On the relation between genetic variation and osteoarthritis

Hollander, W. den

Stellingen behorend bij het proefschrift getiteld

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1. The canonical multiple testing correction penalty applied in genome-wide genetic association studies is demonstrable overly strict, as appears from the identification of *CRLF1* as osteoarthritis susceptibility gene.
   This thesis

2. Whilst expression of the *DIO2* gene and DNA methylation levels at the locus reflect the pathological state of articular cartilage in osteoarthritis, a static entity such as the underlying genetic sequence is required to distinguish causality from mere correlation.
   This thesis

3. The loss of the chondrocyte's maturational arrested state observed in osteoarthritic cartilage appears mediated by changes in genome wide DNA methylation.
   This thesis

4. The observation of vast differences across the DNA methylation landscape between knee and hip articular chondrocytes implies the necessity of distinct approaches when cartilage tissue is to be (re-)generated *in vitro* for clinical purposes.
   This thesis

5. Future studies that focus on the integration of genomic, epigenomic and transcriptomic data for the identification of molecular mechanisms underlying osteoarthritis require markedly larger sample sizes alongside improved methodology compared to now.
   Adapted from ***A Tsezou, Osteoarthritis & Cartilage, volume 22 issue 12,*** **2014**

6. The observed missed heritability of complex genetic diseases is near being unveiled, arguably driven by the advances in high dimensional data generation and analysis techniques such as functional genomics and Mendelian randomization.
   Adapted from ***F Dudbridge, Genetic Epidemiology, volume 40 issue 4,*** **2016**

7. Investigating whether the epigenome of affected tissues is reflected in the circulation would accommodate the urgent and unmet need to develop predictive biomarkers that provide early warnings of osteoarthritis.
   Adapted from ***A Mobasheri et al., Osteoarthritis & Cartilage, volume 25 issue 25,*** **2017**

8. DNA methylation can mediate or modulate the transcriptional outcome of genetic risk alleles and, as such, relate susceptibility alleles to disease outcome.
   Adapted from ***LN Reynard, Seminars in Cell & Developmental Biology, volume 62,*** **2017**

9. The world is still a weird place, despite my efforts to make clear and perfect sense of it.
   Hunter S. Thompson, ***Songs of the Doomed: More Notes on the Death of the American Dream*****, 2012** *There in which the scientific method is the utmost powerful tool we have to dissect and understand reality, it elegantly does so while leaving nature's surprising beauty untouched.*

10. The highest forms of understanding we can achieve are laughter and human compassion.
    Richard Feynman, ***What Do You Care What Other People Think?*****, 1988** *Academic research is predominantly driven by curiosity, from which the results enable us to increase wellbeing in various corners of human existence. We should, however, not lose sight of who we are and what we actually do; mere social primates striving for happiness.*

11. Don't worry, don't be afraid, ever, because this is just a ride.
    Bill Hicks, ***Revelations*****, 1993** *Us humans tend to lose the meta-awareness of having embarked on a journey of certain kind. While passionate dedication is valuable in maintaining a high aim, it need not be a prerequisite of living a true and meaningful life. In that regard, neither failure, set- nor throwbacks serve a distraction thereof.*