FORWARD
The National Databank for Rheumatic Diseases

RHEUMATOLGY RESEARCH FOUNDATION
AWARD RECIPIENT

Genetic variants in cannabinoid receptor 2 are associated with perceived effectiveness of cannabis in treating RA-related pain.

Relationship Between Genetic Variants in Cannabinoid Receptor 2 and Self-Reported Effectiveness of Cannabis for Pain Management in Rheumatoid Arthritis

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BACKGROUND

- Cannabinoid receptor 2 (CB2) is a member of the cannabinoid receptor family and is encoded by the CNR2 gene
- CB2 receptors are found primarily in immune cells, and their activation exerts anti-inflammatory effects
- Variants in CNR2 have been linked to pain, autoimmune disorders, and depression
- Objective: to examine relationships between CNR2 variants and self-reported effectiveness of cannabis in the treatment of RA-related pain

METHODS

- Data were provided by adults with RA participating in FORWARD who provided blood samples and reported use of cannabis or cannabis-derived products for the purpose of treating arthritis-related pain
- Genotyping was performed with the Illumina Infinium Global Screening Array
- CNR2 variants with minor allele frequencies greater than 0.05 were included in the analysis (rs4625225, rs7512349, and rs9424399)
- Multivariable logistic regression was used to determine whether the presence of the minor allele in each variant was associated with self-reported effectiveness of cannabis
- Models were adjusted for age, sex, race, cigarette smoking history, RA duration, BMI, glucocorticoid use, NSAID use, opioid use, Rheumatic Disease Comorbidity Index (RDCI), history of depression, and Patient Activity Scale II (PAS-II)

RESULTS

- A total of 134 participants met inclusion criteria, of whom 79 (59%) found cannabis effective in treating their RA-related pain
- Respondent characteristics are presented in Table 1 and genotype distributions of the three variants are presented in Table 2
- Adjusted models indicated that for all three variants, the presence of at least one copy of the minor allele was associated with reduced odds of finding cannabis effective for pain management compared to those homozygous for the major allele (Figure 1)

CONCLUSION

- Our results indicate that the perceived effectiveness of cannabis in the treatment of RA-related pain varies significantly by CNR2 genotype
- The three variants are in linkage disequilibrium (Figure 2) and are also all silent, so a related variant not assessed by the array used in this study may be causative of the identified relationship
- These results highlight the possible impact of genetic variations on the therapeutic potential of cannabis for arthritis pain management, which may be relevant for personalized medicine as legalization and medicinal use of cannabis continue to become more widespread in the United States
- Further research is warranted to confirm these findings, to elucidate underlying mechanisms, and to better understand the relationships between CB2 and pain, cannabis use, and any potential immunomodulatory effects

Table 1. Characteristics of study participants by self-reported effectiveness of cannabis in RA pain management.

Characteristic	Not Effective n=55	Effective n=79
Age, years, mean (SD) *	68.9 (9.7)	64.3 (10.9)
Female, %	88.9	92.4
White race, %	94.5	91.0
Hx cigarette smoking, %	41.8	40.5
RA duration, years, mean (SD)	25.1 (13.5)	24.8 (11.7)
BMI, kg/m^2, mean (SD)	28.7 (6.6)	27.5 (6.3)
Glucocorticoid use, %	25.5	14.1
NSAID use, %	27.3	30.8
Opioid use, %	20.0	20.5
RDCI, 0-9, mean (SD)	2.2 (1.8)	2.2 (2.0)
Hx depression, % *	54.5	73.4
PAS-II, 0-10	3.7 (1.9)	4.4 (2.1)

Statistically significant differences (t-test or chi-square, $p<0.05$) are marked with an asterisk (*). BMI=body mass index; NSAID=non-steroidal anti-inflammatory drugs; RDCI=Rheumatic Disease Comorbidity Index; PAS-II=Patient Activity Scale II

Table 2. Genotype distributions of the investigated CNR2 variants.

Variant	Genotype	n (%)
rs4625225	TT	83 (62)
	TC	48 (36)
	CC	3 (2)
rs7512349	TT	89 (66)
	TC	43 (32)
	CC	2 (1)
rs9424399	AA	88 (66)
	AG	43 (32)
	GG	3 (2)

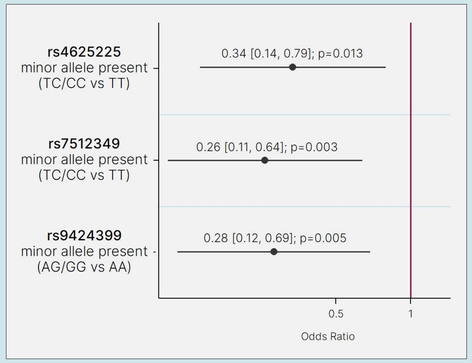

Figure 1. Adjusted odds ratios and 95% confidence intervals for each minor allele's association with reported effectiveness of cannabis in treating RA-related pain. Each model was adjusted for age, sex, white race, cigarette smoking history, calendar year, RA duration, BMI, glucocorticoid use, NSAID use, opioid use, Rheumatic Disease Comorbidity Index (RDCI), history of depression, and Patient Activity Scale II (PAS-II).

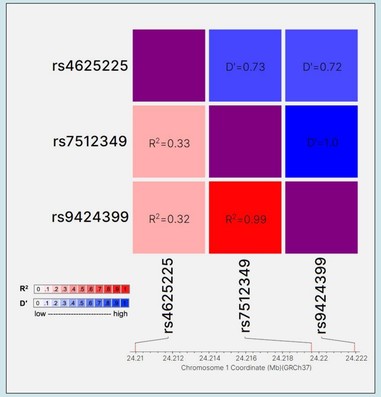

Figure 2. Heatmap of pairwise linkage disequilibrium statistics for the three variants. Created with LDlink using European reference populations.

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