@TheGBLab 2015 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, as well as 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.

Visual Reviews of the Genetics of Dementia, PD and ALS

Our understanding of the genetics of disease has seen tremendous advances over the last decade or so. Many of these advances were possible due to the identification of novel disease causing genes and risk modulating ones. Because so many genes have been identified recently we recognized a need for easy to read publications with the most relevant information available for these genes. To that end we published a trilogy of papers as Cell SnapShots. We started with the Genetics of ALzheimer's Disease, then updated the Genetics of Parkinson's Disease and lastly published a review of the Genetics of ALS and FTD. In all papers, and in addition to listing the genes involved in each condition, we tried to expand on known functions of those genes and their effect sizes on the respective phenotype. We think these are very useful not only for novel people in the field, but also as the primary place to look for when researching genes linked to these diseases.

NeuroX: a Tool for Genetics of Neurodegenerative Diseases

In 2015 we published the paper that accompanies the NeuroX genotyping array, a tool that was born from the collaborative efforts of several dozen researchers and Illumina. As we drill down into the frequency spectrum of genetic variants, we also require tools that are rapid and cost-effective allowing us to genotype several thousand samples in relatively short periods of time. These were the main reasons behind the creation of this array. NeuroX is built on the backbone of Illumina's ExomeChip, which contains approximately 240,000 markers, mostly coding and of lower frequency in the general population. On top of this content we added about 24,000 variants we considered interesting for a number of reasons: 1) they were associated in recent GWAS of neurological disease; 2) they never reached significance, but were suggestive; 3) rare variants that were found during our exome and genome sequencing efforts; 4) known neurological disease causing mutations; 5) variants that were known eQTLs in the brain. At a price point of ~$45 or £30 and with a 12-sample format, NeuroX is the perfect tool for any study in a new cohort of neurological disease or replication of previous studies. Our large-scale genetic studies in DLB were based on NeuroX (see more below and here). The array has been incredibly successful and a second, new and improved, version is currently in the works.

Department Molecular Neuroscience
University College London

Mutations in *PNKP* as a Common Cause of Ataxia

Recessive forms of ataxia are a very heterogeneous group of diseases, not only clinically, but also genetically. In 2014 we had started a collaboration with a Portuguese group who had performed a 10 year nationwide, population-based, systematic survey of ataxia. In this cohort were identified 9 families with a homogeneous form of recessive ataxia with oculomotor apraxia (AOA). The integration of whole-genome genotyping and whole-exome sequencing data from these families led to the identification of the same, completely segregating, homozygous *PNKP* (polynucleotide kinase 3'-phosphatase) mutation, c.1123G>T (p.Gly375Trp), in three of the studied families. When looking at the same gene in the remaining families, we identified homozygous or compound-heterozygous mutations in five other families (see here for details). PNKP is a dual-function enzyme with a key role in different pathways of DNA-damage repair. Mutations in this gene had previously been associated with an autosomal-recessive syndrome characterized by microcephaly; early-onset, intractable seizures; and developmental delay (MCSZ). The finding of *PNKP* mutations associated with recessive AOA extends the phenotype associated with this gene and identifies a fourth locus that causes AOA. Additionally, and since the families were identified in a nationwide, population study, we were also able to conclude that mutations in *PNKP* are the most common cause of AOA in the Portuguese population and that AOA4 is the second most common form of recessive ataxia following Friedrich's ataxia, in the country.

Heritability and Genetic Correlation in DLB

Last year we performed the first large-scale genetic study in DLB. This showed us that DLB shares not only clinical and pathological determinants with both PD and AD, but also shares common genetic risk factors. For two of those loci, however, the association profiles in DLB were starkingly different than the ones seen in PD. This year we have taken this study a step further and performed a formal calculation of the genetic correlation between DLB and both PD and AD. Our estimates point to a very similar correlation between DLB/AD and DLB/PD, suggesting that from a purely genetic perspective, DLB is as similar to AD as it is to PD. This is only true when the *APOE* locus is excluded from the analysis, given its very strong effect in both AD and DLB. In addition to testing for correlation, we also estimated the heritability of DLB – identifying how much of DLB in our cohort is due to genetic variability between our cohort of cases and controls. We estimated that the heritability of DLB is ~30%; very similar to the heritability calculated by us and others for PD and slightly lower than the heritability estimated for AD. These results provide us with a couple of important clues for future studies: DLB has a strong genetic component and because it shares so much with the other common diseases, DLB must be more common than currently estimated.

de novo Mutations in Parkinson's Disease

The purely genetic forms of Parkinson's disease are rare and the majority of patients are sporadic. There are, however, a significant number of these sporadic cases that present with an early onset of disease, very similar to what occurs in familial forms. We hypothesized that a portion of these cases might be due to *de novo* mutations. To test this hypothesis, we collected 21 parent-child trios (for a total of 63 individuals studied: 21 early-onset PD cases together with their healthy parents). We excluded any potential recessive forms of disease and performed exome-sequencing in all individuals. The rationale was that any genetic variants identified in the probands that was not present in either parent, would be a candidate for causing the disease. In addition to our dataset, we also had ~1,200 PD cases that had already been exome-sequenced, providing us with a quick and inexpensive replication cohort. We identified 20 confirmed *de novo* mutations in the 21 trios. Of the genes identified to carry *de novo* mutations, *PTEN*, *VAPB* and *ASNA1* are supported by various sources of data to be involved in PD. We show that these genes are reported to be within a protein-protein interaction network with PD genes and that they contain additional rare, case-specific mutations in our independent cohort of PD cases. These results suggest that a new genetic mechanism may be involved in causing apparently sporadic forms of PD.

Overview of Movement Disorders Genetics

In 2015, together with Susanne Schneider and backed by Springer, we prepared a book with an overview of the genetics of movement disorders. We divided it into three sections: 1) Technical and scientific aspects; 2) Clinical aspects with guidance towards work-up; and 3) Ethical and legal aspects of genetic testing in clinical and research settings. We were fortunate to bring together a fantastic group of authors that contributed each of the chapters. It was great fun putting this together and the final result greatly exceeded our expectations.

Expanding our case collection

One of our main goals continues to be to collect and recruit cases for our studies. These range from families with rare diseases, to sporadic cases of common diseases such as Alzheimer's disease. We have collected over 50 samples with rare, undiagnosed diseases. All of these have either been exome or genome sequenced and many have whole-genome genotyping data as well. We have also expanded our collection of dementia cases, with an emphasis on DLB. Here we have been able to increase our neuropathological cohort to over 1,500 cases. All of these have been genotyped on a large array and were also exome sequenced. Additionally, we have generated exome sequencing data on about 1,000 PD cases, bringing the number of sequenced PD samples in our consortium (IPDGC) to closer to 3,000.

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