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

1. Associate Metabolite Levels with Clinical Outcomes
2. GWAS for Metabolite Levels to Identify Genes Associated with Metabolite Concentrations
3. Functionally validate the Genes Identified during GWAS
4. Replicate the Gene/SNPs in Other Studies
Mayo PGRN
Citalopram-Escitalopram Clinical Trial

800-Patient Trial

Follow-up phone call at Weeks 24

**Week 0** (Baseline)
- Consent
- Clinical assessment
- Start at escitalopram 10 mg or citalopram 20 mg
- DNA and baseline metabolomics blood draw

**Week 4**
- Clinical assessment
- Potential dose increase to 20 mg or 40 mg, depending on symptoms.
- Blood draw for metabolomic and plasma drug level assays

**Week 8**
- Clinical assessment
- Blood draw for metabolomic and plasma drug level assays

- 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

<table>
<thead>
<tr>
<th>Plasma Serotonin</th>
<th>Clinical Outcomes</th>
<th>Remission</th>
<th>Response</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>4 weeks</td>
<td>8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$p = 0.012$</td>
<td>$p = 0.028$</td>
<td>$p = 0.007$</td>
</tr>
<tr>
<td>Changes after 4 weeks</td>
<td></td>
<td>$p = 0.011$</td>
<td>$p = 0.041$</td>
<td>$p = 0.026$</td>
</tr>
<tr>
<td>Changes after 8 weeks</td>
<td></td>
<td>$p = 0.069$</td>
<td>$p = 0.147$</td>
<td>$p = 0.037$</td>
</tr>
</tbody>
</table>

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

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


* Co-first Authors.
Baseline Plasma Serotonin GWAS

- TSPAN5
  - $p = 7.84 \times 10^{-9}$

- ERICH3
  - $p = 9.28 \times 10^{-8}$


* Co-first Authors.
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/)

* Co-first Authors.
**ERICH3 Locus Zoom**

- rs11580409  
  \( p = 1.12 \times 10^{-07} \)
- rs696692  
  \( p = 9.28 \times 10^{-08} \)
- rs11210490  
  \( p = 8.43 \times 10^{-06} \)
**ERICH3 SNPs Information**

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

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

**Linkage Disequilibrium (LD) Analysis in Caucasian**

<table>
<thead>
<tr>
<th>SNP</th>
<th>Proxy</th>
<th>Distance</th>
<th>R Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11580409</td>
<td>rs11210490</td>
<td>59198</td>
<td>0.437</td>
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</tbody>
</table>

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

* Co-first Authors.
**ERICH3** Non-Synonymous SNP Function

**GT**: Wild Type
**L1056V**: rs11580409 (A>C)
**P264A**: rs11210490 (G>C)

**MG132**: Proteasome inhibitor, (carbobenzoxy-Leu-Leu-leucinal)
**3MA**: Autophagy inhibitor, (3-methyladenosine)

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ERICH3 KD, OE and Serotonin Concentrations in Cell Culture Media

hNSC-derived Neurons

- **Neg siRNA**
- **ERICH3 siRNA KD**

[Graph showing concentration of serotonin in ng/mL for Neg siRNA and ERICH3 siRNA KD.]

* *p < 0.05

SK-N-BE(2) Neuroblastoma

- **EV**
- **ERICH3 OE**

[Graph showing concentration of serotonin in ng/mL for EV and ERICH3 OE.]

**p < 0.01


* Co-first Authors.
**ERIC3 SNPs and Clinical Outcomes in SSRI GWAS**

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

<table>
<thead>
<tr>
<th></th>
<th>PGRN-AMPS</th>
<th>ISPC</th>
<th>STAR*D</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11580409 (ERIC3)</td>
<td>0.16</td>
<td>0.022</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**PGRN-AMPS:** Mayo Clinic Pharmacogenomics Research Network-Antidepressant Medication Pharmacogenomics Study  
**ISPC:** International SSRI Pharmacogenomics Consortium  
**STAR*D:** Sequenced Treatment Alternatives to Relieve Depression

*Co-first Authors.
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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