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

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Abstract

Background:
In the United States, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have an estimated efficacy of 35-45%, and many patients may trial three or four antidepressants before achieving response and/or remission. Pharmacogenomics tests are an important clinical utility in addressing the less than expected response rate, particularly the gene encoding for the expression of serotonin transporters on the presynaptic neurons, solute carrier family 6 member 4, or *SLC6A4*. One promoter single-nucleotide polymorphism (SNP), rs4795541, is commonly reported in pharmacogenomics tests, however alternative promoters SNPs such as rs25531 and rs25532 may also influence serotonin transporter expression and are not reported in commercial pharmacogenomics tests.

Objective:
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 of *SLC6A4*.

Methods:
15 individual DNA samples were chosen at random from Botton et Al. and short-read data and long-read data were compared using descriptive analysis. Data collected was ordinal due to base pair repeat lengths being non-continuous. Antidepressant use was not required for inclusion.

Results:
Three promoter regions of variable length whose SNPs were identified in Botton et Al. are noted to be of variable length. 4/15 (26.7%) of the individuals had a noted discordance between short read sequencing and long read sequencing. The most commonly seen genotype of rs4795541, rs25531, and rs25532 was LS, AA, CC. 11/15 (73.3%) of the individuals carried at least one S allele in rs4795541.

Conclusion:
The *SLC6A4* variable number tandem repeat promoter region is polymorphic and a critical area for pharmacogenetics testing of SSRI medications. With advances in long read technology, specific SNPs can be categorized together as haplotypes with a strong utility in clinical interpretation and applications in treatment decisions pertaining to pharmacotherapy and antidepressant use. Pharmacogenetics tests must use long read technology and methods, like the SMRT sequencing application, to accurately assess *SLC6A4* and must include the three SNPs outlined (rs4795541, rs25531, and rs25532) for clinical use today and in the future as more is understood about their clinical significance together.