

ADPP 01

Metabolic Phenotyping of First Degree Relatives of Patients with Type 1 Diabetes

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No conflict of interest



Medizinische Universität Graz



Topics

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- Study design
- Metabolomics—a short introduction
- Metabolomics—sample analysis
- Metabolomics—results
- Conclusion/Next steps

Study Design and Aims

- ADPP (Austrian Diabetes Prevention Program)–Step 1
 - “Identification of new biomarkers and β cell antigens in type 1 diabetic subjects and their first-degree relatives”
 - Total number of subjects: 423 (3 groups, 1 visit)
- Primary Study Aim
 - Detection of biomarker for β -cells from T1D patients
 - Metabolomics analysis
- Secondary Aim
 - Identify new putative antigens of the auto-immuno-processes of T1D

Study Demographics

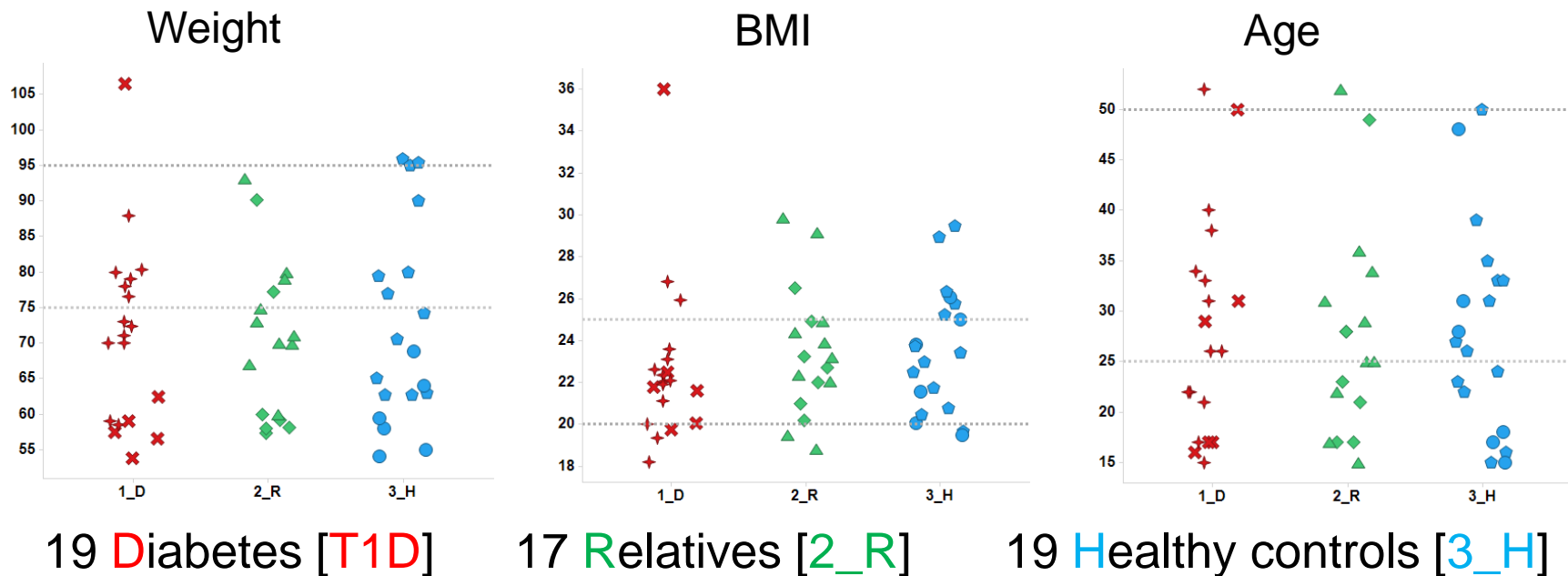
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- 55 subjects selected from 423
 - 19 **Diabetes Type 1 patients [T1D]** (newly diagnosed, duration < 3 months; all insulin treated)
 - 17 **First degree relatives [2_R]** (only one related to T1D subject)
 - 19 **Healthy controls [3_H]** (unrelated healthy controls)

	T1D	2_R	3_H
number	19	17	19
age (median + IQR)	26 (19-34)	27 (20-33)	28 (21-34)
BMI (median + IQR)	22 (21-23)	23 (21-25)	23 (22-25)
sex (% female)	32%	32%	41%
C-Peptide [ng/ml] (median + IQR)	0.725 (0.39-0.081)	0.97 (0.795-1.17)	1.45 (0.9-1.8)
HBA1C (median + IQR)	8.4 (7.6-8.9)	5.2 (5.0-5.4)	5.1 (4.85-5.1)

Successful Matching of Subjects

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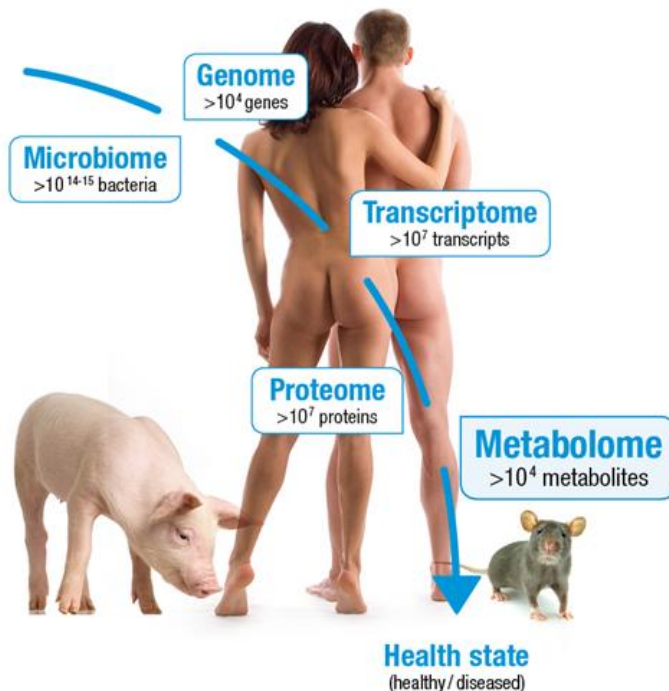
Metabolomics

Environment

Food, physical exercise, stress,
radiation, toxins, pathogens

Metabolome

- ✓ integrates interactions of distinct omics
- ✓ allows detection of compensatory mechanisms prior to symptoms
- ➔ challenging analytics established at HEALTH



Metabolomics Sample Analysis

■ Sample Extraction of EDTA Plasma

- 80% cold methanol overnight¹

■ Sample Analysis by MS

- with HILIC-HRMS (Orbitrap) in ~40 min per sample

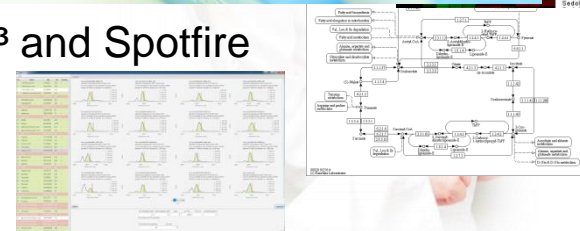
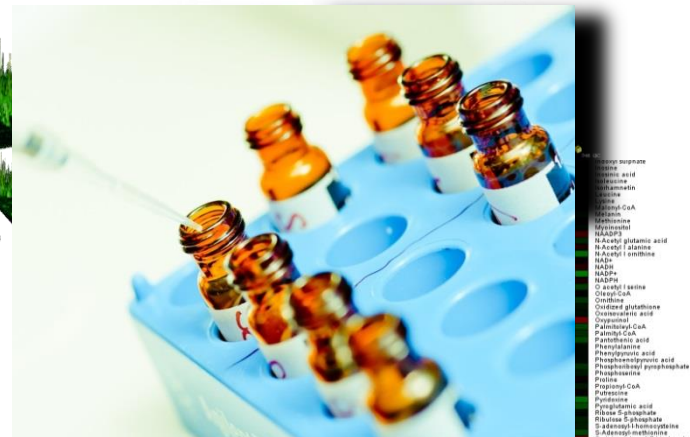
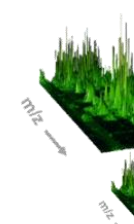
- pooled QC samples and blanks

■ Data Analysis (Targeted/Untargeted)

- Targeted with in house build software PeakScout^{2,3} and Spotfire

- Untargeted: 4483 features (metabolite signals)

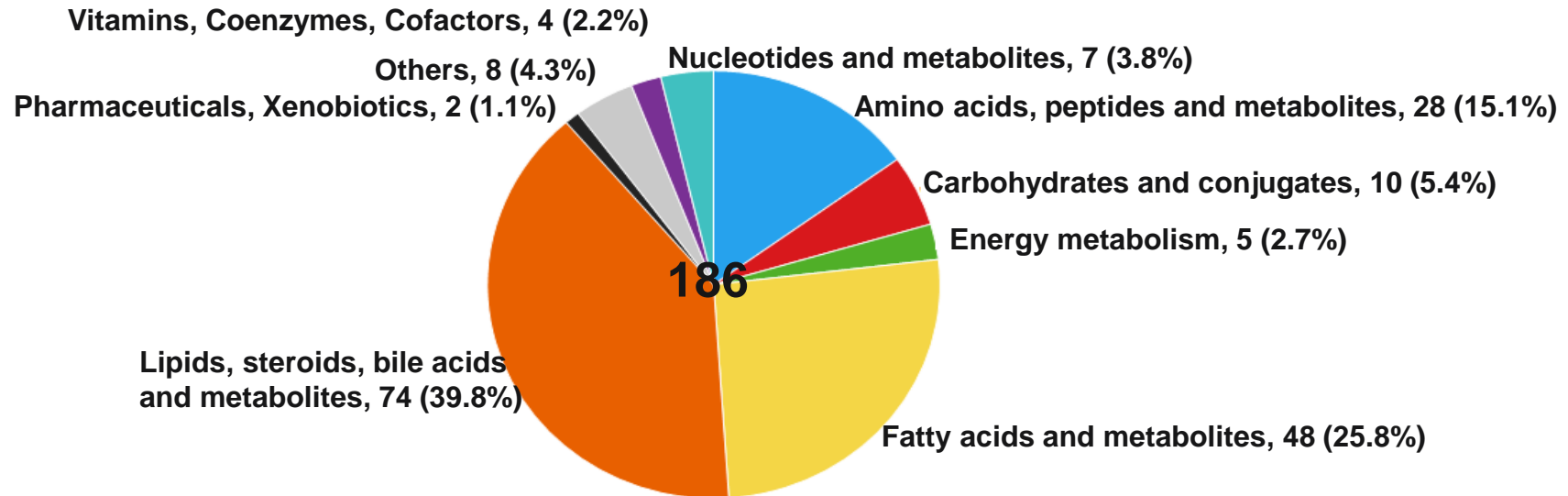
- extensive and thorough data quality controls (7.4% median relative standard deviation)



Targeted Data Analysis- Deep biological insights/biomarker identification

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■ Broad coverage of all important metabolic classes

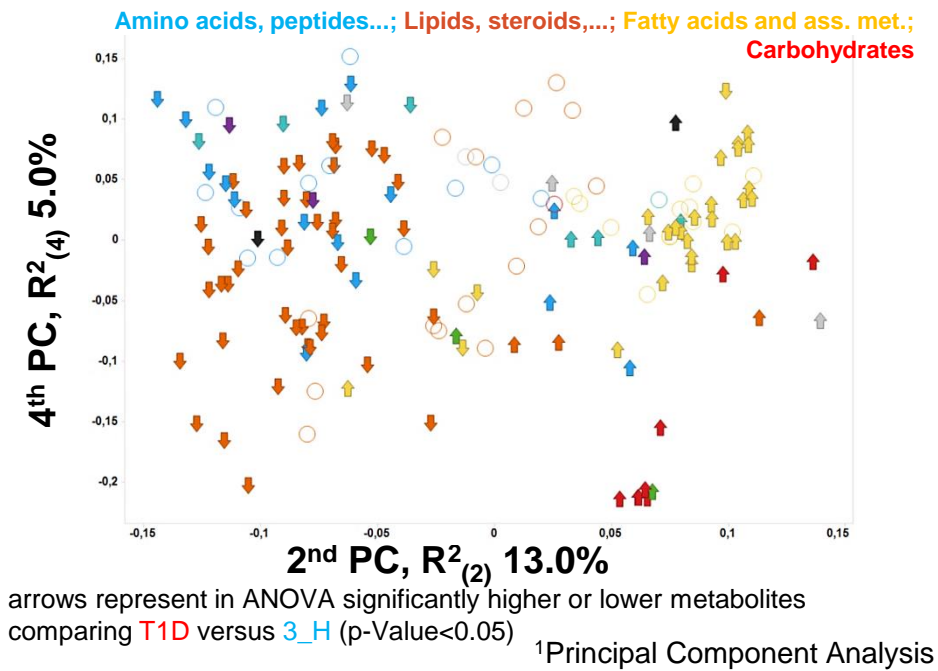
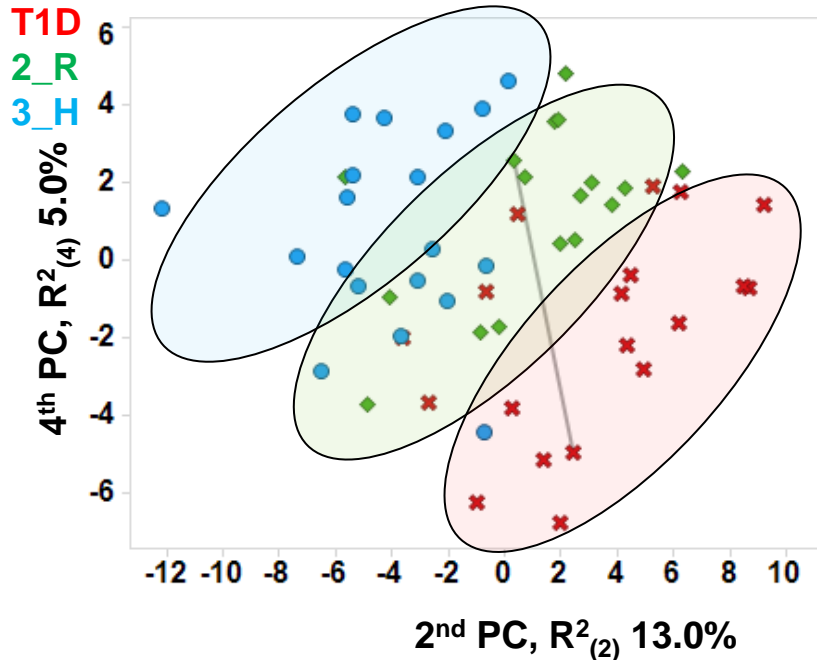


Multivariate Statistical Analysis

PCA¹ Overview

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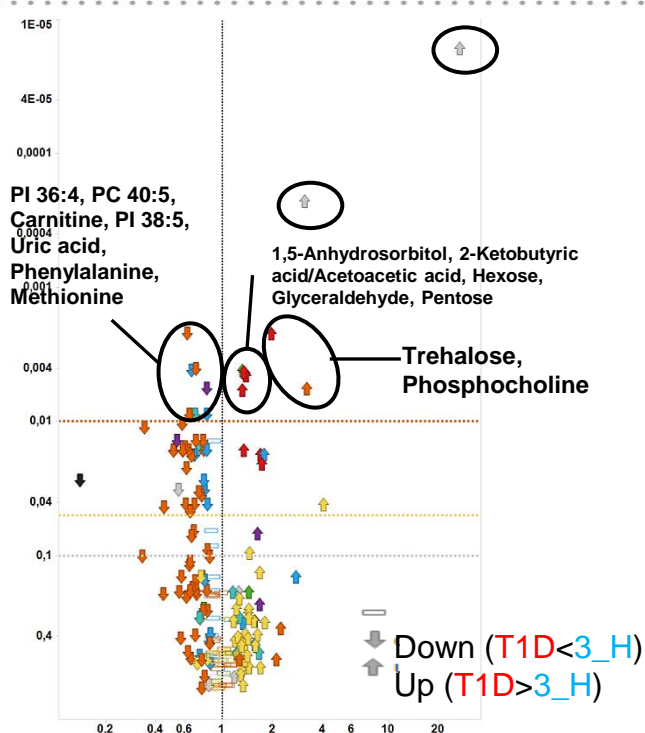
- 55 subjects (19 Diabetes, 17 Relatives, 19 Healthy) & 156 multi-variate-analysis metabolites (connection line marks the only directly related pair)



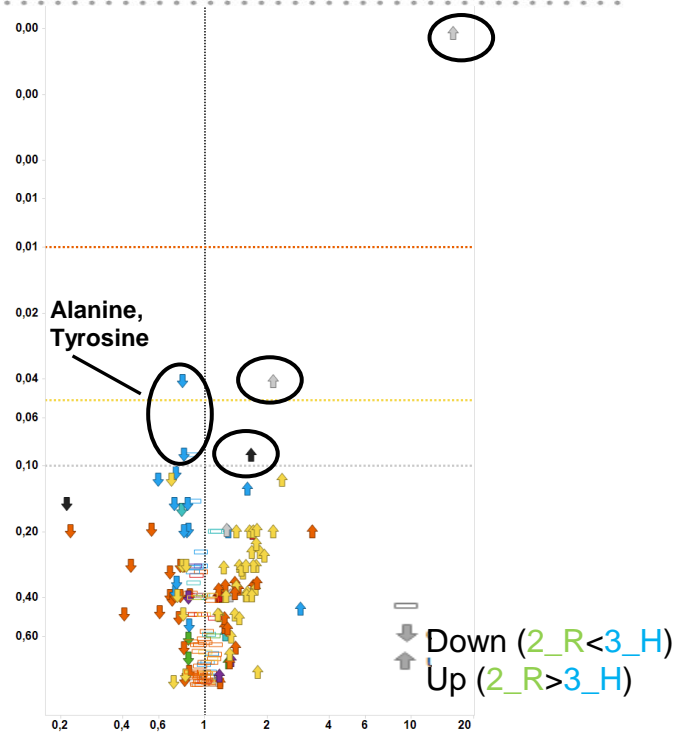
Univariate Statistical Analysis ANOVA Volcano Plots

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Diabetes - Healthy



Relatives - Healthy



Conclusion

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- 14 metabolites differ strongly between groups
 - many observed differences consistent with literature
 - some are not yet described
- relatives are metabolically distinct from healthy and trend towards T1D
- At the current state it remains open, what exactly impacts the metabolome of the relatives and seemingly puts them at risk, but avoids in some cases T1D

Next Steps

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- Major Question- is it an effect of:
 - an epiphenomenon
 - causal differences
 - phenotype differences
 - „innocent bystanders“
- Next Steps:
 - Validation of results in other laboratories
 - Validation of compounds with other analytical methods
 - Validate findings in other cohorts

Metabolomics Team

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