle, United Kingdom; ⁶King's College London Centre for Rheumatic Diseases, Department of Inflammation Biology, London, United Kingdom; ⁷Hospital Universitario de la Princesa (IIS-IP), Rheumatology, Madrid, Spain; ⁸University of Glasgow, Immunology, Glasgow, United Kingdom; ⁹Pfizer, Inflammation & Immunology Research Unit, Cambridge, United States of America; ¹⁰Karolinska Institutet and Karolinska University Hospital, Rheumatology, Stockholm, Sweden; ¹¹Newcastle upon Tyne Hospitals NHS Foundation Trust, Health and Bioinformatics, Newcastle upon Tyne, United Kingdom; ¹²University of Glasgow, Infection Immunity & Inflammation, Glasgow, United Kingdom; ¹³Hospital Clínico San Carlos, Rheumatology, Madrid, Spain; ¹⁴Medical University of Vienna, Rheumatology, Vienna, Austria

Background: Patients who achieve remission promptly could have a specific genetic risk profile that supports regaining immune tolerance. The identification of these genes could provide novel drug targets.

Objectives: To test the association between RA genetic risk variants with achieving remission at 6 months.

Methods: We computed genetic risk scores (GRS) comprising of the RA susceptibility variants¹ and HLA-SE status separately in 4425 patients across eight datasets from inception cohorts. Remission was defined as DAS28CRP < 2.6 at 6 months. Missing DAS28CRP values in patients were imputed using predictive mean matching by MICE. We first tested whether baseline DAS28CRP changed with increasing GRS using linear regression. Next, we calculated odds ratios for GRS and HLA-SE on remission using logistic regression. Heterogeneity of the outcome between datasets was mitigated by running inverse variance meta-analysis.

Results: Evaluation of the complete dataset, baseline clinical variables did not differ between patients achieving remission and those who did not (Table 1). Distribution of GRS was consistent between datasets. Neither GRS nor HLA-SE was associated with baseline DAS28CRP (OR 1.01; 95% CI 0.99-1.04). A fixed effect meta-analysis (Figure 1) showed no significant effect of the GRS (OR 0.99; 95% CI 0.94-1.03) or HLA-SE (OR 0.8CRP87; 95% CI 0.75-1.01) on remission at 6 months.

Table 1. Summary of the data separated by disease activity after 6 months.

	all	Remission at 6 months	No remission at 6 months
N	4425*	1558	2430
Age, mean (sd)	55.38 (13.87)	55.17 (14.09)	55.62 (13.59)
Female %	68.98%	65.43%	70.73%
ACPA+ %	61.94%	63.53%	61.67%
Baseline DAS28, mean (sd)	4.76 (1.22)	4.47 (1.23)	5.1 (1.15)

*not all patients had 6 months data

A. Meta-analysis on the RA-GRS and HLA with remission at 6 months

B. Meta-analysis on the RA-HLA SE with remission at 6 months

Figure 1. A. Inverse weighted meta-analysis of (A) the GRS + HLA and (B) the HLA SE. Includes the dataset name (Study), test estimate (TE), the standard error of treatment estimate (seTE), odds ratio (OR), 95% confidence intervals (95%-CI) and the weights of the fixed effect model. I^2 percentage of variation across studies due to heterogeneity. τ^2 states the variance of the true effect size.

Conclusion: In these combined cohorts, RA genetics risk variants are not associated with early disease remission. At baseline there was no difference in genetic risk between patients achieving remission or not. Studies encompassing other genetic variants are needed to elucidate the genetics of RA remission.

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Acknowledgements: This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777357, RTCure. This project has received funding from Pfizer Inc.

Disclosure of Interests: Samantha Jurado Zapata: None declared, Marc Maurits: None declared, Yann Abraham Employee of: Pfizer, Erik van den Akker: None declared, Anne Barton: None declared, Philip Brown: None declared, Andrew Cope: None declared, Isidoro González-Álvarez: None declared, Carl Goodyear: None declared, Annette van der Helm - van Mil: None declared, Xinli Hu Employee of: Pfizer, Thomas Huizinga: None declared, Martina Johansson: None declared, Lars Klareskog: None declared, Dennis Lendrem: None declared, Iain McInnes: None declared, Fraser Morton: None declared, Caron Paterson: None declared, Duncan Porter: None declared, Arthur Pratt: None declared, Luis Rodríguez Rodríguez: None declared, Daniela Sieghart: None declared, Paul Studenic: None declared, Suzanne Verstappen: None declared, Leonid Padyukov: None declared, Aaron Winkler Employee of: Pfizer, John D Isaacs: None declared, Rachel Knevel Grant/ research support from: Pfizer

DOI: 10.1136/annrheumdis-2021-eular.1042

POS0349

SEQUENCE COMPLEMENTARITY BETWEEN SARS-CoV-2 GENOME AND HUMAN NONCODING RNAS ASSOCIATED WITH IMMUNOLOGICAL DISORDERS: AN IN SILICO PIVOTAL STUDY

R. Talotta¹, S. Bahrami², M. J. Laska². ¹University of Messina, Clinical and Experimental Medicine, Messina, Italy; ²Aarhus University, Clinical Medicine, Aarhus, Denmark

Background: Recent evidence shows that human cells may produce several noncoding (nc)RNAs in response to viral infections. Among them, a central role has been attributed to long noncoding (lnc)RNAs, more than 200 nucleotides in length, which are also crucially involved in cancer and autoimmunity. LncRNAs epigenetically control the transcription of genes presiding over cell proliferation, differentiation, migration and apoptosis, by directly or indirectly binding cellular or foreign nucleic acids, including viral genomes.

Objectives: The objectives of this study were to evaluate *in silico* the presence of a nucleotide sequence complementarity between the RNA genome of Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) and human ncRNA genes and to analyze any associations between SARS-CoV-2 gene-matching ncRNAs and human diseases.

Methods: The FASTA sequence of each of the 11 SARS-CoV-2 isolate Wuhan-Hu-1 genes (ORF1ab, ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF10, S, E, M, N) was retrieved from NCBI.nlm.nih.gov/gene (reference sequence NC_045512.2). The ensembl.org library for human ncRNA genes was interrogated for any base-pair match and detected human ncRNAs analyzed for their functional activity. Finally, the associations between ncRNAs and human diseases were searched on GWAS databases (<https://www.ebi.ac.uk/gwas> and <https://www.genecards.org>).

Results: A total of 252 matches between SARS-CoV-2 genes and human ncRNAs were recorded (ORF1ab: 28; ORF3a: 9; ORF6: 50; ORF7a: 31; ORF7b: 16; ORF8: 23; ORF10: 5; S: 24; E: 17; M: 32; N: 17). With the exception of two small nuclear RNAs (RNVU1-4 and RNVU4-74P corresponding to ORF6 and ORF10, respectively), all of them were lncRNAs, mostly expressed in testis and central nervous system under physiological conditions. Percentage of alignment ranged from 91.30% to 100%, with a mean nucleotide alignment length of 17.5±2.4. Polymorphic variants of these transcripts have mostly been reported in patients with neuropsychiatric disorders, cancer and dysmetabolism. Of note, we found 13 and 15 complementarities with lncRNAs associated with immune-mediated diseases Table 1. and immunological pathways (IL-2, IL-6, IL-12, IL-12R, IL-13, IL-17, M-CSF, CXCL-10, TRAIL-R2 and IgG glycosylation), respectively.

Conclusion: This pivotal study shows that SARS-CoV-2 genes contain complementary sequences to human ncRNAs in turn associated with several diseases, including autoimmunity. The biological effects of this interaction remain to be elucidated.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.1077