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Core gene identification using gene expression

PhD thesis

to obtain the degree of PhD at the
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on the authority of the
Rector Magnificus Prof C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Wednesday 2 December 2020 at 18.00 hours

by

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Propositions

1. Genome-wide association studies have successfully uncovered the genetic architecture of numerous complex traits, but additional layers of data are required to uncover the molecular mechanism leading to disease.

2. Bulk gene expression datasets reflect their cell types or tissue of origin, and the resulting patterns need to be accounted for when identifying (causal) disease genes to avoid false positive results.

3. The process of healthy aging can be described as a change in cell populations in blood, rather than a change in gene expression within the cells.

4. Because each methodology has its flaws, integrating multiple independent lines of evidence is essential for trustworthy results.

5. Despite evolutionary constraints, local genetic regulation of gene expression can have large effects. Therefore, such cis-regulation is of limited use when understanding common complex diseases.

6. Common and rare disease genetics are traditionally viewed as independent areas of research, but they are at two ends of the same spectrum and can benefit from each other's insights.

7. While disease associations are generally small, their consequences ultimately lead to disease. Large population-based biobanks are required to detect the subtle patterns that lead to the development of disease.

8. In as far as they exist, finding core genes for common complex diseases will be the key to understand and treat these diseases.

9. Biology is infinitely complex: each cell in each organ in each (diseased or healthy) individual is unique. Every level complexity will expose more information, leading to new questions and knowledge.

The more we know, the more we know we don't know
(attributed to Aristotle)

10. Modern science is collaborative, and better for it.

"The scientific enterprise as a whole does from time to time prove useful, open up new territory, display order, and test long-accepted belief. Nevertheless, the individual [or team] engaged on a normal research problem is almost never doing any one of these things. Once engaged, [their] motivation is of a rather different sort. What then challenges [them] is the conviction that, if only [they are] skillful enough, [they] will succeed in solving a puzzle that no one before has solved or solved so well."

Thomas Kuhn, *The Structure of Scientific Revolutions*

Square brackets indicate modified from the original to acknowledge the diversity and collaborative nature of modern science.

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