Metabolic Profiles and Disease Risk

IRAS Studies, March 7, 2015

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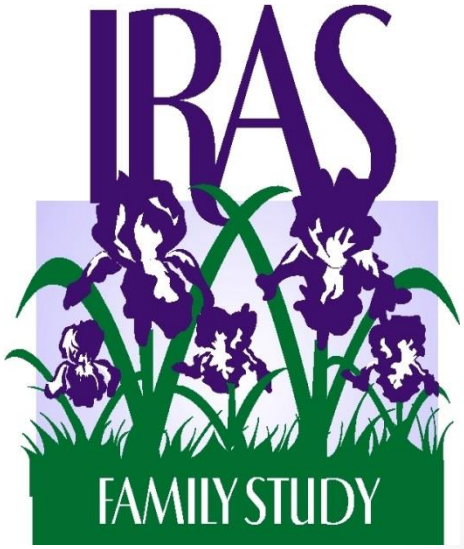


Study Goals

IRAS (Classic): Examine the relationship between directly measured insulin sensitivity and carotid atherosclerosis, across the range of glycemic status and ethnicity.

IRAS Family: Examine the genetic and environmental basis of insulin resistance and abdominal adiposity in a minority, family-based cohort

Wagenknecht LE, et al. The Insulin Resistance Atherosclerosis Study (IRAS): Objectives, design and recruitment results. Ann Epidemiol 1995;5:464-472.

Henkin L, et al. Genetic epidemiology of insulin resistance and visceral adiposity. The IRAS Family Study design and methods. Ann Epidemiol 2003;13(4):211-217.

Comparison of IRAS Studies

IRAS (Classic)

- Individuals, age 45-65
- Hispanic/AA/White from 4 regions
- Selected across range of glycemic status
- Primary phenotypes* include FSIGT & carotid IMT
- Metabolomics (baseline non-DMs)
- Baseline 1992-1994, and 5-yr f-up

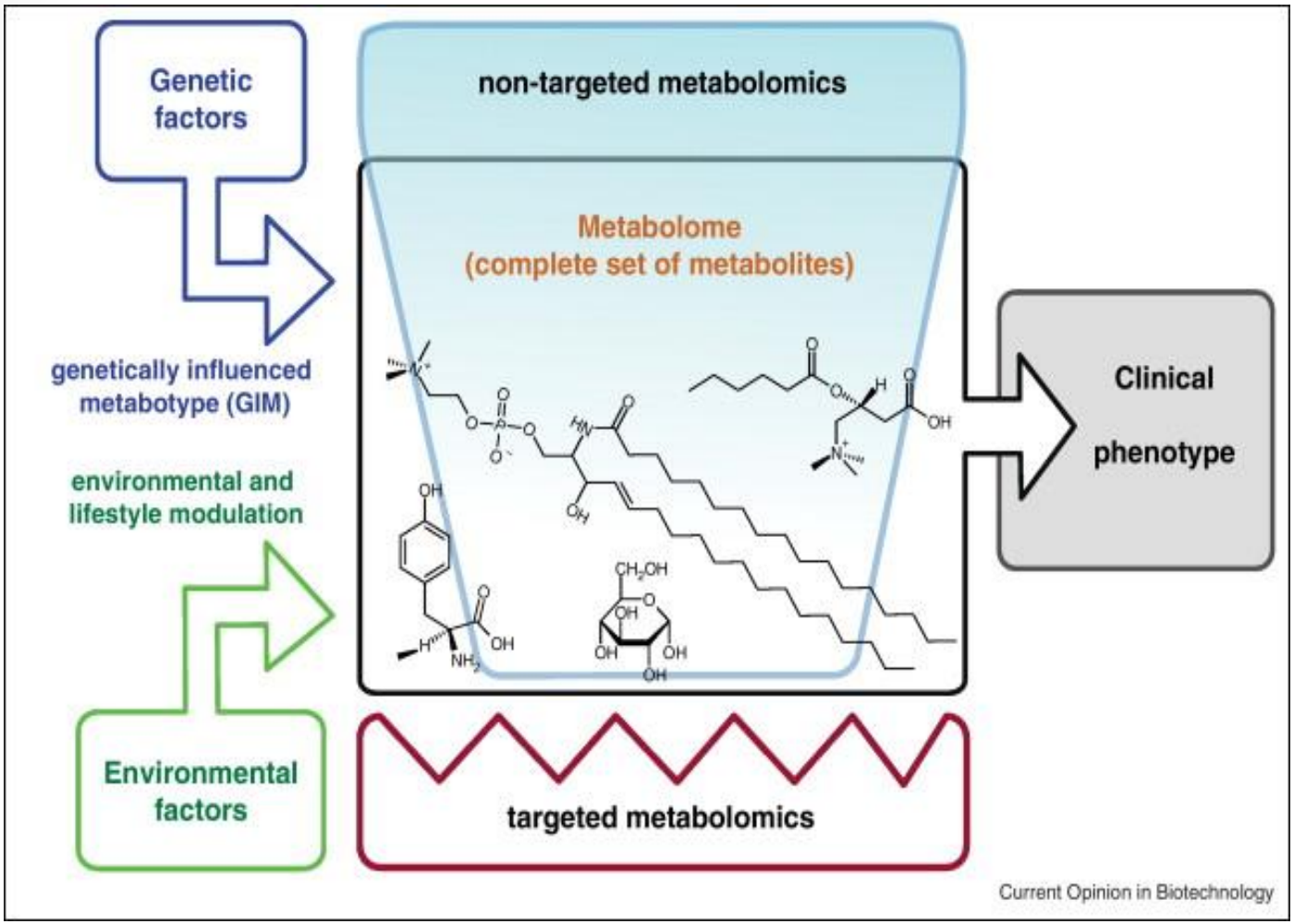
IRAS Family

- Large families, age 18-81
- Hispanic/AA from 3 regions
- Selected for large families from IRAS
- Primary phenotypes* include FSIGT & adiposity by CT scan
- Metabolomics (all)
- Baseline 1999-2002, and 5-yr f-up

**Full list of phenotypes and baseline characteristics is provided in meeting book.*

Emerging Technologies: Metabolomics as an example

- Individual serum metabolites and clusters of metabolites have been shown to predict risk of metabolic diseases (e.g., diabetes) independent of known risk factors
- Well-characterized cohorts can contribute:
  - Genetic and environmental factors
  - Clinical phenotypes (insulin sensitivity, obesity, diabetes, atherosclerosis)
  - Multiple ethnic/race groups, with observed differences in metabolites



Systems Biology Network

Adamski et al., Curr Opinion Biotech 2013; 24:39-47

IRAS Metabolites & Outcomes

- Metabolomics:
  - IRAS: 93 targeted metabolites: fatty acids, sterols, bile acids, amino acids, acylcarnitines (*in 750 baseline non-DM)*
  - IRAS Family: up to 2300 named compounds, underway at Metabolon, plus targeted panel (*in all participants)*
- Outcomes:
  - Incident diabetes, hypertension
  - Change in insulin sensitivity, atherosclerosis, weight
  - Cross-sectional measures of BMI, VAT, SAT, liver fat, fat and lean mass

Emerging Technologies: Strengths and Challenges

- Large numbers of metabolites lead to strengths and challenges:
  - (+) Identify a variety of biologic pathways
  - (-) Increase the type 1 error rate
  - (+) Provide opportunity for a variety of analytic approaches (large N and lack of independence among them)
  - (+/-) Hypothesis-generating approaches
  - (-) Biological role of many metabolites not well-characterized

- Conclusion: there is value in cross-cohort collaboration for replication, analytic strategies

Issues for Cross-Cohort Studies of Emerging Technologies: Metabolites and Outcomes

- Harmonization of metabolite panels
- Harmonization of disease outcomes
- Analytic strategies
- Data sharing/IRB
- Leadership/authorship
- IP/emerging technologies