Development of a Genetic Risk Score for Pain in Rheumatoid Arthritis

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BACKGROUND/OBJECTIVES

- Pain is often the most significant symptom of rheumatoid arthritis (RA), but it is multifactorial and does not always correlate with other markers of disease activity
- Singe nucleotide polymorphisms (SNPs) related to central and peripheral pain processing have been associated with fibromyalgia (FM), which commonly coexists with RA
- We hypothesized that a composite genetic risk score (GRS) based on 42 SNPs associated with FM* would be associated with higher patient-reported pain scores in RA

*Janssen et. al., (2021), *An Acad Bras Ciênc*. 93(suppl 4)

METHODS

- Patients with RA and genotyping data were included from two independent cohorts:
  - 1) FORWARD (National Databank for Rheumatic Diseases)
  - 2) Veterans Affairs RA registry (VARA).
- Pain was assessed in both cohorts on a visual analogue scale (range 0-10).
- We used multivariable linear regression to determine relationships between each SNP and baseline pain, using FORWARD as the training dataset.
- We generated a GRS for pain for each individual (from both cohorts) as the sum of their risk alleles weighted by the effect size estimate (regression coefficient) for each SNP.
- Linear regression was used to assess the associations of GRS with baseline pain and with disease activity in FORWARD (training dataset) and VARA (validation dataset), adjusting for age, sex and race.
- Similarly, associations of GRS with pain and disease activity during longitudinal follow-up were determined using linear regression incorporating generalized estimating equations.

RESULTS

- Included 756 participants from FORWARD (mean age 56.8 years, 89.4% female) and 2,176 participants from VARA (mean age 71.7 years, 11.0% female) who had both genetic and VAS pain data
- Several SNPs were associated with pain scores in each cohort, but no single SNP was associated in both cohorts.
- Both FORWARD and VARA participants in the highest GRS quartile had significantly greater baseline pain but the effect was more modest in the validation dataset (**Figure 1**).
- Participants in the highest GRS quartile from both cohorts also had greater longitudinal pain (**Table 1),** baseline disease activity (**Table 2)** and longitudinal disease activity (**Table 3**)

Figure 1. Genetic Risk Score quartile is associated with greater baseline pain in two independent cohorts.

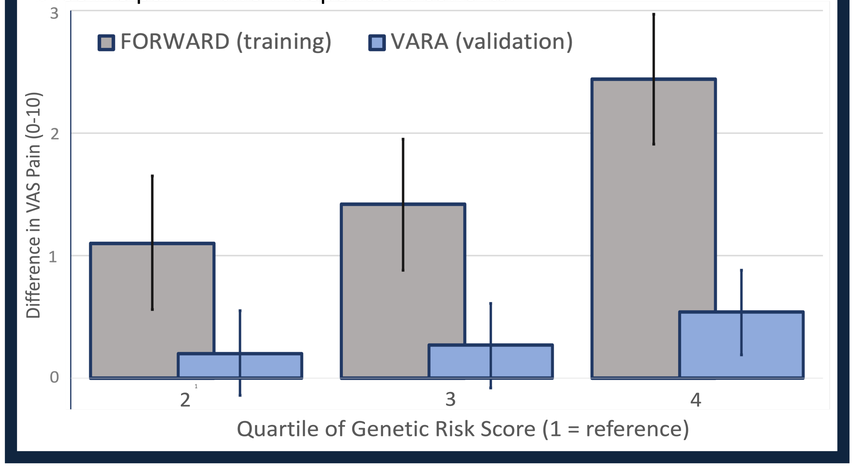

Table 1. GRS quartile is associated with longitudinal pain scores in two independent cohorts.

GRS Quartile	FORWARD (VAS Pain) (N = 756, obs. = 9797) β (95% CI)	P	VARA (VAS Pain) (N = 2176, obs. =) β (95% CI)	P
1	ref	--	ref	--
2	0.59 (0.17,1.01)	<0.01	0.05 (-0.2,0.28)	0.68
3	0.91 (0.48,1.34)	<0.01	0.21 (-0.12,0.35)	0.10
4	1.51 (1.08,1.94)	<0.01	0.33 (0.10,0.58)	0.01

* Adjusted for age, sex, race

Table 2. GRS quartile is associated with baseline disease activity scores in two independent cohorts.

GRS Quartile	FORWARD (PAS-II) N = 758 (obs. = 9797) β (95% CI)	P	VARA (RAPID3) N = 2097 (obs. = 21972) β (95% CI)	P
1	ref	--	ref	--
2	0.43 (0.07, 0.8)	0.02	0.28 (-0.31, 0.87)	0.35
`3	0.78 (0.41, 1.16)	<0.01	0.43 (-0.15, 1.02)	0.15
4	1.17 (0.8, 1.55)	<0.01	0.77 (0.18, 1.35)	0.01

* Adjusted for age, sex, race

Table 3. GRS quartile is associated with longitudinal disease activity scores in two independent cohorts.

GRS Quartile	FORWARD (PAS-II) N = 756 β (95% CI)	P	VARA (RAPID3) N = 1780 β (95% CI)	P
1	ref	--	ref	--
2	0.79 (0.35, 1.23)	<0.01	0.46 (-0.33, 1.26)	0.25
3	0.97 (0.54, 1.40)	<0.01	0.40 (-0.39, 1.19)	0.32
4	1.28 (1.26, 2.13)	<0.01	1.06 (0.33, 1.26)	<0.01

* Adjusted for age, sex, race

- GRS was not associated with swollen joints, C Reactive Protein levels, or physician global scores in VARA

CONCLUSIONS

- **A genetic risk score based on previously identified pain-related SNPs predicted greater RA pain in an external independent cohort**
- Comprehensive genetic risk scores may eventually provide meaningful clinical value for understanding pain in RA patients with increasing insight into pain-related genetics and advanced methods such as machine learning

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