Characterizing short tandem repeat expansions in Tourette syndrome

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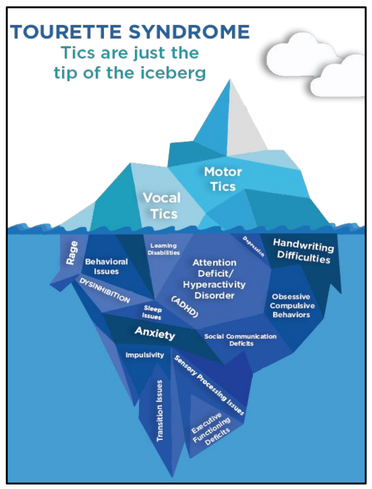
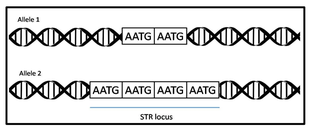
Background

- Short tandem repeats (STRs) are repeated DNA sequences of 1-6 base pairs and are considered to be a large source of genetic variation in humans
- Expansions in repeat length (RL) are known to cause a number of brain disorders





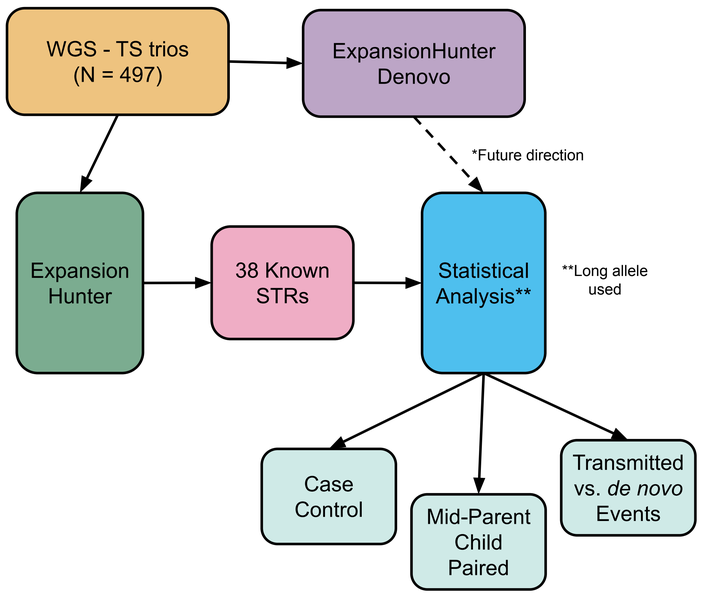
- Tourette syndrome (TS) is a neurological and neurodevelopmental disorder with an early age of onset (5-10yrs)
- Family studies estimate heritability to be 70%
- The role of STRs in TS disease susceptibility remains unknown

Methods

Table 1. Cohort overview of 497 family trios

		Sample Demographics				
		Father	Mother	Female Child	Male Child	Total
Diagnosis	TS	57	26	108	392	583 (38.9%)
	non-TS	442	472	—	—	914 (61.1%)
	Total	499 (33.3%)	498 (33.3%)	108 (7.2%)	392 (26.2%)	1,497

Figure 1. Workflow diagram



Results

Figure 2. Example of *TCF4* realignment via ExpansionHunter

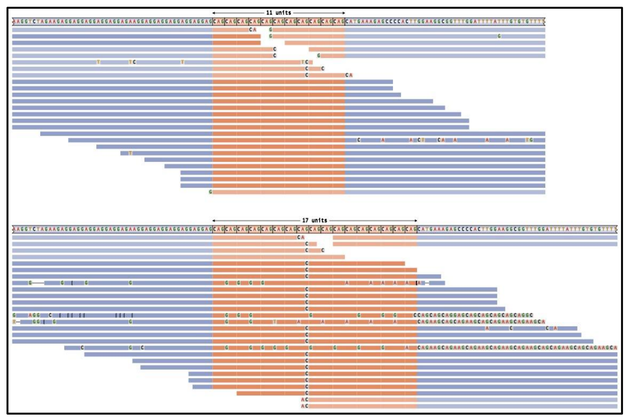


Figure 3. *TCF4* RL was highly correlated between mid-parents and probands

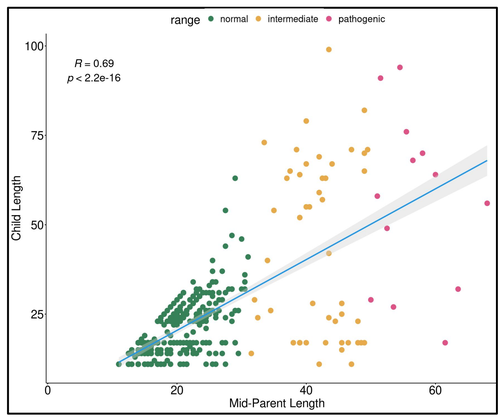


Figure 4. *AFF2* on chromosome X showed sex-specific RL correlation

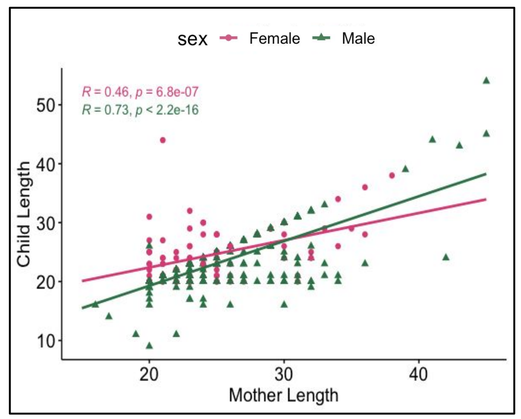
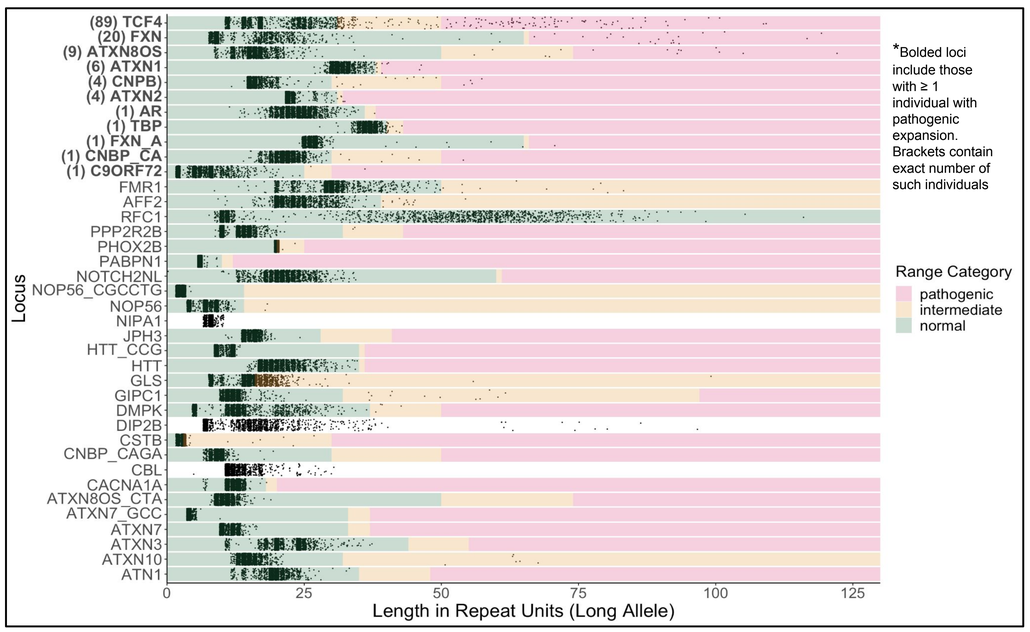


Figure 6. Samples with pathogenic expansions were identified in 11 known STRs



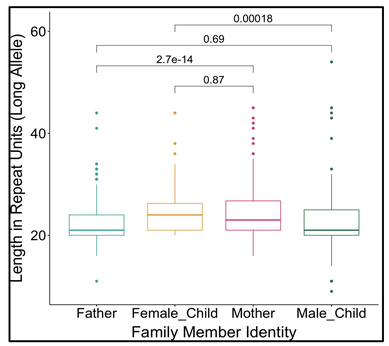
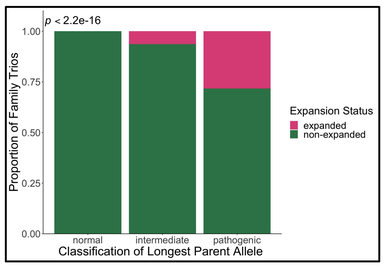


Figure 5. RL estimations on chromosome X were biased between sexes

Figure 7. Trend analysis demonstrated more frequent *TCF4* expansions in probands whose parents had longer expansions



Conclusion

- Our current analysis of 38 known STRs demonstrates a significant correlation between parental and proband allele lengths
- However, no known STR expansions are significantly associated with TS
- ExpansionHunter overestimates RL on sex chromosomes in females as compared to males
- Increased occurrence rate of *TCF4* expansions compared to other loci suggests a potential role in TS susceptibility; future examinations are needed
- Further genome-wide investigation, rather than targeted analysis, of STR loci is needed to examine their causal relationship to TS and understand the impact of novel STR expansions on disease susceptibility

Acknowledgements

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Citations: Tstesos *et al.* (2023), Depienne & Mandel (2021), Chintalaphani *et al.* (2021), Dolzenko *et al.* (2017), tourette.org, https://www.pathologyoutlines.com/topic/molecularshttandreptgenotyp.html