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Massively parallel next generation sequencing to investigate the cis-acting genetic modifiers of somatic instability in Huntington's disease

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Huntington Disease (HD) is an extremely variable inherited neurodegenerative disorder caused by expansion of an unstable CAG trinucleotide repeat in the huntingtin gene (*HTT*). Somatic instability in HD exhibits an age-dependent, expansion-biased and tissue-specific pattern and the highest level of somatic instability is found in tissues that are most susceptible to the disease pathology. Therefore, the aim of this project was to test the hypothesis that somatic instability of the HD CAG repeat plays a major role in disease pathology by quantifying somatic instability in the number of CAG repeats by next generation sequencing (NGS) technology in buccal cell DNA. We developed a high-throughput sequencing pipeline to sequence and genotype *HTT* alleles from blood and buccal swab DNA of the Scottish and Venezuelan populations, respectively. A total of 210 individuals from the Scottish general population and 742 HD patients and unaffected individuals from the Venezuelan HD cohort were sequenced on the MiSeq platform. We established that it was possible to sequence and genotype the CAG repeats, the polymorphic CCG repeat and the flanking sequences. Our data highlight the utility of NGS technology as an approach to genotype *HTT* alleles, detect sequence variants and quantify somatic instability of the CAG repeat. Our data emphasise that the somatic instability in HD is age-dependent and expansion-biased, also could be a major factor in disease progression and could be a potential therapeutic target in HD.

Biography

Asma M Alshammari is currently working as a senior specilisit in Human Molecular Genetics at Kuwait Medical genetics Centre. She has completed her PhD in Human Molecular Genetics from University of Glasgow.

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