Applications of GxE interactions in cardiovascular diseases

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Outline

- Background
- Candidate gene-based GxE interaction studies
- GxE studies based on GWAS hits
- GEWAS (GWIS)
- Using data from randomized clinical trials
- Genotype-based recall studies
The GWAS revolution in numbers

Genome-wide association studies 2005-2010
A revolution for the genetics field?

- Publications
- SNPs
- Cumulative SNPs

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My disclaimer: Broad interest in CVD and T2D genetics and epidemiology

Identification of causal variants

- Resequencing
- Ethnic diverse samples
- eQTL analyses
- Bioinformatics

Abundance of novel loci

- Larger and larger GWAS meta-analyses will identify more loci

Identification of more novel loci

- Mendelian randomization
- Risk prediction studies
- Genotype-based recall

Translational genomic medicine

Mechanistic studies

- Animal model systems
- Cellular studies
- Detailed physiological studies in human

Today, I will talk about...
Even highly heritable traits are under some degree of environmental control

Heritability estimates of height range from 0.87 to 0.93 in men, and from 0.68 to 0.84 in women

Even highly heritable traits are under some degree of environmental control

The Great Chinese Famine during 1959–1961 led to lower body height in adulthood

Comparisons of individuals with same genetic background living in different environments indicate GxE interactions


Definition of GxE interaction

Genetic effects on [disease] traits that differ in magnitude [and sometimes direction] across environmental contexts

By courtesy of Prof. Paul Franks
GxE interaction studies based on candidate genes

- Studies based on biological hypotheses
- Extensive attempts with few replicated results
- Close to 5,000 candidate gene studies of coronary heart disease before 2006 in PubMed
  - Of these were 192 SNPs in 102 genes shown to be associated in at least two studies, but few (APOE, ALOX5AP) have been robustly associated
  - However, many negative studies and huge publication bias
- Similar or even worse situation for GxE interaction studies based on candidate genes
Plenty of non-replicated examples of GxE in the CVD literature

“We have shown that physical activity may counterbalance the effect of a genetic predisposition to increase body weight, body fat, and obesity. Obese individuals with the BAR-2 Gln27Gln genotype may benefit from physical activity to reduce their weight. Genotyping may be a useful tool to target prevention such as physical activity, to individuals that have highest benefit from it.”


“Primiparous homozygous carriers of the G protein 3 825 TT allele, a thrifty genotype, are at high risk of obesity and post‐pregnancy weight retention if they do not exercise regularly.”

Why did candidate gene-based GxE interaction studies fail?

- Abundance of false positives
  - Multiple testing without appropriate corrections
  - Lack of replication
  - Publication bias

- Abundance of false negatives
  - Underpowered studies
    - Too small sample sizes
    - Over-optimistic expectations of effect sizes
    - Suboptimal assessment of environmental variables
  - Large degree of between-study heterogeneity

- Suboptimal hypotheses due to limited biological knowledge
Along came the GWAS era...
Published Genome-Wide Associations through 12/2010, 1212 published GWA at $p \leq 5 \times 10^{-8}$ for 210 traits

Plenty of loci to follow-up in GxE studies...
...of various traits
Example: *FTO* was identified in 2007 as an obesity locus.
Example: *FTO*-physical activity

Whereas other studies do not support this notion


Figure 1 Association of FTO SNP rs9939609 with adiposity traits depends on physical activity level in European-American and African-American men. (a) BMI, (b) waist circumference, and (c) skinfolds.
So, what should we believe and what to do?

- As in the old school candidate gene-based studies, we again have issues with:
  - Between-study heterogeneity
  - Inadequate power due to too small sample size in relation to effect sizes
  - Imprecise and varying assessment of environmental variables
  - Publication bias

- A better approach if we want to study established loci is meta-analyses of many studies (or to use very large samples)
  - This is currently ongoing for FTO-PA interactions (N~250,000)
Interactions of dietary whole grain intake with fasting glucose– and insulin–related genetic loci in individuals of European decent: a meta-analysis of 14 cohort studies (N=48,000)

Interactions of glucose- and insulin-related loci with zinc intake on fasting glucose (N~45,000)

However, GWAS main effects might not be the best candidates for interactions
Why ignoring the environment (as in main effect GWAS) might be a problem in identifying loci involved in GxE interactions

By courtesy of Prof. Paul Franks
Why ignoring the environment (as in main effect GWAS) might be a problem in identifying loci involved in GxE interactions.

Assuming no GxE when GxE exists (ignoring E)

By courtesy of Prof. Paul Franks
Gene-Enviroment-Wide Association Studies (GEWAS)

- Kraft *et al.* developed a joint test that investigates the association between an outcome and a genetic locus, while allowing for possible effect modification by an environmental variable.
- Manning *et al.* have extended this joint test to a meta-analysis context allowing simultaneously testing the genetic main effect adjusting for confounders, and potential interactions between each genetic locus and an environmental variable.
- This joint meta-analysis (JMA) is an effective screening tool when the underlying interaction model is unknown and, importantly, retains power when there is no interaction effect.

\[
Y = \text{Intercept} + \beta_{\text{cov}} + \beta_{G} + \beta_{E} + \beta_{G*E} + e
\]
Genome-wide SNP*BMI interaction on fasting glucose and insulin (N=88,771)

Ref: Manning AK, et al. Novel application of a genome-wide approach that accounts for body mass index (BMI) and SNP by BMI interaction on fasting glycemic traits reveals new genetic variants implicated in insulin resistance. Submitted.
Genome-wide SNP*physical activity and SNP*BMI on 2-hour glucose

- Discovery stage of 14,323 individuals → 39 SNPs reaching P<10^-5 for JMA or interaction P-value brought forward
- Replication in ~20-26k individuals
- Analyses and interpretation ongoing

Ref: Scott RA, unpublished data
GxE studies in the context of randomized clinical trials

- Observational studies are useful to discover unknown GxE interactions, especially if the effects occur over long time and are of small size.

- However, due to well-recognized problems with reverse causation, confounding and bias, we may want to consider using randomized designs also in the context of GxE interaction studies.
Post-hoc analyses of existing RCTs: Examples from Diabetes Prevention Program (DPP)

Findings from original study:
Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.

Genotype-based recall studies

- Refers to a design where genetic information is used to group individuals into strata for comparisons
- The sampling frame is usually a large cohort study, where you can re-contact individuals that have certain genetic profiles for further studies
- For example, one can identify homozygotes of rare variants with large effect, or draw individuals from the extremes of the distribution of a genetic risk score
Genotype-based recall trials

By courtesy of Prof. Paul Franks
Example of a genotype-based recall study:
Genetic Risk Information for Primary Prevention (GRIPP)
Genotype-based recall study: Rationale

- To translate complex-trait genetics to the clinical setting, it is essential to show that genetic information affect clinical decisions regarding diagnosis or treatment.
- Genotype-based recall studies are designed to show that the effect of a clinical intervention differs depending on the genotype of an individual (i.e. a GxE interaction).
- Such studies could provide an important rationale for genetically-informed targeted treatment in personalized medicine.
A lot of work ahead...

- There are multiple important ways forward in complex trait genetics that will have important impact on clinical medicine in due time
  - Additional loci can and should be identified
  - Biology of the already established loci needs to be understood
  - The role of genetic information for risk prediction and stratification needs to be further explored

- Identification of more novel loci
  - Resequencing
  - Ethnic diverse samples
  - eQTL analyses
  - Bioinformatics
  - GxE and GxG studies
  - Pathway analyses
  - Gene-based analyses
  - Studies of pleiotropy

- Reuse of GWAS data
  - Larger and larger GWAS meta-analyses will identify more loci
  - Mendelian randomization
  - Risk prediction studies
  - Genotype-based recall

- Mechanistic studies
  - Animal model systems
  - Cellular studies
  - Detailed physiological studies in human

- Abundance of novel loci
  - Identification of causal variants
  - Mechanistic studies
  - Translational genomic medicine

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Thanks for your attention!
Questions or comments?