Advancement of Y-markers with Rapidly Mutating Y-STR (RM-Y STR)

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Abstract:

In forensic genetics, the research of Y-chromosomal markers has evolved dramatically, especially with the use of rapidly changing Y-STRs (RM-YSTRs). Short tandem repeats on the Y chromosome, or Y-STRs, are frequently employed in forensic casework, population studies, and genealogical research. They have proven to be useful in distinguishing male lineages. But this field has undergone a revolution with the introduction of RM-YSTRs, which show mutation rates 10-100 times higher than those of traditional Y-STRs. Particularly when closely related males are involved, these highly changeable markers offer improved resolution in distinguishing between male cousins, providing more precision in complex kinship analyses. This review paper examines the origins, traits, and forensic uses of RM-YSTRs, emphasizing how they enhance the Y-chromosome analysis's discriminating ability. The multi-copy RM YSTR markers DYF399S1, DYF387S1, DYF404S1 and DYF403S1 can be tough to interpret for main two reasons: first, an imbalance in the amplified peaks can make genotyping incorrect; and second, slippage peaks, which can account for up to 20% of the

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allelic peaks, are frequently seen because of their hyper-mutability, the widely used Y-STRs loci exhibit high polymorphism in most populations, with mutation rates ranging from 10−4 to 10−2 per locus present in every hereditary generation (Y-Chromosome STR Haplotype Reference Database, YHRD). We also examine the incorporation of RM-YSTRs into databases, their significance for population substructure, and their use in forensic and anthropological contexts for paternal ancestry tracking. This study highlights the significance of Y-marker analysis with RM-YSTRs in contemporary forensic by providing a thorough overview of the field's accomplishments through the consolidation of current research. Within 7 of the 8 locations studied globally, RMYSTRs showed higher maximal haplotype diversity and discriminating power [16]. It has been proposed that the RM Y-STRs are innovative markers that can expand the application of Y-chromosomal technology beyond male individualization and paternal lineage differentiation and also combining RM-YSTR data with other genetic markers may improve our comprehension of human genetic diversity and its historical and legal implications.

Keywords: STR, Y-STR, SRY gene, NRY region, RM-Y STR, Mutation rate

INTRODUCTION

The Y chromosome's unique features, such as paternal inheritance and there is no recombination for the majority of its length, make it an effective tool for tracing and comparing the paternal lineages of human populations. A wide range of polymorphic markers are currently present on the non-recombining region of the Y chromosome, from base substitutions, deletion and addition variations, which are uncommon but unique occurrences in evolution and typically occur in pairs, to faster-mutating polymorphisms. Determining an

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individual's sex is the main purpose of the Y chromosome. It has the SRY (Sex-determining Region Y) gene, which causes the testes to mature and male hormones to be produced[1]. These events result in the development of main and secondary sexual characteristics in males. With over 58 million base pairs, the Y chromosome is substantially smaller than the X chromosome[2]. It is smaller in size, but it still has all the necessary genes for male fertility and spermatogenesis[3]. Its gene pool shrank throughout time, leaving it with only 50–200 functional genes, compared to the X chromosomes around 1,000. The SRY (Sex-determining Region Y) gene, which is located on the Y chromosome, causes the testes to form and so starts the development of masculine features. Male primary and secondary sexual traits develop as a result of it[4].

The Y -STRs markers are useful in situations of sexual assault. Cell samples from the victim and sample combinations of the attacker's semen are frequently used as evidence in sex crimes. Traditional methods are able to distinguish sperm from the female components, but total dissociation isn't usually attained[5]. In furthermore, sample combinations made from vasectomized or male azoospermia prevents separations based on sperm. Polymorphic sequences that are arranged into large arrays with tandem repeats scattered make up the majority of the Y chromosome of human, also known as the long arm. Individual human Y chromosomes have been described using other hypervariable regions and RFLP analysis of these spanning several thousand base pairs [6].

A group or family of Y chromosomes related by descent is known as a haplogroup, and its identity is of great importance. Single nucleotide polymorphisms (SNPs) have a pattern that can be evaluated and directly determine Y haplogroups. However, identifying the haplogroup by direct SNP testing can occasionally be a time-consuming procedure[7]. Y-STRs have a particular inheritance pattern

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that makes them useful in population studies, forensic genetics, and genealogy[6]. Haplotypes must be appropriately grouped according to the donor's population origin since Y-chromosome-specific STR markers are sensitive to population divergence[8]. This led to the decision to combine various continental Y-STR datasets in May 2004 i.e.YHRD(Y chromosome haplotype reference database)[9].

Numerous investigations have shown that male lineage differentiation and haplotype diversity Y-STRs, as assessed with the current available Y-STR sets, can both be enhanced by including extra Y-STRs that have been carefully determined[10]. A large portion of the Y chromosome, referred to as the non-recombining region (NRY), with the exception of the pseudoautosomal regions (PARs) at the ends, does not recombine with the X chromosome during meiosis. Repetitive DNA sequences and mutable structural variations are highly concentrated in the Y chromosome[11]. Higher mutation rates are caused by repetitive sequences' increased susceptibility to replication mistakes and instability during cell division[8]. Because of their slower mutation rates, traditional Y-STRs are not as good at differentiating between male lineages that are closely related. Rapidly Mutating Y-STRs (RM-YSTRs) provide greater resolution for these applications, which has become a significant breakthrough[12].

Given that the Y chromosome is getting smaller over time, some experts have estimated that it may vanish in a few million years[13]. The Y chromosome stabilized and ceased shedding genes after a period of rapid shrinking, according to comparative research on Y chromosomes in other species (such as rats and chimpanzees). There are ideas that alternative mechanisms, such as other chromosomal adaptability and gene relocation, might take over to determine male sex or fertility if the Y chromosome disappeared[13].

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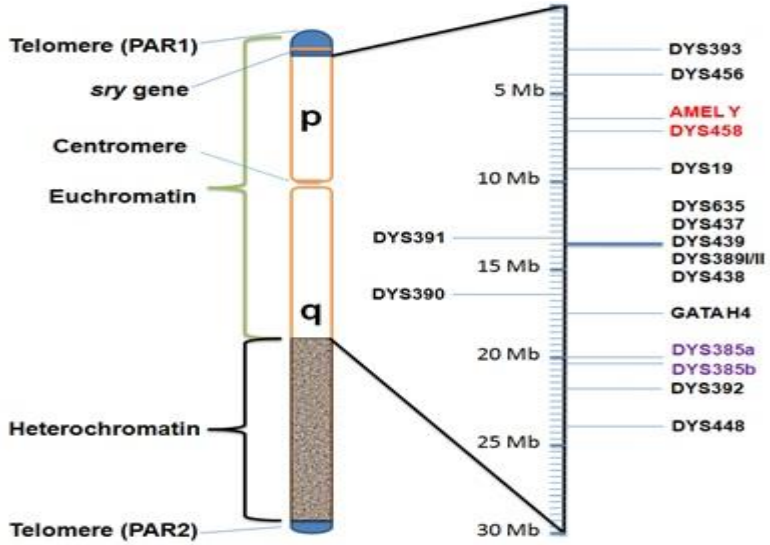
UNDERSTANDING RM-YSTR

Ballantyne et al. introduced the idea of "rapidly mutating" Y-STR loci. However, fast changing Y-STR sites also increase the likelihood of mutation within the same male lineage[10]. Fig. 1 depicts a Rare Case of DYS385 Monoallelism along with Amel Y deletion[14].

Fig. 1



Because the majority of Y-STRs loci in the available kits that currently have relatively low mutation rates and so exhibit relatively few alleles, in some populations there is not enough variation present in Y-STRs that are enough to discern between closely linked/related

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guys, or even males who are distantly related. It has been possible to identify Y-STR loci with higher mutation rates—referred to as rapidly mutating (RM) Y-STR loci—that may offer greater discriminative ability in differentiating related males[15].

The seven highly mutating or rapidly mutating Y-STR markers are DYF387S1a/b, DYS449, DYS518, DYS570, DYS576, and DYS627 respectively. Specifically located on the Y chromosome, Rapidly Mutating Y-STR (RM-YSTR) markers or loci exhibit higher rates of mutation than traditional Y-STRs[16]. Because these loci have a high mutation rate (between 10^{-2} and 10^{-3} mutations per generation), they are useful for differentiating between close male relatives[17].

Most commonly used RM-YSTR markers are:

1. DYS570: One of the Y chromosome's Rapidly Mutating Y-STR (RM-YSTR) loci is the DYS570 marker[18]. Its high mutation rate makes it beneficial for distinguishing between closely related male people, which makes it valuable in genetic genealogy, population research, and forensic science. Typically has **6-12 alleles** depending on the population studied and the specific allele definition[19].

2. DYS576: inherited from father to son and located on the Y chromosome, most especially in the non-recombining region. A high mutation rate (between 10^{-2} and 10^{-3} mutations each generation) indicates that it is one of the Y-STR markers that evolves more quickly. Commonly has **6-11 alleles**. The variation is influenced by the population and the mutation rate[20].

3. DYS627: has a considerable mutation rate (between 10^{-2} and 10^{-3} mutations per generation), which makes it a useful marker for distinguishing between guys who are closely related[19]. It is used to distinguish between brothers, cousins, or more distant relatives in

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cases when standard Y-STR markers would not offer sufficient diversity to divide people in a paternal line. Usually exhibits **7-13 alleles**, reflecting its rapid mutation rate and diversity[18].

4. DYS612: When paternal relatives have profiles that are similar based on normal Y-STR markers, it adds another level of resolution. DYS612 is utilized in genetic genealogy to track paternal ancestry through the identification of mutations that transpire over a comparatively brief period of time. Generally has **5-10 alleles**, with the number varying by population[21].

5. DYS518: Because of its high variability, it works well in situations where a more stringent level of differentiation between male suspects or persons is required for paternity testing[20]. It helps to solve family trees, especially when there is a common paternal ancestor across several generations of males. Typically shows **7-12 alleles** across different populations[22].

6. DYS449: In genetic genealogy, DYS449 plays a crucial role in tracing paternal ancestry and identifying recent mutations that occurred within a few generations[21]. In population genetics, DYS449 is also employed to investigate the organization of different populations throughout time, paternal migratory patterns, and male lineage diversity. Often has **5-9 alleles**, though this can vary based on the specific population and the observed mutations[9].

The fastest slowly mutating locus (DYS458) mutates 1.5 times quicker than the slowest quickly evolving locus (DYS449), and the mutation rates of several gradually mutating Y-STR loci are extremely similar to DYS458's [12]. The fastest mutating locus (DYS518) among the rapidly mutating loci only mutates 1.5 times faster than the slowest quickly mutating locus (DYS449). By comparison,

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DYS458, the fastest slowly changing Y-STR, mutates 17.6 times quicker than DYS438 (the slowest slowly mutating Y-STR). Regarding mutation rates, those "slowly mutating" loci have far higher variation than those "rapidly mutating" loci[12].

APPLICATIONS AND ADVANCEMENTS OF RM-YSTR

a. Forensic Analysis:

Suspects in forensic cases are frequently related, such as brothers, cousins, or father and son. Due to their lower mutation rates, traditional Y-STRs are not as useful for differentiating between members of the same paternal lineage. Because they are more likely to detect changes between related males, RM-YSTRs provide a solution[23].Their increased mutation rates range from 0.5% to 2.7% every generation. For instance, it's critical to precisely identify the offender in cases of sexual assault where male DNA is found at the crime scene, particularly if there are family members who could be suspects[23]. With the increased resolution that RM-YSTRs offer, forensic experts can distinguish between male relatives who could otherwise seem the same when utilizing conventional Y-STRs[24].

When the putative father and his family members are potential candidates, paternity testing can get complicated. RM-YSTRs increase the number of markers that are more likely to change over successive generations, which increases the accuracy of such tests[12]. This capacity aids in the exclusion or confirmation of paternity in situations where conventional indicators might not be sufficient. In forensic research, RM-YSTRs have become a potent marker that can provide better results in cases involving closely related males and intricate paternity disputes[25][17].

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b. Genealogical Studies:

The study of family lines, migration patterns, and human history is greatly aided by genetic markers. Because Y-STRs are inherited directly from father to son, they have long been used to trace paternal ancestry[26]. However, when it comes to differentiating between male lineages that are closely related, the lower mutation rates of conventional Y-STRs frequently fall short of offering enough precision[27]. This restriction has been overcome by rapidly mutating Y-STRs i.e. (RM-YSTRs), which provide increased precision in demographic and genealogical research[27].

When certain branches of a family tree are unclear, RM-YSTRs might be especially helpful in solving genealogical riddles. For example, genetic analysis employing RM-YSTRs can provide hints regarding familial ties when historical records are lacking or unclear[28]. According to Tariq Zeyad et al., the population of the UAE and the Saudi Arabia East [Arab] population grouped together, suggesting a closer genetic relationship and it stood in relation to other pertinent populations[29]. In summary, compared to all other investigations done on the same population, the Yfiler1 Plus multiplex kit demonstrated a better power of discrimination. This study took into account the first investigation into this community using 27 Y-STR loci[29]. The study's population analysis's geographic distribution is accurately reflected in the genetic distance findings.

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c. Anthropological and Population Studies:

In anthropological research, RM-YSTR markers are frequently utilized to track paternal lineage across generations. Researchers can assess the degree of relatedness among male people by comparing their RM-YSTR profiles[30]. This information is useful for researching social structures, kinship, and population migration trends across cultural boundaries.

Understanding the divergence of paternal lineages in particular is aided by RM-YSTRs in the evolution of humans. They can provide light on human dispersal events by assisting in the identification of the geographic and temporal origins of particular Y-chromosome lineages[31].

In patrilineal societies, where inheritance and lineage are traced through the male line, RM-YSTR analysis can shed light on societal dynamics[12]. Scholars are able to deduce ancient social structures and patterns of marriage by looking at the Y-STR profiles of various ethnicities.

In population genetics, RM-YSTRs are used to examine genetic variation both within and between populations[16]. These markers' rapid mutation rate makes it possible to discover changes between populations or subgroups that are closely related with greater precision[30].

It is possible to monitor past mixing events and migration trends with RM-YSTRs[16]. Researchers can conclude historical population migrations and interactions by examining the distribution of RM-YSTR haplotypes among various groups.

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Commercial Kits for RM-YSTR Analysis

For RM-YSTR analysis, a number of commercial kits are available; these kits are developed to amplify and examine the Y-STR loci that are mutating quickly. These kits provide high-resolution paternal lineage information and are utilized in genetic research, forensic labs, and genealogical investigations.

S. No.	**Name of kit**	**Manufacturer**	**Applications**
1.	Yfiler™ Plus PCR Amplification Kit	Applied Biosystems	Designed for high-throughput analysis, it has markers that offer RM-YSTR as well as standard information[32].
2.	PowerPlex® Y23 System[34]	Promega Cooperation	It has a strong discriminating capacity for male lineage identification and is utilized in forensic applications[33].
3.	MPS Y-STR Typing Kit	Promega Cooperation	This kit amplifies numerous Y-STR markers, including RM-YSTR loci, at the same time using multiplex PCR[36].
4.	Y Chromosome STR Analysis Kit	New England Biolabs (NEB) company	Provides a variety of Y-STR markers, including RM-YSTRs, for thorough Y-chromosome analysis[37].
5.	Y-STR Genotyping Kit	Several suppliers, including Promega and Applied Biosystems	A variety of Y-STR markers are available, frequently encompassing RM-YSTRs enabling in-depth paternal lineage research[38].

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ADVANCEMENTS OF RM-YSTR MARKERS POPULATION WISE:

Below are some studies that highlights how RM-YSTR markers have been applied to different populations, leading to significant advancements in understanding paternal lineage, migration patterns, and genetic diversity within these groups. Here's a table summarizing the advancements of RM-YSTR markers across various populations:

Table: 1

Population	Key Advancements	Key findings	Applications	References
European**[18]**	High-resolution male lineage distinction of closely related lineages is present.	detection of regional differences in Y-chromosome diversity	In genealogical investigations, paternal lineages are more easily traced.	Roewer et al.,2001
African**[6]**	Unique RM-YSTR mutations specific to sub- Saharan African populations	The data provides strong research proof that the RM Y-STR markers is highly effective in distinguishing between closely and distantly linked males.	enhanced comprehension of the distribution of lineages throughout Africa	Kaye N et al., 2011
Asian**[11]**	New Y-STR loci that is included in the Yfiler-Plus kit do not exhibit substantial signs of population history, according to the analysis of population consistent with that of the Yfiler system.	A Korean population has likewise shown decreased mutation rates at DYS387S1 and DYS518; however, larger mutation rates were noted at DYS449 and DYS570.	Used to resolve complex genealogical and paternal lineage cases	Y. wang et al., 2015

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Native American**[19]**	**Y chromosome evidence favors a single-migration theory, suggesting that all major Native American groups may have a common ancestor.**	the relationship between gene flow and genetic drift that has occurred in Beringia and in the Americas created the collection of modern Native American Y frequencies of chromosomal haplogroups	**information brought fresh perspectives on the ancestry of Native American tribes' genetic makeup.**	Zegura et al., 2004
Middle Eastern**[20]**	The Arabian Peninsula has Y-chromosome diversity mapped at high resolution.	The pattern of population substructuring was found to be mostly explained by geography, notwithstanding minor differences in the link between genetic and geographical distance.	The pattern of population substructuring was found to be mostly explained by geography, notwithstanding minor differences in the link between genetic and geographical distance.	Eida Almohammed et al., 209
Pacific Islander**[21]**	In isolated populations, fast mutations indicative of recent founder effects have been detected.	The ensuing haplotypes' phylogenetic analysis reveals ethnically distinct groupings that existed before Australia and Papua New Guinea were settled.	The DYS390 STR provides the chance to look into the specific allele that underwent a mutational alteration.	Peter Forster et al., 1998

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CHALLENGES AND LIMITATIONS OF RM-YSTR

RM-YSTRs have drawbacks in spite of their benefits. Higher mutation rates can occasionally result in homoplasy, which can make it more difficult to interpret results when the same mutation arises independently in separate lineages. Not all forensic labs may be equipped to do RM-YSTR analysis on a regular basis, and it requires specific understanding and confirmation[12].

RM-YSTRs necessitate more complex investigation and interpretation because of their high rates of mutation. Due to the considerable variability, it may be difficult to discern between real paternal ties and random matches brought on by mutations[39].

The use of RM-YSTRs in forensic labs or genealogical studies may be hampered by their limited availability and validation, especially in areas or institutions with limited resources for advanced genetic testing[31].

Due to noise introduced into the genetic data, the high mutation rates of RM-YSTRs can occasionally mask long-term evolutionary patterns in population research. It might be difficult to derive precise conclusions regarding population history as a result of misinterpreting migration patterns, population structure, and historical linkages[40].

The wider acceptance and effectiveness of RM-YSTR markers in a range of applications will depend on addressing these constraints by ongoing study, validation, and the creation of standardized methodologies.

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DISCUSSION

In many populations, it will be necessary to determine the RM Y-STR haplotype frequencies to estimate the match probabilities required in situations when non-exclusion RM Y-STRs are used to establish the constellation. But even prior to When such data are produced, the RM Y-STR set should prove beneficial in forensic casework by emphasizing clusters of exclusion[10]. The multi-copy RM YSTR markers DYF399S1, DYF387S1, DYF404S1 and DYF403S1 can be tough to interpret for main two reasons: first, an imbalance in the amplified peaks can make genotyping incorrect; and second, slippage peaks, which can account for up to 20% of the allelic peaks, are frequently seen[15]. Because of their hypermutability, the widely used Y-STRs loci exhibit high polymorphism in most populations, with mutation rates ranging from 10−4 to 10−2 per locus present in every hereditary generation (Y-Chromosome STR Haplotype Reference Database, YHRD)[17].Using the newly developed fast-evolving marker DYFS3871S1, it was possible to identify a second mutation that improved discrimination. DYF3871S1 typically has a high value for differentiating between unrelated people[26].

The usefulness of RM-YSTRs, however, varies according to the unique traits and background of every population group. RM-YSTRs have made it possible to do more accurate genealogical research in European groups[40], and they have shed light on past migratory patterns and social structures in African cultures[10]. In other areas, RM-YSTRs have helped map intricate population dynamics, identify founder effects, and solve difficult genealogical issues in places like Asia, Native America, the Middle East, and the Pacific

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Islands. These developments highlight the value of RM-YSTRs in demographic and genealogical research, however because of the possible difficulties posed by their high mutation rates, care must be taken when interpreting these markers[24].

CONCLUSION

There are numerous benefits to using RM-YSTRs in forensic science. For example, RMYSTRs require fewer markers (13 markers) than Y filer (17 markers). Furthermore, in 7 of the 8 locations studied globally, RMYSTRs showed higher maximal haplotype diversity and discriminating power [16]. It has been proposed that the RM Y-STRs are innovative markers that can expand the application of Y-chromosomal technology beyond male individualization and paternal lineage differentiation[41]. In forensic casework, the use of RM-YSTRs has demonstrated promise in solving intricate paternity cases, locating male suspects in criminal investigations, and more precisely tracking paternal ancestry[42]. Furthermore, RM-YSTRs provide sophisticated tools for researching population dynamics, migration patterns, and the evolution of human populations in anthropological and genealogy research[27]. The development and standardization of RM-YSTR panels will probably continue as research advances, improving their accessibility and dependability for forensic laboratories across the globe[25]. Furthermore, combining RM-YSTR data with other genetic markers may improve our comprehension of human genetic diversity and its historical and legal implications[24].

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