@TheGBLab 2018 Annual Report

Neurodegeneration & Genomic Sciences

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At TheGBLab our work is focused on understanding genomic variability and its impact on disease/phenotype. Our main areas of interest are neurodegenerative diseases in general, with a particular focus on the most common diseases: Alzheimer's, Parkinson's and Dementia with Lewy Bodies. To study these conditions we apply state-of-the-art genomic technologies in both large cohorts of cases, and on families where these diseases segregate. The former approach tends to inform us regarding disease modulating variants, while the latter is suited to identify disease causing variants. In addition to disease-based research, we also have a longstanding interest in the role of benign genetic variability.

Alzheimer's disease genetics

A main focus of our work over the years, the genetics of AD received once again a significant amount of effort in our lab. We've performed the first comprehensive genetic study of familial AD in the Finnish population. This is an important set of results, particularly since we now recognise the Finnish population as having a distinct genetic background when compared to other southern European populations. Because of this, understanding the genetics of dementia in this population is important and has implications for other populations.

The very first result of the application of exome-sequencing to dementia, was the identification of *NOTCH3* mutations in AD cases in 2010. This year, we've performed a detailed survey of genetic variability in leukodystrophy genes in AD. These data suggested a role for *NOTCH3* and *CSF1R* variants in AD.

We have also co-authored a paper showing that loss-of-function variability in *ADAM17* may be associated with late-onset familial AD and we applied polygenic risk scores from the latest AD meta-analysis to determine if we could discriminate between cases and controls in a cohort of well defined sampes. Our results showed a ~75% discriminative power in this setting, which is an improvement over using *APOE* alone.

Lastly, in reply to a small observational study of 16 subjects harbouring *TREM2* variants that suggested that the presence of an ε4 *APOE* allele was necessary for the development of AD pathology in TREM2 p.R47H carriers, we studied a large cohort of AD cases (ADSP and ADGC datasets), including a substantial number of neuropathologically confirmed subjects, to conclusively show that Alzheimer's disease pathology exists in a significant number of cases carrying only the *TREM2* p.R47H, without the presence of *APOE* ε4 alleles.

This year we also published two separate reviews in AD: the first was an overview of AD genetics, which included the most recent data from large consortium studies; the second was a review of the role of *TREM2* in AD and other neurodegenerative diseases, focusing on data generated over the last 5 years since its identification as a strong risk factor for AD. It was a really interesting exercise to see the amount of work that has been devoted to understanding this gene that is critical for AD.

Parkinson's disease genetics

Similarly to AD, we've performed a substantial amount of work in Parkinson's disease this year. We've co-authored a manuscript showing that genetic variants in *LRP10* are unliley to cause PD in a large European-American cohort. We've also co-authored a study detailing the frequency of loss-of-function variants in the *LRRK2* gene in Parkinson's disease. Here, we show that *LRRK2* haploinsufficiency does not cause or protect against PD, which is an important finding as we continue to work to understand the biological consequences of the genetic variability involved in this disease.

Lastly, we've shown that coding variability in *GBA* is responsible for the GWAS signal at this locus. Particularly, the p.E365K and p.T408M variants, which do not cause Gaucher disease when homozygous, are the drivers of the GWAS association signal.

Dementia with Lewy Bodies genetics

In DLB, 2018 was another truly fantastic year. The year started with the publication of the first GWAS in this disease. A remarkable piece of work that could not have been accomplished without the efforts of a large international consortium. Here, we show that common genetic variability plays a role in this disease and that the genetic architecture of DLB is likely to be distinct from PD and AD. In just a year this paper has already been cited over 19 times, which shows that it has been impactful in the field. We have also performed the first comprehensive study of copy number variability in DLB, showing suggestive evidence that CNVs may be involved in disease. Similarly to what occurred in PD, we have also looked at the potential role of *LRP10* genetic variants in DLB and failed to identify any evidence for this association. Lastly, we performed a review of the current state of genetic research in DLB.

Rare diseases

Despite our main projects being in common neurodegenerative diseases, one area which we have always had an interest in is the study of rare or orphan diseases. 2018 was no exception. We co-authored the description of genetic variants in *ZFHX2* as the cause of a rare pain insensitivity phenotype, which provides us with novel therapeutic targets for this condition. We have also described a splice-site mutation in *AP4S1* as the cause of spastic paraplegia type 52 with polymicrogyria.

This is an important manuscript as it expands the phenotype associated with SPG52. Similarly, we also published the description of a family with Brown-Vialetto-Van Laere syndrome, expanding the phenotype associated with mutations in *SLC52A3*.

Van Andel Research Institute

2018 was the year that we decided to move from the UK back to the US. This wasn't an easy decision; we had spent over 8 years at UCL, where we felt like we were a productive and successful lab. But we found at VAI a vibrant and supportive community and that really convinced us to move across the Atlantic once again. The last few months of 2018 were certainly less productive science-wise, as we planned the move of lab and people, but we're expecting for things to pick back up from very early in 2019 when our group is back together in a single location. We are very much looking forward to the new opportunities, collaborations and manuscripts coming out of our lab at VARI in beautiful West Michigan.

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