Erik B. van den Akker

Which : 1436W
When : Wednesday, Nov. 7 3:15 pm - 4:15 pm
Where: Moscone Center, Exhibit Halls ABC

Meta-analysis of co-regulated subnetworks in transciptomics data: towards functional marker profiles of human ageing

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Age associated modules within co-expression networks may provide a molecular basis for identification of mechanisms underlying age related diseases. However, age-changes in gene expression profiles typically have low signal-to-noise ratios that seriously hamper a solely data driven approach. We cope with this aspect in two ways. First, we employ a meta-analysis approach on multiple large-scale expression studies for constructing the co-expression network and detecting age associated modules therein. Second, we project the co-expression network onto the Protein-Protein Interaction (PPI) network spanned up by predicted or experimentally validated functional relations between genes to improve the confidence and interpretation of observed co-regulated subnetworks. For the analysis we created a gene expression compendium of 2,539 subjects in an age range of 15 to 95 years belonging to three published expression studies measured in peripheral blood or lymphocytes: SAFHS, IFB cohort and DILGOM. Single gene meta-analysis showed functional enrichment for N-linked glycosylation, besides a few other broadly defined terms. Our approach based on co-regulated subnetworks (CoRSuN), on the contrary, detected 70 age associated CoRSuNs, including a highly significant module containing T-cell differentiation markers ($p = 1.3 \times 10\text{-}143$). To investigate whether the detected CoRSuNs mark ageing up to the highest ages, we tested them for association with age in 50 middle-aged and 50 ninety-year-old participants from the Leiden Longevity Study. This confirmed age-changes in five CoRSunNs, including the T-cell CoRSuN, independent of lymphocyte and monocyte cell counts. Since the T-cell differentiation markers are established markers of T-cell lineages, their expression may point to proportions of T-cell subpopulations, rather than to a molecular mechanism. We therefore adjusted the age-associated CoRSuNs for the first principle component of the T-cell differentiation CoRSuN now revealing 15 out of the 70 subnetworks, including a ribosomal ($p = 9.7 \times 10\text{-}4$) and mitochondrial module ($p = 4.1 \times 10\text{-}5$). We conclude that age-changes in the blood transcriptome likely reflect changes in T-cell populations, potentially confounding the genomic analysis into ageing mechanisms. Furthermore, we demonstrate that de novo grouping of genes using co-expression networks in conjunction with a PPI network yields functional gene modules as relevant markers of human ageing up to very high ages.

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Joris Deelen

Which : 2035T
When : Thursday, Nov. 8 2:15 pm - 3:15 pm
Where: Moscone Center, Exhibit Halls ABC

Telomere length in human blood cells and the prediction of survival

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Telomere length (TL) in human leukocytes declines with age and several studies have shown that decreased TL is associated with increased mortality, although not in all studied populations. Previous studies had a relatively small sample size and follow-up in larger populations is warranted. In addition, it is not clear whether telomere shortening measured in blood cells marks merely a history of cell division induced by infections or whether there is a causal contribution of length reduction to mortality. We measured TL in peripheral blood of 870 nonagenarian siblings (mean age 93 years), 1,580 of their offspring (mean age 59 years) and 725 spouses thereof (mean age 59 years.) from the Leiden Longevity Study. These participants have been followed up for vital status during 7.56 years on average. Mean TL was measured as a ratio (T/S) of telomere repeat length (T) to the copy number (S) of the single-copy gene 36B4. There was no difference in TL between the offspring and spouses (P = 0.927), so we could analyse them as one group. Survival analysis, using Cox regression, in the nonagenarians showed that longer telomeres are associated with better survival into very old age (HR = 0.66, P = 0.028). This effect is even more pronounced in the offspring and their spouses (HR = 0.24, P = 0.001). To determine whether the association could be based on TL marking a history of infections, we determined the association between TL and markers for immune response (white blood cell counts, hsCRP and incidence of CMV infection) and a marker for cell replication (IGF1/IGFBP3) in the offspring and spouses. We conclude that decreased TL is significantly associated (P < 0.05) with decreased neutrophil counts, basophil counts and IGF1/IGFBP3 ratio, increased lymphocyte counts and a higher incidence of CMV infection. When the survival analysis of TL among the nonagenarians was adjusted for the mentioned parameters of cell replication and immune response, we found that TL still showed an independent association with survival (HR = 0.60, P = 0.007). We conclude that TL predicts survival in very old and middle age and that this effect is independent from markers for immune response and cell replication. This observation is currently being replicated in independent cohorts in which we will also determine the impact of known genetic determinants of TL on survival.

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Which : 459F
When : Friday, Nov. 9 2:15 pm - 3:15 pm
Where: Moscone Center, Exhibit Halls ABC

Genome structure, variation and function.
Analysis of structural variation in the Genome of the Netherlands (GoNL) project

The Genome of the Netherlands (GoNL) is a national collaboration that aims at characterizing genetic variations in the Dutch population of 250 families. Here we report on the pilot results of the structural variation analysis for 18 families. Our analysis employs several methodologies for detection of different types and size ranges of variants. Using GATK Unified Genotyper, we identified 1,459,968 small indels of which 23% are novel compared to 1000 Genomes phase 1 data, and 86% overlap with Pindel's short indel calls. In silico functional analysis indicates that 819 are causing premature stop codons and frameshifts in 749 genes. A combination of 4 approaches, read depth (CNVnator, DWAC-Seq), read pair (123SV, BreakDancer and GenomeSTRiP), split-read (Pindel), and de novo assembly (SOAPdenovo, CLC) ensures detection of structural variants of different types and size ranges. For example, we identified a 1.8 kb insertion absent in genome reference, but common in Dutch population (allele frequency=42%), while rare (5%) in 1000 Genomes project. Homozygous DNA segments were identified using PLINK and VCFtools. We performed hundreds of PCR/Sequencing assays to determine false-positive rate for each tool and to establish de novo mutation rate of indels and structural variants. The set of wide size range, multi-type, high-quality SVs calls, together with GoNL SNP set (reported separately) describes common genomic variants in the Dutch genomes. This variation catalogue is essential for understanding population history, interpretation of GWAS and analysis of other studies involving West-European samples.

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