@TheGBLab 2016 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, Parkinson 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

The application of whole-exome sequencing to the study of Alzheimer's disease has been the major recent contributor to the identification of genetic factors associated with the disease. We have used this approach to study a cohort of neuropathologically confirmed AD cases and healthy subjects from the UK. Data resulting from this effort have been analysed focusing on the GWAS regions previously associated with AD in order to assess the possibility of rare coding variants in these regions also having an effect on disease, and also with a focus on genes involved in the APP-Abeta metabolism. In the first study, a potential protective factor for AD was identified in ABCA7, which warrants a detailed follow up in a larger and independent cohort. The second study confirmed that common coding variability in the 29 APP-Aβ related genes studied were not a critical factor for AD development.

As part of an international collaboration studying early-onset AD cases we examined the role of TYROBP genetic variants in Alzheimer's disease. The results obtained suggest that rare coding genetic variants in this gene are more common in AD cases than in controls, although larger studies are needed to confirm this association. In efforts led by the University of Nottingham to study a cohort of sporadic EOAD cases, NeuroX data (see below for a description of this platform) were used to perform a mutation analysis of 16 genes linked to familial forms of neurodegeneration and, paired with Sanger sequencing, were used to identify mutations in exons 16 and 17 of APP.

We expect that the ongoing use of genotyping platforms focused on rare variability, the increase in the number of samples being studied, and the expansion of whole-genome wide studies to underserved populations will lead to the identification of novel genetic factors in AD. With the same goal we are also continuing our efforts to expand the ongoing collaborative work looking at sequencing data from AD and controls from different European groups.

Dementia with Lewy Bodies

In 2016 we continued our work studying the genetics of Dementia with Lewy Bodies (DLB). We saw the publication of the manuscript we wrote in 2015, detailing our findings of heritability of DLB and its genetic correlation with PD and AD. These were important results, conclusively showing that there is a strong genetic component to DLB. To determine if our DLB cohort is contaminated with frontotemporal dementia cases, which would be plausible given some of the overlaps in clinical presentation, we assessed our samples for the most common genetic cause of FTD and FTD/ALS. Screening for the C9orf72 expansion in our DLB cohort revealed no pathogenic expansions in any of our pathologically diagnosed cases (see details here).

This year was also the 10th anniversary of the Lewy Body Society. This was celebrated with a day-long meeting in Newcastle - the “birthplace of DLB” in Europe. It was a great meeting with a very good mix of scientist- and laypeople-led discussions. Hopefully this was only the first of a series of more regular DLB-devoted meetings in the UK.

New genes for Parkinson’s disease?

During the last year two genes were published as being causative for Parkinson’s disease. We were part of the team that found homozygous mutations in VPS13C as a rare cause of autosomal recessive Parkinson's disease in work that was led by the International Parkinson’s Disease Genomics Consortium. This was an interesting result since common variability in the same gene had previously been found to be associated with modulating risk for the disease. It is not the first time we see this type of event (rare variability causing disease and common variability modulating risk), the same is also true for in PD, but it is remarkable how this finding was only conclusively made after the integration of disparate datasets (GWAS and sequencing in this case).

The second gene published was TMEM230. This finding is centred on a family in which the genetic cause had been previously identified as segregating mutations in another gene (DNAJC13). The same family was re-analysed by a different research group and mutations in TMEM230 were suggested to be the genetic cause instead. We had a look in our own data and found no evidence for the involvement of this gene in Parkinson’s disease - from a purely genetic perspective. The authors of the initial description of the family have also disputed the results linking TMEM230 with Parkinson’s disease (see comment here and reaction paper here). More than pinpointing the gene itself, these results highlight how difficult it is to identify genetic causes of disease. When a new gene is identified there is a burden of proof that needs to be met and this clearly is not accomplished in all instances.

Rare diseases

Despite our main projects being in neurodegenerative diseases, one area which we have always had an interest in is the study of rare or orphan diseases. In 2016 we made a concerted effort to create a program that would allow us to focus on this type of disorders. Our Rare Disease Program was mainly designed to help families who either don't have access to state-of-the-art genomic technologies through their Health Systems, or have only available a subset of these technologies. Because this is not the main area of study of our lab we are only able to perform a limited number of these projects, which are selected after detailed review of all available information (e.g. phenotype, previous laboratory testing, availability of family members and population genetic data for that genetic ancestry, etc). In 2016 we included a total of 14 families and we were able to identify the genetic cause of disease in 6 families. These included novel or extremely rare mutations in CTSF, MAGEL2, TBCK, RARS2, SLC20A2 and PTH1R.

We found this program to be extremely rewarding and plan to expand it in the following years.

Canine models of rare diseases

In 2016 we have also started to study rare neurological diseases in dogs. Kiterie Faller, a research fellow in the the lab visiting from the University of Glasgow, has led this effort by using whole-genome sequencing in dog breeds affected by different disorders. The first results of this program have now been published, reporting an MFSD8 mutation as the cause of neuronal ceroid lipofuscinosis in two littermate Chihuahua dogs.

NeuroX2 (a.k.a. Neuro Consortium Array)

In 2015 we published the paper that accompanies the NeuroX genotyping array, a platform designed to study neurodegenerative disease samples. We saw great interest from the community and the number of samples genotyped on this array worldwide greatly exceeded our expectations. In 2016, together with Illumina, we developed an improved version of this genotyping platform. The content has been tweaked and updated, the price point is lower and the total number of markers has increased. For more details on the array and content see the datasheet here. The array is a tremendously cost-effective approach to genome-wide genotyping, particularly for cohorts that have not yet been genotyped on any other platforms, but also for replicating results from larger GWAS-type studies. One thing we were successful at doing was incorporating probes for the APOE E2, E3, E4 haplotype, which means that it is now possible to get APOE and genome-wide genotyping at price point that rivals standard APOE genotyping alone.

Awards and recognition

It is always exciting to see our work recognized. In 2016 we were honored to receive recognition from the two main dementia UK Charities: Jose was awarded the 2016 Leader in Dementia Research by winning the Alzheimer's Society Dementia Research Leader Awards, and Rita was the first ever winner of the Alzheimer's Research UK Young Investigator of the Year Award.

Dementia Research Institute awarded to UCL

2016 ended with the fantastic announcement that UCL had won the bid to host the UK Dementia Research Institute (DRI) hub. The DRI is a new, national research institute dedicated to understanding the underlying diseases, transforming treatments and improving the lives of people living with dementia. It has a starting budget of £250 million and is led by the Medical Research Council with founding charity partners (Alzheimer's Society and Alzheimer's Research UK). We have played a small role during this application and are looking forward to the benefits such a strong initiative will bring to everyone living with dementia.

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