Background: Immunogenicity is a leading cause of treatment failure to TNF inhibitors, and also affects drug safety. Variations in HLA class II genes have been suggested to predispose to anti-drug antibody formation (ADA), but characterization of biologically relevant HLA haplotypes, based on high-resolution genotyping, is lacking.

Objectives: To assess associations between HLA loci and formation of ADA to infliximab across different immune mediated inflammatory diseases.

Methods: Patients with immune mediated inflammatory diseases on infliximab therapy (N=612; 181 spondyloarthritis, 120 rheumatoid arthritis, 72 psoriatic arthritis, 114 ulcerative colitis, 80 Crohn’s disease and 45 psoriasis) participating in the Norwegian Drug Monitoring (NOR-DRUM) trials (1, 2) were included in the present analyses. Neutralising ADA were assessed with an automated fluorescence assay at each infusion. Next generation sequencing-based HLA typing was performed. Associations with ADA formation were assessed at locus, allele, haplotype and amino acid level. Peptide binding predictions for infliximab were performed.

Results: ADA were detected in 147 patients (24%). Significant associations were shown between ADA and several HLA loci, whereas conditional analyses indicated HLA-DQB1 (p=1.4x10^-6) as the primary risk locus. Highest risk of ADA formation was seen for patients carrying at least one of the HLA-DQ2 haplotypes; DQB1*02:01–DQA1*05:01 and DQB1*02:02–DQA1*02:01 (OR 3.18, 95% CI 2.15 to 4.69, p=5.9x10^-9) (Figure 1). These findings were consistent across diagnoses (Table 1), and remained significant when adjusting for other possible predictors of ADA. Computational predictions indicated that both these HLA-DQ2 haplotypes could strongly bind two peptide motifs (INTSEVED and VYACE-VTHQ) in the infliximab heavy and light chain.

Table 1. HLA-DQ2 carrier frequencies according to the different disease phenotypes and for all diagnosis combined

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HLA-DQ2 carrier-frequency among patients with ADA formation</th>
<th>HLA-DQ2 carrier-frequency among patients without ADA formation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (N=120)</td>
<td>0.316</td>
<td>0.134</td>
<td>0.02</td>
</tr>
<tr>
<td>PsA (N=72)</td>
<td>0.55</td>
<td>0.231</td>
<td>0.01</td>
</tr>
<tr>
<td>SPA (N=181)</td>
<td>0.364</td>
<td>0.182</td>
<td>0.02</td>
</tr>
<tr>
<td>UC (N=114)</td>
<td>0.556</td>
<td>0.264</td>
<td>0.006</td>
</tr>
<tr>
<td>CD (N=80)</td>
<td>0.429</td>
<td>0.303</td>
<td>0.33</td>
</tr>
<tr>
<td>Py (N=45)</td>
<td>0.867</td>
<td>0.267</td>
<td>0.0004</td>
</tr>
<tr>
<td>All disease</td>
<td>0.469</td>
<td>0.217</td>
<td>5.9x10^-9</td>
</tr>
</tbody>
</table>

Conclusion: The risk of ADA to infliximab was three-fold higher in patients carrying the HLA-DQ2 risk haplotypes across diseases. A biological role for the HLA-DQ2 molecules encoded by the two different HLA-DQ2 risk haplotypes in the formation of ADA was further supported by peptide binding predictions. These novel findings provide promise for future incorporation of HLA-DQ2 testing to facilitate personalised treatment decisions.

REFERENCES:

Disclosure of Interests: Marte K. Viken: None declared, Benedicte A. Lie: None declared, Kristin Kaasen Jørgensen: None declared, Johan Maersk Hansen: None declared, Line Henriksen: None declared, Martin S. Højberg: None declared, Jette Widerlund: None declared, Charles J. Saint: None declared, Aage B. Lykke: None declared, Cato Mørk Spekversboen Bjørlykke: None declared, Marte K. Viken: None declared, Bitte Stenager: None declared, Øystein Sandanger: None declared, VTHQ) in the infliximab heavy and light chain.

Figure: Kaplan-Meier survival curve in time to ADA formation (years) for the significant HLA-DQB1*02:01-DQA1*05:01 and HLA-DQB1*02:02-DQA1*02:01 haplotypes and HLA-DQ2

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Figure: Kaplan-Meier survival curve in time to ADA formation (years) for the significant HLA-DQB1*02:01-DQA1*05:01 and HLA-DQB1*02:02-DQA1*02:01 haplotypes and HLA-DQ2

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ARTHRITIS PATIENTS AND NON-ARTHRITIS CONTROLS

The Psoriatic Arthritis 5-Thermometer scales (PsA-5Ts) scoring and calculation rule aim of improving its diagnostic accuracy.

There are a variety of composite disease activity monitoring methods and patient-centered metrics available for psoriatic arthritis (PsA). The Psoriatic Arthritis 5-Thermometer scales (PsA-5Ts) is a new tool, proposed, with the aim of improving its diagnostic accuracy.

Objectives: The goal of this research was to evaluate data on the measurement qualities of the PsA-5Ts, a composite measure of disease activity in PsA patients, in a real-world scenario (Figure 1).

While the variance in grip strength is mostly explained by sex and between-person variation for all subject groups, the proportions of explained variance for measured hand function is not similar between diseases. In all groups > 50% of the variation in measured hand function remains unexplained by the variables used. Especially in arthritis patients, HAQ explained less than 25% of the variance in measured hand function. Grip strength can be considered a poor surrogate for hand function in this context due to its large gender dependence. The explainability of MHO variation largely by HAQ indicates that it has limited potential to provide further information beyond overall functional impairment. In contrast, the large between-person variation in MPUT likely indicates unexplored movement patterns of hand motion that may be further dissected using sensor-based analyses (2) and can help identify movement components a potential for an in-depth assessment of subtle hand-function alterations in inflammatory arthritis.

REFERENCES:

Table 1. Variance proportions for each of the four study groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hand function (MPUT)</th>
<th>Grip strength</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PsA</td>
</tr>
<tr>
<td>MHO</td>
<td>3.4</td>
<td>39.0</td>
</tr>
<tr>
<td>ID</td>
<td>34.8</td>
<td>36.2</td>
</tr>
<tr>
<td>Age</td>
<td>0.0</td>
<td>13.8</td>
</tr>
<tr>
<td>HAQ</td>
<td>35.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Dominant hand</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Sex</td>
<td>12.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Residual</td>
<td>13.3</td>
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</tbody>
</table>

Conclusion: While the variance in grip strength is mainly explained by sex and between-person variation for all subject groups, the proportions of explained variance for measured hand function is not similar between diseases. In all groups > 50% of the variation in measured hand function remains unexplained by the variables used. Especially in arthritis patients, HAQ explained less than 25% of the variance in measured hand function. Grip strength can be considered a poor surrogate for hand function in this context due to its large gender dependence. The explainability of MHO variation largely by HAQ indicates that it has limited potential to provide further information beyond overall functional impairment. In contrast, the large between-person variation in MPUT likely indicates unexplored movement patterns of hand motion that may be further dissected using sensor-based analyses (2) and can help identify movement components a potential for an in-depth assessment of subtle hand-function alterations in inflammatory arthritis.

Figures:

Figure 1. Overall (N=299) proportions of variance for (A) hand function by Moberg Pick-Up Test (MPUT) and (B) grip strength. Dominance = dominant hand, HAQ = health assessment questionnaire, ID = Individual, MHO = Michigan Hand Questionnaire.

Acknowledgements: This study was supported by the German Research Council (DFG 1483 – Project-ID 442419336, INST 90 / 985-1 FUGG, FOR2438/2886; SFB1181), the German Ministry of Science and Education (project MASCARA), the European Union (H2020 GA 810316 - 4D-Nanoscope European Research Council Synergy Project) and Novartis Germany GmbH.

Disclosure of Interests: None declared
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POS0009

SUBJECTIVE ASSESSMENT OF PHYSICAL FUNCTION DOES NOT SUFFICIENTLY EXPLAIN MEASURED HAND FUNCTION AND GRIP STRENGTH IN ARTHRITIS PATIENTS AND NON-ARTHRITIS CONTROLS

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Background: Monitoring disease activity in patients with inflammatory arthritis is essential for effective treatment. While the health assessment questionnaire (HAQ) is commonly used to assess physical function, additional functional tests, such as isometric grip strength and the Moberg Pick-Up-Test (MPUT), provide objective measures for hand function and allow assessing hand function across different diseases (1). It remains unclear to date, if measured hand function is already reflected by the HAQ, as the most widely used patient reported outcome measure of physical function in arthritis.

Objectives: To estimate the proportion of hand function and grip strength variability explained by HAQ, patient-reported hand function, and between-person variation in patients with inflammatory arthritis and non-arthritic controls.

Methods: Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis without PsA (PsO) and healthy controls (HC) were investigated. Subject characteristics (age, sex, disease) and HAQ were recorded. Hand function was assessed by vigeometric grip strength, MPUT, and a patient-reported tool (Michigan Hand Questionnaire, MHO). Mixed pure-random-effect linear regression models were used to estimate the proportion of variance in measured hand function or grip strength explained by subject characteristics (age, hand dominance, sex, reported hand function, disease group).

Results: 299 subjects were tested, 101 with RA (Age: 59.1±13.3 years, BMI: 27.2±5.5 kg/m², HAQ-DI score: 0.4±0.6), 92 with PsA (Age: 58.8±11.6 years, BMI: 29.6±1kg/m², HAQ-DI score: 0.6±0.7) and 106 non-arthritic controls (51 with PsO (Age: 47.3±14.1 years, BMI: 29.8±3.7kg/m², HAQ-DI score: 0.4±0.6) and 55 HC (Age: 54.6±16.5 years, BMI: 25.2±3.5kg/m², HAQ-DI score: 0.1±0.2). Overall variation of MPUT is mostly accounted for by between-person variation (43.1%), followed by HAQ (20.3%) and MHO (20.2%) (Figure 1A). Overall variation in grip strength is mostly accounted for by sex (59.8%), between-person variation (21.1%) and HAQ (11.3%) (Figure 1B). Overall variation in MHO is mostly accounted for by HAQ (59.2%) and residual variation (28.3%). Study group specific result are summarized in Table 1.

Table 1. Variance proportions for each of the four study groups.

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<td>0.0</td>
</tr>
</tbody>
</table>

The PsA-5Ts is calculated based on 5 numerical thermometer scales questions. Each scale is assessed as a number between 0 and 15.

Figure 1. The Psoriatic Arthritis 5-Thermometer scales (PsA-5Ts) scoring and calculation rule

The PsA-5Ts final value = PsA-5Ts 1 (palmar numeric thermometer value (range 0-10) x 5) + PsA-5Ts 2 (digits numeric thermometer value (range 0-10) x 2) + PsA-5Ts 3 (palmar function numeric thermometer value (range 0-10) x 2) + PsA-5Ts 4 (digit problems numeric thermometer value (range 0-10) x 4)