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| **Biostatistics- Genetics**  Work Package 14A |
| **Objective(s)**: |
| The aim of this work package was to develop and apply state-of-the-art genetic data analysis methods to DPUK cohorts, with the goal of testing and demonstrating the utility of informatics portals for integrated analyses within a newly created genetics portal.  More specifically, the objectives centred on developing and applying state-of-the-art stratification methods to DPUK cohorts. It also aimed to provide exemplar statistical analyses to test and demonstrate the utility of the informatics portal for integrated analyses.   1. Develop genetic risk stratification analyses for AD using polygenic score and other analytical techniques, through collation of existing GWAS and new replication data. These analyses would be extended to other forms of dementia and neurodegeneration to include PD, MND and others. 2. Provide exemplar statistical analyses to test and demonstrate the utility of the informatics portal for integrated (across cohort) analyses. Analyses will include linking research results data to routinely collected data within cohorts and data linking individuals between cohorts. 3. To create a results database focusing on genetics, genomics and associated data. |
| **Overview Summary:** |
| This work package focused on developing and applying state-of- the art genetic data analysis methods to DPUK cohorts to demonstrate the potential of informatics portals for conducting integrated genetic analyses. It led to the successfully development of the [DPUK Genetics Portal](https://portal.dementiasplatform.uk/AnalyseData/GeneticsPlatform#:~:text=The%20DPUK%20Genetics%20portal%20provides,Registry%20and%20Genetic%20Data%20Browser.) to operate alongside the [DPUK Data Portal](https://portal.dementiasplatform.uk/) and [Imaging Portal](https://portal.dementiasplatform.uk/AnalyseData/ImagingPlatform). The team has successfully generated novel findings in the genetic risk for dementias and implicated other inflammation biomarkers in the prediction of dementia. |
| **Executive Summary:** |
| The aim of this work package was to develop and apply state-of-the-art genetic data analysis methods to DPUK cohorts, with the goal of testing and demonstrating the utility of informatics portals for integrated analyses within a newly created genetics portal. This is an important step towards future data analysis culture because data portals provide simplified and remote access for researchers to a large number of cohorts that would be otherwise prohibitive to distribute and analyse due to security and computational restrictions. During the process the team identified challenges associated with data sharing and attempted to come up with solutions. As part of the project, it generated many novel findings into the genetic risk for dementias, as well as implicating other factors such as inflammation biomarkers or comorbidities for the prediction of dementia. At the time of submitting this report eleven papers in peer-reviewed journals have been published, with a further two papers in review. Nineteen presentations have been given at conferences and workshops regionally, nationally, and internationally.  The team has successfully developed a genetics portal, one new algorithm has been created as a result of this project, four DPUK study requests have been made, and more than £500,000 of further funding has been acquired. This project enabled the support of several Early Career Researchers to work in the field of dementia research and provided them with opportunities to communicate their research in the wider field.  The team concluded that data portals are a very promising new tool for dementia research, and supplied recommendations to improve the DPUK portal for future projects and researchers. |
| **Summary of Outputs**: (as per Researchfish categories) |
| **Publications:** |
| **Primary Research Findings**:  1)Escott-Price et al. 2015. **Common polygenic variation enhances risk prediction for Alzheimer's disease.** *Brain* 138(12), pp. 3673-3684. doi: 10.1093/brain/awv268  2)Escott-Price et al. 2015. **Polygenic risk of Parkinson disease is correlated with disease age at onset.** *Annals of Neurology* 77(4), pp. 582-91. doi: 10.1002/ana.24335  3)Leonenko et al., Escott-Price **Polygenic risk and hazard scores for Alzheimer's disease prediction.** *Ann Clin Transl Neurol*. 2019;6(3):456–465. 2019(1) 18. doi: 10.1002/acn3.716  4)Leonenko et al., Escott-Price (2019) (2) **Genetic risk for alzheimer disease is distinct from genetic risk for amyloid deposition** *Ann Neurol.* 2019 Sep;86(3):427-435. doi: 10.1002/ana.25530.  5)Baker et al., Escott-Price **POLARIS: Polygenic LD-adjusted risk score approach for set-based analysis of GWAS data.** *Genet Epidemiol*. 2018;42(4):366–377. doi: 10.1002/gepi.22117  6)Grozeva etal., Sims (2019) **Benefits and challenges of rare genetic variation in Alzheimer's disease.** *Current Genetic Medicine Reports* 7 (1), pp. 53-62. doi: 10.1007/s40142-019­0161-5  7)Guerreiro et al. (2016). [**Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases**.](http://orca.cf.ac.uk/84792) *Neurobiology of Aging* 38, article number: 214.e7–214.e10. doi: 10.1016/j.neurobiolaging.2015.10.028  8)Escott-Price et al. (2018). [**Polygenic risk for schizophrenia and season of birth within the UK Biobank cohort**.](http://orca.cf.ac.uk/109757) *Psychological Medicine* doi: 10.1017/S0033291718000454  9)Ahmad et al. (2018.) **Disentangling the biological pathways involved in early features of Alzheimer's disease in the Rotterdam Study.** *Alzheimer's and Dementia.* doi: 10.1016/j.jalz.2018.01.005  10)Morgan et al. (2017.) **The correlation between inflammatory biomarkers and polygenic risk score in Alzheimer's Disease.** *Journal of Alzheimer's Disease* 56(1), pp. 25-36. doi: 10.3233/JAD-160889  11)Bellou et al., Escott-Price (2020) **Polygenic risk and pleiotropy in neurodegenerative diseases.** *Neurobiology of Disease.* doi: 10.1016/j.nbd.2020.104953  12) Baker andEscott-Price (2020) Polygenic Risk Scores in Alzheimer’s Disease: Current Applications and Future Directions. Frontiers in Digital Health (in press)  13)Bellou et al., Escott-Price (2020) **Age-dependent effect of APOE and polygenic component on Alzheimers’ disease.** *Neurobiology of Aging. (in press)*  **Invited Reviews:**  14)Emily Baker et al. (2015) **Common polygenic variation enhances risk prediction for Alzheimer's disease**. *Brain* 138(12), pp. 3673-3684. doi: 10.1093/brain/awv268  15)Escott-Price et al. (2015) **Polygenic risk of Parkinson disease is correlated with disease age at onset**. *Annals of Neurology* 77(4), pp. 582-91. doi: 10.1002/ana.24335  16)Leonenko et al. (2019) **Polygenic risk and hazard scores for Alzheimer's disease prediction**. *Ann Clin Transl Neurol*. 2019;6(3):456–465. 2019(1) 18. doi: 10.1002/acn3.716  17)Leonenko et al. (2019) **Genetic risk for alzheimer disease is distinct from genetic risk for amyloid deposition**. *Ann Neurol*. 2019 Sep;86(3):427-435. doi: 10.1002/ana.25530. Epub 2019 Jul 1.  18)Baker et al. (2018) **POLARIS: Polygenic LD-adjusted risk score approach for set-based analysis of GWAS data**. *Genet Epidemiol*;42(4):366–377. doi: 10.1002/gepi.22117  19)Grozeva (2019) **Benefits and challenges of rare genetic variation in Alzheimer's disease**. *Current Genetic Medicine Reports* 7 (1), pp. 53-62. doi: 10.1007/s40142-019­0161-5  20)Guerreiro et al. (2016). **Genome-wide analysis of genetic correlation in dementia with Lewy bodies, Parkinson's and Alzheimer's diseases**. *Neurobiology of Aging* 38, article number: 214.e7–214.e10. doi: 10.1016/j.neurobiolaging.2015.10.028  21)Escott-Price et al. (2018). **Polygenic risk for schizophrenia and season of birth within the UK Biobank cohort**. *Psychological Medicine*. doi: 10.1017/S0033291718000454  22)Ahmad et al. (2018). **Disentangling the biological pathways involved in early features of Alzheimer's disease in the Rotterdam Study**. *Alzheimer's and Dementia* doi: 10.1016/j.jalz.2018.01.005  23)Morgan et al. (2017). **The correlation between inflammatory biomarkers and polygenic risk score in Alzheimer's Disease**. *Journal of Alzheimer's Disease* 56(1), pp. 25-36. doi: 10.3233/JAD-160889  24)Leonenko et al. (2019) **Genetic risk for Alzheimer’s disease and for amyloid deposition is distinct**. *Annals of Neurology*. doi: 10.1002/ana.25530  25)Kunkle et al. (2019) **Meta-analysis of genetic association with diagnosed Alzheimer's disease identifies novel risk loci and implicates Abeta, Tau, immunity and lipid processing**. Nature genetics, 51:414–430  26)Richards et al. (2019) **The relationship between polygenic risk scores and cognition in schizophrenia**. *Schizophrenia Bulletin*. doi: 10.1093/schbul/sbz061  27)Hardy and Escott-Price (2019) **Genes, pathways and risk prediction in Alzheimer’s disease**. *Human Molecular Genetics*. doi: 10.1093/hmg/ddz163  28)Guerreiro et al. (2019) **Heritability and genetic variance of dementia with Lewy bodies**. *Neurobiology of Disease*. doi: 10.1016/j.nbd.2019.04.004  29)Baker et al. (2019) **Gene-Based Analysis in HRC Imputed Genome Wide Association Data Identifies Three Novel Genes for Alzheimer's Disease**. *PloS One*. doi: 10.1371/journal.pone.0218111  30)Leonenko et al. (2019) **Polygenic Risk and Hazard Scores for Alzheimer’s disease prediction**. *Annals of Clinical and Translational Neurology*. doi: 10.1002/acn3.716  31)Escott-Price et al. (2019) **Genetic analysis suggests high misassignment rates in clinical Alzheimer’s cases and controls**. *Neurobiology of Aging*; 77:178-182.  32)Escott-Price et al. (2019) **Polygenic Risk Score Analysis of Alzheimer’s Disease in Cases without APOE4 or APOE2 Alleles**. *Journal of Prevention of Alzheimer’s Disease*. doi: 10.14283/jpad.2018.46  33)Harrison et al. (2020) **From polygenic scores to precision medicine in Alzheimer’s Disease: A systematic review**. *Journal of Alzheimer's Disease* (in press) |
| **Collaborations & Partnerships** |
| The team has coordinated a genetics network within DPUK. This network includes the following Principal Investigators: Carol Brayne, John Hardy, Peter Passmore, Kevin Morgan, John Powell, Simon Mead and Clive Holmes. Following the implementation of this network, permissions have been gathered to incorporate a variety of data to the DPUK Genetics Database and have incorporated pre-existing genetic data via upload to the DPUK analytical site.  Some of the work undertaken has led to the development of new collaborations in the neuroimmunology field and been important in defining the new work proposed in this area for new DPUK funding due to start in 2021. |
| **Further Funding** |
| 1. Leveraging human genetics to identify target populations for dementia therapeutics (VEP PI), £200,134; 01/03/20-28/02/23; (UKDRI (Eisai/DRI joint initiative 2. Translating Individual Alzheimer Genetic risk into disease phenotypes (VEP PI), £371,564; 01/05/20-30/04/23; JPND (MRC) 3. Polygenic risk scores for neurodegeneration and Alzheimer’s pathophysiology (VEP PI), £247,055; 01/09/20-31/08/21); (UK DRI) |
| **Next Destinations** |
| * Christian Bannister – Digital Health Labs * Elisa Majounie – British Columbia Cancer Agency * Aura Frizzati – Swansea University Post-doctoral Researcher * Georgina Menzies – Cardiff University Lecturer * Nandini Badarinarayan – NHS Informatics Service * Ganna Leonenko – Dementia Research Institute * Detelina Grozeva – Post-doctoral researcher Division of Psychological Medicine * Roswithas Hopkins - Dementia Research Institute * Lauren Luckcuck – Centre for Aging and Dementia Research * Janet Harwood – Post-doctoral researcher Division of Psychological Medicine |
| **Engagement Activities** |
| **Scientific:**  Emily Baker, PhD Student (Supervisor – Prof Valentina Escott-Price)  Poster at AAIC Conference – July 2017  Poster at ASHG Conference – October 2017  Ioanna Katzourou, PhD Student (Supervisor – Prof Valentina Escott-Price)  Abstract at AAIG Conference – July 2019  Abstract at AAIG Conference – July 2020  Karen Crawford, PhD Student (Supervisor – Prof Valentina Escott-Price)  Abstract at AAIG Conference – July 2019  Thomas Rowe, PhD Student (Supervisor – Prof Valentina Escott-Price)  Abstract at AAIG Conference – July 2020  Emily Baker – ECR  Abstract at ESHG Conference – June 2019  Abstract at AAIG Conference – July 2020  Eftychia Bellou – ECR  Abstract at AAIG Conference – July 2019  Abstract at ICAPD Conference – April 2020  Abstract at AAIG Conference – July 2020  Ganna Leonenko – ECR  Abstract at ASHG Conference – October 2018  Abstract at ASHG Conference – October 2019  Abstract at ESHG Conference – June 2020  Georgina Menzies - ECR  DPUK Genetics Platform presentation – AAIC July 2017  Presentations at cohort workshops – May and September 2017  Presentations at cohort workshops – December 2017 and February 2018  Presentation at the MRC oversight board in London  Detelina Grozeva - ECR  Poster presentation at European Society of Human Genetics Conference 2019  **Public:**    **2016**   * May 2016 Dementia week, seminar series * June 2016 Sci Screen presentation, Cardiff University * June 2016 Science Café talk * Mobile roadshow with interactive showcase space for lived experience and discussion. e.g. Delegates used the dementia goggles in a Virtual Reality system that makes you feel like you are very old. Our field team ran the event, delivering memory tests, tests of spatial awareness, and recruit participants. CADR with MRC CNGG/NCMH at Wales Gene Park's Genetics and Genomics Conference (22 June 2016). * Used mobile roadshow to deliver interactive space, as above. British Science Festival 10 & 11 September 11am-4pm * Used mobile roadshow to deliver interactive space, as above. Young Onset Dementia: Different Impact, Positive Solutions conference 27th September * Field Team delivered interactive presentation directly to public. Public response to scientific discovery * CADR presentation to Minister who was visiting Swansea University 15 August * CADR annual public conference 5 October 2016 City Hall, Cardiff * Welsh Talk (Cardiff, 21/11/2016)   **2017**   * 25/04/2017 Church Talk, Cwmbran * June 2017: Talk on ‘Dementia’ for Aberystwyth Probus group. (General public) * September 2017: Study day for Llandaff Diocese, Church of Wales, on Dementia Friendly Churches. (General public) * July 2017: Novel approach to gene-based analysis of Alzheimer’s Disease informed by genetics of psychiatric disorders. Baker E and Escott-Price V * October 2017: POLARIS: Polygenic LD-Adjusted Risk Score Approach for Analysis of GWAS Data. Baker E, Sims R, Williams J and Escott-Price V * BBC Wales: The work of brain banks and the people who donate to them to help with research. * October 2017: Foundations Autumn Roadshows (Nottingham 50 people 20 public, Southampton 50 people 20 public, London 60 people 25 public, Manchester 40 people 10 public) * CADR stand at Ageing Well in Wales workshop Swansea 7th February 2018 * 10/10/2017 CADR Conference   **2018**   * 08/02/2018 Will members of my family develop Alzheimer's disease? * February 2018: Will members of my family develop Alzheimer’s disease? * March 2018: Genetics of Dementia Summit. Williams * March 2018: UK DRI at Cardiff. Williams * April 2018: UK DRI at Cardiff * April 2018: Wales This Week: Memory Matters * 17/05/2018 CADR stand at Dementia Action Week open day * 18/10/ 2018 CADR Annual Conference: Connect 'for' Ageing and Dementia Research   **2019**   * 20/01/2019 Buckingham Palace 50th Anniv. Investiture Prince of Wales * 20/02/2019 Whiteley Retirement Village * 05/03/2019 Davies C Newton Nottage Mother's Union (Porthcawl) monthly meeting talk about Alzheimer's Research * 05/03/2019 Ministerial Lab Visit * 25/03/2019 5 Million Genome Analyses * 21/03/2019 Russell group tour of laboratories * 03/04/2019 Fund raising for the dementia revolution * 21/05/2019 Cardiff University Dementia Research stall at Memoria performance by Re-Live * 29/05/2019 BDR training day at Cardiff * 30/05/2019 Cheltenham Festival of Science * 05/06/2019 ARUK Annual Conf 2019 * 17/06/2019 AAIC Los Angeles - Multiplex Model of Alzheimer's * 19/06/2019 European Society of Human Genetics Conference "Copy number variation in Alzheimer’s Patients" * 19/06/2019 Kerr Lecture, Walton Centre, Liverpool * 19/06/2019 European Society of Human Genetics Conference "Next Generation Exome Sequencing in a Large Sample of Alzheimer’s Patients" * 26/06/2019 UK-Korea Neuroscience Symposium * 18/07/2019 Talk to Mother's Union regarding the research conducted by the Dementia Research Team * 19/07/2019 MRC CNGG celebration dissemination video * 31/07/2019 AMS fellowship workshop * 12/08/2019 RCPsych Neuropsychiatry Conf * 11/09/2019 MRC Centre Celebratory Event * 20/09/2019 Royal Society visit * 22/10/2019 Alzheimer's Society Lab Visit * 23/10/2019 VIB/KUL Distinguished Lecture Series * 27/11/2019 JPND Genetic Architecture of Alzheimer's   **2020**   * 01/01/2020 ARUK sponsored Pint of Science Event * 23/01/2020 Newspaper Article Western Mail. Multiplex Model of Alzheimer's * 25/02/2020 From Multiomics to mechanisms |
| **Influence of policy, practice, patients & the public** |
| The potential of polygenic scores was specifically mentioned by the UK Minister of Health in discussing future medical practice (2019). |
| **Research Tools & Methods** |
| The group has led on the development of polygenic risk scoring methodology and published extensively on this topic. Details of progress in the development of algorithms is given below. |
| **Research Databases & Models** |
| This work has led to the development of algorithms.  Alzheimer's Disease Polygenic Risk Profiling - This model used data from a powerful dataset comprising 17 008 cases and 37 154 controls obtained from the International Genomics of Alzheimer’s Project (IGAP). Alzheimer’s disease (AD) Polygenic risk scores were generated for 3177 cases and 7277 controls (GERAD data) and tested whether the alleles identified to associate with disease in IGAP sample are significantly enriched in the cases relative to the controls in the GERAD sample. The disease prediction accuracy was investigated in a sample of 3049 cases and 1554 controls (for whom APOE genotype data was available) by means of sensitivity, specificity, area under the receiver operating characteristic curve (AUC) and positive and negative predictive values. The best prediction accuracy AUC = 78.2% (95% confidence interval 77–80%) was achieved by a logistic regression model with APOE, the polygenic score, sex and age as predictors (Escott-Price V. et al. 2015,2017). |
| **Intellectual property & licencing** |
| None |
| **Medical products, interventions & clinical trials** |
| None |
| **Artistic & creative products** |
| None |
| **Software & technical products** |
| The team has published a PRS methodology: (Baker et al. (2018) **POLARIS: Polygenic LD-adjusted risk score approach for set-based analysis of GWAS data**. *Genet Epidemiol*;42(4):366–377. doi: 10.1002/gepi.22117). The POLARIS set‐based analysis tool is available to download from github.com/BakerEA/POLARIS. The tool is written in Python and will operate on any computing platform. |
| **Spin outs** |
| None |
| **Awards & recognition** |
| None |
| **Other outputs & knowledge/future steps** |
| These research findings implicate new pathways to the development of common Alzheimer's disease. The work is likely to have a considerable impact on the future understanding of disease mechanism and therapeutic targets. |
| **Use of facilities & resources** |
| GERAD consortium genetic and basic cohort phenotype data has been uploaded to the DPUK Data Portal. |
| **Most successful outcome and what it means for future dementia research**: |
| Development and validation of AD polygenic risk scoring. Genomic profiling will become pivotal in selecting therapies based on individual risk. To achieve high diagnostic accuracy, polygenic risk scoring should be linked with biomarkers, clinical and environmental information and tested for accuracy in groups of people targeting disease specific functional mechanisms. |
| **Lessons learned**: |
| Data sharing is essential for bioinformatics analyses and to make best use of research findings. The current challenges of data sharing are well known but are impacting negatively on progress by delaying the research (data analysis and methodology development) in the AD and dementia field. |
| **Other:** |
| The full research report from the team can be made available by contacting DPUK staff. |
| **Date of Report:** |
| 14 August 2020 |