then demonstrate the potential for this methodological approach to improve power for discovery of associated SNPs by integrating GWAS of (continuous) measures of symptoms of Attention deficit/hyperactivity disorder (ADHD; MIM 143465) from the Early Genetics & Lifecourse Epidemiology Consortium (EAGLE) with the latest GWAS of ADHD diagnosis from the Psychiatric Genomics Consortium'(PGC).
Discussion: We anticipate that this method will facilitate locus discovery in genome-wide meta-analyses of psychiatric disease by encouraging valuable contributions from existing and future studies of the genetics of corresponding continuous traits.
Disclosure: Nothing to Disclose.

62. THE STATISTICAL PROPERTIES OF GENE-SET ANALYSIS FOR GWAS DATA

Christiaan de Leeuw[1], Benjamin Neale[2], Tom Heskes[3], Danielle Posthuma[5]

[1]CNRC, Vrije Universiteit, Amsterdam
[2]Analytic and Translational Genetics Unit
[3]Radboud University Nijmegen
[4]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University Amsterdam, The Netherlands; Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands

Background: With the rapid increase in sample sizes available for genome-wide association studies, it has become clear that many traits of interest are highly polygenic in nature and involve a large number of genetic variants with small individual effects. Gene-set analysis has been developed to evaluate if and how these variants relate to specific biological functions. A variety of tools is available to perform such analysis, but the statistical properties of specific methods as well as of gene-set analysis in general are still not widely known. Here we present an extensive statistical review of gene-set analysis to address'this.
Methods: A total of eleven stand-alone gene-set analysis methods were used, including both self-contained and competitive approaches. In addition five more methods were implemented in R, representing the standard statistical models that are the basis of most gene-set analysis methods. Four sets of large-scale simulations were used to evaluate these methods: validation simulations to determine rates of type 1'error and spurious associations; power simulations to assess the relation between statistical power and a range of parameters, including sample size; power simulations to assess the impact of heterogeneity between samples on power in a meta-analysis context; and a variety of simulations to investigate threats to the interpretation of statistically significant gene-set associations.
Results: The validation simulations show that self-contained gene-set analysis has a strong tendency to report spurious associations when analysing a polygenic phenotype, especially for larger gene sets and as the sample size increases. Competitive gene-set analysis does not have this vulnerability but most competitive methods do exhibit biases in their type 1'error rates, with only MAGMA and INRICH showing consistently well-controlled error rates. The power simulations reveal that the power for competitive gene-set analysis is strongly dependent on the heritability of the phenotype, and that increasing sample sizes leads to only a moderate and diminishing improvement in power. However, heterogeneity between samples can be used to potentially boost power as'well.
Discussion: This statistical review demonstrates a number of important properties of gene-set analysis in general and specific methods in particular. It establishes that self-contained analysis cannot provide reliable results for polygenic phenotypes, and that most competitive methods have hidden flaws as well. It further reveals that obtaining sufficient statistical power requires more than merely increasing sample'sizes.
Disclosure: Nothing to Disclose.

63. CROSS-DISORDER HERITABILITY ANALYSIS OF 23 BRAIN DISEASES REVEALS NOVEL PATTERNS OF SHARED GENETIC BACKGROUND BETWEEN PSYCHIATRIC AND NEUROLOGICAL DISEASES

Verneri Anttila[1], Benjamin Neale[2]

[1]Massachusetts General Hospital
[2]Analytic and Translational Genetics'Unit

Background: The broad and continuous nature of psychiatric phenotypic spectra has been clinically recognized for a long time, and the nosological overlaps which follow have been in recent years shown to extend into genetics as well. Now, new heritability-based methods provide a comprehensive test with which to perform large-scale quantification of such overlaps, both to evaluate the degree of sharing between psychiatric diseases and as a tool to evaluate their comorbidities with other brain diseases and phenotypes of interest.
Methods: Many neurological and psychiatric diseases have considerable epidemiological co-morbidity. In the Brainstorm project, we set out to combine as much of the available GWAS data from brain diseases as possible. We used a novel heritability method, LD score regression, which allows us to compare the extent of local linkage disequilibrium with association results from each disease to quantify the extent of shared molecular genetic basis of these diseases, and to evaluate the genetic co-morbidity patterns both within the major categories and the extent to which they cross the neurology/psychiatry boundary. Our aim was to use this unprecedented dataset to explore the co-morbidity of common genetic risk factors in order to gain insights into the molecular basis of these phenotypic co-morbidities. The analyzed data includes the currently available genome-wide association datasets from the Psychiatric Genetics Consortium, together with similar data from a number of neurological genetics consortia, totaling roughly 217,000 cases, as well as roughly 700,000 population-matched controls.
Results: We found that in general, psychiatric diseases in general tend to have considerable risk-increasing co-morbidity with a variety of other psychiatric diseases, notably with schizophrenia and major depression showing considerable co-morbidity with most of the studied psychiatric