

RT-QuIC

Optimisation, harmonisation and standardisation of the analysis of disease associated prion protein in cerebrospinal fluid (CSF) by real-time QuIC, in the diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD).

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PI: Dr Alison J.E. Green, The National CJD Research & Surveillance Unit, Centre for Clinical Brain Sciences, University of Edinburgh, Scotland, UK

1) Aims of the consortium: Real-time Quaking Induced Conversion (RT-QuIC) is a recently developed technique that can detect the aggregation of abnormal mis-folded proteins. Scientific studies reported in 2011 and 2012 suggested that RT-QuIC could be used as a sensitive and specific diagnostic test for sporadic Creutzfeldt-Jakob disease (sCJD): a rare protein mis-folding disorder. The aim of our project was to establish RT-QuIC in a number of European countries and ensure that the RT-QuIC technique was optimised and standardised within European laboratories. We also wanted to ensure that the results obtained were harmonised throughout Europe and by the inclusion of non-European countries such as Japan, Canada and Australia to ensure that RT-QuIC was harmonised on an international basis.

2) Methods: We established two CSF RT-QuIC workshops, trained scientists, exchanges reagents such as recombinant PrP and CSF samples and undertook two international CJD Ring-trials.

3) Key results: Our achievements were to establish RT-QuIC in 3 Italian laboratories (Rome, Milan and Bologna), 1 Belgium laboratory (Antwerp), 1 French laboratory (Paris) and 1 German laboratory (Munich). This involved training personnel and sending out reagent packs to each laboratory to help establish the technique. Once the technique was established we worked together to standardise and optimise the RT-QuIC technique in terms of methodology, such as amounts of recombinant prion protein substrate required, shaking speed, temperature and buffer composition. In addition we established the criteria for a positive result. After the RT-QuIC technique was optimised and standardised we undertook two international ring-trials to ensure the RT-QuIC technique was harmonised between 11 international laboratories. This involved sending out sets of identical cerebrospinal fluid (CSF) samples to each laboratory to ensure identical results were obtained. The results of these ring-trials were near complete agreement between European and Non-European laboratories. We have created a standardised protocol for the RT-QuIC. In addition to the above work in optimising the RT-QuIC technique each laboratory has collected data regarding the diagnostic utility of CSF RT-QuIC for the diagnosis of sCJD. The sensitivity of RT-QuIC ranges from 73%-91% and the specificity is currently 100%.

4) Significance and impact of results: In light of the high degree of sensitivity and specificity of a positive CSF RT-QuIC result for sporadic CJD, CSF RT-QuIC was included as part of the diagnostic criteria for sporadic CJD by the European Centre for Disease Control (ECDC) funded European CJD Surveillance Network in 2017. CSF RT-QuIC is now accepted as a part of the diagnostic work-up of patients with suspected sporadic CJD worldwide.

5) Future challenges: An ECDC funded international ring trial for CSF RT-QuIC involving 13 different laboratories was set up in October 2019. In addition an international collaborative study has been commissioned to investigate the impact of CSF RT-QuIC on the surveillance of sporadic CJD by the World Health Organisation.