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CASE REPORT

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Multistep microsatellite mutation in the maternally transmitted locus *D13S317*: a case of maternal allele mismatch in the child

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Abstract Examination of a case of a paternity dispute with 17 autosomal short tandem repeats (STR) loci revealed a mismatch of the maternally transmitted allele at the locus *D13S317* in the questioned child. The composition of the alleles of this locus in the mother, questioned child and suspected father was 8/8, 11/11 and 8/11, respectively. The sequence analysis of the regions flanking the locus *D13S317* and peak height measurements of the paternal, maternal and child alleles at this locus excluded the possibility of null allele as a cause of the allelic mismatch inherited by the child. The results suggested expansion of the microsatellite repeat motif, TATC by three repeat units as a probable cause for the allelic mismatch in the child. This is a rare case of maternally transmitted multistep microsatellite mutation reported for the first time for this locus in the forensic DNA analysis. The mutation rate at *D13S317* locus in maternal and paternal meiosis was 0.04 and 0.14%, respectively, and overall mutation rate was 0.15%. The probability of maternity and paternity were 0.999999 and 0.999999, respectively, for all the 17 autosomal STR loci analyzed. Furthermore, the sequence of two hypervariable regions of mitochondrial DNA, HV1 and HV2 and the maternal alleles of six X chromosome STR loci in the questioned child matched completely with the mother. These results conclusively proved that the mother and suspected father are the biological parents of the questioned child.

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Introduction

Microsatellites, also known as short tandem repeats (STR), are tandem repeats of 2 to 7 bp and account for 3% of the human genome [12]. More than one million microsatellite loci are estimated to be present in the human genome and they are among the most variable types of DNA sequence in the genome [28]. DNA profiling of STR loci is a very powerful tool in parentage establishment and forensic identification. Microsatellite mutation (gain or loss of repeats in the alleles) mainly caused by replication slippage [20, 25] at one or more loci results in allelic mismatch in the questioned child and thus, complicates forensic inference. Such an allelic mismatch which is incompatible with Mendelian inheritance due to deviations in size from parental alleles may result in the exclusion of the putative father in the case of paternal allelic mismatch or in the exclusion of the biological mother in the event of maternal allelic mismatch at a single segregation of an otherwise compatible STR result. Data from other DNA markers become essential to resolve the noncongruence between parental and offspring genotypes. Most widely used markers in combination with the autosomal STRs in such aberrant situations are HV1 and HV2 hypervariable regions of mitochondrial DNA which are inherited by the offspring from the biological mother [7] and Y chromosome-derived STRs which are inherited from the biological father to resolve maternity and paternity disputes, respectively [13, 14]. In forensic literature, most of the reported allelic mismatches are confined to paternally derived alleles as mutation rate in males are several fold higher than females [3]. In the present study, we report a multistep microsatellite expansion in the maternal autosomal STR locus *D13S317* causing an allele mismatch in the child. We also

conclusively assign the maternity of the questioned child using two hypervariable regions (HV1 and HV2) of mitochondrial DNA in combination with autosomal and X chromosome STRs analysis.

Materials and methods

Samples and DNA Extraction

Blood samples of the persons were collected in sterile vials with ethylenediaminetetraacetic acid (EDTA) at the Laboratory of DNA Fingerprinting Services of Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India to establish the paternity of the child. The DNA was extracted from the samples by standard phenol/chloroform method [24]. The quantity of DNA in the samples was estimated by electrophoresis on a 0.8% agarose gel.

Polymerase chain reaction (PCR) and sequence analysis

The DNA samples were amplified for 17 autosomal STR loci using AmpF*l*STR Profiler Plus, Identifiler (Applied Biosystems, Foster City, USA), and PowerPlex (Promega Corporation, Wisconsin, USA) kits as per the manufacturer's instructions and six X chromosome STR loci using published primer sequences [27, 31] as per the method therein. The mitochondrial DNA hypervariable regions HV1 and HV2 were amplified using published primer sequences [11] as per the method therein.

For sequencing analysis of the STR locus *D13S317*, a new primer pair localized largely outside the common amplicons was designed according to the GenBank sequence information (G09017). The forward and reverse primer sequence information is as follows:

1. Forward primer: 5′-TGGGATGGGTTGCTGGACA TGG-3′
2. Reverse primer: 5′-AAAACATATTCAGAGAGCTT GAA-3′

The PCR amplification was performed in a 25-μl reaction volume containing 50-ng DNA, 200-μM dNTPs, 6 pmol each primer, 2.5-U AmpliTaq Gold (Applied Biosystems) and 1× PCR buffer with 1.5-mM $MgCl_2$. Thermal cycling conditions were 95°C for 10 min and then 27 cycles of 94°C for 30 s, 60°C for 1.25 min, 72°C for 30 s and 72°C for 6 min final extension. To determine whether the child is a genuine homozygote at *D13S317* or an ostensible homozygote as a result of loss of an allele, the peak heights of the alleles at *D13S317* in the questioned child, mother and father were measured in relation to the internal locus (*TPOX*), at which all the three were homozygous. All the amplification reactions were performed on an ABI GeneAmp PCR System 9700.

GeneScan and genotyping

All the PCR amplicons for STR analysis were run on the ABI 3100 Automated Genetic Analyzer and analysis was carried out using GeneScan and Genotyper software.

Table 1 Genotype of the mother, the questioned child and the suspected father for autosomal STR loci and maternity and paternity indices

S. No.	Locus	Mother	Questioned child	Suspected father	Maternity index	Paternity index
1	*Penta E*	14, 16	14, 15	11, 15	31.25	8.47
2	*Penta D*	9, 11	11, 12	10, 12	1.94	6.49
3	*D8S1179*	10, 16	15, 16	12, 15	8.20	3.55
4	*D21S11*	27, 29	27, 28	28, 29	27.78	3.29
5	*D7S820*	10, 11	10, 12	11, 12	1.92	3.31
6	*CSF1PO*	9, 12	11, 12	10, 11	1.05	2.02
7	*D3S1358*	15, 18	16, 18	15, 16	8.77	2.27
8	*THO1*	6, 9.3	6, 6	6, 7	1.48	1.48
9	*D13S317*	8, 8	11[a], 11	8, 11	1.92	1.92
10	*D16S539*	13, 13	13, 13	12, 13	7.87	3.94
11	*D2S1338*	17, 19	19, 20	20, 20	1.30	1.86
12	*D19S433*	13, 13	13, 15	12, 15	1.18	1.63
13	*VWA*	17, 18	16, 17	15, 16	2.03	2.65
14	*TPOX*	8, 8	8, 8	8, 8	3.94	3.94
15	*D18S51*	15, 16	13, 16	13, 14	3.12	4.80
16	*D5S818*	13, 13	11, 13	11, 11	3.16	1.28
17	*FGA*	20, 23	20, 23	21, 23	5.05	4.17
	Amelogenin	X, X	X, Y	X, Y		

[a]The mutated allele showing mismatch with the mother

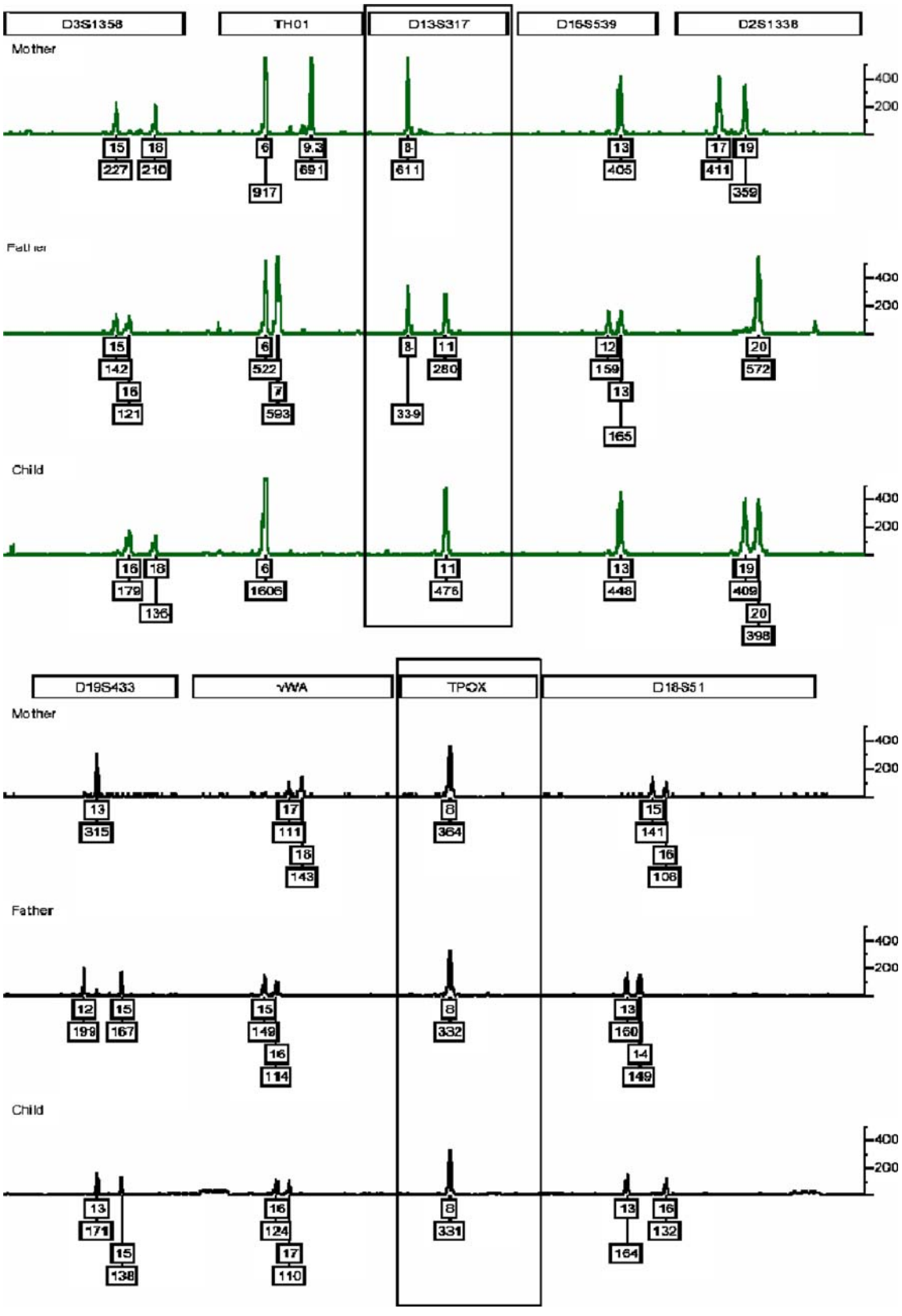


Fig. 1 Electropherogram of genotypes with peak heights of the mother, the questioned child and the suspected father at test locus *D13S317* with internal control locus *TPOX* (shown in *boxes*)

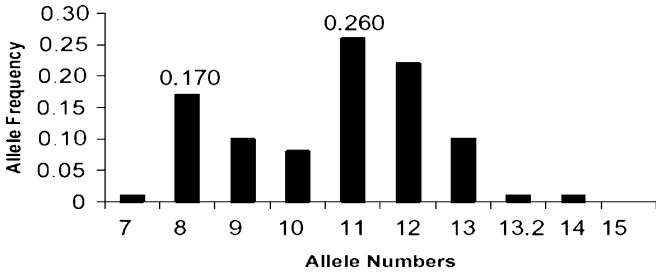


Fig. 2 Allele frequency distribution at *D13S317* locus in Indian population from which the samples were derived for the study (*N*=114)

Sequencing of *D13S317* alleles and HV1 and HV2 regions of mitochondria

The PCR allelic products of *D13S317* locus were purified on a 6% polyacrylamide gel electrophoresis (PAGE). The DNA was eluted from the gel with elution buffer (0.5 M ammonium acetate, 1-mM EDTA, pH 8.0) and the DNA was precipitated in 100% ethanol. The PCR products of HV1 and HV2 regions of mitochondria were purified by treating with 1 U of shrimp alkaline phosphatase (MBI Fermentas, USA) and 2 U of exonuclease I (NEB, USA) at 37°C for 15 min and at 80°C for 15 min to inactivate the enzyme. Prior to sequencing, the purified products were quantified by electrophoresis on a 2% agarose gel. Sequencing PCR was performed on 50-ng DNA of each of the purified products using Big-Dye Terminator (Applied Biosystems, Foster City, USA) kit as per the manufacturer's instructions using forward primers of respective loci for HV1 and HV2 mitochondrial regions [11] and using forward and reverse primers for *D13S317* locus. After sequencing PCR, the PCR products were precipitated in 100% ethanol followed by 70% ethanol wash. The purified products were run on an ABI 3100 Automated Genetic Analyzer (Applied Biosystems, Foster City, USA) and the sequence analysis was carried out using sequencing analysis software.

Statistical analysis

The maternity and paternity indices and probabilities of maternity and paternity of the mother, suspected father and questioned child were calculated using the method on the

Forward sequence of D13S317 locus in questioned child

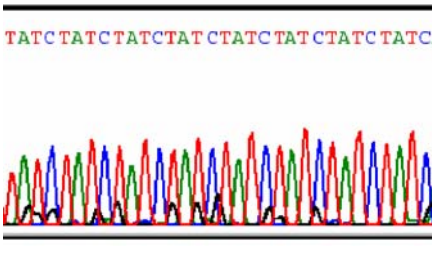
GCCT**ACAGAAGTCTGGGATGTGGA**GGAGAGTTCATTTCTTTAGTGGGCATCCGTGA
CTCTCTGGACTCTGACCCATCTAACGCCTATCTGTATTTACAAATACATTATG*TATCT*
*ATCTATCTATCTATCTATCTATCTATCTATCTATCTATC*AATCATCTATCTATCT**TTCTGTC**
TGTCTTTTTGGGCTGCCTATGGCTCAACCCAAGTTGAAGGAGGAGATTTGACCAAC
AATTCAAGCTCTCTGAATATGTTTTANNNANNNNNNNN

Reverse sequence of D13S317 locus in questioned child

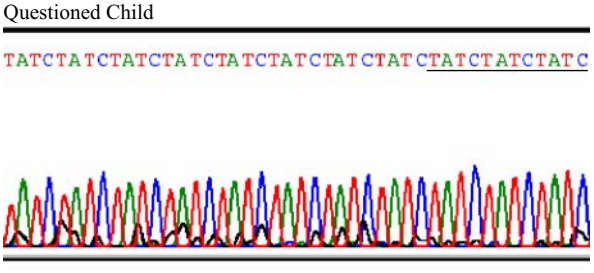
GTTGAGCCATAGGCA**GCCCAAAAAGACAGAC**AGAAAGATAGATAGATGATT*GATA*
*GATAGATAGATAGATAGATAGATAGATAGATAGATAGATA*CATAATGTATTTGTAAATAC
AGATAGGCGTTAGATGGGTCAGAGTCCAGAGAGTCACGGATGCCCACTAAAGAAAT
GAACTCTCC**TCCACATCCCAGACTTCTGT**GATACCATGTCCAGCAACCCATCCCAA
NNATNANNNNNNNNNGGTCNNGCNGNNNGNNATNGCGCTNCCN

A

Mother



Questioned Child



B

Fig. 3 **a** Forward and reverse sequences of *D13S317* locus with flanking regions in the questioned child. GDB PCR primer sequence is in *bold* letters and Promega Powerplex 16 kit primers sequence is underlined [16]. The STR regions are shown in *italics*. **b** The expansion of micro-satellite repeat motifs in the questioned child is underlined in electropherogram.

basis of Bayesian mathematics [23]. The allele frequency of the Indian population from which the samples have been derived (unpublished data) was used to calculate the maternity and paternity indices. The likelihood ratio of paternity for *D13S317* locus was calculated using the statistical method described by [4].

Results and discussion

The initial analysis of the DNA from the mother, the suspected father and the questioned child with 17 autosomal STR loci showed a mismatch of one maternal allele at *D13S317* locus in the questioned child (Table 1). The alleles for the *D13S317* locus in the mother, the questioned child and the suspected father were 8/8, 11/11 and 8/11, respectively (Fig. 1). The frequency of alleles 8 and 11 in the Indian population from which the samples were derived for the study were 0.170 and 0.260, respectively (Fig. 2). The allele 11 showed the highest frequency. If the mother and the suspected father were the biological parents of the questioned child, the expected alleles of the child would be 8/11. As the mother/child mismatch was found with opposite homozygosity and the allele differing in three repeats, two likely possibilities were considered: (1) Virtual opposite homozygosity can be caused by dropout of the allele 8 in the questioned child due to SNPs in the primer binding region. Sequencing those sites and construction of alternate primers would elucidate such cases as has been investigated by [10]. In a recent study, it has been reported that in more than 80% of the cases, G to A transition in the reverse binding region results in allelic dropout [9]. (2) An alternate possibility assumes the existence of a real null allele caused by a sequence deletion. To check the former possibility, the primers were designed for the sequences located outside the ABI, Promega and GDB primer binding sequences all of which amplified only allele 11 in the questioned child (Fig. 3). Furthermore, the sequence analyses using the newly designed primers showed complete forward and reverse primer-binding regions of GDB primers of *D13S317* locus in the mother, the questioned child and the father genotypes. These results excluded the possibility of sequence variation or presence of SNPs in the primer-binding region as a cause of allele dropout in the questioned child. The alternate possibility that the null allele has resulted due to sequence deletion was examined by comparing the peak heights of the alleles of the questioned child, mother and suspected father at *D13S317* locus in relation to the internal homozygote locus (*TPOX*) as control (Fig. 1). The allele 11 in the questioned child showed a peak height almost twice that of the heterozygous father excluding the possibility of a null allele [19] (Table 3). The other possibility that the mother under study is not the biological mother of the questioned child is unlikely as at least two [22] or three [8] independent exclusions are required to demonstrate the biological parenthood of the child. The maternity and paternity indices were calculated for all 17 autosomal STR loci (Table 1) and probabilities of maternity and paternity were 0.999999 and 0.999999, respectively, indicating the high probability of the mother and father being the biological parents of the questioned child. The likelihood ratio of paternity for the mutated locus *D13S317* was 4.5×10^{-5} and this value is comparable with the other case of microsatellite mutation [4]. Hence, we invoked the possibility of mutation in the microsatellite motif of the mismatched allele and we sequenced the alleles of the STR locus *D13S317*. The forward sequence of the child showed $(TATC)_{11}$ allele, whereas, the mother harboured the $(TATC)_8$ allele and the father showed a heterozygous $(TATC)_8/(TATC)_{11}$ alleles, and conversely, the reverse sequence showed $(GATA)_{11}$, $(GATA)_8$ and $(GATA)_8/(GATA)_{11}$ alleles for the questioned child, mother and

Table 2 Genotype of the mother and the questioned child for six X chromosome STR loci

S. No.	Locus	Mother	Questioned child
1	*GATA172D05*	10, 11	10
2	*HPRTB*	11.2, 12.2	12.2
3	*DXS8377*	46, 49	46
4	*DXS101*	25, 25	25
5	*HuMARA*	16, 18	16
6	*DXS7423*	13.2, 13.2	13.2

Table 3 Ratio of peak heights of the alleles of the questioned child, the mother and the suspected father at *D13S317* locus in relation to the internal homozygote locus (TPOX) as control

Locus *D13S317*	Genotypes	Allele 8	Allele 11
Mother	Homozygous	1.0	–
Father	Heterozygous	0.55	0.58
Child	Homozygous	–	1.0
Locus *TPOX*	Genotypes	Allele 8	
Mother	Homozygous	1.1	
Father	Homozygous	1.0	
Child	Homozygous	1.0	

Table 4 Distribution of age of mothers and fathers at the time of conception

Age at conception (years)	Number of mothers (%)	Number of fathers (%)
14–19	78 (15.3)	62 (12.2)
20–25	164 (32.2)	64 (12.5)
26–31	163 (32.0)	84 (16.5)
32–37	64 (12.5)	98 (19.2)
37–42	37 (7.3)	96 (18.8)
43–48	4 (0.7)	43 (8.4)
49–54	–	37 (7.2)
55–60	–	7 (1.4)
61–66	–	5 (1.0)
67–72	–	8 (1.6)
73–78	–	4 (0.8)
79–84	–	2 (0.4)

father (Supplementary Fig. 1). The sequence analysis revealed a multistep mutation in the microsatellite 5′–3′ motif (TATC) of D13S317, which might have occurred during maternal meiosis due to slippage of DNA polymerase during DNA replication [20, 25]. This is probably a rare case of maternally transmitted multistep microsatellite mutation at this locus as we have not come across such mutations at this locus in forensic DNA analyses in published literature. The previous studies show that single-step mutations account for ~90% of STR mutation events, followed by double-step mutations and a very limited number of multistep mutations [3]. The majority of mutations were observed at compound microsatellites and the ratio of expansion of repeats to contraction of repeats was about 4:1 [17]; that of [15] was 10:4. However, in both of the studies, differences were not significant and sample size was small. The threshold allele size is 4 for tetra and pentanucleotide repeats for slippage mutation, which ranges from 10^{-6} to 10^{-3} for 5 to 19 tetra repeat motif and 10^{-7} to 10^{-4} for 5 to 14 penta repeat motif [18]. Mutation of step size 1 is 65%, step size 2 is 23% and step size greater than 2 is 12% [30]. In the present study, the maternal allele seems to mutate at higher frequency. The higher frequency of alleles with 11 tetranucleotide repeat motifs at this locus in the population studied supports this observation (Fig. 2). The multistep mutation in the homogeneous track of tetranucleotide repeats observed in the present study is consistent with the previous reports, which has shown strong correlation of higher mutation rate with the long perfect repeat motifs [3]. In paternity testing, the mutation rate observed for STR locus *D13S317* in maternal meiosis is several fold lower (0.04%) as compared to paternal allele (0.14%) and overall mutation rate (0.15%) http://www.cstl.nist.gov/strbase/mutation.htm). This is because of relatively fewer numbers of meiotic divisions during oogenesis as compared to spermatogenesis assuming that most mutations are replication dependent [3, 6]. In our laboratory, we have analysed 510 paternity cases and observed four parent–child mismatches out of which one was maternal (reported in the present study) and three were paternal (unpublished), yielding an overall mutation rate of 7.85×10^{-3}. The age distribution of mothers and fathers at the time of conception is shown in Table 4 [21]. [3] have reported a ratio of 17:3 of paternal vs maternal mutants. [29] have also observed ~5:1 to 6:1 ratios in Centre d'Etude du Polymorphisme Humain (CEPH) reference families. Similar observations have also been made in other species in which higher rate of mutations for males have been documented [5, 26]. Hence, it is not surprising that there are fewer reports on microsatellite variations involving maternal alleles in forensic analysis.

Furthermore, in parentage assignment particularly in paternity testing, whenever a single locus mismatch is observed, it is always suggested to do additional analysis to confirm the parentage (American Association of Blood Bank (AABB), http://www.aabb.org). Therefore, we analyzed sequences of HV1 and HV2 regions of mitochondria (Supplementary Fig. 2) and X chromosome STR loci of the questioned child and mother (Table 2). The maternal X chromosome STR alleles and the sequences of HV1 and HV2 regions of mitochondria in the questioned child matched with those of the mother. However, there still remains a possibility that the biological mother, her sister and any of her other maternal relatives may have similar alleles of X chromosome STR loci and sequences of HV1 and HV2 regions of mitochondria. However, as per the case history, the child is born by sexual intercourse of the suspected father with the mother; therefore, the possibility of any other sexual relationships can be excluded. The study conclusively proved that the mismatch of the alleles of *D13S317* locus in the child with the mother is due to mutation in the microsatellite motif, and the mother and the suspected father are the biological parents of the child.

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