A novel biomarker for insight into ALS disease mechanisms and progression

RESEARCH TEAM:

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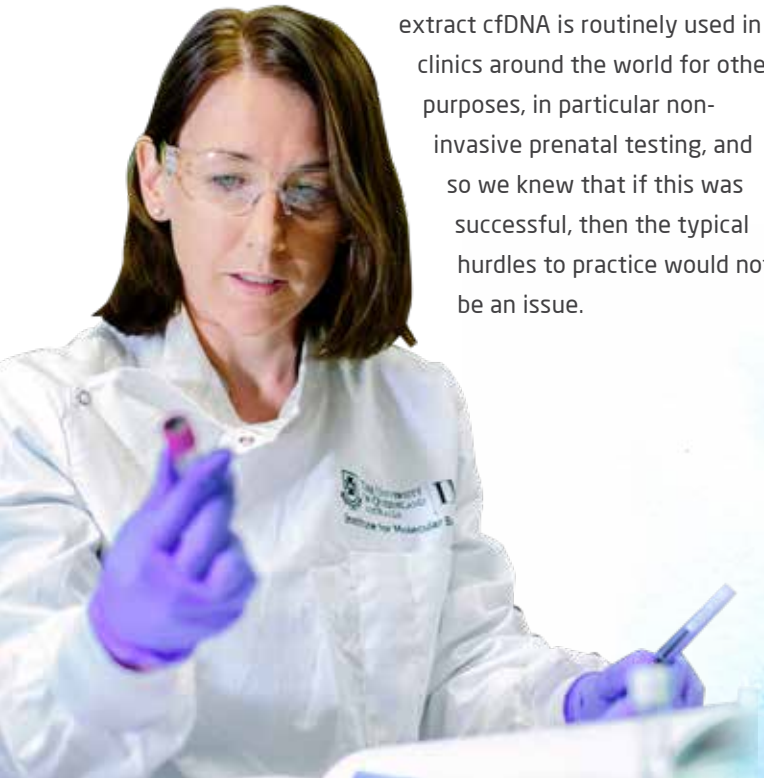
Research

ALS is typically a fast-progressing disease but most people with the condition will experience a relatively slow, 12-month long diagnostic process. There is no single biological marker that can distinguish the condition to avoid this issue and support early multidisciplinary interventions and clinical trial enrolment. In 2016, Prof Wray's (Australia) and Assoc. Prof Zaitlen's (USA) teams were collaborating on other projects and came up with a relatively new idea to investigate cell-free DNA (cfDNA) as a biomarker for ALS to address this problem. cfDNA is simply the product of cellular turnover, in which DNA gets released into the circulation. Given the progressive, changing condition of someone with ALS, we hypothesized that the blood cfDNA profile would be unique compared to someone with a different condition, or a healthy control. We started to develop methods to profile the cfDNA detected in blood to determine where the cfDNA was coming from (the originating tissue/cell) by comparing the detected cfDNA with references of known tissues markers. Our question was to determine if an ALS specific cfDNA signature could be detected, ultimately leading to a blood test that could be used for diagnosis or tracking disease progression. The technology to extract cfDNA is routinely used in clinics around the world for other purposes, in particular non-invasive prenatal testing, and so we knew that if this was successful, then the typical hurdles to practice would not be an issue.



Outcome

Thanks to initial funding support from the Brain Foundation, we have been able to progress our preliminary idea, results and methods to determine if a unique profile of cfDNA in ALS patients can identify and track disease. Our methods were to profile cfDNA, predict that cfDNA in blood originates from a variety of tissue/cell-types, and that it may consist of a higher proportion from skeletal muscle in ALS cases compared to controls (with small numbers of samples analysed using an unbiased, whole-genome approach). The methods and preliminary findings have been made publicly available (bioRxiv/Github) and are now peer-reviewed in a well-regarded genomics journal Nature Communications. Assoc. Prof Zaitlen and his team at the University of California are now preparing an efficient, high-throughput capture to profile the tissue-informative regions of the genome. This will allow us to efficiently profile a large number of ALS samples, alongside other neurological cases and controls for sensitivity testing and further profile refinement. This is running across two international clinics, here at UQ and in parallel at UCSF, to ensure the methods and techniques are robust. We are excited that the project has now been rapidly increased in size with subsequent funding received from FightMND to support the additional sample collections and profiling for outcomes to be produced by 2022-end. We look forward to sharing these results with the community and very much hope that this will make significant inroads into improving the diagnosis and tracking of those with ALS.