Towards the Implementation of Genetic Testing
for Antipsychotic-Induced Weight Gain

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www.pharmacogenetics.ca
Antipsychotic-induced weight gain

Mean weight (kg) after 6-10 weeks of treatment (Lett ... Müller, 2012)
Current trial-and-error approach

<table>
<thead>
<tr>
<th>Response</th>
<th>Side Effects</th>
<th>Success</th>
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Only 25% chance of treatment success at first trial
"...and you cannot change a thing, as you are completely controlled by your genes."
...out of 3 billion basepairs per person
SIMPLE TRAIT

\[ G \rightarrow \text{Phenotype} \]

Responsible for a minor portion of medical diseases (~1-5%)
**COMPLEX TRAIT**

Phenotype

Responsible for the majority of medical diseases (~95%)
Response & side effects

Additional factors

Pharmacokinetics

Pharmacodynamics

e.g., CYP2C19, CYP2D6

Dopamine, Serotonin, etc.

Gender, Nutrition

Age, Compliance, Fitness

Smoking, Ethnicity
Genetic analyses

- Cytogenetics
- Selected genotyping
- Full Sequencing

ATTGAGAAATGCAATGTCATACATG
GTTAAGTAATTGCTATTGATCACTT
ACTAGTTATGCAATTTGGGCAAATT
ATTTTGACTGTGACTCCCAGTTTAG
TTAGTTATG
Antipsychotic-induced Weight Gain: Genome Wide Study

This GWAS was done on N=180 youths age 7 to 16 treated with antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) for disruptive behaviour. Nearly all gained weight to some degree. (Correll CU et al., JAMA, 2009).

‘Manhattan’ Plot of minus log p-values
(Malhotra A, (...) Müller DJ, Kennedy JL (in press, Arch Gen Psych)
Melanocortin-leptinergic pathway

For more details: Please stay tuned!

Coming up: Presentation from Eva Brandl
Future perspectives

• Results need to be replicated in independent samples; new samples need to be collected

• Progresses in DNA sequencing, functional analyses and bioinformatics need to be incorporated

93% prediction

Lan et al., 2008
FROM HUMAN GENETICS AND GENOMICS TO PHARMACOGENETICS AND PHARMACOGENOMICS: PAST LESSONS, FUTURE DIRECTIONS

Pharmacogenetics, pharmacogenomics and personalized psychiatry: Are we there yet?

Global pharmacogenetics: giving the genome to the masses

Pharmacogenetics-based therapeutic recommendations — ready for clinical practice?
THE DECISION TREE

TAKING CONTROL OF YOUR HEALTH IN THE NEW ERA OF PERSONALIZED MEDICINE

THOMAS GOETZ
Response & side effects

Additional factors

Pharmacodynamics

Dopamine
Serotonin etc.

Pharmacokinetics

e.g., CYP2C19, CYP2D6

Gender, Nutrition, Age, Compliance, Fitness

Smoking, Ethnicity
Mayo Clinic, Rochester, US
(example for CYP2D6 PM)

### Drug Report (Antidepressants)

<table>
<thead>
<tr>
<th>USE AS DIRECTED</th>
<th>USE WITH CAUTION</th>
<th>USE WITH CAUTION AND WITH MORE FREQUENT MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Duloxetine 1</td>
<td>Amtriptyline 6</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Mirtazapine 1</td>
<td>Bupropion 6</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Trazodone 1</td>
<td>Clomipramine 6</td>
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<tr>
<td>Sertraline</td>
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<td>Desipramine 6</td>
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<tr>
<td></td>
<td></td>
<td>Prozac 6</td>
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<tr>
<td></td>
<td></td>
<td>Tofranil 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine 6</td>
</tr>
</tbody>
</table>

### Drug Report (Antipsychotics)

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<tr>
<td>Quetiapine</td>
<td>Clozapine 1</td>
<td>Aripiprazole 6</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Olanzapine 1</td>
<td>Haloperidol 6</td>
</tr>
<tr>
<td></td>
<td>Risperidone 1</td>
<td>Perphenazine 6</td>
</tr>
</tbody>
</table>
**Patient referral** to Dr. Müller or RA – Screening for inclusion/exclusion
(eg capacity, medical history, ethnicity)

RA contacts patient (for informed consent) and study entry:
SCID, PANSS, HAMD, CGI, BAS, AIMS, UKU (modified), body weight and BMI

Six weeks follow-up:
PANSS, HAMD, CGI, BAS, AIMS, UKU (modified), body weight and BMI
+ Blood draw for plasma levels + PIP-FQ (Physicians)

Three month follow-up:
PANSS, HAMD, CGI, BAS, AIMS, UKU (modified), body weight and BMI
Study exit
CYP2D6 Genotype

- Poor Metabolizers (PM): 1
- Intermediate Metabolizers (IM): 5
- Extensive Metabolizers (EM): 16
- Ultra Rapid Metabolizers (UM): 1
Satisfied with Information

How satisfied were you with the information provided to you?

<table>
<thead>
<tr>
<th>Option</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Satisfied</td>
<td>19</td>
</tr>
<tr>
<td>Satisfied</td>
<td>8</td>
</tr>
<tr>
<td>Neutral</td>
<td>4</td>
</tr>
<tr>
<td>Unsatisfied</td>
<td></td>
</tr>
<tr>
<td>Very Unsatisfied</td>
<td></td>
</tr>
</tbody>
</table>
Patient Satisfaction

Did you ask your patient if he/she has been satisfied with the research study?

- Very Satisfied: 8
- Satisfied: 12
- Neutral: 1
- Unsatisfied: 1
- Very Unsatisfied: 7
- Not Applicable: 0
Information Helped with Treatment

If any treatment recommendation was given to you, to what extent has this been helpful in your further treatment decisions?

- Very Helpful: 12
- Helpful: 8
- Neutral: 6
- Not Helpful
- Very Unhelpful
Summary

- Our findings indicate significant associations with gene variants of the melanocortin-lptinergic pathway with antipsychotic induced weight gain (AIWG)
- Clinical algorithms need to be validated in order to implement genetic testing for AIWG
- Currently, testing of CYP2D6 and CYP2C19 appears to be a promising „first step“ in order to implement genetic testing in the clinical arena
- Our study at CAMH has demonstrated that such testing is well received by both physicians and patients and that it was perceived to be helpful for treatment decisions (see also poster from Janna Notario)
Acknowledgments

"I am a 67 year old woman who has had depression as long as I can remember. (…) I had asked my doctor if there were blood tests for the medication. I was disappointed to discover there were no tests. I came across an article about your research with DNA and (…) a more precise approach to medication.

I hope I see the day that I can take medication that will help me be joyful. Keep up the good work.”