

Impact of SNP variation at the *SLC6A4* promoter region and base pair repeat lengths in 15 de-identified American individuals.

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BACKGROUND

- In the United States, selective serotonin reuptake inhibitor (SSRI) antidepressants have an estimated efficacy of 35-45%.
- Many patients may trial three or four antidepressants before achieving response and/or remission or may have to combine treatments for response and/or remission.
- Pharmacogenomics tests are utilized in shared clinical-decision making processes to manage pharmacotherapy in disease states such as depression, anxiety, and more.
- Current pharmacogenomics tests only evaluate one single-nucleotide polymorphism (SNP) related to the *SLC6A4* promoter region, while at least three significant promoter region SNPs have been identified.
- It is clinically and experimentally unclear if the only SNP tested for, rs4795541, is the only significant promoter involved in *SLC6A4* expression.

OBJECTIVES

- To examine the potential impact of SNP variation on pharmacogenomics test accuracy and predictability
- To examine and explain the complexity of discrepancies found within pharmacogenetics tests

METHODS

Study Design:

- Observational, cross-sectional

Study Population:

- Coriell DNA samples, other miscellaneous short-read samples including 1KG, GeT-RM, and PacBio.

Data Source:

- Botton et Al. paper derived de-identified USA resident long-read DNA samples
- Data collected is ordinal data and will be expressed as median \pm IQR

METHODS

Study Measures:

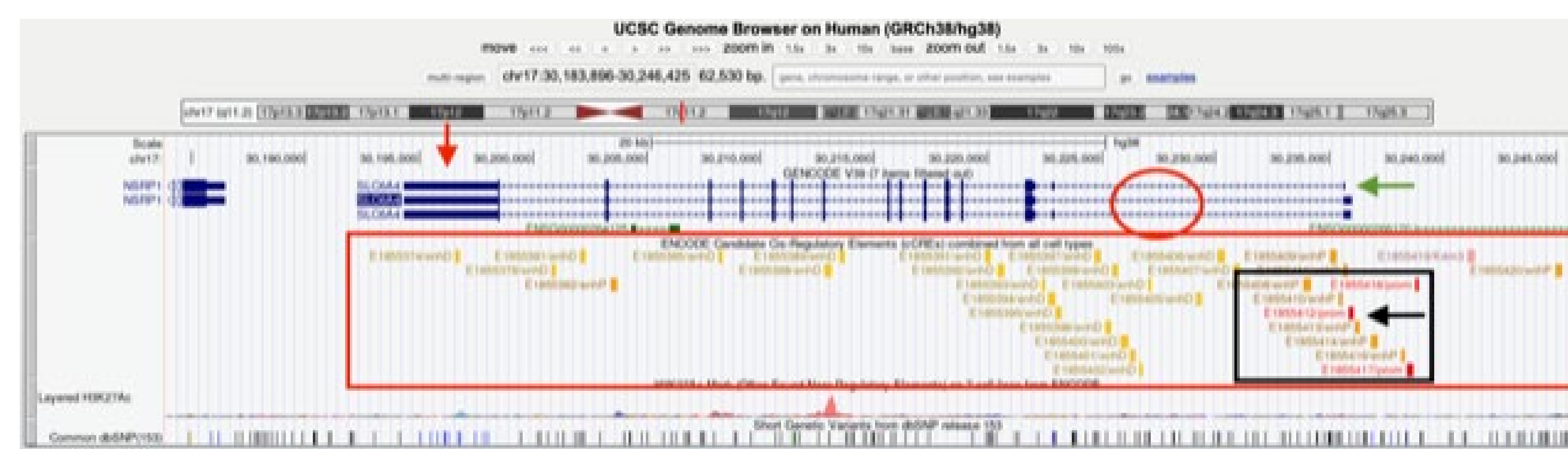
- Independent Variables: SNP variation at three areas of interest, as indicated in rs4795541, rs25531, and rs25532
- Dependent Variable: Length of SNP variant at rs4795541, rs25531, and rs25532

Data Analysis:

- Data is collected from Botton et Al. paper who used a novel long-read small-molecule real-time (SMRT) sequencing technique
- Samples are chosen at random but required both short read and long read sequencing data.
- Excel algorithms are used to conduct median and IQR.

RESULTS

Figure 1. *SLC6A4* promoter region from UCSC, annotated



- This shows the 3 isoforms of the *SLC6A4* gene. The left-pointing arrows show that transcription goes right to left (gene is on minus strand of DNA). The green arrow points to the first exon, while the red arrow points to the last exon. There are three exon splicing variants of *SLC6A4*. This image shows that the entire gene spans around 60,000 base pairs. Everything is scaled, so the blue, yellow and red boxes actually contain hundreds to thousands of nucleotides. The red rectangle shows the locations of cis-regulatory elements - yellow for enhancers and red for promoter binding sites for transcription factors and enzymes. The black arrow in the black box shows the region that is tested for promoter length, and was sequenced by Botton et Al. Notice this promoter region is immediately upstream of the first exon, which is also subject to 3 different types of splicing. At the bottom of the image are SNP locations. Notice that all three promoter regions have SNPs associated with them.

Figure 2. Discordance between short and long reads

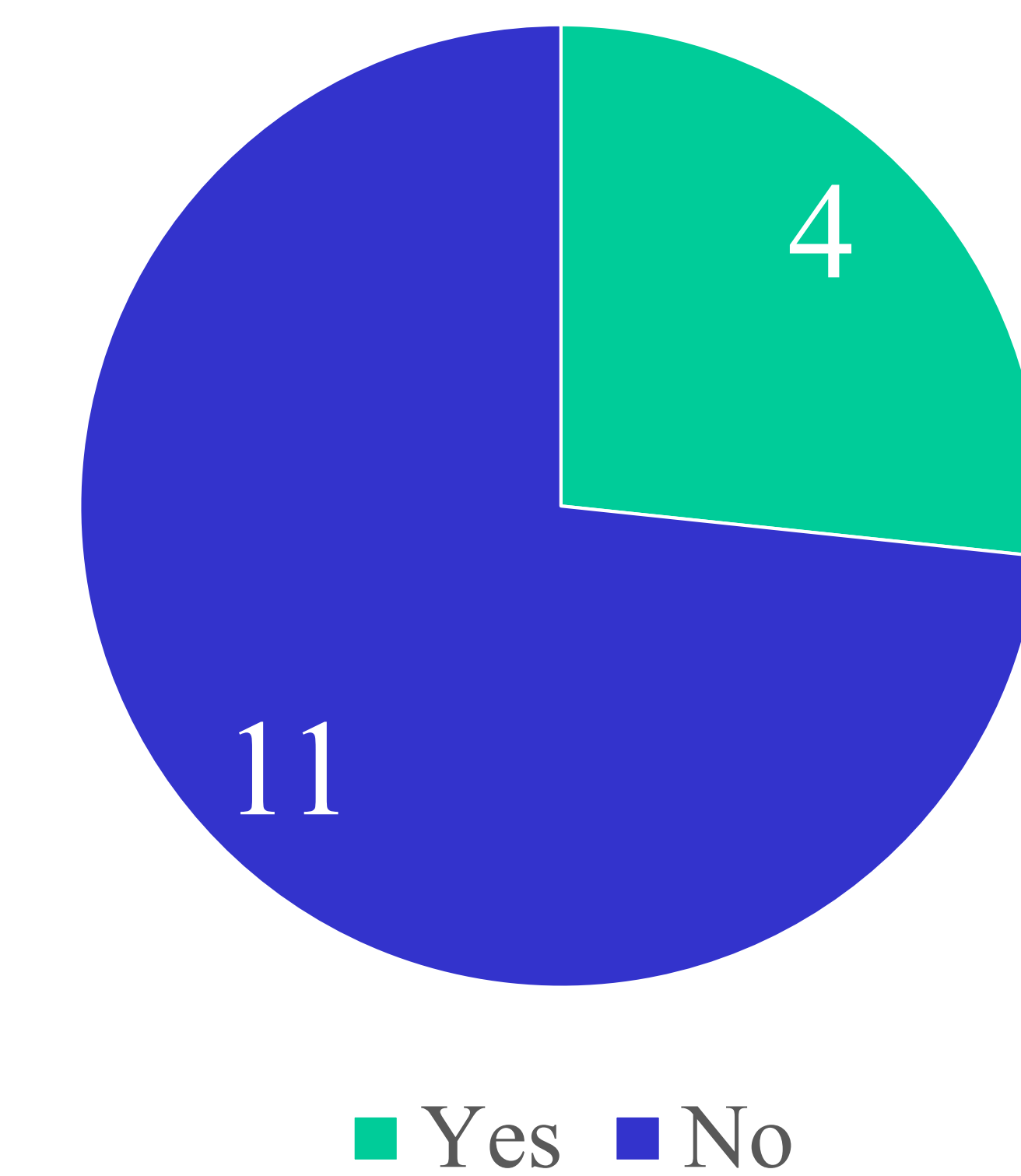


Figure 3. Combined Table S2 and S5 from Botton et Al.

n	sample	rs4795541	rs25531	rs25532	diplotype	Additional variants detected by long-read SMRT sequencing					
						rs76568780	rs77638792	rs56087640	rs1408618839	rs25530	rs1462091560
1	HG00276	LL	AG	CC	LAC/LGC				CT		
2	HG00436	LL	AA	CC	LAC/LAC	AA	AA				A/delA
3	HG01190	LS	AG	CC	LGC/SAC						
4	NA07000	LS	AA	CT	LAC/SAT						
5	NA07029	SS	AA	TT	SAT/SAT						
6	NA10831	SS	AA	CC	SAC/SAC						
7	NA10847	SS	AA	CT	SAC/SAT						
8	NA11839	LS	AA	CT	LAC/SAT						
9	NA12145	LS	AA	CC	LAC/SAC					CT	
10	NA18526	LS	AG	CC	LGC/SAC						
11	NA18855	LXL	AA	CC	LAC/XLAC						
12	NA18942	LS	AG	CC	LGC/SAC						
13	NA19174	SXL	AA	CC	SAC/XLAC						
14	NA19176	LL	GG	CC	LGC/LGC						
15	HG01089	SS	AG	CC	SAC/SGC						

CONCLUSION

- The *SLC6A4* variable number tandem repeat promoter region is polymorphic and a critical area for pharmacogenetics testing for SSRI medications.
- Pharmacogenetics tests must use long read sequencing techniques and report at least the three SNPs included in Botton et Al. (rs4795541, rs25531, and rs25532).
- By including all three SNP using long read technology, these pharmacogenomics test results can inform decisions about pharmacotherapies later on for the patient as well, especially as more is clinically understood about the *SLC6A4* promoter region variation and expression.