Relationship Between the Fatty Acid Desaturase 2 (FADS2) Gene Variant rs174583 and Lipid Levels in Subjects with Schizophrenia

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Role of Cholesterol in CVD

- Most common cause of cardiovascular disease (CVD) is atherosclerosis
- The endothelium regulates many elements of cardiovascular health
- Endothelial dysfunction increases CVD risk
  - Regardless of presence of vascular disease
N-3 Fatty Acids, AAP Use, and Endothelial Functioning

- AAP = atypical antipsychotic
- RHI = reactive hyperemia index
- Higher value = better endothelial function
- AAP non-users = positive relationship between O3FA intake and RHI (p= 0.007)
- AAP users = no relationship (p> 0.6)
Study Objectives

- To determine the relationship between the *FADS2* rs174583 genotypes and both lipid levels and endothelial function in patients diagnosed with schizophrenia receiving antipsychotic treatment
  - Control for omega-3 fatty acids (O3FA) dietary intake
  - Assess for AAP interaction
**Methods**

**STUDY DESIGN:** Cross-sectional analysis

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis NOS</td>
<td>• Inability/unwilling to provide informed consent</td>
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<tr>
<td>• 18-90 years old</td>
<td>• Active substance abuse</td>
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<tr>
<td>• Antipsychotic treatment ≥ 6 months</td>
<td>• Excluding alcohol abuse</td>
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<td>• Use of illicit substances in past month</td>
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<td>• T2DM prior to AAP use</td>
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</table>
Methods

Subjects meeting study criteria (8-hr fast)

Endothelial Function (EndoPat 2000; Itamar)

Genetic Analysis (rs174583 C/T)

Assessments
- Medication History Interview
- Smoking and Physical Activity
- 24-hr Food Recall x 3

Laboratory Measures (Metabolic Syndrome screening)
Subject Demographics

- No differences were found among listed variables, statin use, or AAP exposure based on FADS2 genotype

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n=143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.11 ± 11.30</td>
</tr>
<tr>
<td>Gender</td>
<td>62% (Male)</td>
</tr>
<tr>
<td>Race</td>
<td>62% (Caucasian)</td>
</tr>
<tr>
<td>Smokers</td>
<td>57%</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>46%</td>
</tr>
<tr>
<td>FADS2 rs174583 genotype</td>
<td>47.6% (CC), 39.8% (CT), 12.6% (TT)</td>
</tr>
</tbody>
</table>
# Results: Lipids and Genotype

<table>
<thead>
<tr>
<th>Laboratory Value (mg/dL)</th>
<th>TT (n=15)</th>
<th>CT (n=52)</th>
<th>CC (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol (TC)</strong> (p= 0.04)</td>
<td>152.4*</td>
<td>165.3</td>
<td>179.3</td>
</tr>
<tr>
<td><strong>LDL</strong> (p= 0.01)</td>
<td>87.13*</td>
<td>97.1</td>
<td>109.3</td>
</tr>
<tr>
<td><strong>TC/HDL</strong> (p= 0.03)</td>
<td>3.11*</td>
<td>3.48</td>
<td>3.73</td>
</tr>
<tr>
<td><strong>HDL</strong> (p= 0.97)</td>
<td>51.0</td>
<td>50.1</td>
<td>50.6</td>
</tr>
<tr>
<td><strong>Triglycerides (TG)</strong> (p= 0.73)</td>
<td>120.6</td>
<td>144.3</td>
<td>138.7</td>
</tr>
</tbody>
</table>

*Statistically significant results
Results: Lipids and N-3 Intake

- The relationships persisted after controlling for O3FA dietary intake
  - TC (p= 0.03)
  - LDL (p= 0.03)
  - TC/HDL (p= 0.03)
- No differences in either O3FA (p= 0.4480) or O6FA (p= 0.2366) intake among genotype groups
  - TT vs. CT and CC
AAPs interacted with the relationship between rs174583 TT genotype and LDL serum levels

- $F_{(3,108)} = 2.89$, $p = 0.03$

<table>
<thead>
<tr>
<th></th>
<th>LDL (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AAP users</td>
</tr>
<tr>
<td>rs174583 TT (n= 18)</td>
<td>96.5 ± 10.3</td>
</tr>
<tr>
<td>rs174583 C allele (n= 125)</td>
<td>107.7 ± 3.8</td>
</tr>
</tbody>
</table>
Results: Endothelial Functioning and AAP Use

- Subjects with the rs174583 TT genotype had better endothelial function
  - t = -2.17, p = 0.032
- AAPs interacted with the above relationship
  - $F_{(3,108)} = 4.94$, p = 0.028

<table>
<thead>
<tr>
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<th>AAP users</th>
<th>AAP non-users</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs174583 TT (n=18)</td>
<td>1.52 ± 0.18*</td>
<td>1.95 ± 0.23</td>
</tr>
</tbody>
</table>

*Meets criteria for endothelial dysfunction (<1.67)
Study Limitations

- Cross-sectional
- Used O3FA dietary intake
- Small sample size
- Did not control for multiple comparisons
- Only one \textit{FADS2} variant examined
  - Currently genotyping for others
Conclusions

- The *FADS2* rs174583 TT genotype = cardioprotective?
  - Reduced lipid levels (TC, LDL, TC/HDL)
  - Higher RHI
- Possible predictor for risk of antipsychotic induced metabolic complications
- AAP interference with cardioprotective relationships
  - LDL and RHI
Future Directions

- Continue genotyping additional variants
- Examine antipsychotic effects on desaturase activity
  - Detailed explanation for current study results
  - Rationale for association of certain antipsychotics and cardiometabolic dysfunction
- Prospective study of fatty acid supplementation
1. Which of the following clinical measurements may be positively affected by the FADS2 rs174583 TT genotype?

a) Glucose
b) Cholesterol
c) Waist Circumference
d) Blood pressure
Self-Assessment Questions

1. Which of the following clinical measurements may be positively affected by the *FADS2* rs174583 TT genotype?
   
a) Glucose  
b) Cholesterol  
c) Waist Circumference  
d) Blood pressure
2. Why is the delta-6-desaturase (*FADS2*) a critical early mediator of n-6 PUFA metabolism?

   a) This enzyme mediates the conversion of α-linolenic acid and linoleic acid to their respective fatty acids leading to decreased inflammatory eicosanoids

   b) This enzyme allows for the preferable conversion of α-linolenic acid to linoleic acid leading to higher production of weakly inflammatory eicosanoids

   c) This enzyme mediates the conversion of eicosapentaenoic acid and arachadonic acid resulting in greater production of docosahexaenoic acid

   d) Polymorphisms in this enzyme have been associated with higher levels of O3FA and lower levels of arachadonic acid resulting in lower production of strongly inflammatory eicosanoids
2. **Why is the delta-6-desaturase (FADS2) a critical early mediator of n-6 PUFA metabolism?**

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   d) Polymorphisms in this enzyme have been associated with higher levels of O3FA and lower levels of arachadonic acid resulting in lower production of strongly inflammatory eicosanoids
n-3 PUFAs

- α-linolenic acid (18:3 n-3)
  - 18:4 n-3
  - 20:4 n-3
  - eicosapentaenoic acid (20:5 n-3)
    - 22:5 n-3
    - docosahexaenoic acid (22:6 n-3)

n-6 PUFAs

- linoleic acid (18:2 n-6)
  - γ-linoleic acid (18:3 n-6)
    - dihomogamma-linoleic acid (20:3 n-6)
      - arachidonic acid (20:4 n-6)

**Delta-6-desaturase (FADS2)**

**Delta-5-desaturase (FADS1)**

Elongase

Weak inflammatory eicosanoids

Strong inflammatory eicosanoids
Questions?

• **Contact Information**
  – kngard@umich.edu

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