Friday June 10, 9:00-10:15

Parallel session 3

Genetic and Molecular Epidemiology

Chairs: Jim Peters & Matty Weijenberg

9:00 Genome-wide association study in patients with posterior urethral valves (O41)
Loes van der Zanden

9:15 The effects of genetic susceptibility and stress-related exposures on depression and anxiety (O42)
Rujia Wang

9:30 Hemoglobin, red blood cell count, platelet count and blood pressure: observational and mendelian randomization analyses (O43)
Zhen He

9:45 Linear regression on martingale residuals enables fast and accurate recurrent event analysis for genome-wide association studies (O44)
Jasper Hof

10:00 Atlas of metabolites and biochemical pathways associated with hepatic triglyceride content in middle aged men and women (O45)
Tariq Faquih

O41. Genome-wide association study in patients with posterior urethral valves.

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Background: Congenital lower urinary tract obstructions (LUTO) are most often caused by posterior urethral valves (PUV), a male limited anatomical obstruction of the urethra affecting 1 in 4,000 male live births. Little is known about the genetic background of PUV. Here, we report the first genome-wide association study (GWAS) for PUV.

Methods: Four cohorts of patients and controls from The Netherlands, Germany, and Poland were included in the current study. Samples were genotyped using Illumina microarrays. After standard quality control steps, imputation and association analyses were performed separately for the different cohorts, after which results were combined in a meta-analysis.

Results: The final meta-analysis included 756 patients and 4,823 on ethnicity matched controls and comprised 5,754,208 variants that were genotyped or imputed and passed quality control in all 4 cohorts. No genome-wide significant locus was identified, but 33 variants showed suggestive significance ($P<1\times10-5$). When considering only loci with multiple variants residing within <10kB of each other showing suggestive significance and with the same effect direction in all 4 cohorts, 3 loci comprising a total of 9 variants remained. These loci resided on chromosomes 13, 16, and 20.

Conclusion: The present GWAS and meta-analysis is the largest genetic study on PUV performed to date. The fact that no genome-wide significant locus was identified, can be explained by lack of power or may indicate that common variants do not play a major role in the aetiology of PUV. Nevertheless, future studies are warranted to replicate and validate the 3 loci that yielded suggestive associations.

O42. The effects of genetic susceptibility and stress-related exposures on depression and anxiety.

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Background: It is unclear whether and to what extent stress-related exposures moderate effects of polygenetic risk scores (PRSs) on depression and anxiety. We aimed to examine such moderation effects for a variety of stress-related exposures on depression and anxiety.

Methods: We included 41,810 participants with both genome-wide genetic data and measurements of depression and anxiety in the Lifelines Cohort Study. Current depression and anxiety were measured by the MINI International Neuropsychiatric Interview. Stress-related exposures included long-term difficulties, stressful life events, reduced social support, childhood trauma, and loneliness, which were measured by self-report questionnaires. PRSs were calculated based on the latest genome-wide association studies for depression and anxiety. We used linear mixed models adjusting for family relationships to estimate the interactions between PRSs and stress-related exposures.

Results: Nine of the ten investigated interactions between the five stress-related exposures and the two PRSs for depression and anxiety were significant (Ps<0.001). Higher exposure to long-term difficulties, stressful life events, reduced social support and loneliness amplified the genetic effects on both depression and anxiety. As for childhood trauma, its interaction with the PRS was significant for depression (P=1.78e-05) but not for anxiety (P=0.32).

Conclusions: Higher levels of stress-related exposures significantly amplify effects of genetic susceptibility on depression and anxiety. With large sample sizes and comprehensive stress-related exposures, our study provides powerful evidence on the interplay between genetics and stress-related exposures on depression and anxiety.

O43. Hemoglobin, red blood cell count, platelet count and blood pressure: observational and mendelian randomization analyses.

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Background: Previous studies have found associations of hemoglobin (HGB), red blood cell count (RBC#) and platelet count (PLT#) with blood pressure (BP). However, whether the associations are causal is not known. The present study aimed to evaluate causal effects of the three traits on BP by employing complementary observational and Mendelian randomization (MR) analyses.

Methods: Observational cross-sectional analyses were conducted by using multivariable logistic (for hypertension) and robust linear regressions (for BP) in the Lifelines Cohort Study (n=110,115). Further, we performed inverse variance-weighted two sample MR analyses (both forward and reverse), combined with multiple sensitivity analyses, to explore the causal effect of the three exposure traits on systolic (SBP) and diastolic BP (DBP) and vice versa, using genetic instrumental variables related to the three exposure traits (HGB, RBC# and PLT#) that had been identified in the UK Biobank (n= 350,475) and genome-wide association study results from the International Consortium of Blood Pressure (ICBP) for SBP and DBP (n= 757,601).

Results: In the MR analyses (per standard deviation increase in exposures), higher HGB (B=0.11, 95% CI=0.07-0.16) and RBC# (B=0.07, 95% CI=0.04-0.10) were associated with DBP. Reverse MR analyses also suggested causal effects of DBP on both HGB (B=0.06, 95% CI=0.03-0.09) and RBC# (B=0.08, 95% CI=0.04-0.11). No associations with SBP were found. The observational cross-sectional analyses supported these findings and yielded fairly similar results. No consistent causal effects of PLT# on SBP and DBP were found.

Conclusion: Our results indicate robust bidirectional causal relationships of HGB and RBC# with DBP, but not with SBP. Causal effects of PLT# on BP were not consistent.

O44. Linear regression on martingale residuals enables fast and accurate recurrent event analysis for genome-wide association studies.

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Background: While many diseases recur after recovery, e.g. recurrences in cancer and infections, research into these recurrences is primarily focused on analysing only time-to-first recurrence, thereby ignoring any subsequent recurrences that may occur after the first. Statistical models for the analysis of recurrent events are available, of which the Cox proportional hazards frailty model is the current state-of-the-art model. However, this model is too statistically complex for efficient application in high-dimensional data analysis such as genome-wide association studies (GWAS). Here, we developed a novel method for the analysis of recurrent event data in GWAS.

Methods: In our method, every DNA variant is tested on association with the recurrent events using a linear regression on martingale residuals. The statistical performance (type I error, power, run time) of our novel method was compared with established recurrent event models using simulated data (N=1,500). Our simulation scenarios ranged over relevant parameters for GWASs on recurrent event data, such as minor allele frequency, average number of recurrences and heterogeneity in recurrence risk.

Results: First results showed that the P-values obtained from our novel method are highly correlated with P-values obtained from a Cox proportional hazards frailty model (rho = 0.9999976). Also, our novel method is more than 5,000 times faster than existing recurrent event models: a recurrent event GWAS for 1 million DNA variants for 1,500 individuals is carried out in 50 seconds, whereas existing recurrent event methods would require 3 days. Finally, our simulations showed that the novel method controls the type I error and that the statistical power is similar to state-of-the-art recurrent event models in all simulation scenarios.

Discussion: We present linear regression on martingale residuals as the first method to perform a valid, accurate and efficient recurrent event analysis in GWAS.

O45. Atlas of metabolites and biochemical pathways associated with hepatic triglyceride content in middle aged men and women.

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Background: Non-alcoholic fatty liver disease (NAFLD) is characterized by the pathological accumulation of triglycerides in hepatocytes and is associated with insulin resistance, atherogenic dyslipidemia, and cardiometabolic diseases. Thus far, the extent of metabolic dysregulation associated with hepatic triglyceride accumulation has not been fully addressed.

Approach: To gain insight in the spectrum of metabolites associated with hepatic triglyceride accumulation, we performed a comprehensive plasma metabolomics screening with 1,363 metabolites in middle aged men and women (N=496) in whom hepatic triglyceride content (HTGC) was measured by 1H magnetic resonance spectroscopy.

Results: Our analyses revealed that 118 metabolites were univariately associated with HTGC (p-value < 6.59×10-5), which were used to generate an atlas of metabolite-HTGC associations. The number of associations and effect sizes were higher in women and further increased after menopause. The atlas comprises of a correlation-based Gaussian graphical model (GGM) and a genome scale metabolic model (GSMM) network. The majority of metabolites, including branched chain amino acids (BCAA), carbohydrates, and lipids, had strong positive associations. Interestingly, some sphingomyelins, glucosyl- and lactosyl- ceramides had negative associations with HTGC in contrast to dihydrosphingomyelins and ceramides. Several unannotated, xenobiotic, and a novel metabolites were associated with HTGC, such as 4-ethylcatechol and metabolonic-lactone-sulfate. The interactive metabolite-HTGC atlas is provided online: https://tofaquih.github.io/AtlasLiver/.

Conclusions: The combined network and pathway analyses showed that HTGC is associated with extensive dysregulation of BCAA metabolism and dyslipidemia. These associations were strongest in women. Our analysis provides a publicly available and comprehensive atlas of biochemical pathways associated with HTGC.