DETECTION OF SHORT TANDEM REPEAT (STR) EXPANSION BY WHOLE GENOME SEQUENCING INCREASES THE DIAGNOSTIC YIELD OF A BRAZILIAN NEUROLOGICAL COHORT

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Introduction: The Brazilian Rare Genomes Project is an initiative from the Israelite Albert Einstein Hospital, partnering with the Brazilian National Health Ministry, which aims to sequence over 8,000 patients and improve rare diseases diagnostic rates in Brazil. So far, we have released over 2,000 reports, with an overall positivity rate of 38%. In order to increase our diagnosis rate, we have used other approaches, including detecting short tandem repeat (STR) pathogenic expansions. STRs are especially involved in neurological diseases, and several of them remain undiagnosed due to the technical challenges. Recent advances in bioinformatics have made possible the detection of repeat expansions from whole genome sequencing (WGS) data, such as ExpansionHunter (EH). **Objective**: We evaluated the clinical utility of detecting STR expansions in WGS data in a cohort of patients with rare neurological diseases of suspected genetic origin. **Methods**: We sequenced 655 samples, using a PCR-free WGS protocol on Illumina Novaseq 6,000 equipment. We selected 15 well-characterized neurological disorders loci (*AR, ATN1, ATXN1, ATXN2, ATXN3, ATXN7, ATXN8OS, ATXN10, C9orf72, CACNA1A, DMPK, FMR1, FXN, HTT, TBP*) and ran EH software. **Results:** We provided the molecular diagnosis to seven more patients by identifying nine expanded alleles in five genes (*ATXN7*, *ATXN8OS, DMPK, FMR1, FXN*), increasing the diagnostic yield of the neurological cohort from 39.2 to 40.3%. All expanded alleles were confirmed by polymerase chain reaction (PCR) or repeat-primed PCR. **Conclusions:** PCR-free WGS data is a valid screening tool for STRs and increases the molecular diagnosis in a cohort of neurological patients.

Keywords: Genetic diagnostic test. Short tandem repeat. Expansion disorders. ExpansionHunter. Whole genome sequencing.