Repeat expansion disorders screening by WGS: strategy and stumbling blocks

Fen Guo; Abhinav Mathur; Ruby Liu; Christin Collins; Lora Bean; Madhuri Hegde
PerkinElmer Genomics, Pittsburgh, PA

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BACKGROUND

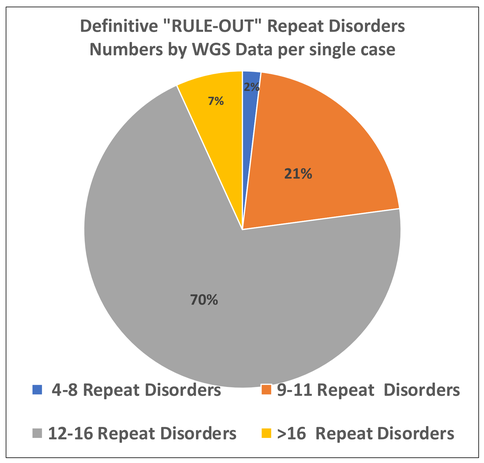
- Repeat expansion disorders are a group of clinically, pathologically, and genetically heterogeneous disease that are caused by expansions of short tandem repeats (STR). More than 40 repeat expansion disorders have been identified, predominantly present with neurological findings like ataxia.
- Diagnostic identification of repeat expansions disorders can be challenging due to the phenotypic overlap between the different STRs and the variation in penetrance and age of onset contributed by the repeat size and the impact of modifier genes.
- The implementation of a single, affordable front-line test that is capable to comprehensively detect/screen all possible causes will enable diagnosis, optimize clinical management/treatment, and allow for accurate genetic counseling of patients with repeat expansion disorders.
- We integrated Short Tandem Repeat (STR) screening into our whole genome sequencing platform. A total of 35 repeat expansion disorders were evaluated from the WGS data.

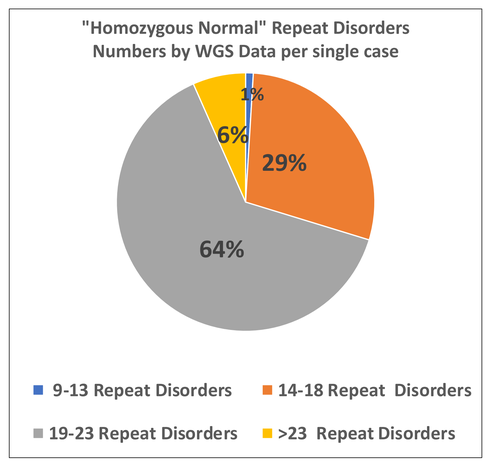
"RULE-OUT" STRATEGY

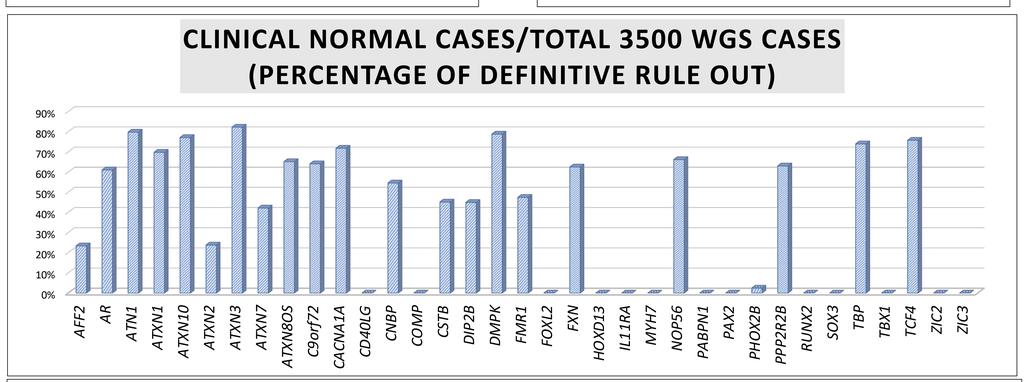
A definitive "rule-out" strategy was utilized to interpret the screening result. STR screening results were defined into three categories:

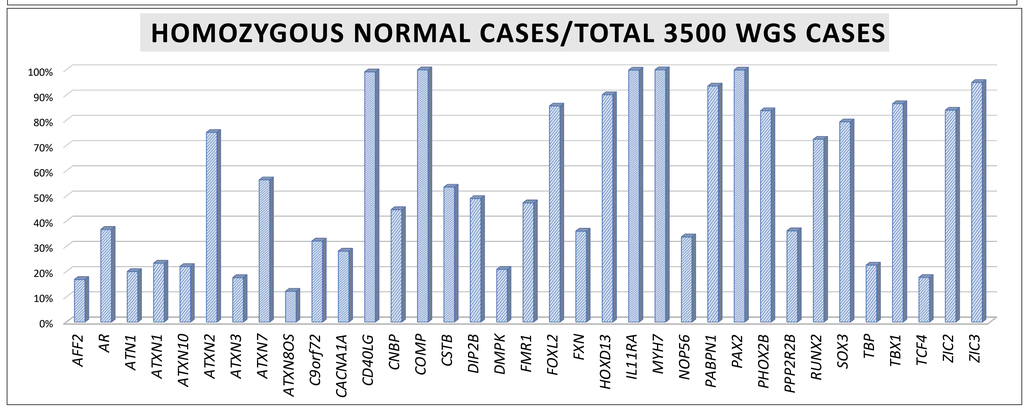
- **Clinically normal** – two distinct heterozygous non-expanded alleles detected and/or one non-expanded allele in male patient for x-linked genes are detected, which indicate these genes are unlikely to be causative, a definitive "RULE OUT" for the corresponding repeat expansion disorders will be given;
- **Homozygous normal–** a single non-expanded allele was detected either because the individual is truly homozygous for the non-expanded allele identified or because the individual carries one non-expanded allele along with an expanded allele which is beyond the current limit of detection. Follow-up is recommended if clinical phenotype is relevant;
- **Inconclusive** – Repeats that cannot be analyzed due to data quality, sequence architecture at the loci and/or the repeat sizes lie outside the normal range. Any potential repeat sized lie outside the normal range will be manually reviewed based on phenotypic relevance. Orthogonal assay confirmation will be needed.

RESULTS









CONCLUSION

- More than 12 repeat expansion disorders (disorders associated with *ATXN3*, *ATN1*, *DMPK*, *ATXN10*, *TCF4*, *TBP*, *CACNA1A*, *ATXN1*, *NOP56*, *ATXN8OS*, *AR* and *C9orf72*) can be definitely ruled out based on the screening data solely among 77.1% of the patients.
- Approximate 53.7% individuals have only a single non-expanded allele detected in more than 20 repeat expansion disorders which additional follow up will be needed due to the possibility of an expanded allele which is beyond the limitation of short-read sequencing.
- A significant high inconclusive result in *TBX1*, *AFF2*, *RUNX2*, *SOX3*, *ZIC2*, *HOXD13*, *PABPN1* and *FOXL2* genes which indicate the GC bias, and the homology issue of these repeat-expansion alleles might contribute to the poor performance.