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# Deletion mapping based on STS-PCR of Y-STR negative Chinese males

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## Abstract

**Background**: In forensic genetic identification, male samples that lack the amelogenin Y-linked gene may be mistakenly genotyped as females. Therefore, in recent years, the Yindel has been integrated into multiplex polymerase chain reaction (PCR) kits designed for sex determination. Nevertheless, it has been observed that certain male individuals still exhibit negative results for these two loci or other short tandem repeat in Y chromosome (Y-STR). **Methods**: Y chromosome short tandem repeat (Y-STR) genotyping was performed to identify the deletion of STRs on the Y chromosome in two Chinese males. This provided a comprehensive assessment of the extent of Y chromosome deletion. The Yp11.2 deletion map was developed using Y-specific sequence-tagged sites (STSs) to verify the extent of the Yp11.2 region deletion and identify the unique deletion type in individuals at a more detailed level. **Results**: Y-STR genotyping revealed the presence of deletions in the DYS570 and DYS576 loci in the two Chinese males. **Conclusions**: We report a novel approach for detecting sites of Y chromosome deletion in Chinese males with *AMELY* drop-out or negative Y-STR loci. Identifying a significant number of sequence-tagged site (STS) loci enables a more systematic determination of the correlation between the deletion of different regions of the Y chromosome and the physiological and pathological characteristics. This allows for the identification of the specific role that each region of the Y chromosome plays in male ontogeny and fertility maintenance. Furthermore, this study's deletion pattern of Y-STRs differed from other previously reported cases. Seventeen selected Y-STSs exhibited a new class of deletion patterns.This study presents a simple and efficient approach using STS loci to investigate the classification of Y chromosome short tandem repeat (Y-STR) deletions and Yp11.2 deletion patterns in Chinese males and their correlation with male fertility.

## Keywords

*AMELY* dropout; Y-STR; STS; Yp11.2 region; Deletion mapping


  

# Mapa de ausencia de Y-STR negativo en hombres chinos basado en STS-PCR


## Resumen

**Antecedentes**: En la identificación genética forense, las muestras masculinas que carecen del gen de la cadena Y de la amelogenina pueden dividirse erróneamente en mujeres. Así, en los últimos años, Y-indel se ha integrado en kits de reacción en cadena de polimerasa múltiple (PCR) para la identificación de género. Sin embargo, se ha observado que algunos individuos masculinos siguen mostrando resultados negativos para estos dos sitios u otros secuencia repetida de tándem corto del cromosoma Y (Y-STR). **Métodos**: Se realizó la genotipado de la secuencia repetida de tándem corto (Y-STR) del cromosoma Y para identificar la ausencia de STR en el cromosoma y en dos hombres chinos. Esto proporciona una evaluación completa del grado de ausencia del cromosoma Y. El mapa de deleciones Yp11.2 fue desarrollado utilizando sitios de marcadores de secuencia Y específicos (STSs) para verificar el grado de deleción en la región Yp11.2 e identificar tipos únicos de deleciones en individuos a un nivel más detallado. **Resultados**: El genotipado Y-STR mostró deleciones en los genes DYS570 y DYS576 en dos hombres chinos. **Conclusiones**: Informamos un enfoque novedoso para detectar sitios de deleción del cromosoma Y en varones chinos con pérdida de *AMELY* o loci negativos de Y-STR. Identificar un gran número de sitios marcado por secuencia (STS) puede determinar de manera más sistemática la correlación entre la ausencia de diferentes regiones del cromosoma Y las características fisiológicas y patológicas. Esto permite identificar el papel específico de cada región del cromosoma Y en el desarrollo individual masculino y el mantenimiento de la fertilidad. Además, el patrón de ausencia de Y-STR en este estudio es diferente al de otros casos reportados anteriormente. Diecisiete y-STSs seleccionados mostraron una nueva categoría de patrones ausentes. Este estudio propone un método simple Y eficaz para estudiar la clasificación de los patrones de Deleción de secuencias repetidas de tándem corto (Y-STR) Y Deleción Yp11.2 en los cromosomas Y masculinos chinos y su correlación con la fertilidad masculina utilizando sitios STS.



## Palabras Clave

Pérdida de *AMELY*; Y-STR; STS; Área Yp11.2; Mapeo de deleciones


## 1. Introduction

The amelogenin (*AMEL*) locus has been widely employed as a gender marker due to the varying sizes of the polymerase chain reaction (PCR) products of the amelogenin X-linked (*AMELX*) and amelogenin Y-linked (*AMELY*). The *AMEL* locus, included in commercial short tandem repeat (STR) multiplex kits, is utilized for forensic DNA profiling and gender diagnosis. However, during a criminal investigation, males with *AMELY* dropouts may be incorrectly identified as females when relying solely on the genotypic outcomes of the *AMEL* locus [1–3].

Therefore, it is recommended that *AMELY* dropout males should undergo Y-chromosome STR (Y-STR) genotyping. However, in some instances, the amplification of Y-STRs yielded negative results. There are typically three situations that can result in the negative amplification of Y-STRs: mutations in the primer-binding site [4, 5], fragment deletion [6–13], or an abnormal Y chromosome [14–17]. The primary cause of negative Y-STR amplification was identified as fragment deletion. Typically, mutations are identified by modifying the amplification kit or by designing novel primers targeting distinct chromosome regions. Eliminating several adjacent Y-STR markers signifies a fragment deletion within the pertinent genomic region. The observed dropout of numerous interspersed Y-STR markers may be attributed to a mosaic deletion. An elevated occurrence of Y-STR deletion indicates the presence of Y chromosome abnormalities [18]. Occasionally, the presence of STRs in the q arm of the Y chromosome may go undetected, typically due to the loss of the Yq region caused by Xp-Yp replacement. In some instances, there is a near absence of all Y-STRs on the Y chromosomes, which suggests that the individual has a 46, XX sex reversal syndrome [19–22].

A sequence-tagged site (STS) is defined as a concise DNA sequence, typically spanning 200 to 500 base pairs, that serves as a unique molecular marker within the genome. The chromosomal locations and nucleotide sequences of STS are known. Because the genome contains a single STS copy, PCR can effectively detect it. Unlike STS markers, Y-STRs are broadly distributed across the Y chromosome. This widespread dispersion complicates the detection of deletion patterns, as it often leads to the failed amplification of Y-STR markers. Therefore, it is essential to identify the STS loci to create a deletion map in the corresponding area, offering a more comprehensive understanding of the deletion pattern of the Y chromosome [23].

As the incidence of cases involving *AMELY* deletion rises, there is concurrently an increase in the diversity of deletions observed in the Yp11.2 region, suggesting a degree of specificity linked to different populations (**Supplementary Table 1**). Hence, it is critical to characterize the Yp11.2 deletion regions. Jobling *et al.* [23] employed 33 Y-specific markers to study 45 *AMELY*-null boys from 12 populations and identified five distinct Yp11.2 deletion patterns: class I, -Is, II, III and IV [23]. Class I is the predominant category and encompasses a range of deletion types. Class I, -Is, II and III deletions are accompanied by deleting adjacent Y-STR loci, such as DYS458 and/or DYS456. It has been reported that three individuals exhibiting the class I deletion pattern in the Chinese population also had a few other deletions that could not be categorized [15, 24]. To examine the potential mutation patterns in the Chinese population, we tested the deletion region located on the Y-short arm of two Chinese males who tested negative for the *AMELY* gene. These tests included Y-STR

analysis, examination of the sex-determining region Y (SRY), and testing of STSs.

## 2. Materials and methods

### 2.1 Samples and DNA extraction

All samples (samples 1 and 2, positive and negative) were funded by the Center for Forensic Science of Jining Medical University. Samples 1 and 2 were *AMELY*-negative males. The extraction of DNA for *AMEL* and Y-STR genotyping and STS testing was performed according to the previously reported method [25].

### 2.2 AMEL and Y-STR genotyping

The autosomal STR and Y chromosome *AMEL* loci were amplified using the Goldeneye 20A PCR Amplification kit (20ADH301, Peoplespot, Beijing, China) and Huaxia$^{TM}$ Platinum kit (2111036, Applied Biosystems, Foster City, CA, USA), following previously published protocol [14]. For males with *AMELY* allele dropout, the Y filer plus kit (1903043, Applied Biosystems, Foster City, CA, USA) and Goldeneye 27YB kit (27YMI101, Peoplespot, Beijing, China) were used to verify the gender of the subjects, as described previously [14]. The amplified products were separated by capillary electrophoresis on an ABI-3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and analyzed using GeneMapper ID-X1.4 software (Applied Biosystems, Foster City, CA, USA).

### 2.3 STS loci screening and primers designing

Samples exhibiting *AMELY* dropout were subjected to further analysis using SRY and STS tests to validate the gender and determine the precise locations of the deletions. The positional information of the SRY and STS markers was obtained from the University of Colombo School of Computing (UCSC) Genome database (http://genome.ucsc.edu/cgi-bin/hgTracks) and the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/nuccore/NC_000024.10?from=2686000&to=7912000&report=genbank&strand=true). The primer sequences and annealing temperatures are listed in Table 1.

### 2.4 PCR amplification and electrophoresis

Gradient PCR was performed to determine the optimal annealing temperature for each primer pair, employing the methodology reported in prior studies [25]. Genomic DNA extracted from blood samples was used as a template for PCR amplification. The thermal cycle conditions and method for separating amplified PCR products have been reported [25].

## 3. Results

### 3.1 Genotyping of AMEL locus and Y-STR

The STR typing of the two males with negative *AMELY* amplification showed *AMELX* amplification but not amplification of *AMELY*. In addition, all autosomal STR loci were successfully detected (**Supplementary Fig. 1**).

The genotypes of 23 Y-STR loci, except the DYS570 and DYS576 loci, were effectively retrieved from the two males using the Yfiler Plus kit and Goldeneye 27YB kit (**Supplementary Fig. 2**). Both males had identical Y haplotypes according to Y-STR genotype profiling. The findings indicated that the negative amplification of *AMELY* was likely due to a deletion in the Yp11.2 region encompassing *AMELY* (*AMELY*-DYS570-DYS576) rather than mutations in the primer binding region or abnormalities in the Y chromosome. The two *AMELY*-negative males were predicted to have the same haplotype (**Supplementary Table 2**). Based on the pedigree analysis, it can be determined that they have a common ancestry.

### 3.2 Analysis of STS and deletion region

Seventeen Yp11.2-specific STSs located between DYS456 and DYS458 were used to refine the deleted region in these individuals (Table 1). Six STSs, comprising DYS399, sY2208, sY2207, sY2220, DYS463A18 and DYS288, were successfully genotyped, whereas BV703954, BV703904, BV703923, sY2137, sY716, DYS256, DYS267, sY2232, sY2233, DYS261 and DYS260 were not detected in both of the *AMELY*-negative males (Table 2). The detection results for STS loci are shown in Table 2.

Based on the data gathered, a detailed map of the absent Yp11.2 region was constructed, as shown in Fig. 1 (Ref. [23]). It was found that the two males lacking the *AMELY* gene exhibited identical deleted regions. The breakpoints were confirmed to be BV703954 (5.08 Mb), BV703904 (5.19 Mb) and DYS260 (7.72 Mb)-sY2220 (7.73 Mb). Notably, both of the *AMELY*-negative males were determined to be fertile.

## 4. Discussion

Prior research has examined several amplification kits encompassing five loci adjacent to *AMELY* in the Yp11.2 region: DYS393, DYS456, DYS458, DYS481 and DYS19 [26]. Deletions involving the *AMELY*-DYS458-DYS19 genetic sequence have been documented. Nonetheless, occurrences where deletions of DYS393 or DYS19 that include the *AMELY* gene are notably rare. The Y-STR genotyping results in this study revealed that all five loci were positive. The Y-STR multiplex amplification kit contained DYS570 (6.86 Mb) and DYS576 (7.09 Mb), closer to *AMELY*. The typing results indicated that both loci were deleted. The individuals did not possess the same Y haplotype as previously described, indicating that the deletion pattern of *AMELY*-DYS570-DYS576 differed from the prior findings [15, 27].

In addition to the five classical deletion categories reported by Jobling *et al.* [23] (2007), alternative Yp11.2 deletion patterns in *AMELY*-negative individuals are increasingly emerging. As an illustration, Takayama reported deleting three segments in Japanese individuals [6]. The study conducted by Jobling *et al.* [23] did not include testing results for Chinese male samples. Currently, the classification data for the unreported types pertaining to Chinese males has been documented only for three samples, all categorized under Class I, as shown

**TABLE 1. Information of STS primers.**

| Markers | Sequence | Product size (bp) | Annealing Temperature (°C) |
|---|---|---|---|
| SRY-F | ACTGGTATCCCAGCTGCTTGC | 228 | 62 |
| SRY-R | AAGAGAATATTCCCGCTCTCCGG | | |
| DYS399-F | CTGTAAACAAGATTGGGC | 326 | 57 |
| DYS399-R | TCCATTTACTTAAAATGG | | |
| BV703954-F | AAGTCATTCAGCAAGTCTCTAGGAG | 353 | 57 |
| BV703954-R | TCTCAGGACAGTCAGAATGACG | | |
| BV703904-F | TAATGTTGGTAGACATCAATGCAG | 394 | 57 |
| BV703904-R | AAATGTTGTCCTTGGGCTTG | | |
| BV703923-F | TCTCTTGTTATGCTTGTTATGCC | 148 | 57 |
| BV703923-R | AAACTGTGAGGACTAAGCTGTGA | | |
| SY2137-F | CTTGCTGATGTCCACCGTC | 255 | 57 |
| SY2137-R | GATCCCCCCAACCCAAAT | | |
| SY716-F | TTCACACAGTGGCTGAATTACTTT | 208 | 57 |
| SY716-R | CATACCAGTGGGTTGCAAAA | | |
| DYS256-F | CTTTGCTAGGTAAGACCCACAA | 300 | 57 |
| DYS256-R | AAGCACGCCTACCTTCACCT | | |
| DYS267-F | TTTTAGAGTCATTGGCCAGG | 132 | 57 |
| DYS267-R | CTCTGAAAAAAAGGCAGCAG | | |
| SY2232-F | AACGTGTCTGGAAAGATGGC | 97 | 57 |
| SY2232-R | CAAAGATGCCTGATTGGCTC | | |
| SY2233-F | GAGGCTCTCAATGCCAA | 82 | 57 |
| SY2233-R | GCAGCTGCTGGTATTCCTTC | | |
| *AMELY*-6-1-F | TGCTGATGTGGTGTGAAGTACA | 745 | 57 |
| *AMELY*-6-1-R | TGTTCCAAAGGTAGAAGAAGGC | | |
| DYS261-F | CTGGACTGCACAAAACAACA | 293 | 57 |
| DYS261-R | AGAATATGGTGGGTGGGACT | | |
| DYS260-F | ACTAAAACACCATTAGAAACAAAGG | 309 | 57 |
| DYS260-R | CTGAGCAACATAGTGACCCC | | |
| SY2220-F | CATAGGAAGGGCAGTGCTTG | 57 | 57 |
| SY2220-R | CCATCAGAGAAGCAAGGAGG | | |
| SY2208-F | GTGAGAAGCCAACAGAAGCC | 55 | 57 |
| SY2208-R | CAGAGTTTTTGTGGGCATGA | | |
| SY2207-F | CCTTCACTCTCCCTCTGACG | 52 | 57 |
| SY2207-R | GGGGAGTCCTCTAAACAGGG | | |
| DYS463A18-F | AATTCTAGGTTTGAGCAAAGACA | 254 | 57 |
| DYS463A18-R | ATGAGGTTGTGTGACTTGACTG | | |
| DYS288-F | TTGCTTTGCTTGTCATTTCAGA | 75 | 57 |
| DYS288-R | CATTACAAATACCTGGACACTG | | |

*SRY: sex-determining region Y; AMELY: amelogenin Y-linked; bp: base pair.*

**TABLE 2. Detection of Y-Specific loci in two male samples.**

| Markers | Sample 1 | Sample 2 | Positon (Mb) |
|---|---|---|---|
| SRY | + | + | 2.79 |
| DYS399 | + | + | 4.99 |
| BV703954 | + | + | 5.08 |
| BV703904 | − | − | 5.19 |
| BV703923 | − | − | 5.27 |
| sY2137 | − | − | 5.42 |
| SY716 | − | − | 5.56 |
| DYS256 | − | − | 5.75 |
| DYS267 | − | − | 6.76 |
| sY2232 | − | − | 6.79 |
| sY2233 | − | − | 6.79 |
| *AMELY*-6-1 | − | − | 6.87 |
| DYS261 | − | − | 7.55 |
| DYS260 | − | − | 7.72 |
| sY2220 | + | + | 7.73 |
| sY2208 | + | + | 7.73 |
| sY2207 | + | + | 7.74 |
| DYS463A18 | + | + | 7.78 |
| DYS288 | + | + | 7.79 |

*SRY: sex-determining region Y; AMELY: amelogenin Y-linked; Mb: million bases. −: negative; +: positive.*

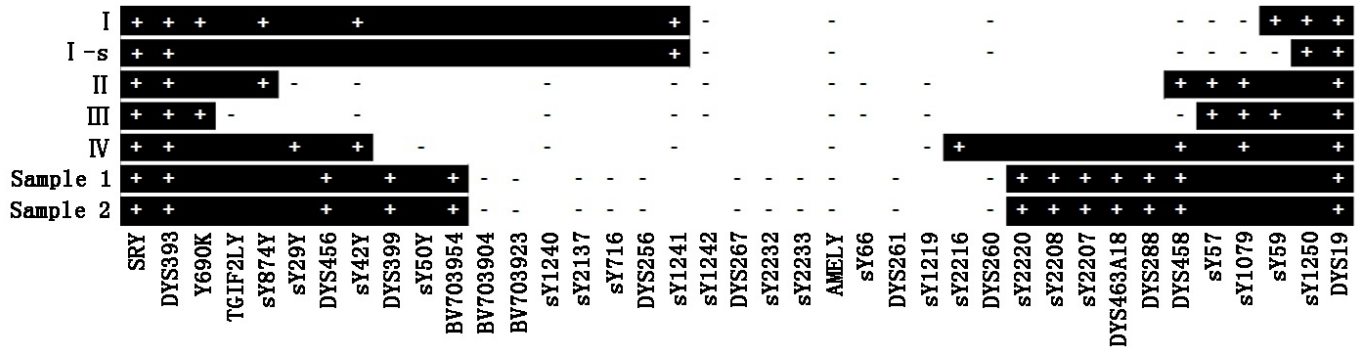


**FIGURE 1. The deletion map comparison with the classification described by Jobling *et al.* [23].** SRY: sex-determining region Y; *AMELY*: *amelogenin Y-linked*.

in **Supplementary Table 1** [19, 28]. However, the current study discovered that the existence of DYS456 and DYS458 indicated that the deletion pattern did not belong to Class I. A deletion map of the Yp11.2 region was developed using 17 STS loci. This map showed that 11 of these loci (BV703954, BV703904, BV703923, sY2137, sY716, DYS256, DYS267, sY2232, sY2233, DYS261, DYS260) were missing from the region between 5.19 Mb and 7.72 Mb on the Yp11.2 region. A deletion spanning approximately 2.52 Mb was identified, situated 1.68 Mb upstream and 0.85 Mb downstream of the AMELY gene. This deletion pattern does not conform to those cataloged in the report by Jobling *et al.* [23], suggesting it represents a novel deletion pattern that has not been previously documented or classified.

Identifying the deleted region is challenging due to the significant similarity between the breakpoints and the X chromosome, which hinders the selection of STS loci. Due to numerous palindromes in the male-specific regions of Y chromosomal deficiency, next-generation sequencing cannot identify these significant deletions.

The absence of genetic markers in the *AMELY* and Y-STR loci within the Yp11.2 region, specifically DYS458 and DYS456, has been extensively documented in the Chinese population. Our objective is to examine the specific type of deletion in the *AMELY* gene using data from prior studies conducted in China (**Supplementary Table 1**). However, there is a scarcity of data regarding the deletion pattern in the Yp11.2 region, and different laboratories have different STS

loci for study. During the experiment, it was discovered that several primer sequences for STSs in the UCSC database were inaccurate or that there was an increased production of non-specific bands during amplification in the Chinese population. This resulted in difficulties in screening STS loci and hindered their wide usage. Therefore, the current investigation and classification of Yp11.2 regional deletion patterns in the Chinese population is complicated. This study has the potential to generate insights for the future screening of STSs, designing primer sequences, and developing amplification kits for specific regions of Y chromosomes. The integration facilitates additional investigation into the classification basis of the *AMELY* deletion and Yp11.2 deletion maps in the Chinese population, providing convenience [29].

The study utilizes STS-PCR technology to identify Y chromosome deletion regions and verify their physiological functions. This approach is not limited to the Yp11.2 region but can also be used in other regions of the Y chromosome. The same method can be employed to screen STS loci in different regions of the Y chromosome and establish a multiplex amplification system. An efficient method for regional division of the Y chromosome and systematic identification of its deletion can rapidly detect Y chromosome deletions in male infertility patients [30, 31], enabling early detection, swift diagnosis, and tailored treatment for male infertility patients.

## 5. Conclusions

In conclusion, this study provides a straightforward and effective method for detecting Y chromosome deletions using STS-PCR. This approach was used to determine the deletion range of Yp11.2 in two Chinese males. It was found that this deletion is a novel form of deletion that does not impact male reproductive capacity.

### ABBREVIATIONS

*AMEL*, *amelogenin*; *AMELX*, *amelogenin X-linked*; *AMELY*, *amelogenin Y-linked*; STR, short tandem repeat; Y-STR, Y chromosome STR; STS, sequence-tagged site; SRY, sex-determining region Y; PCR, polymerase chain reaction; UCSC, University of Colombo School of Computing; NCBI, National Center for Biotechnology Information.

### AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article (and **Supplementary material**).

### AUTHOR CONTRIBUTIONS

QQP—designed the research study, analyzed the data and wrote the manuscript. KWH, MLG and YWH—performed the research. YQW—provided help and advice on first draft of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Bloodstains and fresh peripheral blood samples were acquired from individuals in the Chinese Han population of Jining City. The informed consent of the patients was obtained in written form. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of Jining Medical School (JNMC-2021-YX-008).

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1938835351987470336/attachment/Supplementary%20material.docx.

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