identified rare damaging mutations (both SNPs and CNVs) in genes previously associated with ASD, including NRXN1.
Results: Common polygenic risk for ASD varies between families with an ASD proband, with some families carrying high risk for ASD, and others carrying low risk. Risk scores in the ASD probands are significantly higher than unaffected family members. We identified several families with low risk for ASD that carry a mutation in NRXN1, suggesting that some individuals will develop ASD as a result of common variation, whereas others with low common polygenic risk may develop ASD as a result of a severe effect variant.
Discussion: Overall, our findings show that it is necessary to explore the mutational spectrum of variants in families by including both common and rare SNPs and CNVs, to fully capture the genetic basis of risk for ASD.

Disclosure: Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2017.08.322

M16. PATHVIEW WEB: USER FRIENDLY PATHWAY VISUALIZATION AND DATA INTEGRATION

Weijun Luo*, Cory Brouwer

University of North Carolina at Charlotte

Background: Pathway analysis is widely used in omics studies. Pathway-based data integration and visualization is a critical component of the analysis. To address this need, we recently developed a novel R package called Pathview. Pathview maps, integrates and renders a large variety of biological data onto molecular pathway graphs. Pathview quickly became a leading tool in pathway visualization, and has been widely adopted by tens of thousands of scientists and dozens of dependent applications worldwide.
Methods: Here we developed the Pathview Web server, as to make pathway visualization and data integration accessible to all scientists, including those without the special computing skills or resources. Pathview Web features an intuitive graphical web interface and a user centered design. We also provide a comprehensive online help system and multiple quick-start example analyses. Even with no special computing training and resources, users may still accomplish pathway based data visualization and integration independently.
Results: The server not only expands the core functions of Pathview, but also provides many useful features not available in the offline R package: 1) The results graphs are interactive and hyperlinked to abundant external annotation data online; 2) The server provides the latest, most complete and accurate pathway definitions and graphs by regular synchronization with KEGG source databases; 3) Users can review, replicate and share their analyses easily with free registered user accounts, which enable collaborative research and reproducible science; 4) Useful user engagement features allow users make comments and suggestions, or ask for help in designated pages. Importantly, the server presents a comprehensive workflow for both regular and integrated pathway analysis of multiple omics data. In addition, the server also provides a RESTful API for programmatic access and conveniently integration in third-party software or workflows.
Discussion: Pathview Web is openly and freely accessible at https://pathview.uncc.edu/.

Disclosure: Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2017.08.323

M17. NOVEL QUANTITATIVE METHOD FOR GENETIC ASSOCIATION TESTING

Gido Schoenmacker*, Tom Claassen, Tom Heskes, Barbara Franke, Jan Buitelaar, Alejandro Arias-Vásquez

Radboud University Nijmegen Medical Centre

Background: Traditional genome-wide association studies perform a per-SNP association test, resulting in millions of tests. To subsequently examine effects at higher levels, gene-based, pathway-based, or polygenic risk approaches are used to aggregate the SNP-level association results. These methods result in a high multiple-testing burden, are vulnerable to inflation due to effects of Linkage Disequilibrium (LD) and gene size, and require time-expensive computing per phenotype. We propose a quantitative scoring method that operates directly on SNP-level data and can be used for any arbitrary genetic region of interest. We hypothesize that (a) our method can robustly identify genetic regions of interest, that (b) our method can be used to explain variance in a similar manner to polygenic risk approaches, and that (c) our method is robust against effects of LD and gene size. These properties ensure that our novel method can be used for genetic association testing.
Methods: Our primary data set consists of the Nijmegen Biomedical Study: 4452 genome-wide genotyped subjects using the Illumina HumanOmniExpress-12 and -24 BeadChip platforms with available Body Mass Index (BMI) measurements. In this data set, we tested the effects of LD by incremental pruning, the effects of gene size by Kolmogorov-Smirnov distribution comparison, and we compared our association results to results obtained using existing genetic association applications (Plink 1.9, Magma 1.04, and PRSice 1.25). Secondly, we compare variance explained for different methods in an Attention Deficit Hyperactivity Disorder (ADHD) discovery (n=2947) and replication (n=785) cohort.
Results: Using our novel method and fewer than 4500 individuals, we find one significantly associated gene for BMI (SNRPC) and several other suggestive genes which are confirmed in literature to be associated with BMI and were not picked up by the other methods tested. Secondly, we find a similar variance explained for ADHD across cohorts compared to the existing method. Lastly, our method is invariant to gene sizes and shows robust results against the effects of LD.

Discussion: Our results show that our novel method can identify true genetic regions of interest for BMI, can explain variance across cohorts for ADHD, and proves robust against the effects of gene size and LD. We identified genes of interest that were missed by existing methods, suggesting that our method could add to existing genetic association tests. More work in larger cohorts is needed to identify in which precise conditions our method can increase power to detect genetic regions of interest, however these first results in both a physical and a psychiatric/behavioral phenotype show promise.

Disclosure: Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2017.08.324

M18. ALLELIC HETEROGENEITY ACROSS PSYCHOTIC DISORDERS AND RELATED PHENOTYPES

Tatiana Polushina[*,1], Vidar Steen[1], Ole Andreassen[2], Stephanie Le Hellard[1]

[1]*University of Bergen*
[2]*University of Oslo*

Background: Major mental illnesses have been shown to overlap at the clinical and genetic levels. The genetic overlaps have been so far explored at the single genetic variants level, but very few studies have explored how independent variants within a locus could contribute to the genetic overlaps. In our study, we intend to increase the information captured from GWASs by focusing on allelic heterogeneity, i.e. the contribution of several independent markers within one genetic locus, within a trait and across related traits.
Methods: Using summary statistics from GWASs of traits related to mental illnesses: psychotic disorders, cognitive traits and brain volumes, we first selected independent genomic regions associated in each traits after conditional regression (Yang et al.[1]). All the genetic variants in LD with the associated signal were included in the genomic regions. We then first explored the overlaps in the regions within traits and across traits. We also scored each genomic region in each of the traits, using the Brown score for each bin, and explored the overlap in the significant regions.
Results: We observed allelic heterogeneity within and across traits. 147 genomic regions were associated with independent markers (not in LD) across several traits. We have established a map of genetic overlaps for these clusters across psychiatric disorders and relevant phenotypes (brain volumes, cognitive and personality traits). The strongest overlaps were observed in pairs: schizophrenia - educational attainment and schizophrenia – bipolar disorder.

We have established a pipeline for identification of allelic heterogeneity across different phenotypes.

Several of the GWAS included were too limited in power to provide significant hits yet, and will need bigger samples to yield more significant results.

Discussion: We identify allelic heterogeneity across traits, demonstrating that some genetic regions harbor independent associations with related phenotypes. Our approach is complementary to studies that explore genetic overlap at the single marker level. This improves our understanding of the impact of genetic factors in main psychotic disorders and related phenotypes, and could help to direct functional studies later.

Disclosure: Nothing to disclose.

Reference

[1] Yang J. et al. Nat. Genet. 2012.

http://dx.doi.org/10.1016/j.euroneuro.2017.08.325

M19. ESTIMATE SPATIOTEMPORAL IMPACT OF BRAIN VARIANTS

Kevin Vervier[*], Jacob Michaelson

University of Iowa

Background: Functional characterization for genetic variants is a major challenge in whole-genome sequencing-based studies. Recent approaches, such as TiSAn (Vervier et al., 2017) or GenoSkyline (Lu et al., 2016), estimate tissue-specific impact of variations, in particular in human brain tissues. However, such annotations do not provide insights on which brain regions or development time points might be especially vulnerable to a given variant.
Methods: In this work, we propose to integrate spatio-temporal gene expression from BrainSpan (BrainSpan, 2014) to estimate what the 'context matrix' of a variant is. Variants found in non-coding regions are represented as a combination of gene expression matrices, where weights are based on associations demonstrated in SLINGER models (Vervier et al., 2016).
Results: We validate our approach on psychiatric disorder datasets, and use temporal patterns to discriminate early- and late-onset damaging variants. Brain region-specific variants also help to identify combined mechanisms of action, in complex traits.
Discussion: Spatio-temporal profiles could also be combined with polygenic risk score approaches, and provide new dimensions to study psychiatric disorders.

Disclosure: Nothing to disclose.

http://dx.doi.org/10.1016/j.euroneuro.2017.08.326

M20. COMBINING POLYGENIC RISK SCORES ACROSS SEVERAL TRAITS CAN IMPROVE SCHIZOPHRENIA RISK PREDICTION