Genetic Variations of Neuroactive Steroid Pathways in Interferon-α-Induced Depression in Patients with Hepatitis C Viral Infection

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INTRODUCTION

- Neuroinflammation is a growing area of interest in depression research. Interferon–alpha (IFN–α) induced depression serves as the most powerful clinical model, as its pathophysiology involves hypothalamic–pituitary–adrenal (HPA) axis activation.
- Neuroactive steroids (NAS), especially progesterone and allopregnanolone, regulate neuroplasticity, neuroinflammation and HPA axis function by interacting with receptors such as progesterone receptor membrane component 1 (PGRMC1), membrane progesterone receptor (mPR) and type A γ–aminobutyric acid (GABAA) receptors.
- Given their ability to modulate HPA axis activity, **neuroactive steroids present a potential therapeutic avenue for IFN–α induced depression**, but the underlying mechanisms remain unexplored.

METHODS

- Participants: 291 patients (134 females, 157 males) with chronic HCV undergoing interferon–α IFN–α therapy
  - Case Group (n = 66): patients who developed IFN–α–induced depression during the treatment
  - Control group (n = 225): patients who didn't developed
- Candidate gene and SNPs: **581 SNPs in 40 candidate genes related to neuroactive steroid biosynthesis and action on the central nervous system (CNS)**
- Statistical Analysis
  - Allelic association tests for SNPs: assess the difference in allele frequencies between cases and controls with empirical p–values
  - Haplotype association tests and stratified analyses by sex: only conducted if the gene reached statistical significance in the allelic association tests.

RESULTS

- Allelic association tests:
  - **rs3121819 in GABRD** (GABA A R subunit Delta) (OR = 1.989, empirical p = 0.0016),
  - **rs12411080 in HSD3B2** (Hydroxy–Delta–5–Steroid Dehydrogenase) (OR = 0.4406, empirical p = 0.0276),
  - **rs11675297 in SRD5A2** (Steroid 5 Alpha–Reductase 2) (OR = 3.218, empirical p = 0.0098).
- Haplotype association test:
  - one significant haplotype in SRD5A2 which the sequence is TTCTCCGCACATT (chi square = 8.781; empirical p–value = 0.0298)
- Stratification by sex did not significantly alter these associations.

Table 2 Characteristics of subjects

|		Case group (N = 66) N (%)	Control group (N = 225) N (%)	p-value
Sex	Female	41 (30.6)	93 (69.4)	*0.003
	Male	25 (15.9)	132 (84.1)	
Age		51.6 ± 11.04	52.12 ± 12.02	0.835
Marriage	Single	14 (87.1)	29 (12.9)	0.114
	Married	52 (78.8)	196 (21.2)	
Education (years)		9.48 ± 4.03	10.6 ± 3.99	*0.030

Table 3 Odds ratio of having IFN-a-induced depression under treatment in relation to SNPs

Pathway	Gene	SNP	Allele	χ2	p-value	Odd Ratio	Empirical p-Value
Neuroactive steroid biosynthesis	SRD5A2	rs11675297	G>A	10.380	0.001	3.218	*0.009
	HSD3B2	rs12411080	G>A	5.126	0.024	0.441	*0.028
Tonic GABAergic Inhibition	GABRD	rs3121819	A>G/T	9.174	0.002	1.989	*0.002

Table 4 Stratified analysis of significant SNPs by sex

Pathway	Gene	SNP	p-value	OR_S	OR_A	OR percentage difference
Neuroactive steroid synthesis	SRD5A2	rs11675297	0.004	2.982	3.218	0.073
	HSD3B2	rs12411080	0.036	0.456	0.441	0.034
Tonic GABAergic Inhibition	GABRD	rs3121819	8.804	1.992	1.989	0.002

Figure 1. Haplotype association test
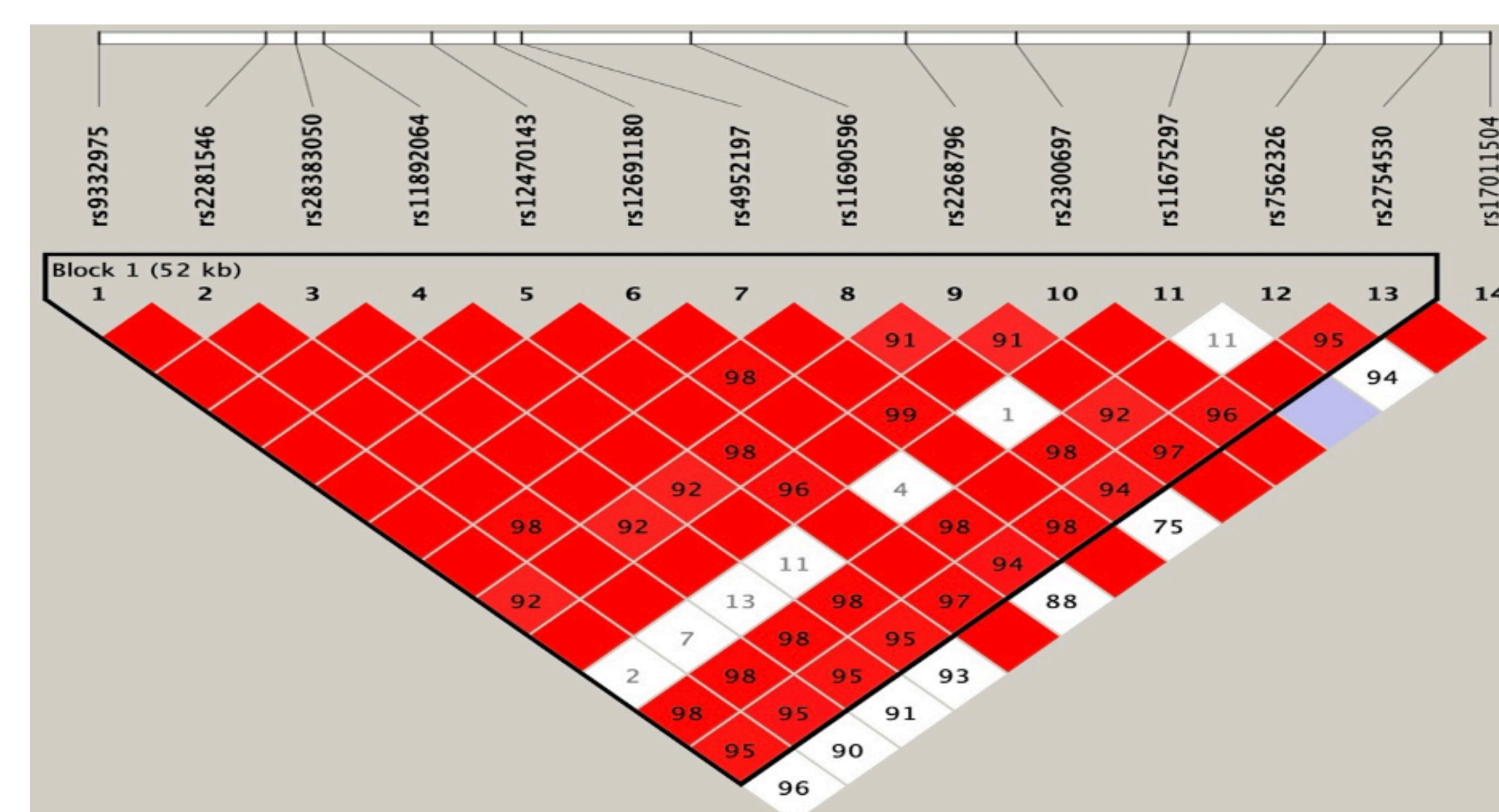
CONCLUSION

- **This study delivers the first genetic evidence linking neuroactive steroid synthesis and GABAergic neurotransmission to IFN–α–induced depression.**
- These findings highlight the neuroactive steroid pathway as a promising target to further investigate the mechanisms and potential treatment strategies for depression.