PgmNr 2565: Beyond SNPs and INDELs: Identifying repeat expansions in an unresolved ataxia exome cohort.

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Ataxias are a group of neurological disorders with tremendous genetic heterogeneity. Around 50-60% of dominant hereditary ataxias are estimated to be caused by repeat expansions while the majority of other ataxias are due to mutations in one of several hundred genes. The diagnostic yield in ataxia patients through exome sequencing has been shown to be around 40-50%, leaving a large number of patients with no diagnosis. The possibility exists of patients with repeat expansions that have not been detected by exome sequencing. With the advent of new bioinformatic algorithms to identify repeat expansions from sequencing data, we sought to identify the presence of such expansions in exome negative ataxia cases.

We re-analyzed exome sequencing data of 183 ataxia patients with no clear pathogenic variants in a curated set of ataxia genes. We utilized the exSTRA R package (Tankard *et al*. 2018, The American Journal of Human Genetics, 103(6), 858–873) to identify repeat expansions in coding regions of certain spinocerebellar ataxia genes (*ATN1, ATXN1, ATXN2, ATXN3, ATXN7, CACNA1A, TBP*). Repeat primed PCR (RP-PCR) was performed to confirm and size the repeat expansions.

exSTRA works by identifying outliers in the cohort. 16 such outliers were initially identified and 3 out of 16 outliers were confirmed to be a true repeat expansion by RP-PCR. Two samples had a full expansion repeat in *CACNA1A* (11,22 repeats) and *ATXN7* (11,76 repeats) respectively and one sample had a reduced penetrance repeat in *ATXN2* (31,32 repeats). We are in the process of performing similar analysis in additional 33 ataxia patients negative by exome sequencing. In addition, we performed a preliminary analysis to screen for the presence of the recently described intronic AAGGG repeat expansion in the *RFC1* gene in patients with cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS). Analysis of off-target reads in 27 samples indicates the presence of the AAGGG repeat in 3 samples that needs to be confirmed by RP-PCR. Our results on these ongoing studies will be presented.

Reanalysis of exome sequencing data appears to be a promising screening tool for the detection of repeat expansions resulting in an increase in diagnostic yield. With the emergence of better detection algorithms, the ability to use exome data for both mutation detection as well as repeat expansions will be useful for diagnostic testing purposes and allow for more comprehensive and cost-effective testing.