



# ***ERICH3* Genetic Variation Associated with Plasma Serotonin and Change in Plasma Serotonin After SSRI Therapy: Pharmacometabolomics-informed Pharmacogenomics**

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# Introduction

- **Major depressive disorder (MDD)** is a common and life-threatening psychiatric disease.
- **Selective serotonin reuptake inhibitors (SSRIs)** are the “standard of care” for MDD drug therapy.
- **Response to SSRIs** is highly variable, with less than half of MDD patients achieving remission.
- Although it is known that inheritance contributes to SSRI response, to this time, very few validated signals have been obtained for SSRI response by using **genome-wide association studies (GWAS)** alone.

# Pharmacometabolomics-informed Pharmacogenomics

Associate Metabolite Levels  
with Clinical Outcomes



GWAS for Metabolite Levels to  
Identify Genes Associated with  
Metabolite Concentrations

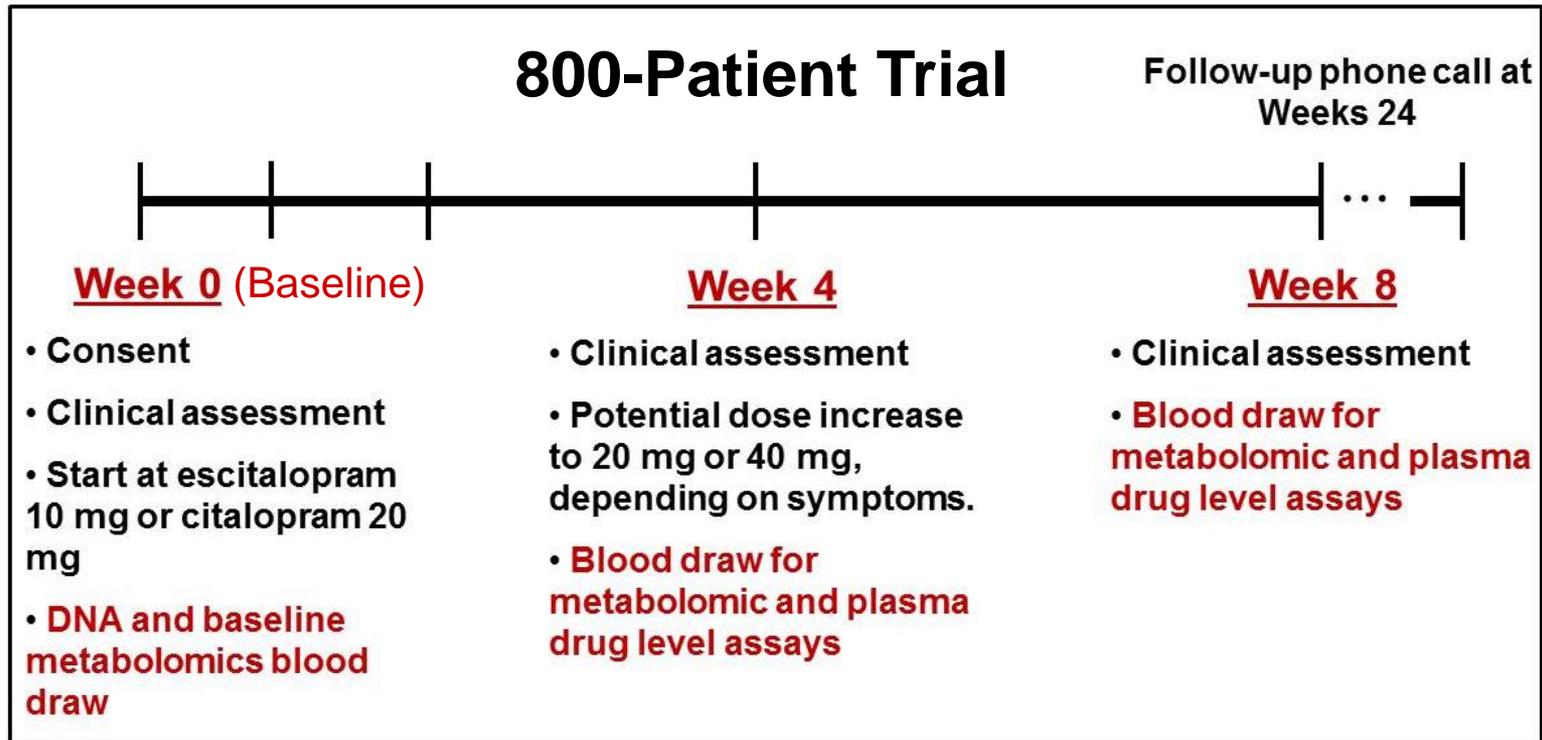


Functionally validate the Genes  
Identified during GWAS



Replicate the Gene/SNPs in  
Other Studies

# Mayo PGRN Citalopram-Escitalopram Clinical Trial



- **918 patient samples** (306 subjects, 3 time points)
- **31 metabolites** assayed by quantitative targeted LCECA platform.

# Plasma Serotonin and Change in Plasma Serotonin were Associated with SSRI Clinical Response

Association of Plasma Serotonin Concentration with Clinical Outcomes

Clinical Outcomes \ Plasma Serotonin	Remission		Response		% Change	
	4 weeks	8 weeks	4 weeks	8 weeks	4 weeks	8 weeks
Baseline	$p = 0.012$	$p = 0.028$	$p = 0.007$	$p = 0.047$	$p = 0.015$	$p = 0.019$
Changes after 4 weeks	$p = 0.011$	$p = 0.041$	$p = 0.026$	$p = 0.060$	$p = 0.021$	$p = 0.024$
Changes after 8 weeks	$p = 0.069$	$p = 0.147$	$p = 0.037$	$p = 0.130$	$p = 0.041$	$p = 0.06$

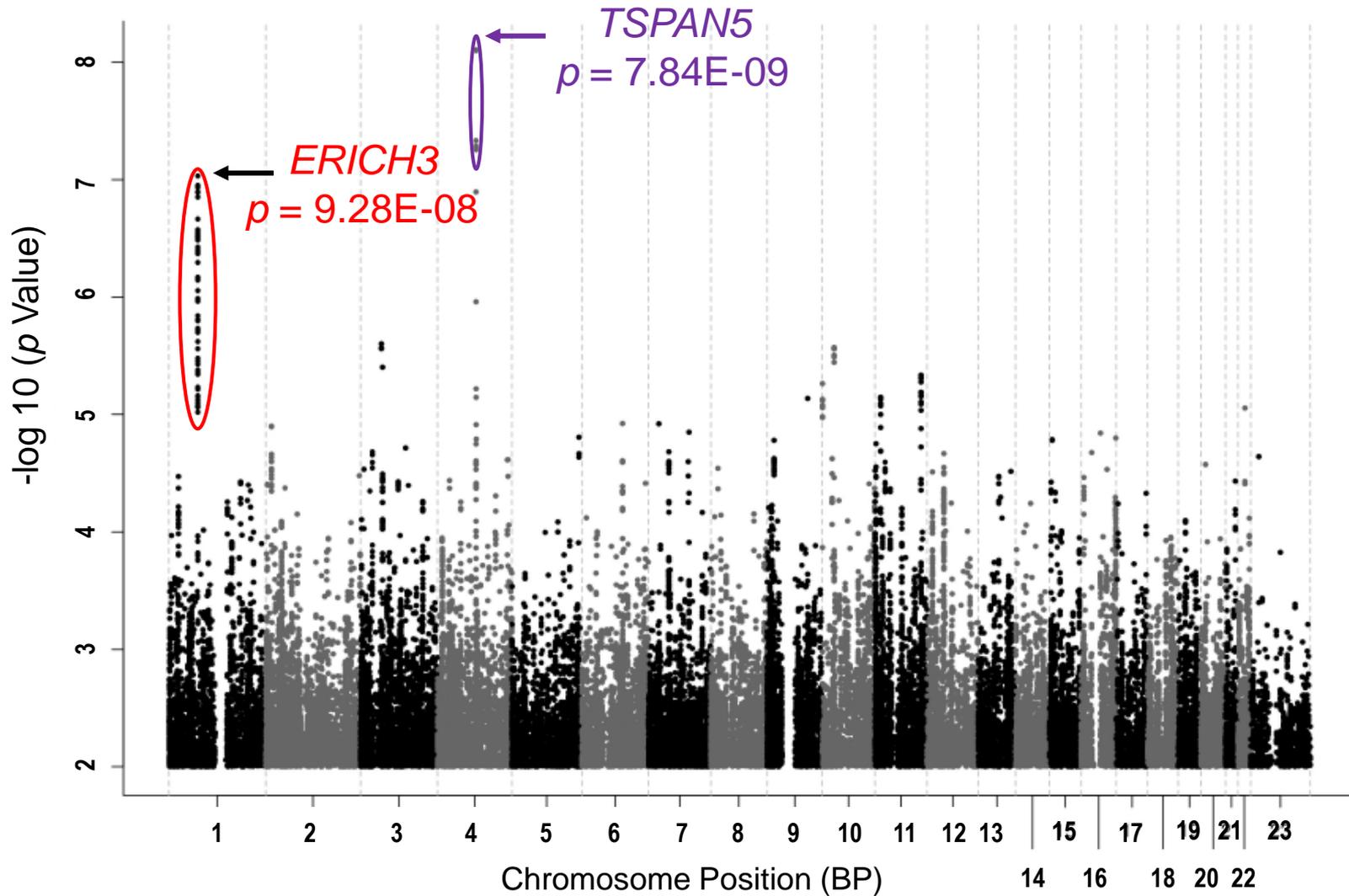
**Remission:** post-treatment QIDS < 5 or HAMD < 7.

**Response:** >50% reduction in depression score.

Gupta M.\*, Neavin D.\*, Liu D.\*, et al. *Molecular Psychiatry*. In press

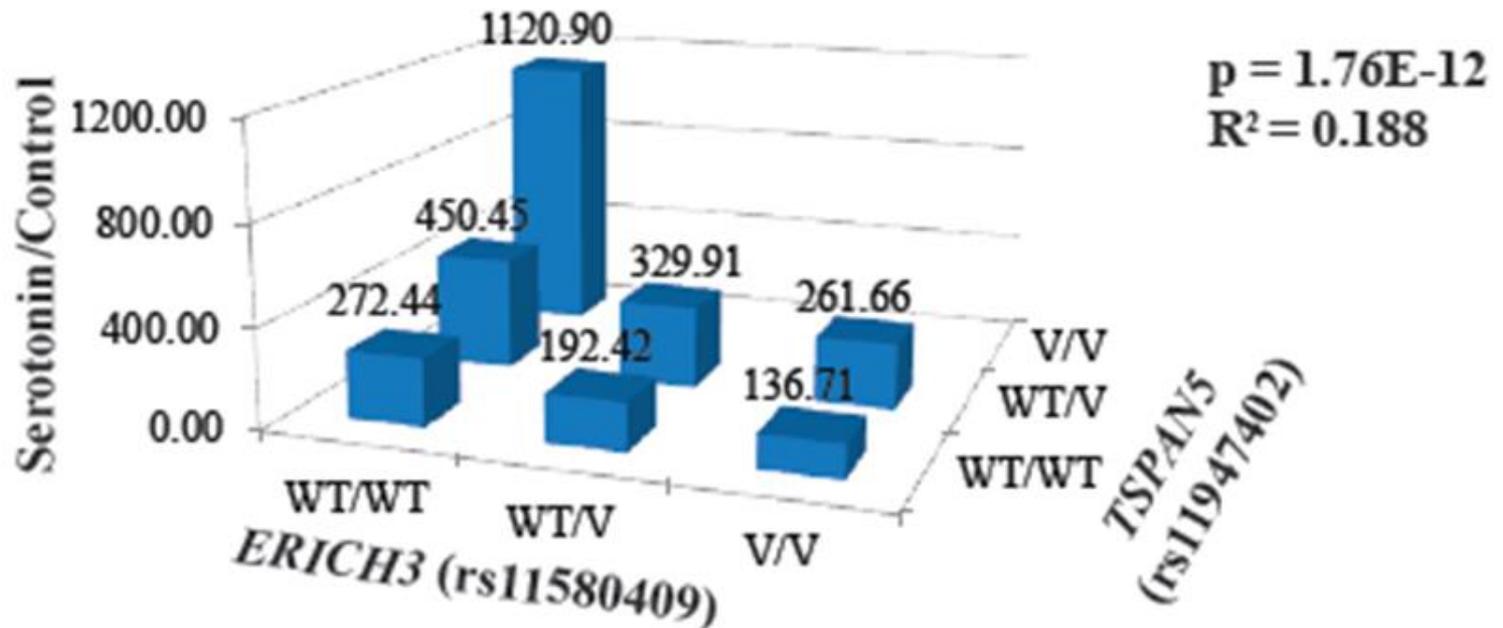
\* Co-first Authors.

# Baseline Plasma Serotonin GWAS



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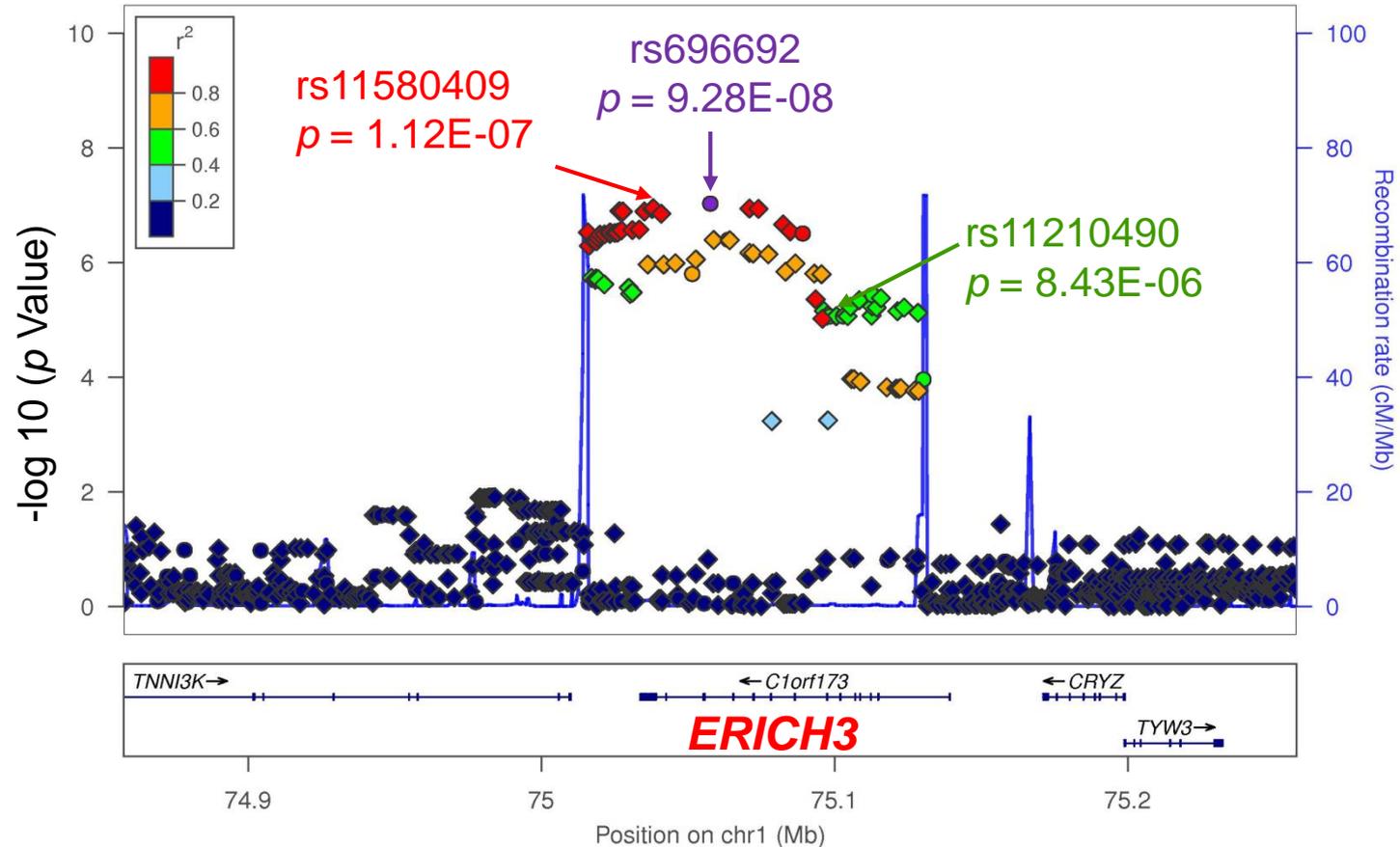
# *ERICH3* and *TSPAN5* SNPs with Baseline Plasma Serotonin Concentrations



*ERICH3* and *TSPAN5* are highly expressed in **brain tissues** base on the GTEx data. (<http://www.gtexportal.org/>)

Gupta M.\*, Neavin D.\*, Liu D.\*, et al. *Molecular Psychiatry*. In press  
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# ERICH3 Locus Zoom



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# ERICH3 SNPs Information

Rank	SNP ID	P Value	Estimate	MAF	N	SNP Location	cDNA Change	AA Substitution
1	rs696692	9.28E-08	-0.46	0.355	290	Intron	NA	NA
2	rs11580409	1.12E-07	-0.46	0.361	290	Exon 14	3166 T>G	L1056V
...	...	...	...	...	...	...	...	...
66	rs11210490	8.43E-06	-0.36	0.467	290	Exon 7	790 C>G	P264A

SNPs were ranked by **p values** in GWAS; **MAF**: minor allele frequency; **AA**: amino acid ; **NA**: not applicable

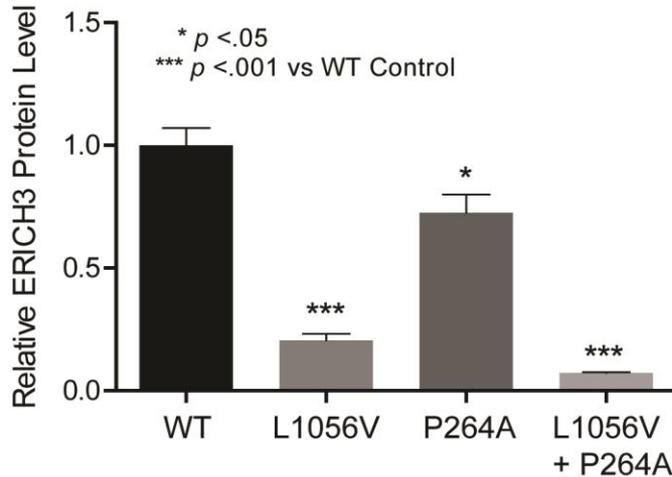
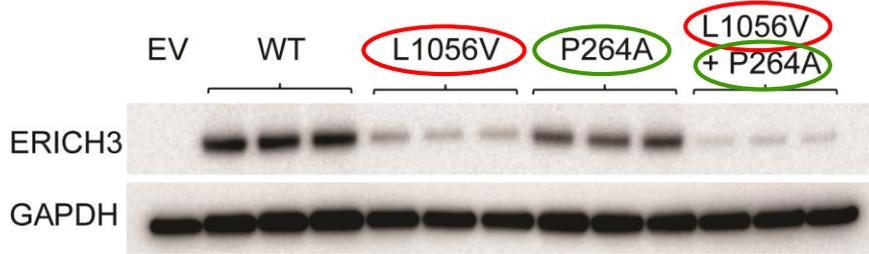
## Linkage Disequilibrium (LD) Analysis in Caucasian

SNP	Proxy	Distance	R Squared
rs11580409	rs11210490	59198	0.437

<https://www.broadinstitute.org/mpg/snap/>

Gupta M.\* , Neavin D.\* , Liu D.\* , *et al.* *Molecular Psychiatry*. In press  
\* Co-first Authors.

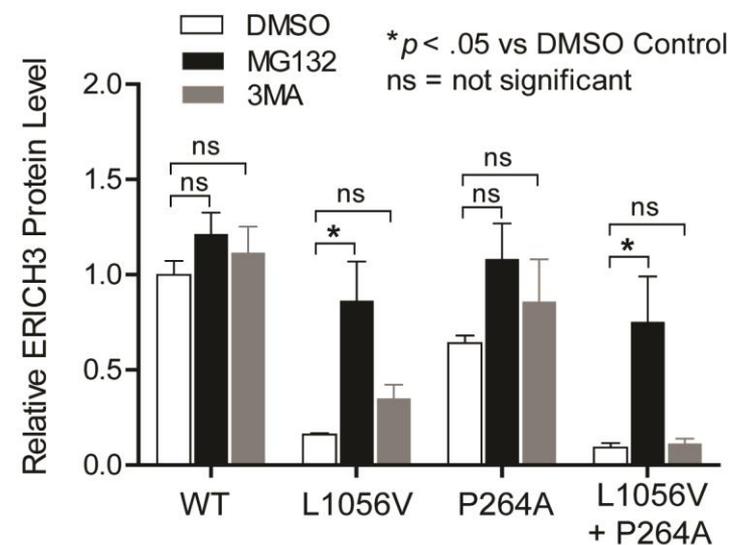
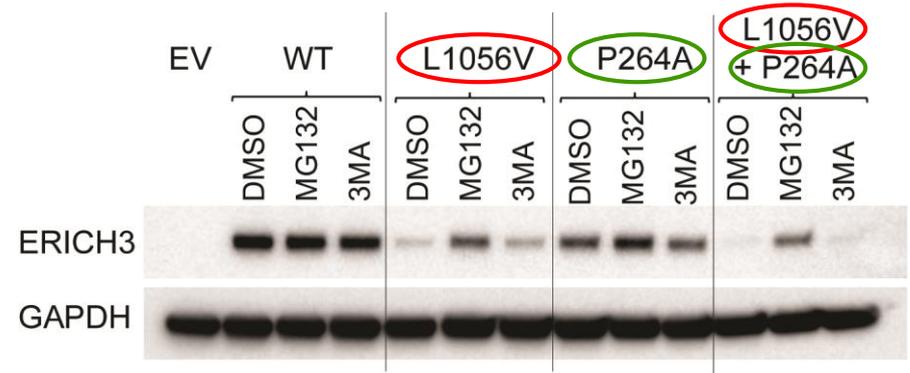
# ERICH3 Non-Synonymous SNP Function



WT: Wild Type

L1056V: rs11580409 (A>C)

P264A: rs11210490 (G>C)



MG132: Proteasome inhibitor,

(carbobenzoxy-Leu-Leu-leucinal) ;

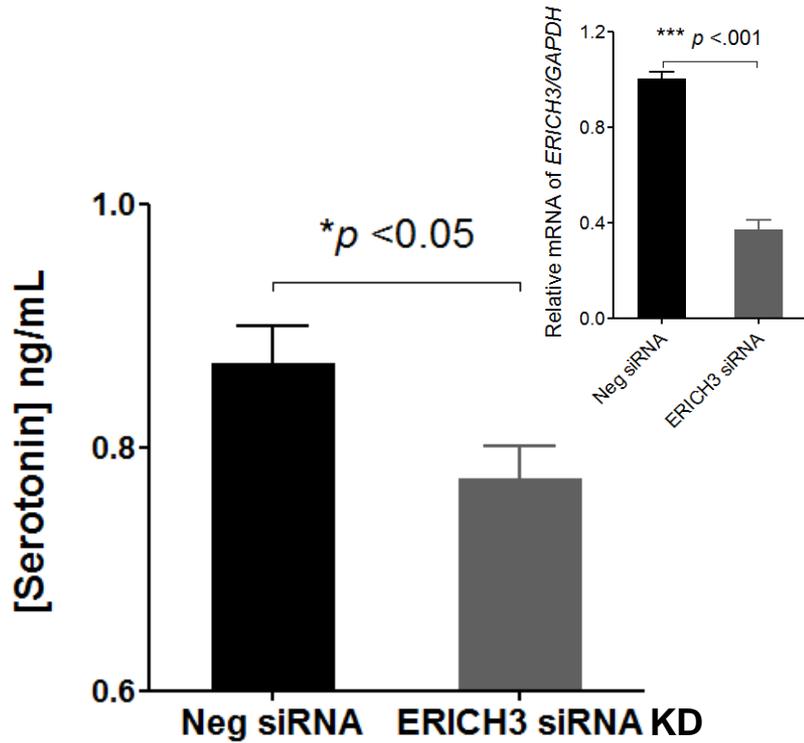
3MA: Autophagy inhibitor, (3-methyladenosine)

Gupta M.\*, Neavin D.\*, Liu D.\*, et al. *Molecular Psychiatry*. In press

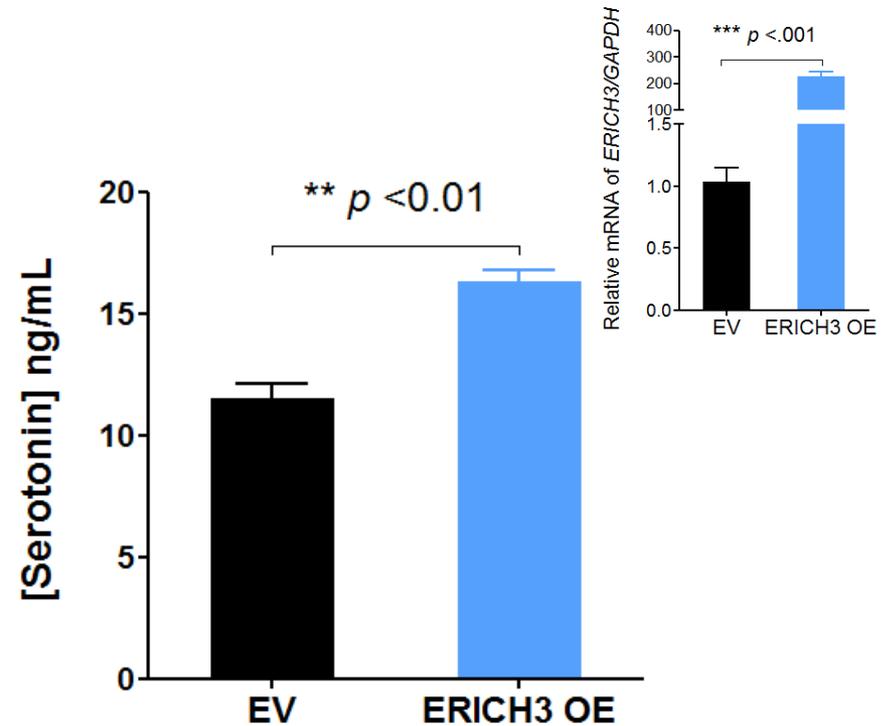
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# ERICH3 KD, OE and Serotonin Concentrations in Cell Culture Media

## hNSC-derived Neurons



## SK-N-BE(2) Neuroblastoma



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# ERICH3 SNPs and Clinical Outcomes in SSRI GWAS

## SSRI Response at Four or Six Weeks Studies and $p$ Values

	PGRN-AMPS	ISPC	STAR*D
rs11580409 ( <i>ERICH3</i> )	0.16	<b>0.022</b>	<b>0.041</b>

**PGRN-AMPS:** Mayo Clinic Pharmacogenomics Research Network-Antidepressant Medication Pharmacogenomics Study

**ISPC:** International SSRI Pharmacogenomics Consortium

**STAR\*D:** Sequenced Treatment Alternatives to Relieve Depression

Gupta M.\*, Neavin D.\*, Liu D.\*, *et al.* *Molecular Psychiatry*. In press

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# Conclusions

- Plasma serotonin concentrations were associated with SSRI clinical outcomes.
- GWAS for plasma serotonin concentrations identified SNPs across the *ERICH3* genes.
- *ERICH3* nsSNPs affect protein quantity and that they are associated with plasma serotonin concentrations and with SSRI response.

# Pharmacometabolomics-informed Pharmacogenomics

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