



Forensic Autosomal Short Tandem Repeats and Their Potential Association With Phenotype

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OPEN ACCESS

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Specialty section:

This article was submitted to
Evolutionary and Population Genetics,
a section of the journal
Frontiers in Genetics

Received: 19 May 2020

Accepted: 17 July 2020

Published: xx July 2020

Citation:

Wyner N, Barash M and
McNevin D (2020) Forensic

Autosomal Short Tandem Repeats
and Their Potential Association With
Phenotype. *Front. Genet.* 11:884.
doi: 10.3389/fgene.2020.00884

Forensic DNA profiling utilizes autosomal short tandem repeat (STR) markers to establish identity of missing persons, confirm familial relations, and link persons of interest to crime scenes. It is a widely accepted notion that genetic markers used in forensic applications are not predictive of phenotype. At present, there has been no demonstration of forensic STR variants directly causing or predicting disease. Such a demonstration would have many legal and ethical implications. For example, is there a duty to inform a DNA donor if a medical condition is discovered during routine analysis of their sample? In this review, we evaluate the possibility that forensic STRs could provide information beyond mere identity. An extensive search of the literature returned 107 articles associating a forensic STR with a trait. A total of 57 of these studies met our inclusion criteria: a reported link between a STR-inclusive gene and a phenotype and a statistical analysis reporting a p -value less than 0.05. A total of 50 unique traits were associated with the 24 markers included in the 57 studies. TH01 had the greatest number of associations with 27 traits reportedly linked to 40 different genotypes. Five of the articles associated TH01 with schizophrenia. None of the associations found were independently causative or predictive of disease. Regardless, the likelihood of identifying significant associations is increasing as the function of non-coding STRs in gene expression is steadily revealed. It is recommended that regular reviews take place in order to remain aware of future studies that identify a functional role for any forensic STRs.

Keywords: short tandem repeat, phenotype, forensic marker, DNA profiling, junk DNA, non-coding STRs

INTRODUCTION

Short tandem repeats (STRs) are short repeated sequences of DNA (2–6 bp) that account for approximately 3% of the human genome (Lander et al., 2001). The number of repeat units is highly variable among individuals, which offers a high power of discrimination when analyzed for identification purposes. It is a widely accepted notion that STRs are non-coding in nature and are therefore not implicated in gene expression (Tautz and Schlotterer, 1994; Ramel, 1997; Butler, 2006; Biscotti et al., 2015). There is increasing evidence, however, that non-coding DNA sequences such as STRs may be involved in gene regulation via various mechanisms, hence being associated with phenotype (Sawaya et al., 2013; Chen et al., 2016).

The first STR markers used in forensic casework were selected in 1994 by the Forensic Science Service (FSS) in the United Kingdom for a quadruplex amplification system consisting of four

Q3 115 tetranucleotide STRs—TH01, vWA, FES/FPS, and F13A1
 116 (Kimpton et al., 1994). These markers were deemed suitable
 117 for PCR amplification due to their simple repeat sequences
 118 and their propensity to display regularly spaced alleles differing
 119 by four bases; however, the quadruplex system did not offer
 120 a high level of discrimination. In 1997, the Federal Bureau of
 121 Investigation (FBI) nominated 13 autosomal STR loci to form the
 122 core of the Combined DNA Index System (CODIS), a database
 123 consisting of profiles contributed by federal, state, and local
 124 forensic laboratories. Two of the markers initially selected by
 125 the FSS (vWA and TH01) were included within the core CODIS
 126 set, whereas FES/FPS and F13A01 were eventually discarded
 127 due to low levels of polymorphism. The core set was reviewed
 128 in 2010 with an additional seven STRs being implemented from
 129 January 1, 2017. The majority of commercially available DNA
 130 profiling kits are manufactured to include the core CODIS STR
 131 loci (Butler, 2006). In accordance with the DNA Identification
 132 Act of 1994, CODIS is bound by stringent privacy protection
 133 protocols, in that the stored DNA samples and subsequent
 134 analyses be used strictly for law enforcement identification
 135 purposes. The DNA Analysis Backlog Elimination Act of 2000
 136 reaffirms that the markers used for forensic applications were
 137 specifically selected because they are not known to be associated
 138 with any known physical traits or medical characteristics.

139 The markers nominated for CODIS were specifically chosen
 140 due to their location within non-coding regions of the genome;
 141 however, claims that non-coding regions play no functional role
 142 have been contested in recent years (Cole, 2007; Kaye, 2007;
 143 Sarkar and Adshear, 2010). There is increasing evidence that
 144 there may be associations between certain STR alleles and medical
 145 conditions (von Wurmb-Schwark et al., 2011; Meraz-Rios et al.,
 146 2014). This should not be confused with situations where alleles
 147 or loci are diagnostic for medical conditions (e.g., trisomy).
 148 Additionally, the ability to infer biogeographical ancestry (BGA)
 149 from forensic STRs is possible (Graydon et al., 2009; Algee-
 150 Hewitt et al., 2016) with investigators using population-specific
 151 STR data as intelligence to guide enquiries (Lowe et al., 2001).
 152 BGA is correlated with some phenotypes such as blue eye
 153 color in Europeans (Gettings et al., 2014) and lighter skin color
 154 with increasing distance from the equator (Relethford, 1997).
 155 However, the STR genotype *per se* is not causative of BGA
 156 phenotype in any direct sense and is mostly associated with
 157 BGA as a result of genetic drift (as STRs for forensic use have
 158 been selected to exhibit Hardy Weinberg equilibrium). In the
 159 event that any CODIS markers are in future found to be linked
 160 to a medical condition or physical trait, the analysis of the
 161 DNA sample must still be used only for identification purposes
 162 pursuant to the DNA Identification Act of 1994.

163 Katsanis and Wagner (2013) assessed 24 CODIS loci for
 164 phenotypic associations, but found no evidence to support
 165 the disclosure of any biomedically relevant information. For
 166 example, despite the fact that the locus TH01 was associated
 167 with as many as 18 traits: from alcoholism to spinocerebellar
 168 ataxia, the authors state that association with these traits does
 169 not necessarily imply that individual genotypes are causative or
 170 predictive of a particular trait. Following this, a statement issued
 171 by the Scientific Working Group of DNA Analysis Methods

[SWGDM] (2013) restated that although alternate discoveries 172
 may be made in the future, current understanding is that the 173
 CODIS loci do not reveal any information beyond identity. 174
 There has only been one STR to date that has been removed 175
 from consideration as a marker used in human identity testing 176
 (Szibor et al., 2005). The STR locus HumARA is located within 177
 a coding region on the X-chromosome and has been linked to 178
 muscular dystrophy. HumARA is a trinucleotide repeat and these 179
 are known to be more prone to disease-causing expansions than 180
 tetranucleotide repeats (Orr and Zoghbi, 2007; Castel et al., 2010; 181
 Hannan, 2018). 182

MATERIALS AND METHODS 183

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 A systematic search of the literature was conducted across 187
 three databases (Web of Science, PubMed, and Google 188
 Scholar) between August and December 2018. Population 189
 data studies, allele frequency studies, validation studies, 190
 technique developments, single case reports, mutation analyses, 191
 off-ladder allele identification, loss of heterozygosity studies, 192
 and locus characterizations were excluded. Additional papers 193
 were located by back referencing relevant or similar studies. 194
 Following the literature search, each STR was analyzed in the 195
 University of California Santa Cruz (UCSC) Genome Browser 196
 (Human GRCh38/hg38 Assembly) using the following tracks: 197
 Mapping and Sequencing—Base Position-dense; STS Markers- 198
 full, Gene and Gene Prediction—GENCODE v29-full; NCBI 199
 RefSeq-pack, Phenotype and Literature—OMIM Alleles-full; 200
 OMIM Pheno Loci-full; OMIM Genes-full; HGMD Variants-full; 201
 GWAS Catalog-full, Regulation—ENCODE Regulation-show; 202
 RefSeq Func Elems-full, Variation—Common SNPs(151)-full; 203
 FlaggedSNPs(151)-full, Repeats—Microsatellite-full; Simple 204
 Repeats-full. The STRs investigated included the 20 CODIS core 205
 loci used by the FBI, three extra loci currently used in Australia 206
 (Penta E, Penta D, D6S1043), and SE33 which is a core STR 207
 in the German national database and has subsequently been 208
 incorporated into several European kits. 209

RESULTS AND DISCUSSION 210

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 213
 A total of 57 association studies sourced from three databases 214
 met our inclusion criteria: a reported link between a STR- 215
 inclusive gene and a phenotype and a statistical analysis reporting 216
 a *p*-value less than 0.05. Fifty unique traits were identified 217
 across the 24 markers (**Supplementary Table 1**). Schizophrenia 218
 was the trait most frequently described with a total of 11 219
 studies reporting data on 14 different polymorphisms potentially 220
 associated with eight loci. Two separate articles investigated the 221
 allelic frequency amongst people who attempted suicide and 222
 reported a significantly higher frequency amongst 10 different 223
 alleles of seven forensic loci. The intronic STR TH01 had 224
 the greatest number of studies with 26 reports describing 27 225
 traits potentially linked to 40 different genotypes. Five of these 226
 studies were investigating a link to schizophrenia, reporting five 227
 polymorphisms that are possibly associated with the disease. 228

229 No studies associating alleles or genotypes with phenotype were
 230 found for Penta E, Penta D, D3S1358, SE33, or D10S1248;
 231 however, one study by Shi et al. (2012) investigated the method of
 232 diagnosing Down syndrome by testing for a trisomy at the Penta
 233 D locus as it is located on chromosome 21. Similarly, six of the
 234 10 articles included for D21S11 were investigating the marker's
 235 efficiency in genetic tests for Down syndrome.

236 Of the 57 articles proposing an association between a forensic
 237 STR and a phenotype, none of them confirmed any particular
 238 genotype to be solely causative of a phenotype. Despite 13
 239 of the STRs being located within a functional gene, there
 240 were no entries in the Online Mendelian Inheritance in Man
 241 (OMIM) database relating any STR-inclusive regions of these
 242 genes with a disease. A stand-out result is the number of
 243 studies reporting an association between a phenotype with
 244 polymorphisms at the TH01 locus.

245 TH01

246 TH01 is located within the first intron of the tyrosine hydroxylase
 247 (TH) gene and is commonly characterized by the repeat motif
 248 [AATG]_n or alternatively by the [TCAT]_n motif, according
 249 to GenBank top strand nomenclature. TH is the rate-limiting
 250 enzyme involved in the biosynthesis of the catecholamines
 251 dopamine, epinephrine, and norepinephrine. Catecholamines
 252 act as both neurotransmitters and hormones that assist in
 253 maintaining homeostasis (Eisenhofer et al., 2004). As such, a
 254 strong relationship has been reported in the literature (Eisenhofer
 255 et al., 2004; Ng et al., 2015) between variations in the expression
 256 of TH and the development of neurological, psychiatric, and
 257 cardiovascular diseases.

258 Previous studies (McEwen, 2002; Antoni et al., 2006; Bastos
 259 et al., 2018) have shown that increased levels of epinephrine
 260 and norepinephrine are expressed in individuals experiencing
 261 acute or chronic stress. Wei et al. (1997) found that individuals
 262 carrying the TH01-9 allele showed the highest levels of serum
 263 norepinephrine amongst a population of unrelated healthy
 264 adults, whereas carriers of the TH01-7 allele showed the lowest.
 265 Barbeau et al. (2003) investigated the relationship between
 266 the number of TH01 repeats and hemodynamic parameters
 267 in subjects at rest and in response to applied stressors. The
 268 results of this study indicate that the 6 and 9.3 TH01 alleles
 269 are associated with a decrease in the hemodynamic responses to
 270 stress, offering a protective effect to individuals carrying those
 271 alleles. Carriers of the TH01-6 allele displayed a lower heart
 272 rate reactivity when exposed to stressors with increasing age
 273 than those without the TH01-6 allele. Furthermore, individuals
 274 carrying TH01-9.3 showed no increase in systolic blood pressure
 275 in response to stress, whereas those not possessing the TH01-
 276 9.3 allele demonstrated a significant increase in systolic blood
 277 pressure reactivity with increasing age. Conversely, the TH01-
 278 7 allele was found to be detrimental to blood pressure in those
 279 with a greater body mass index (BMI). Subjects carrying TH01-
 280 7 displayed a higher resting systolic blood pressure as BMI
 281 increases and increased heart rate reactivity in response to
 282 stressors with increasing BMI.

283 TH01-7 was also reported to be significantly more prevalent
 284 in patients prone to depression (Chiba et al., 2000). The TH01-8
 285

allele was found more frequently in suicide attempters (Persson 286
 et al., 1997), individuals with depression (Serretti et al., 1998), 287
 and individuals with delusional disorder (Morimoto et al., 2002). 288
 Persson et al. (2000) investigated the influence of the number of 289
 TH01 repeats on 30 personality dimensions. Subjects possessing 290
 the TH01-8 allele scored higher in the neuroticism facets with 291
 significant differences observed between individuals displaying 292
 anger, hostility and vulnerability (Persson et al., 2000), compared 293
 to non-TH01-8 allele carriers. Nine repeats at the TH01 locus 294
 were associated with delusional disorder (Morimoto et al., 2002) 295
 and extraversion (Tochigi et al., 2006). Furthermore, Yang et al. 296
 (2011) conducted a number of association studies in China 297
 and reported that the frequency of TH01-9.3 was higher in 298
 those displaying suicidal behavior, and TH01-10 was significantly 299
 overrepresented in individuals demonstrating violent behavior 300
 including sexual assaults (Yang et al., 2010) and in males with 301
 impulsive violent behavior (Yang et al., 2013). TH01 was also 302
 linked to various disease states such as schizophrenia (Jacewicz 303
 et al., 2006b), predisposition to malaria (Gaikwad et al., 2005; 304
 Alam et al., 2011), sudden infant death syndrome (SIDS) 305
 (Klitschar et al., 2008; Courts and Madea, 2011), and Parkinson's 306
 disease (Sutherland et al., 2008). 307

308 As previously mentioned, TH catalyzes the conversion 308
 of tyrosine to levodopa (L-DOPA) which is then converted 309
 to dopamine. Dopamine can be further converted into 310
 norepinephrine and epinephrine. *In vitro* experiments have 311
 previously demonstrated that TH01 can regulate TH gene 312
 transcription, displaying a quantitative silencing effect (Albanese 313
 et al., 2001). TH01 alleles inhibited transcription proportionally 314
 to the number of repeats. Given that so many vital functions 315
 rely on the presence of dopamine and its metabolites (Wei 316
 et al., 1997; Meiser et al., 2013), malfunctions of dopaminergic 317
 pathways have been associated with the development of 318
 numerous psychological diseases (Meiser et al., 2013), and in 319
 this review, TH01 was largely connected with schizophrenia 320
 (Kurumaji et al., 2001) and Parkinson's disease (Meiser et al., 321
 2013). The longer TH01-9.3 and TH01-10 alleles, predicted to 322
 yield less dopamine, were found more frequently in individuals 323
 displaying traits indicative of dopaminergic dysfunction 324
 such as impulsive violent behavior (Yang et al., 2013), sexual 325
 assault (Yang et al., 2010), and addiction (Sander et al., 1998; 326
 Anney et al., 2004). 327

328 Some contradictory associations were observed between TH01 328
 and certain phenotypes. For instance, De Benedictis et al. 329
 (1998) reported a significant association of >9 TH01 repeats 330
 with longevity in male Italian centenarians. Contrariwise, von 331
 Wurmb-Schwark et al. (2011) were unable to replicate this result 332
 when using the same study design on a German population, 333
 just as Bediaga et al. (2015) were also unable to confirm an 334
 association in a northern Spanish population. Similarly, there 335
 are conflicting reports on the association of TH01-9.3 with 336
 SIDS across European populations. In 2008, Klitschar et al. 337
 (2008) found that the frequency of the TH01-9.3 allele was 338
 significantly higher in SIDS patients than in controls in a German 339
 population. This association was further confirmed by Courts 340
 and Madea (2011). On the contrary, Studer et al. (2014) were 341
 unable to replicate this result in a Swiss population. Further 342

population-based association studies are needed to confirm the existence of associations between TH01 and these phenotypes.

None of the studies investigating TH01 have identified any of the associated genotypes as being causative of disease; therefore, the associations mentioned should only be considered as possible or potential. Many of the traits reported to be associated with TH01 are multifactorial, meaning they are affected by both genes and the environment, such as in the case of Parkinson's disease (Meiser et al., 2013) and schizophrenia (Zhuo et al., 2019).

Potential Associations of Other STR Markers

Schizophrenia is a complex heritable mental health disorder characterized by delusions, hallucinations, and impaired social cognition. It is understood that schizophrenia is polygenic with disease burdening alleles being distributed across multiple loci (Giusti-Rodríguez and Sullivan, 2013; Zhuo et al., 2019). Consistent with this notion, our study revealed that schizophrenia was associated with the greatest number of STRs: FGA, TH01, vWA, D2S441, D2S1338, D8S1179, D16S539, and D18S51. One study (Jacewicz et al., 2006a) found that longer repeats in D18S51 and D2S1338 were significantly more frequent in patients than in controls. This trend is consistent with the expansion of trinucleotide repeats in other major psychiatric disorders. Although the inherent complexity of the disease has posed a challenge to researchers, neurotransmitter abnormalities have long been acknowledged as a major contributing factor in the pathogenesis of schizophrenia (Mäki et al., 2005; Modai and Shomron, 2016).

Genetic mutations alone are not enough to trigger the onset and development of schizophrenia; therefore, further research is required in order to explore how genetic risk factors interact with environmental risk factors in the development, onset, and progression of the condition.

Venous thromboembolism (VTE) is a disorder defined by the occurrence of deep vein thrombosis and/or pulmonary embolism. vWF is a glycoprotein that plays a role in platelet adhesion during coagulation; therefore, it is understood that alterations in serum levels of vWF can contribute to thrombosis disorders (Laird et al., 2007). Meraz-Rios et al. (2014) found that vWA-18, TPOX-9, and TPOX-12 were observed more frequently in individuals with venous thrombosis in the Mexican mestizo population. Furthermore, vWA and TPOX have been associated with chronic myeloid leukemia (Wang et al., 2012).

Trisomys

Down syndrome, or Trisomy-21, can be diagnosed by the presence of a third allele at chromosome 21. This trisomy can be present at any polymorphic marker found on chromosome 21, and there are several studies evaluating the use of D21S11 and Penta D as effective markers in Down syndrome detection (Yoon et al., 2002; Liou et al., 2004; Shi et al., 2012; Guan et al., 2013). Similarly, D18S51 and D13S317 can be used as genetic markers to diagnose the presence of Edwards syndrome (Trisomy-18) and Patau syndrome (Trisomy-13), respectively. Trisomys are an example of a causal association as all individuals with three

chromosomes will be affected. While the presence of an extra allele at chromosomes 13, 18, or 21 does not reveal a medical condition unknown to the donor, it does provide additional identifiable information to investigators.

Cancer

Forensic STRs have been used as genetic markers in several studies to screen for cancer-related alleles. Hui et al. (2014) found that two pairs of alleles (D8S1179-16 with D5S818-13 and D2S1338-23 with D6S1043-11) were found more frequently in gastric cancer patients. Furthermore, a study from China identified a significant association between homozygous alleles at D6S1043 and an increased risk of invasive cervical cancer (Wu et al., 2008). Loss of heterozygosity (LOH) is a genetic mutation that results in the loss of one copy of a heterozygous gene, often resulting in cancer due to loss of functional tumor suppressor genes. LOH in different cancer tissues have been observed at a number of forensic loci such as CSF1PO, FGA, vWA, D3S1358, D5S818, D8S1179, D13S317, and D18S51 in patients with laryngeal cancer (Rogowski et al., 2004). LOH may alter the results of a DNA profile and should be taken into consideration in cases where only cancerous tissue is available for analysis (Peloso et al., 2003; Zhou et al., 2017).

Qi et al. (2018) conducted a study investigating the possibility of using genetic markers rather than related genes to screen for predisposition to lung and liver cancer. This study used CODIS markers to examine the theory of programmed onset which hypothesizes that the occurrence of a chronic disease is independent of age and may instead depend on a programmed onset pattern. The results showed a significant difference in the occurrence of lung cancer between those who carried the D18S51-20 allele and those who did not, and the incidence of liver cancer between those carrying D21S11-30.2 and D6S1043-18 alleles and those who did not. While these results demonstrate CODIS markers being used to predict an individual's predisposition to cancer, there are an extensive number of cancer-related genes in the genome; therefore, the risk of breaching genetic privacy with this information remains low.

Y and X STRs

The Y chromosome has accumulated male advantage and fertility genes (Lahn and Page, 1997; Graves, 2006) and so it is possible that phenotypes associated with maleness are associated with Y STRs. X-linked phenotypes (as a result of recessive genes on the X chromosome) are more prevalent in males (because there is no dominant Y chromosome homolog) so there may also be associations with X STRs. In fact, X-linked genes have recently been shown to influence male fertility and sex ratio of offspring in mice (Kruger et al., 2019).

Association Versus Causation

The association of a STR with a trait or disease does not infer causation. Moreover, some alleles seem to have opposite effects: TH01 allele 9.3 may help with stress (Zhang et al., 2004) but also has a potential link with suicide (Persson et al., 1997; Yang et al., 2011). A genetic variant is considered causative when it is known that the presence of the variant will produce an effect that in turn

causes disease (Hu et al., 2018). None of the associations reported in this study offer proof of causation (except for trisomies), rather they propose a general relationship between some STRs used in forensic applications and a phenotype. These relationships may also be explained by confounding variables, bias, or by chance in cases where a significant finding is unable to be replicated by another study. In fact, this review could be seen as a reflection of the broader so-called “replication crisis” in science (Schooler, 2014). Many of the studies reported in this review may not have sufficiently mitigated against the “multiple comparison problem” where a number of comparisons will be significant by chance. By setting our *p*-value threshold to 0.05, we run the risk that 5% of significant results are significant by chance.

Many of the traits that can be predicted by genetic analysis are the result of epistatic interactions between genes and environmental factors. When considering the associations in this review, it is not reasonable to suggest that an individual possessing the more frequently observed allele associated with a trait will express a specific phenotype. There are many underlying mechanisms involved in the development of complex diseases and while the risk of forensic STRs being found to expose revealing medical information is minimal, the presence of a particular allele may indicate heightened potential or risk for a phenotype.

Molecular Mechanisms

While it remains true that forensic markers are located within non-coding regions, there is growing evidence that STRs in introns and up- or down-stream of genes may affect phenotype. STR mutations in the 5′ untranslated region (UTR) are known to modify gene expression, probably because they serve as protein binding sites (Li et al., 2004). Mutations in the 3′ UTR result in extended mRNA which can be toxic to the cell (Li et al., 2004; La Spada and Taylor, 2010). There are 13 CODIS STRs located in introns (Supplementary Table 2). Mutations in introns can affect mRNA splicing which can result in gene silencing or loss of function (Li et al., 2004; La Spada and Taylor, 2010). The TCAT repeat in the first intron of TH01 acts as a transcription regulatory element *in vitro* (Meloni et al., 1998). Albanèse et al. (2001) reported a reduction in transcriptional activity of TH as the TCAT repeat number varied from three to eight. STRs are also found at high density in promoter regions and it is highly likely that some are implicated in gene expression by modulating spacing of regulatory elements (Gemayel et al., 2012;

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There is now etiological support for STRs as causative agents for disease in that they are quite plausibly epigenetic regulators for gene expression when located in introns or up- or down-stream of genes. This may increase prior support for the hypotheses of association and thus reduce the required significance level, as described by Kidd (1993), which is a counter to the “multiple comparison problem” discussed earlier.

CONCLUSION

While the results of this study did indicate a large number of phenotypic traits associated with forensic STRs, none were found to be independently causative or predictive of disease. Nevertheless, as there are numerous reported instances of tetranucleotide repeats being implicated in disease and molecular mechanisms have been demonstrated, there remains a strong chance that this inference may change in the near future. One limitation of this study was the sole use of the UCSC genome browser. Future studies may benefit from using a wider range of resources and investigating additional markers such as SNPs in flanking regions, mtDNA and Y-STRs. In the event that a statistically significant association, causal or predictive relationship is discovered, it is not necessarily a valid cause for removal from STR panels, but additional protective measures, such as tightening legislation surrounding genetic privacy, may need to be considered to prevent abuse of this information.

AUTHOR CONTRIBUTIONS

NW designed the study, performed the literature review and wrote the manuscript. MB conceived the project, designed the study, and reviewed and edited the manuscript. DM conceived and managed the project, designed the study, and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fgene.2020.00884/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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