From Nutrigenetic Testing to Personalized Nutrition: When Challenges become Opportunities

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<tr>
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Overview

✓ Nutrigenomics: evolution of a paradigm
✓ Challenges in nutrigenomics (science)
✓ Transforming challenges into opportunities
✓ Conclusion
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Titus Carus Lucretius, around 60 BC

Even those idiosyncrasies with regard to drugs and articles of food which are summed up in the proverbial saying that what is one man's meat is another man's poison presumably have a chemical basis.
Pre-nutrigenomic era

One size fits all – regardless genetic differences

Dietary guidelines designed accordingly & still in place:

- Age
- Sex
- Pregnancy

Health outcomes → Nutrient intakes → Upper tolerable limits (UL) → Dietary Reference Intakes (DRI)
Nutrigenomic era

Currently applied paradigm

Genetic variation in one gene

Establish nutrition targets

...but this approach is biased in most cases because:
The metabolic homeostasis for a nutrient is controlled by multiple genes.
- Multiple variants in multiple genes need to be included (gene-gene interactions). (Challenge 1)
- Gene-environment interactions need to be accounted for. (Challenge 2)

The associated outcome (health status) with genetic make up could vary dramatically with the nutrient level (gene-nutrient interactions). (Challenge 3)

DNA structure – RNA transcription is not dependent only upon single nucleotide polymorphisms (assessed by most genetic tests commercially available).
- Insertions-deletions (in-del) & copy number variations (CNV) (Challenge 4)
- DNA methylation (epigenetic) (Challenge 5)

Assessment of efficacy to normalize nutrient metabolism: use of metabolomic platforms, commercially available. (Challenge 6 – cost issue)
Challenge 1: gene-gene interactions

Nienaber-Rousseau et al, Gene 2013

Current effect: F(4, 1765) = 4.0798, p = 0.0027
Vertical bars denote 95% CI
Challenge 2: gene-environment interactions

Fig. 3. The figure presents simulated phenotypic data for three genotypic groups (Gene = 0, 1, 2, indicating groups of individuals who carry 0, 1, or 2 copies of a particular allele), each shown in a different color. The four-parameter model corresponds to the case in which the interaction term is modeled by a cross-product term only. Although a significant interaction is detected, the corresponding linear regression lines do not match the data points, and the slopes are incorrectly ordered from 0 to 1 to 2 on the basis of the constraints imposed by the use of the cross-product term to model the interaction. Thus, although the model would produce a significant interaction, the regression lines implied by the model inaccurately represent the data and would be misleading as to the nature of the interaction. The data can be accurately reproduced by an extended parameterization of the regression model (six-parameter model) as detailed in Aliev et al.’s (2014) study.

Candidate Gene–Environment Interaction Research: Reflections and Recommendations

Challenge 3: gene-nutrient interactions
Challenge 3: gene-nutrient interactions
Challenge 3: gene-nutrient interactions

![Graph showing predicted HDL-C levels vs. fat intake (% total energy) for different LIPC genotypes (TT, CT, and CC).]

Figure 1 | The importance of gene-environment interactions — an example. Predicted values of high-density lipoprotein cholesterol (HDL-C) are shown for different hepatic lipase (LIPC) genotypes at different total levels of dietary fat intake (data from REF. 7). Low fat intake (band A) combined with the TT genotype results in the highest HDL-C level. For a moderate fat intake (band B), there is no relationship between genotype and HDL-C level. For a high fat intake (band C), the TT genotype has the lowest HDL-C level. Gene–environment interactions are therefore important in identifying genetic and environmental determinants of medically relevant phenotypes such as HDL-C levels; depending on the dietary fat intake, one could conclude that the TT genotype produces high (band A) or low (band C) HDL-C levels, or that it is not associated with HDL-C levels at all (band B).
Challenge 4: copy number variations
CNVs in salivary amylase (AMY1)

N | Median | Mean | SD
---|--------|------|-----
High starch | 133 | 7 | 6.72 | 2.35
Low starch | 93 | 5 | 5.44 | 2.04

Diet and the evolution of human amylase gene copy number variation

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Challenge 5: DNA methylation (epigenetics)

**Figure 5.** *Fads2* promoter methylation negatively correlates with its gene expression in maternal livers. Bivariate fit analysis (using a linear model) was performed on paired variables, between *Fads2* promoter methylation and gene expression. Regression analysis indicated a significant and negative correlation between the two variables, independent of the dietary groups, with a coefficient of determination ($R^2$) of 0.25.
Opportunity 1: gene-gene interactions

- Consider building algorithms using multivariate approaches.

- Consider the use of haplotypes instead of genotypes.
Opportunity 2: gene-environment interactions

- Does the model work in different populations with different environments?
- If not, re-adjust based on the outcomes in local population

Colin Khoury "The conservation and use of crop genetic resources for food security", PhD Thesis
Opportunity 3: gene-nutrient interactions

- Assess the genotype–outcome relationship over a range of intakes: use metabolically challenging intake levels

- Use the appropriate population (not “primed” to the challenge).
  - Food for thought: shall I use a US population for a folate supplementation study? No (folate fortification introduces bias). US population is already supplemented.
  - Which population to use for a deficiency study?
Opportunities 4&5: in-del, CNVs, DNA methylation

- Include in the model such variations & DNA methylation
Conclusion

DNA structure

Point variations
In-dels & CNVs
DNA methylation

Different environmental settings (nutrition included)

Model 1
Model 2
Model “n”

Prediction 1
Prediction 1
Prediction “n”
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