

Disease-associated variations of autosomal STR loci: minireview

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The human genome is constantly undergoing various types of mutations. Some of them seem to be inherited, while others occur spontaneously under the influence of external environmental factors. Some diseases are caused by mutations that are inherited from the parents. Currently, the investigation of new reliable markers for the prediagnosis of hereditary diseases is one of the urgent issues. Several of these markers are identified by genome-wide association studies (GWAS), others by candidate gene approach (CGA), as well as by individual experimental studies. The current article provides a summary of research related to the study of the association of STR markers that are included in human identification kits with various diseases. The key idea of this article was to highlight the alleles as well as several trisomies that are associated with Down's and Edwards' syndromes located in the coding region, mainly variants of loci (CSF1PO, TPOX, THO1, vWA, FGA, etc.) inside the genes, which are associated with diseases. Based on the experimentally obtained results these markers can serve as additional diagnostic tools. Moreover, these markers can be used in family planning policy.

Keywords: *STR loci, mutation, genome instability, trisomy, loss of alleles, disease-associated alleles, cancer, Down syndrome, Edward syndrome*

From fertilization to birth, from birth to death, the human genome undergoes changes as a result of mutations that occur continuously throughout life. Some of these mutations are neutral, while others are aggressive or harmful. Excessively aggressive or harmful mutations cause the death of the carriers, or carriers suffer from various pathologies. Compared to normal variations, some of the pathogenic variations are eliminated directly, while others did not transmit to future generations. In comparison to normal (neutral) variations, pathogenic variations are less widespread and can rarely consolidate their place in the population either randomly or transiently. A previous study conducted by Mustafayev et al. revealed the mutations that were detected during paternity tests in the Azerbaijani population (Mustafayev et al., 2019). In this

review, the analysis of studies related to the detection of associative relationships of specific alleles/variations of STR loci with various diseases in different populations was shown.

One of the main reasons of changes is dynamic mutations, and it is important to study the mechanisms of formation, nature and role of all fixed variations that are presented in the genome in the form of repeated sequences (Pearson et al., 2005). In general, the instability and polymorphisms of the genomes is a universal phenomenon. According to the extent of occurrence, two types of genome instability were distinguished:

- 1) Chromosome instability (CI) - mainly cancer cells, extra chromosomes and chromosome losses creating an abnormal karyotype, all kinds of chromosomal

rearrangements, etc. This type of instability can be inherited during cell divisions and continuously presented as new variations in further generations.

- 2) Microsatellite instability (MI) is polymorphic pathogenic changes occurring directly in different types of microsatellite DNA sequences.

Currently observed variations are mostly normal ones. The examples of common normal variations at the chromosomal level are reported below:

- 1) The size of the heterochromatin regions at the centromeres of chromosomes 1, 9, 12, and 16 and the long arm of the Y-chromosome can change;
- 2) The short arms of acrocentric chromosomes 12, 13, 14, 15, 21, and 22, whose centromeres are located very close to one of the ends of the arms, showed significant variability in size. Usually, the so-called satellite part, which is connected to the main part of the chromosome with a thin short "thread", can be observed in the most distal (farthest) area.
- 3) While cells are cultured under conditions that make DNA replication difficult (for example, lack of thymidine or addition of DNA-polymerase inhibitor aphidicolin), the variability of "fragile chromosome" regions (fragile sites) becomes evident (uncoiled chromatin pieces). Most of the fragile chromosomal regions are normal variations, except for a few ones (for example, the fragile sites FraXE and FraXF that are directly linked to mental retardation are pathogenic).

Genome variations occur due to changes in the number of copies of tandem repeat sequences, full or partial insertions/deletions and point mutations (SNP). Recently, 325 (>400) million SNPs have been detected in the human genome using the array-comparative genomic hybridization (ACGH) method, of which 15 million have a frequency of more than 1% among world populations. The HapMap project (2003, 2010) reported >1447 regions with high variability within the sequences of at least 1 Kb in length in the human genome. In total, these regions possessed with the length of ~360 Mb and

cover ~12% of the genome. The average size of highly variable segments was 250 Kb. Short variations were identified using the paired-end mapping technique and appeared to be more common in the genome (Korbel et al., 2007).

SNPs appeared in both normal and pathogenic changes due to their ability to occur everywhere in the genome – in coding and non-coding elements, as well as in all types of repeats via all possible ways (insertions, deletions, substitutions, trans- and inversions, etc.).

Microsatellites, known as short tandem repeats (STRs) and consisting of 2–6 bp in their core sequences, are small-size DNA sequences with multiple repeats that make up approximately 3% of the human genome (Lander et al., 2001; STRBase (SRD-130), 2023). Repeated core units of polymorphic STR loci, that located mainly in non-coding regions of the genome and vary widely (Butler, 2006; Biscotti et al., 2015). However, there are STRs localized in intron and promoter regions. STRs located in promoter regions are associated with transcription regulatory elements and participate in transactivation (Sawaya et al., 2012; Chen et al., 2016). Possessing with high level of polymorphism, makes these markers like SNP and STR valuable in solving various problems. Examples of such areas of application include interspecies and intraspecies differentiation studies (Deniskova et al., 2016), prenatal clinical studies (Agarwal et al., 2014; Li et al., 2021), preimplantation screening of β -thalassemia (Sharifi et al., 2019), in the determination of kinship relationships at the level of sister and brother (Chakraborty, 2016; Tang et al., 2012), in controversial maternity/paternity and human identification tests (Pinto et al., 2013; Lee et al., 2015; Ramsos and Valloni, 2015), in forensic and population studies (Anghel et al., 2015; Eskandarion et al., 2015; Gurkan et al., 2015; Huang et al., 2015; Tan et al., 2017; He et al., 2018a, 2018b; Amirian et al., 2019; Anwar et al., 2019; Khubrani et al., 2019; Nowroski et al., 2019; Aalbes et al., 2020; Kakkar et al., 2020; Kumawat et al., 2020; Mammadov et al., 2020; Pilav et al., 2020; Sahoo et al., 2020; Badiye et al., 2021), in sequence-based assignments (Tao et al., 2021), etc.

The main reason for doubting the association of several blind STR loci with certain diseases in the most of this kind of studies is the use of genome-wide screening. For example, there is a Marshfield panel (Weber set 10) that scans over 400 STRs in the human genome, including TPOX, D7S820, D8S1179, D13S317, D16S539, and D19S433 (Ghebranious et al., 2003). Therefore, the existence of association between alleles of THO1, which is known for its negative reputation, in a number of patients with schizophrenia (Meloni et al., 1995a, Thibaut et al., 1997) and bipolar disorder (Meloni et al., 1995b), was reported. However, it is known that other researchers did not confirm these associations (Burgert et al., 1998, McQuillin et al., 1999). Recent studies have shown that individuals carrying the 7 allele of THO1 were less nicotine dependent, although these data are not definitively confirmed (Anney et al., 2004).

F.Gao and colleagues (Gao et al., 2013) studied the association of microsatellite STR loci polymorphism (ATCC)n1, D1S1621, and (ATCC)n2 located in introns 1, 8, and 9 of the DISC1 (Disrupted-in-schizophrenia-1) gene with the risk of developing of the schizophrenia in a Chinese Han population. The study was conducted on 310 schizophrenic patients and 400 controls. It was found that the frequency of alleles 12 of (ATCC)n1, 11 and 12, 13 and 15 of D1S1621, and 10 of (ATCC)n2 was significantly higher in schizophrenic patients than in controls, in comparison to alleles 9 and 10 of (ATCC)n1, and alleles 16, 17 and 18 of D1S1621.

Trisomy-21, known as Down syndrome, can be characterized by the presence of three alleles at any polymorphic marker on chromosome 21 (Liou et al., 2004). STR locus D21S11 is a more correct test to identify the trisomy-21 (Pertl et al., 1994). In addition, evaluation of trisomy-18 (Edwards syndrome) in prenatal samples was performed with the D18S51 marker (Yoon et al., 2002). Moreover, loss of heterozygosity (for any reason, an allele located on one of the homologous chromosomes becomes a "null" allele, causing highly homozygous genotype(s)) or a high level of allelic imbalance (for the same reason, causing multiallelic genotype(s)) in some cases was assumed to be associated with cancer (Rubocki et al., 2000).

In 2021 K.Wang et al. (2021) reported a rapid prenatal diagnosis method of Down (trisomy 21) and Edward (trisomy 18) syndromes by amplification of multiplet STR loci via designed fluorescent-labeled primers (STR-FQ-PCR). The non-invasive prenatal diagnostic technology (NIPT) method was tested on 64 amniotic fluid samples for the presence of trisomies 18 and 21, and the results were compared with karyotype and chromosomal copy number variation (CNV) analysis. The aneuploidy test gave a positive result in 61 samples, 14 of which showed Edward's syndrome, and 47 showed Down's syndrome. In total 460 STR locus genotypes were detected, of which 84 related to Edward's syndrome and 376 to Down's syndrome. Chromosomal karyotype analysis showed that all detected samples were chromosomal aneuploidy - 15 of them with trisomy 18, including 14 homozygous and 1 chimeric type, 49 with trisomy 21, including 47 homozygous and 2 chimeric type. CNV analysis revealed 62 cases of chromosomal aneuploidy, 14 of which were trisomy 18 and 48 for trisomy 21. The authors concluded that the detection accuracy rate of STR-FQ-PCR technology was 95.31%, and for karyotype analysis that was 100%. For non-chimera and non-structural abnormal samples, the results of karyotype analyses and that of STR-FQ-PCR technology were 100% identical.

S.F. Alharbi et al. (2022) amplified STR loci with specific primers in 15 chronic myeloid leukemia patients and 15 healthy individuals and showed that alleles 9 and 9.3 of the tyrosine hydroxylase 1 (THO1) STR marker were more frequently detected in leukemia patients.

STR loci also showed instability in other forms of cancer. This is mainly related to DNA repair systems. For example, such associations were found in lung cancer (Zhang et al., 2018), lung and liver cancer (Qi et al., 2018), gastric cancer (Hui et al., 2014), in papillary thyroid cancer (Dang et al., 2020), in esophageal cancer (Kaifi et al., 207), and in leukemia (Filoglu et al., 2014; Bawazir et al., 2019).

Z.L. Wang et al. (2012) detected the association between allele frequency of 15 autosomal STR loci included in the AmpFLSTR™ Identifiler™ PCR Amplification Kit marker set and chronic myeloid leukemia

(CML). The study was conducted on 745 healthy subjects and 132 patients with CML. Comparison of allele frequencies between the patient and healthy groups revealed statistically significant differences ($P < 0.05$) of three STR markers, CSF1PO, vWA and TPOX.

H.Dasnhow and colleagues (2018) proposed a new method called STRetch, which allowed the detection of all pathogenicity-causing STR expansions in the genome, and allowed finding new ones. The method was based on information obtained from genome-wide short reads (sequencing) of known and novel pathogenic loci. The STRetch is the source-available software (github.com/Oshlack/STRetch).

X.Qi and colleagues (2018) conducted a study to analyze the possibility of screening lung and liver cancer susceptibility by using genetic markers rather than genes that are directly associated with the disease. The study revealed statistically significant associations of allele 20 of D18S51 with lung cancer, as well as allele 30.2 of D21S11 and allele 18 of D6S1043 STR marker with liver cancer. These analyses showed that STR markers that are included in the CODIS system can predict susceptibility to cancer.

A study by L.Hiu et al. (2014) revealed that among young individuals with gastric cancer, allele 23 of D2S1338 and allele 11 of D6S1043, as well as allele 16 of D8S1179 and allele 13 of D5S818 showed higher frequency in pairs.

N. Wyner and colleagues (2020) reviewed 107 articles on the association of forensic STRs with phenotype and found 24 markers for 50 unique traits that are related to that in 57 articles. The THO1 marker was associated with 40 different genotypes for 27 traits, five of which showed that THO1 was associated with schizophrenia. Although none of these traits were directly independent causes or predictors of the disease, the statistical significance of the association was nevertheless high.

N.von Wurmb-Schwark and colleagues (2011) conducted a study related to the genetic association of the THO1 STR marker that showed the tyrosine hydroxylase 1 (THO1) gene as a candidate gene for human longevity in the Italian population. In this article, 471 elderly (97-110 years old) and 462 young controls (19-75 years old) living in Germany were studied, but the

expected association was not detected. Nevertheless, the allele frequencies between the studied groups and the previously published study were consistent. However, significant differences in the frequencies of the THO1 allele 9.3 were observed between Germans and Italians, which confirmed the fact that the frequency of this allele decreased in the West-East and North-South directions throughout Europe.

Based on the experimental results, S.Alam and colleagues (2011) hypothesized that the 9th allele of the THO1 STR locus is associated with susceptibility to malaria (*Plasmodia falciparum*). Note that the THO1 microsatellite locus is located in the human immunoregulatory region and close to the β -globin gene.

M.A.Meraz-Ríos et al. (2014) studied the association of STR loci with venous thromboembolism (VTE) disease in 177 patients and 531 healthy controls. The study showed that allele 18 of the vWA microsatellite of the von Willebrand factor α -fibrinogen gene as well as alleles 9 and 12 of the thyroid peroxidase gene TPOX microsatellite were significantly associated with VTE disease. In addition, this risk was higher in individuals with both vWA-18/TPOX-12 (95% CI, OR=1.02-3.64) and vWA-18/TPOX-9 (95% CI, OR=4.93-21.49).

G.Sutherland and colleagues (2008) performed haplotype analysis of the IGF2-INS-TH gene cluster and revealed that the haplotype of IGF2-rs680, INS-rs689 SNPs and the TH-6 allele were not significantly presented in idiopathic Parkinson patients (OR=0.42, 95% CI, 0.25-0.72, $P=0.001$).

In addition, several studies showed the statistically significant association of the allele 9.3 of the THO1 STR locus with sudden infant death syndrome (SIDS) (Klitschar M, 2008; Courts C, Madea B, 2011).

Chun Yang et al. (2022) studied the association of 20 autosomal STR loci with the schizophrenia disease. The study was conducted on 355 schizophrenics and 473 healthy males. Although statistical differences were found in the distribution of genotypes and alleles of D13S317, D5S818 loci between two groups, and no difference was found in the remaining 18 STR loci. Univariate analysis showed that there were statistically significant differences in the

distribution of the (10, 11) genotype and allele 11 of the D13S317 locus and the (7, 10) genotype and allele 7 of the D5S818 locus ($P < 0.005$ compared to the control in both cases) between two experimental groups. Based on the obtained results it could be assumed that the above-mentioned genotypes and alleles of D13S317 and D5S818 STR loci were associated with the risk of developing schizophrenia in males.

Longevity is a complex and multifactorial phenomenon, determined by genetic, epigenetic, environmental, stochastic, and other factors. The main purpose of the research conducted by N.G. Bediaga et al. (2015) was to show the statistically relevant association between polymorphism of hypervariable STR loci such as HUMTHO1 (THO1) and HUMCSF1PO (CSF1PO) that are used in forensic practice and longevity. In a way to study 21 autosomal STR loci polymorphisms, 304 people aged 90 and over and 516 younger controls of European origin living in northern Spain were studied. The study confirmed the previously obtained results of the THO1 and CSF1PO STR loci. In addition, there were significant differences in the distribution of alleles for a total of 6 STR loci, of which the D12S391, D22S1045, and D2S441 STR loci were also significantly associated with longevity. This can be explained by the fact that the genetic pattern of longevity is more complex and depends on multiple genetic factors.

Profiling of disease-associated STR loci is associated with several challenges related to the length of reads, which affect the accuracy of the results. This limitation is mainly due to the generation of repeated reads (especially in loci consisting entirely of C and G). To partially overcome these limitations, H.Tang and colleagues (Tang et al., 2017) performed a sequencing-based whole genome profiling analysis of disease-associated alleles of hypervariable STR loci in 12,632 individuals. For this purpose, the authors improved the existing TREDPARSE software package for 30 known diseases and showed that this program is superior to any other program.

Study by N.A.Al.Sharhan et al. (2022) revealed the evaluation of loss of heterozygosity and microsatellite instability (MI) in circulating extracellular DNA (exDNA) in individuals with

breast cancer using human identification STR markers (AmpFlSTR MiniFiler Human Identification Kit). The study was conducted on 41 patients and 40 healthy women. As a result of the study of the DNA profiles of patients and controls, statistically significant differences were reported in the frequencies of allele 8 of the D7S820 locus, alleles 29, 30.2 and 32.2 of the D21S11 locus, and allele 11 of the CSF1PO locus, as well as the loss of heterozygosity in the profiles. The study showed that the application of exDNA microsatellite instability in early diagnosis of breast cancer can provide effective results.

In order to assess the integral stability and degradation rate of tumor-specific genomic DNA, E.E.Nikulina and colleagues (2022) performed STR loci profiling of DNA isolated from plasmacytomas of archived materials. The study was conducted on 10 patients (7 women, 3 men, average age 53.5) who were treated for advanced plasmacytoma multiple myeloma (MM) in 2013-2021. As a result of the study, 4 out of 10 people were observed for loss of heterozygosity (HL) caused by duplication or deletion of one of the two alleles on chromosomes 1 (1q42), 6 (6q14), 7 (7q21.11), 13 (13q31.1) and 21 (21q21.1).

It is known that a three-allelic pattern was observed in the genotyping of STR loci during several diseases (e.g. Down's syndrome). X.Y.Ma and colleagues (Ma et al., 2023) revealed the abnormal triallelic patterns that create difficulties and uncertainties in assessing the accuracy of the results of actual forensic cases performed with autosomal STR loci. The article also reviewed the types, formation mechanisms, frequency of occurrence, genetic pattern, and quantification of triallelic patterns in autosomal STR (Ma et al., 2023).

C.Lei and colleagues (Lei et al., 2023) for the first time proposed a new system for the detection of aneuploidy and its erroneous chromosomal origin, which caused spontaneous abortions during 2018-2020. Compared to low-pass G-banding karyotyping, the proposed system increased the detection rate of chromosomal abnormalities in 500 unexplained recurrent spontaneous abortions to 56.4%. In this study, a total of 386 STR loci located on twenty-two autosomes and two sex chromosomes (X and Y chromosomes) were developed, which can help

distinguish triploidy, uniparental diploidy, and maternal cell contamination, as well as determine the parental origin of extra chromosomes. It was not possible to perform this for the cases of miscarriages with existing methods. Moreover, it was revealed that among the errors testing for aneuploidy, trisomy was the most frequently detected error (33.4% overall, and 59.9% in the extra chromosome group). In trisomy samples, 94.7% of extra chromosomes were of maternal origin, and 5.31% were of paternal origin. The proposed new system improved the method of genetic analysis of miscarriages by providing additional reference information for the clinical management of pregnancy (Lei et al., 2023).

Recently, most STR loci were considered "junk" DNA since they were located in non-coding regions of the genome and were not able to express any phenotype. As was mentioned above in some populations STR markers that are used in forensic practice were associated with a number of diseases. Chinese scientists J. Yang and colleagues (2022) examined the association between three facial characteristics (single or double eyelid, with or without epicanthus, unattached or attached earlobe) and 15 STR loci in 721 unrelated Han individuals. In order to predict the presence of phenotypic relationship, additionally 1,993 unrelated individuals were included in the study, and STR and geographic data of 27,199 individuals whose results were available in the literature were collected. During the analysis, the correlation between facial characteristics and STR markers was not observed. Although the results were statistically significant for alleles at only two STR loci, allele 19 of D2S1338 and allele 18 of FGA (statistical confidence after Bonferroni correction $P=0.0032$, $P=0.0030$, respectively), the predictive validity was low. Principal component analysis for STR and biogeographic data showed that the first three components could explain 87.7% of the variation, but the prediction accuracy was only 25.2%.

CONCLUSIONS

In all these reviewed studies, some microsatellite STR markers, mainly used in forensic medicine to solve identification issues of

genetic examinations in criminal and civil cases have an association with cancer, schizophrenia, hypertension, muscular dystrophy, Edwards' and Down's syndromes, cardiovascular and other diseases. The loss of alleles and the difference in frequency of alleles between sick and healthy were frequently observed in analyzed scientific studies. In addition, many studies were conducted to study the association of STR markers that are currently used in forensic medicine practice with diseases such as different types of cancer, predisposition to schizophrenia, etc as well as in their early diagnosis. In conclusion, despite the fact that in different populations various and contradictory results were obtained, the use of STR markers in disease identification is a relevant and promising tool.

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