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Maternal allele mutation: Slippage synthesis furnishing evolutionary trend

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Abstract

Gain or loss of repeat motifs leads to an allelic mismatch in the disputed child which is a deviation from the Mendelian inheritance, thereby leading to a paternal mismatch of putative father or exclusion of mother in case of maternal allelic mismatch. This allelic mismatch at one or more loci is a major cause of forensic inferences. The biological samples of the case were genotyped using Powerplex®- Fusion 5C system kit and Investigator® Argus X-12 QS kit as per recommendations of the manufacturer. In this case, identification of a putrefied dead body with 22 autosomal STR loci, primarily analyzed by Powerplex®- Fusion 5C system kit divulged a maternal mismatch at locus D13S317. Alleles at the locus D13S317 allegedly belonging to the father of the deceased and the mother were observed as 10/11, 11/11 and 10/10 respectively. To rule out allelic mismatch at this particular locus, 12 X-STR loci were amplified, in which all the maternal alleles of deceased completely matched with the mother. This case study indicates the extension of one microsatellite repeat motif (TATC) at locus D13S317 in the population of Rajasthan. The reported mutation rate was 0.14% and 0.04% at locus D13S317 in paternal and maternal meiosis respectively.

Keywords: Paternity; X-STR; Maternal mutation

1. Introduction

Geographically, Rajasthan is situated in the North-western region of India. On the west side, it shares geographical boundaries with Punjab and Sindh provinces of Pakistan and towards the south-west, south, east and north, it shares boundaries with Gujarat, Madhya Pradesh, Uttar Pradesh, Haryana and Punjab[1] (Fig.S1). Rajasthan is a part of one of the oldest civilizations (India). According to Census 2011, Rajasthan has 5.66% of the total population of India. Microsatellite mutation at the STR locus D13S317 has not been reported in the population of Rajasthan so far. This case report marks a breakthrough in the observation of microsatellite mutation in the studied population. Genetic diversity including autosomal and Y-STRs on the population of Rajasthan is well established by some authors [2], [3], [4]. Indian sequencing datasets are underreported globally although India has 17% of the world population having extensive genetic diversity so it is very important to report any microsatellite mutations in the Indian scenario.

Variations in the microsatellite motif due to polymerase slippage cause an increase or decrease in the length of one or more loci. In the present study, gain or loss of repeat motifs led to an allelic mismatch in the questioned child which is a deviation from the Mendelian inheritance, thereby leading to a paternal mismatch of putative father and exclusion of mother in case of maternal allelic mismatch. This allelic mismatch at one or more loci leads to forensic inferences. This inconsistency is observed in standard trios (alleged father, mother and child) as well as motherless duos (alleged father and child). The inconsistency noted in the result was due to maternal allele mutation in the deceased. Mutation at primer binding site or paternal germline, null allele, chimerism or malignant cells in the sample tissues is the most common reasons for such inconsistencies[5], [6]. The possibility of a null allele can be ruled out with the help of measurement of peak heights of the maternal, paternal and child alleles at the locus D13S317 as the peak height of allele 11 in the

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deceased is almost twice that of the heterozygous father. In this study, the extension of the maternal autosomal microsatellite motif at the locus D13S317 is reported. Maternity of the questioned child has been conclusively established with the help of maternal X-STR loci.

2. Material and methods

The samples related to the case were received at the DNA division, State Forensic Science Laboratory, Jaipur, Rajasthan for routine casework analysis. Blood samples of individuals were collected after obtaining written informed consent and as per the declaration of Helsinki and following the institutional guidelines. DNA was isolated using Bone DNA Extraction and DNA IQTM kit (Promega, CA, USA- Promega) on Maxwell FSC extraction system (Promega) as per protocol recommended by the manufacturers.

Reference samples of the case were directly subjected to amplification as done in our previous studies [7]. Quantity analysis of the isolated DNA was performed with the help of QuantifilerTM Trio quantification kit (Thermo Fisher Scientific, CA, USA-Thermo) on Quant Studio 5 system (Thermo). Amplification of the 22 autosomal STRs along with Amelogenin was performed by using PowerPlex® Fusion 5C system kit (Promega) and 12 X-STR markers (DXS10103, DXS8378, DXS10101, DXS10134, DXS10074, DXS7132, DXS10135, DXS7423, DXS10146, DXS10079, HPRTB and DXS10148) Investigator® Argus X-12 QS Kit (19300 Germantown Road Germantown, MD 20874) on ABI Thermal cycler 9700 (Thermo) as per the prescribed protocol of the manufacturer except for the half-reaction volumes.

Fragment analysis of the PCR amplicons was performed on the Genetic Analyzer 3500 (Thermo) as per the manufacturer's recommended protocol. Data obtained was analyzed using the GeneMapperTM ID-X software v1.6 (Thermo).

3. Results and discussion

The initial examination was performed by PowerPlex® Fusion 5C system kit (Promega). The result of amplification of the 22 autosomal STRs along with Amelogenin for the trio is presented (Table 1). Paternal and maternal mismatch at various STR loci has been reported by several workers[8], [9], [10], [11]. Genotype at the locus D13S317 in father, deceased and mother was 10/11, 11/11 and 10/10 respectively (Table 3). The probable allele of the deceased should be either 10/10 or 10/11 in the case of Mendelian inheritance. Homozygote genotype (11/11) of the child revealed that one extra motif (TATC) at locus D13S317 expanded due to the slippage of the polymerase. So the length of the maternal origin allele became 44 bp instead of 40 bp. The frequency of alleles 10 and 11 in the studied population is 0.092 and 0.274, respectively (Fig. S2). Mother-child double incompatibility at vWA and D5S818 loci have been reported by Narkuti et al. 2010.

Table 1 Genotype of the father, deceased and mother with Paternity index.

S.No	Locus	Mother	Questioned Deceased	Father	Paternity Index
1.	D3S1358	16,17	16,17	16,17	1.76
2.	D1S1656	8,13	13,13	11,13	3.85
3.	D2S441	11,12	11,12	11,14	
4.	D10S1248	14,16	15,16	15,15	
5.	D13S317	10,10	11,11	10,11	1.82
6.	PENTA-E	9,12	9,14	14,17	7.46
7.	D16S539	8,14	9,14	9,11	3.01
8.	D18S51	14,14	14,15	14,15	3.01
9.	D2S1338	18,20	18,21	21,24	1.28
10.	CSF1PO	11,11	11,11	11,12	1.644
11.	PENTA-D	10,10	10,11	10,11	2
12.	TH01	6,9.3	9,9.3	7,9	1.97

13.	vWA	17,19	16,17	15,16	2.08
14.	D21S11	29,30	28,29	28,29	3.81
15.	D7S820	7,8	7,10	10,12	2.26
16.	D5S818	11,12	12,12	12,12	2.97
17.	TPOX	9,11	11,11	8,11	1.33
18.	DYS391	-	-	10	
19.	D8S1179	10,16	10,13	13,15	3.33
20.	D12S391	18,21	18,21	18,23	2.83
21.	D19S433	13,13	13,14	14,15.2	1.94
22.	FGA	20,26	21,26	21,24	3.76
23.	D22S1045	11,16	11,11	11,17	
24.	AMELOGENIN	X,X	X,X	X,Y	

Table 2 Genotype of the deceased and mother for 12 X-STR Loci.

S.No	Locus	Mother	Questioned Deceased	Father
1	DXS10103	18,19	18,18	18
2	DXS8378	11,11	10,11	10
3	DXS10101	28.2,32	32,33	33
4	DXS10134	35,38.3	36,38.3	36
5	DXS10074	17,19	15,19	15
6	DXS7132	11,13	13,14	14
7	DXS10135	27,29	25,27	25
8	DXS7423	15,16	14,15	14
9	DXS10146	26,28	25,26	25
10	DXS10079	18,19	17,19	17
11	HPRTB	13,14	14,14	14
12	DXS10148	18,26.1	18,26.1	26.1

Table 3 Genotypes of father, deceased and mother at the discrepant loci

Locus	Father	Questioned Deceased	Mother	Mutation rate	PI	Marker size range(bp)
D13S317	10,11	11,11	10,10	0.15%	1.82	193-250

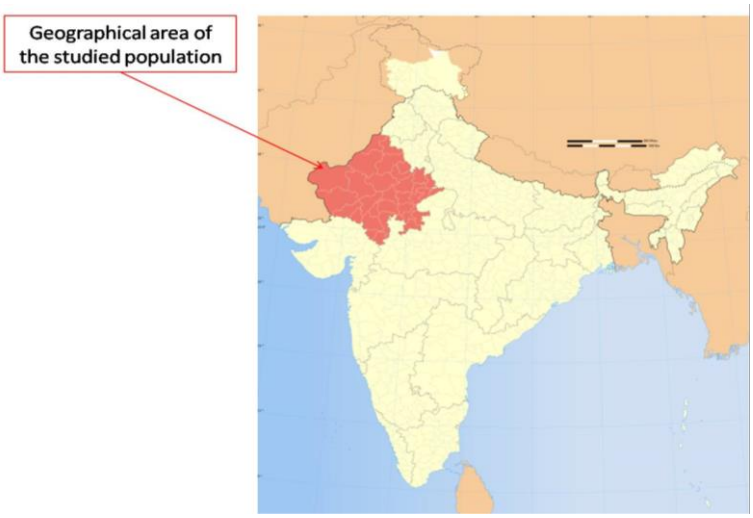

Figure 1 Geographical location of the Rajasthan, India.

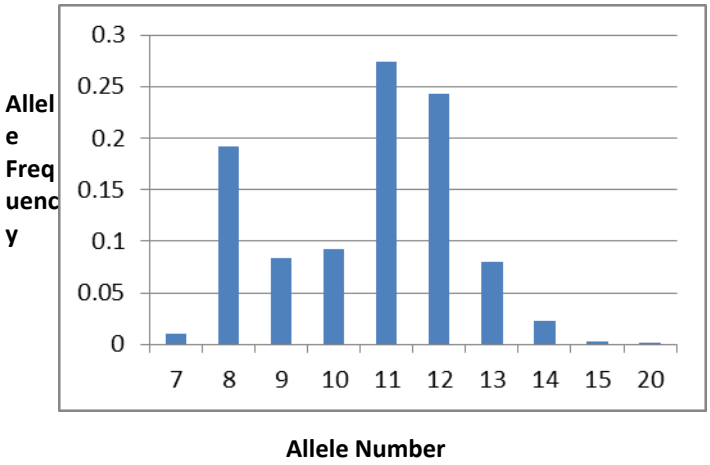

Figure 2 Allele frequency distribution at D13S317 locus in the studied population.

The expansion of one motif at the loci D13S317 might have occurred during the process of oogenesis. Combined Paternity Index (CPI) was also calculated as 3.3x107. Moreover, in cases of paternity testing when a mismatch is noticed at a single locus, supplementary analysis methods should be used to confirm the current parentage and therefore, X-STR analysis was performed in this study.

4. Conclusion

In the case of the girl child, X-STR amplification kit is required for exploration and therefore Y-STR amplification kit cannot be used to resolve the maternal mismatch in this case. The use of Y-STR markers in the exclusion of a paternity testing has been well established by Junge et al. 2006. Investigator® Argus X-12 QS Kit was used to rule out the inconsistency between child and mother at the locus D13S317. This kit amplifies 12X chromosome STR loci (DXS10103, DXS8378, DXS10101, DXS10134, DXS10074, DXS7132, DXS10135, DXS7423, DXS10146, DXS10079, HPRTB and DXS10148) which are depicted in the Table - 2.The use of 12 X-STR loci invariably increases the discrimination power. The result of the 12 X-STR loci in the mother and child was a complete match. Hence the case study highlights the usefulness of X-chromosome STR data for interpreting marginal paternity cases

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

Written informed consent was obtained for the study as per the "declaration of Helsinki"

Author's contribution

AK and RK designed the study, and the manuscript drafted by AK which was reviewed by GK and RKK. All authors reviewed and approved the final manuscript.

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