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DOI:
10.1136/annrheumdis-2021-222007

Document Version
Accepted author manuscript

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
Annals of the rheumatic diseases

Citing this paper
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ADAMTSS as a therapeutic target for osteoarthritis: Mendelian randomisation study

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Osteoarthritis (OA) is a progressive disease for which there is no effective disease modifying therapy. It is characterized by articular cartilage degradation with uncontrolled proteolytic extracellular matrix destruction. The major proteoglycan in the extracellular matrix – aggrecan – is primarily cleaved by the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family of genes [1]. ADAMTSS knockout mice have less severe cartilage destruction after induced joint instability compared to wild-type counterparts [2]. However, ADAMTSS regulation differs in humans [1], for whom the therapeutic role of ADAMTSS inhibition is yet unclear. Although several ADAMTSS inhibitors have been patented, the sole phase II trial (NCT03595618) did not demonstrate benefit for imaging or pain outcomes in knee OA.

Natural variation in the gene that encodes a protein drug target can offer insight into the clinical effects of perturbing that target pharmacologically [3]. The random allocation of genetic variants at conception means that such Mendelian randomisation (MR) analyses are robust to the confounding and reverse causation that can hinder causal inference in traditional epidemiological study designs [4]. As genetic proxies for ADAMTSS function, we selected uncorrelated \((r^2<0.05)\) missense (protein coding) variants within the ADAMTSS gene that have been previously associated with plasma ADAMTSS levels at genome-wide significance \((p<5\times10^{-8})\) in a study of 997 European ancestry individuals [5]. We considered the association of these missense variants with higher plasma ADAMTSS levels to represent biological support that they adversely affect protein function to increase circulating protein levels. The genetic associations of the variants with OA were investigated in the largest genome-wide association study meta-analysis to date (177,517 cases; 649,173 controls), which also considered subtypes: knee (62,497 cases), hip (36,445), spine (28,372) and hand (20,901) [6]. MR estimates for both variants were combined using the inverse variance-weighted method. Colocalization analysis was performed to investigate possible genetic confounding through linkage disequilibrium underlying any observed MR associations. Full details are provided in Supplementary Materials.

Two missense variants (rs2830585 and rs226794, full descriptions in Supplementary Materials) were used as genetic instruments for plasma ADAMTSS levels. Each standard deviation increase in plasma ADAMTSS (proxying reduced activity) was significantly associated with reduced risk of all OA types (odds ratio [OR] 0.983, 95%CI 0.972-0.993; \(p=0.005\)), hip (OR 0.969; 0.949-0.990; \(p=0.004\)) and hand (OR 0.960; 0.925-0.997; \(p=0.032\)) OA (Figure 1). For each outcome, the posterior probabilities of a shared causal variant driving plasma ADAMTSS levels and OA were greater in magnitude than the probability of distinct causal variants (Supplementary Table S2).
Results of this genetic investigation support ADAMT55 inhibition as a therapeutic target for reducing OA risk. A key limitation of our study is that the precise effects of the two considered missense variants on ADAMT55 function are unknown and our assumption that higher protein level reflects reduced function is unproven. However, mechanistic studies of ADAMT55 make the alternative causal direction (reduced ADAMT55 function being detrimental for OA) biologically unlikely. Further studies are needed to replicate these findings in other ancestries and to test for the presence of effect heterogeneity of targeting ADAMT55 across OA subtypes.

A plethora of animal and in vitro human chondrocyte studies have highlighted ADAMT55 as a promising drug target over the past two decades, yet little supportive evidence has yet emerged from human studies. Using large-scale population genetic data, this study provides evidence of a causal effect of ADAMT55 on clinical OA phenotypes, beyond biomarker or cellular surrogates. Studies of drug development programmes have highlighted that targets with genomic support have a higher rate of success. In summary, results of this genetic analysis support ADAMT55 as a promising disease modifying OA drug that should be prioritised in clinical development.
**Figure 1**: Mendelian randomisation estimates of the effect of genetically proxied ADAMTS5 inhibition on osteoarthritis and its subtypes.

<table>
<thead>
<tr>
<th>Group</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=177,517)</td>
<td>0.983</td>
<td>[0.972; 0.993]</td>
</tr>
<tr>
<td>Knee (n=62,497)</td>
<td>0.982</td>
<td>[0.960; 1.004]</td>
</tr>
<tr>
<td>Hip (n=36,445)</td>
<td>0.969</td>
<td>[0.949; 0.990]</td>
</tr>
<tr>
<td>Hand (n=20,901)</td>
<td>0.960</td>
<td>[0.925; 0.997]</td>
</tr>
<tr>
<td>Spine (n=28,372)</td>
<td>0.978</td>
<td>[0.955; 1.001]</td>
</tr>
</tbody>
</table>

**Data availability statement**

All data used in this study are publicly available, with relevant citations detailed.

**Patient consent for publication**: Not required, as publicly available summary data that had already obtained informed participant consent were used.

**Patient and Public Involvement**: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Ethics approval**: This analysis used publicly available summary statistics that had already obtained ethical approval.

**Acknowledgements**

SSZ is supported by a National Institute for Health Research Clinical Lectureship. VK is supported by the Academy of Finland Project 312123, and European Union’s Horizon 2020 research and innovation programme under Grant Agreement No 848158. APM is supported by Versus Arthritis (grant reference 21754). DG is supported by the British Heart Foundation Research Centre of Excellence (RE/18/4/34215) at Imperial College London and by a National Institute for Health Research Clinical Lectureship (CL-2020-16-001) at St. George’s, University of London.

**Conflicts of Interest**

DG is employed part-time by Novo Nordisk outside of the submitted work. All authors declare no conflicts of interest that could bias this work.
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