Genome-wide association study of genetically independent phenotypes identifies shared genetic factors associated with chronic musculoskeletal pain

Yakov A. Tsepilov[1,2,*], Maxim B. Freidin[3,*], Alexandra S. Shadrina[1,2], Sodbo Z. Sharapov[1,2], Elizaveta E. Elgaeva[1,2], Jan van Zundert[4,5], Lennart C. Karssen[6], Pradeep Suri[7,8,9,10], Frances M.K. Williams[3], Yurii S. Aulchenko[1,2,6,11]

[1]Novosibirsk State University, Novosibirsk, Russia [2]Institute of Cytology and Genetics, Novosibirsk, Russia [3]King's College London, London, UK [4]Maastricht University Medical Centre, Maastricht, The Netherlands [5]ZOL Genk/Lanaken, Belgium [6]PolyOmica, 's-Hertogenbosch, the Netherlands [7]VA Puget Sound Health Care System, Seattle, USA [8]Department of Veterans Affairs Office of Research and Development, Seattle, USA [9]University of Washington, Seattle, USA [10]Clinical Learning, Evidence, and Research (CLEAR) Center, University of Washington, Seattle, USA [11]Department of Complex Genetics, Care and Public Health Research Institute, Maastricht University, The Netherlands

*MF and YT contributed equally to this work.

e-mail: tsepilov@bionet.nsc.ru

Background

Pain and, especially, chronic pain that lasts for 3 and more consecutive months has a negative impact on all aspects of human life. However, little is known about the mechanisms of chronic pain onset. In part, it is caused by the fact that genetic studies of pain are complicated by the high complexity and heterogeneity of the phenotype. Nevertheless, recent studies have shown that chronic pain is a complex genetic trait with heritability in between 30% to 60%. Moreover, it was found that various types of chronic pain have some genetic factors in common. In this research, we applied principal component analysis (PCA) to reduce the heterogeneity and reveal shared genes and pathways for distinct, though related, pain phenotypes.

Aim

Reveal the main genetic component that underlies the risk of chronic musculoskeletal pain observed at four different sites locations: back, neck/shoulder, hip, and knee, using data from the UK Biobank.

Materials and methods

Figure 1. Overview of the study. European ancestry individuals provided the matrix of genetic covariances and orthogonal transformation coefficients. The four chronic musculoskeletal pain phenotypes were decomposed into four genetically independent phenotypes (GIPs). Orthogonal transformation coefficients were further used to construct GIPs in the replication cohorts of European, African, and South Asian ancestry individuals. For each GIP, GWAS results were obtained. Replication of associations and in silico functional analyses were based on the meta-analyses of GWAS for the replication cohorts and European ancestry cohorts, respectively. For replicated loci, the most likely causal genes were prioritized.
DEPICT, Data-driven Expression Prioritized Integration for Complex Traits framework; GIP, genetically independent phenotype; PC, principal components; SMR/HEIDI, Summary data-based Mendelian Randomization analysis followed by the Heterogeneity in Dependent Instruments test; FUMA, Functional Mapping and Annotation of Genome-Wide Association Studies platform.

Results

- Four GIPs for four chronic musculoskeletal pain types were evaluated (Figure 2).
- 9 loci were shown to be associated with GIPs, 6 of them were replicated (Table 1).
- 13 genes located near the lead SNPs were prioritized in the identified loci; they were shown to be related to musculoskeletal disorders, nervous system and skeletal development.
- Significant enrichment for the terms related to nervous system and its development was shown for GIP1-associated SNPs.
- Strong genetic correlations between GIP1 and various anthropometric, morphological, socio-demographic and psychiatric human traits were identified (Figure 3).

Table 1. Top SNPs associated with GIPs.

GIP	Lead SNP	Chr:position	Ref/Alt/EA	Nearest gene	Discovery cohort			Meta-analysis of 3 replication cohorts	
					β	P	EAF	β	P
GIP2	[illegible]	[illegible]	C/T	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	T/C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	T/C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	T/C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	G/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	G/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP2	[illegible]	[illegible]	G/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP2	[illegible]	[illegible]	G/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GIP1	[illegible]	[illegible]	G/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Replicated associations are shown in bold.

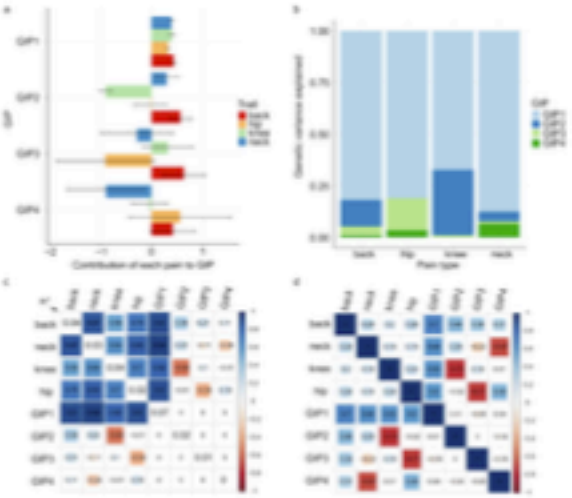

Figure 2. Genetically independent phenotypes (GIP) for chronic musculoskeletal pain. a. Barplots depicting the contribution of the four chronic musculoskeletal pain traits to each GIP. The bars represent orthogonal transformation coefficients, and the whiskers indicate their 95% confidence intervals. **b.** Genetic variance of the studied chronic musculoskeletal pain explained by four GIPs. **c.** Estimated matrix of genetic correlations between the four chronic musculoskeletal pain phenotypes and GIPs. The diagonal elements represent estimates of SNP-based heritability (h2) on the observed scale for each trait. **d.** Matrix of phenotypic correlations between the four chronic musculoskeletal pain phenotypes and GIPs (estimated for pain phenotypes and predicted for GIPs). Estimates for c, d were obtained using the discovery cohort of European ancestry individuals (N = 265,000).

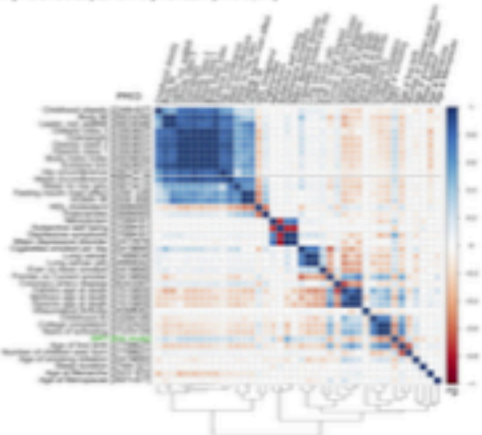

Figure 3. Matrix of genetic correlations between GIP1 and human complex traits. Color depicts the sign and absolute value of the genetic correlation coefficients (rg). Genetic correlations between GIP1 and all presented traits were statistically significant (P < 3.39e-05).
HDL, high density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; PMID, PubMed ID number of the literature source providing GWAS summary statistics.

Conclusion

We suggest that main genetic principal component (GIP1) represents a biopsychological base of chronic pain, related to physiological and psychological aspects and likely reflecting pain perception and pain processing.

Acknowledgements

This study was supported by the European Community's Seventh Framework Programme funded project PainOmics (Grant agreement # 602736) and by the Russian Ministry of Science and Education under the 5-100 Excellence Program. The research has been conducted using the UK Biobank Resource (project # 18219).

The study was published:
Tsepilov, Y.A., Freidin, M.B., Shadrina, A.S. et al. Analysis of genetically independent phenotypes identifies shared genetic factors associated with chronic musculoskeletal pain conditions. Commun Biol 3, 329 (2020). https://doi.org/10.1038/s42003-020-1051-9