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CASE REPORT

Inference of maternal uniparental disomy of the entire chromosome 2 from a paternity test

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Abstract

Atypical situations arise during the constant resolution of paternity cases, which constitute challenges requiring additional genetic systems and non-standard methods. We report a paternity case presenting three alleged father (AF)-child incompatibilities for the markers TPOX, D2S441, and the indel locus B02 (11/11 vs 8/8; 14/14 vs 10/10; 2/2 vs1/1, respectively). Considering the presence of mutations/null alleles, the residual paternity indexes (PI) obtained with 23 autosomal short tandem repeats (STRs) and 38 indels suggest that the AF is the father (PI = 1.94e+011). Although the presence of few incompatibilities also could imply paternity of the AF brother, this hypothesis was less probable (PI = 3.20e+9) (W = 98.4 vs 1.6%, respectively). The inclusion of 23 Y-STR loci confirmed the paternity relationship in this case (global PI = 6.08e+15). However, the two multistep STRs and one indel incompatibilities allow discarding the mutation possibility. On the other hand, the confirmation of the homozygous STR genotypes with two different human identification kits and the low probability to find three null alleles (3.10e-8) allow rejecting the null allele presence hypothesis. Conversely, the child's homozygous genotype for maternal alleles in four markers located in the p and q arms of the chromosome 2 (TPOX, D2S441, D2S1338, and B02) suggests that maternal uniparental isodisomy better explains the relationship despite the presence of three paternal incompatibilities. In brief, when multiple incompatibilities are observed in paternity testing, the chromosomal location of the excluding loci and the use of additional genetic systems can be crucial to get confident kinship conclusions.

Keywords Paternity tests · Uniparental isodisomy · Paternity index · Indels · STRs · Human identification

Introduction

DNA analysis with short tandem repeat (STR) loci presently constitutes the main human identification (HID) tool all around the world [1]. However, replication and disjunction inaccuracies along with technical pitfalls to analyze the human genome can modify the well-known Mendelian inheritance pattern, which complicates the interpretation to establish kinship biological relationships [2]. For instance, the relative high mutation rate of the STR loci is frequently responsible of paternity test exclusions. However, knowledge of biological processes causing STR mutations, such as the replication slippage framed into the stepwise mutation model (SMM) [3], allows recognizing and interpreting these findings [4, 5]. Among the technical pitfalls during the HID process, mutations in the primer annealing site can prohibit the PCR amplification of some alleles, also known as null alleles [2]. An alleged father carrying null alleles in HID markers will be detected as a false homozygous, and he could be excluded in a paternity test when he passes on the null allele to his child, who will appear as homozygous for the maternal allele.

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Similar to the incompatibilities by mutation, statistical approaches have been implemented to interpret the null allele presence in paternity tests [6]. However, some atypical situations arise during the continuous resolution of paternity cases, which constitute challenges that require the inclusion of additional genetic systems and non-traditional interpretation. In this work, we report one paternity case where a deeper genetic and statistical analysis was necessary to explain the paternal relationship despite the presence of three father-child incompatibilities, which allowed suggesting a maternal uniparental isodisomy for the chromosome 2.

Material and methods

DNA was extracted using the DNA IQ system kit (Promega Corp). Genotypes were obtained for a total of 24 STR loci included in the Powerplex® Fusion and/or Globalfiler systems, namely D3S1358, D1S1656, D2S441, D10S1248, D13S317, PENTA E, D16S539, D18S51, D2S1338, CSF1PO, PENTA D, TH01, vWA, D21S11, D7S820, D5S818, TPOX, DYS391, D8S1179, D12S391, D19S433, FGA, D22S1045, and SE33, plus amelogenin. Due to the presence of two incompatibilities (TPOX, D2S441), the PowerplexY-23 system was analyzed in the father and child including the following Y-STRs: DYS19, DYS389I, DYS389II, DYS390, DYS391, DYS392, DYS393, DYS385a/b, DYS439, DYS437, DYS456, DYS635, DYS438, GATA-H4, DYS448, DYS481, DYS549, DYS553, DYS643, DYS458, DYS570, and DYS576. We followed the amplification and capillary electrophoresis conditions recommended by the suppliers, using the corresponding allelic ladders. For the genotyping process, the softwares GeneMapper v3.2 (Applied Biosystems, Foster City, CA) and GeneMapper® ID-X v1.4 (Thermo Fisher Scientific) were used in the ABI Prism 3130 and 3500 Genetic Analyzers, respectively. For deeper analysis, the genotype for 38 autosomal HID indels was obtained according to the protocol described by Pereira et al. (2009) [7]. Alleged father and mother signed a written informed consent authorizing the publication of this case; personal data will be preserved at all time.

Paternity indexes (PI) were computed with the Familias 3.0 software [8]. For this purpose, we used allele frequencies of population studies in Mexico reporting forensic parameters for both Powerplex® Fusion and Globalfiler kits [9], and for the 38 HID-indel system [10], respectively. In the software Familias 3.0, the mutation probability was evaluated only in two STR loci (TPOX and D2S441) by means of the SMM (unstationary) with default parameters (range 0.1; rate 21e −006) and an overall mutation rate of 0.005. Similarly, the null allele probability used the minimum allele frequency (5/2N) for estimations. The paternity indexes (PI) were estimated from the comparison of probabilities for three hypothesis: (1) Alleged father (AF) is the father of the child, (2) a random man is the father of the child, (3) A brother of the AF is the father of the child. Equal prior probabilities (0.5) for and against paternity were assumed to calculate the respective probabilities of paternity (W). Finally, we used the YHRD tool available in this database to evaluate the kinship index based on the Y-STR haplotype (https://yhrd.org/kinship) [11].

Results

A DNA paternity test was carried out with the autosomal STR kits, which displayed two father-child incompatibilities, for TPOX (11/11 vs 8/8) and D2S441 (14/14 vs 10/10) (Table 1). However, following the International Society of Forensic Genetics (ISFG) recommendations [12], we estimated the residual PI indicating a real kinship relationship assuming the probable presence of mutations/null alleles (PI = 2.2107e+8) (Table 1). Although the presence of few incompatibilities also could be explained because the brother of the AF is the father of the child, this hypothesis was lesser probable (PI = 2.8358e+7). The biological relationship between the AF and child also was paternally corroborated with the PowerplexY-23 system (Supplementary Table S1). Although the father and child homozygosity suggests the null allele presence, amplification with different autosomal HID kits did not support this possibility. In addition, these null alleles are not listed in the STRbase of the National Institute of Standard and Technologies (http://strbase.nist.gov/NullAlleles.htm). Similarly, although multistep STR mutations are underrepresented due to the classification bias toward shorter mutations [13], two simultaneous incompatibilities would be poorly explained by mutation because they would imply three and four mutational steps, respectively [2]. Conversely, the two observed incompatibilities and the homozygous state of the child for three STRs located in the chromosome 2 (TPOX, D2S441, and D2S1338) suggest that uniparental isodisomy is the best explanation for this case. It must be noticed that the child shares one allele with his mother for every locus (Table 1). In order to confirm this hypothesis, we obtained the genotype for the 38 HID indel systems (Supplementary Table S2). Interestingly, the alleged father-child incompatibilities displayed one exclusion in the unique locus of this genetic system located in the chromosome 2 (B02 2/2 vs. 1/1, respectively). Once more, the PI of the AF was larger than those of the AF brother hypothesis (PI = 874.6 vs 112.9, respectively), and the child was homozygous for one maternal allele, supporting the maternal uniparental isodisomy hypothesis for this case.

Based on all the 61 autosomal loci analyzed herein, we contrasted the random man versus AF and AF brother hypotheses, which supported—again—that AF is the father of the child (PI = 1.94e+11 vs. 3.20e+09, respectively). In posterior probability (W), these values represent 98.4% for the AF

Table 1 Genotype for 23 autosomal STRs obtained with the Powerplex Fusion and Globalfiler kits of the pedigree with probable maternal uniparental disomy in the chromosome 2

Locus	Alleged father (AF)	Child	Mother	AF-child similarity	AF paternity index (PI)[b]	AF brother paternity index (PI)[c]
D3S1358	16,17	15,17	15,15	15	3.51759324	2.25879662
D1S1656	13,16	15,16	15,16.3	16	2.32126277	1.66063138
D2S441[a]	10,10	*14,14*[a]	11,14	Exclusion	*0.03277687*	0.51401682
D10S1248	13,14	12,14	12,13	14	1.2667849	1.13339245
D13S317	12,13	9,12	9,9	12	2.25733634	1.62866817
Penta E	14,14	11,14,15	11,11	14	11.2359551	6.11797753
D16S539	10,12	12,12	12,12	12	1.86289121	1.4314456
D18S51	15,17	15,24	15,24	15	2.84982935	1.92491468
D2S1338[a]	17,19	*19,19*[a]	19,20	19	2.20167327	1.60083664
CSF1PO	10,11	11,12	11,12	11	0.76569678	0.88284839
Penta D	12,12	10,12	9,10	12	6.99300699	3.9965035
TH01	7,8	8,9.3	6,9.3	8	7.46268657	4.23134328
VWA	16,19	16,19	16,18	19	6.57030223	3.78515112
D21S11	31.2,31.2	30,31.2	30,30	31.2	8.65800866	4.83974026
D7S820	11,11	11,11	11,11	11	3.28623069	2.14311535
D5S818	11,12	11,11	7,11	11	1.11358575	1.05679287
TPOX[a]	8,8	*11,11*[a]	11,11	Exclusion	*0.01827075*	0.50738077
D8S1179	13,14	13,13	13,13	13	1.48676777	1.24338388
D12S391	18,19	19,19	19,24	19	1.95397816	1.47698908
D19S433	13,13	13,16.2	16.2,16.2	13	5.68504832	3.34252416
FGA	20,24	20,20	20,21	20	7.06214689	4.03107345
D22S1045	15,16	16,16	15,16	16	21.2765957	11.1382979
SE33	16,26.2	16,32	18,32	16	5.8171666	3.4085833
AMEL	X,Y	X,Y	X,X	–		
				Total PI	*2.2107e+08*	*2.8358e+07*

[a] STR loci located in chromosome 2 where the child is homozygous and display two incompatibilities

[b] Alleged father is the father of the child

[c] Brother is the alleged father of the child

paternity, regarding 1.6% for the AF brother paternity (Table 2). Considering that AF is the father, because brothers share the same Y-haplotype, the AF paternity probability would be almost 100% when the Y-linked genetic evidence is added to the autosomal evidence (PI = 6.0795e+15) (Table 2). Combination of information from autosomal and Y-chromosome markers is in agreement with the ISFG recommendations [12]. Conversely, the probability to observe three null alleles was estimated in 3.099e−8 based on minimum allele frequencies reported in population studies [9, 10], and that each null allele was passed on from the father to the child (0.5^3). This negligible probability indicates that the maternal uniparental isodisomy hypothesis is more plausible in this case. Interestingly, the entire chromosome 2 probably is implied given that the incompatible loci are in p and q arms (Fig. 1).

Uniparental isodisomy cases in paternity testing have been scarcely reported in the literature, particularly for smaller

Table 2 Global paternity index obtained considering the null allele presence

	Alleged father (AF)	AF brother (hypothetical)
Autosomal PI (23 STRs *plus* 38 indels)[a]	1.9423e+11	3.2031e+09
Autosomal W (%)[b]	98.3776%	1.6224%
Y-linked PI (23 Y-STRs)	3.1301e+4	
Global PI (autosomal *plus* Y-STRs)[b]	6.0795e+15	

[a] Two exclusions detected for TPOX and D2S441 loci, and one exclusion detected for the B02 indel

[b] Prior odds equal to 0.5

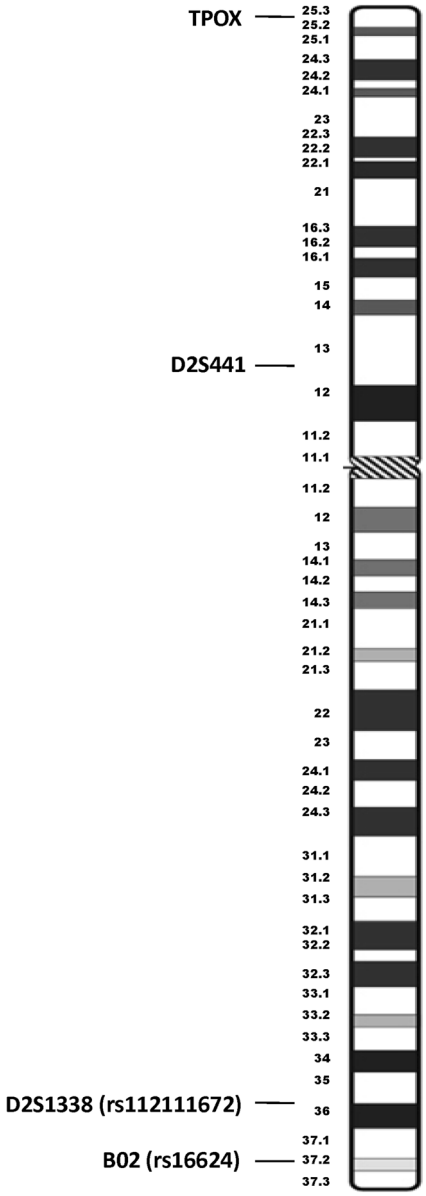

Fig. 1 Chromosomal position of the loci analyzed in this paternity test where child is homozygous for maternal alleles, suggesting the entire chromosome 2 is involved in the maternal uniparental isodisomy (MUPD)

chromosomes, such as the 6 [14], 16 [15], and 21 [16]. To our knowledge, for the chromosome 2, only one partial maternal uniparental isodisomy [17] and one entire paternal uniparental isodisomy [18] cases have been reported, without apparent clinical problems [19]. Unfortunately, although clinical evaluation would be recommended in this case, the family was not available for additional follow-up. In brief, the genetic evidence obtained in this paternity case confirmed a father-child relationship despite the presence of three autosomal incompatibilities. Deeper analysis of these incompatibilities involving markers located in the chromosome 2 allowed concluding a maternal uniparental isodisomy as the more plausible explanation for these results.

Compliance with ethical standards

Alleged father and mother signed a written informed consent authorizing the publication of this case; personal data will be preserved at all time.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Jobling MA, Gill P (2004) Encoded evidence: DNA in forensic analysis. Nat Rev Genet 5(10):739–751
2. Butler JM (2005) Biology of STRs: stutter products, non-template, addition, microvariants, null alleles and mutation rates, in: Forensic DNA typing: biology, technology, and genetics of STR markers, Elsevier Academic Press:p.123–144
3. Jin L, Chakraborty R (1995) Population structure, stepwise mutations, heterozygote deficiency and their implications in DNA forensics. Heredity, 74:274–285
4. Chakraborty R, Jin L, Zhong Y (1994) Paternity evaluation in cases lacking a mother and nondetectable alleles. Int J Legal Med 107: 127–131
5. Luque JA, Valverde JL (1996) Paternity evaluation in cases lacking a mother and nondetectable alleles. Int J Legal Med 108:229
6. Wagner AP, Cree S, Kalinowski ST (2006) Estimating relatedness and relationships using microsatellite loci with null alleles. Heredity 97:e336e–e3345
7. Pereira R, Phillips C, Alves C, Amorim A, Carracedo A, Gusmão L (2009) A new multiplex for human identification using insertion/deletion polymorphisms. Electrophoresis 30: 3682–3690
8. Kling D, Tillmar AO, Egeland T (2014) Familias 3—extensions and new functionality. Forensic Sci Int Genet 13:121–127
9. Ramos-González B, Aguilar-Velázquez JA, Chávez-Briones ML, Delgado-Chavarría JR, Alfaro-Lopez E, Rangel-Villalobos H (2016) Population data of 24 STRs in Mexican-Mestizo population from Monterrey, Nuevo Leon (Northeast, Mexico) based on Powerplex® Fusion and GlobalFiler® kits. Forensic Sci Int Genet 21:e15-e17
10. Martinez-Cortes G, Gusmao L, Pereira R, Salcido VH, Favela-Mendoza AF, Muñoz-Valle JF, Inclan-Sánchez A, López-Hernandez LB, Rangel-Villalobos H (2015) Genetic structure and forensic parameters of 38 Indels for human identification purposes in eight Mexican populations. Forensic Sci Int Genet 17:149–152
11. Willuweit S, Roewer L (2015) The new Y chromosome haplotype reference database. Forensic Sci Int Genet 15:43–48
12. Gjertson DW, Brenner CH, Baur MP, Carracedo A, Guidet F, Luque JA, Lessig R, Mayr WR, Pascali VL, Prinz M, Schneider PM, Morling N (2007) ISFG: recommendations on biostatistics in paternity testing. Forensic Sci Int Genet 1(3–4):223–231
13. Slooten K, Ricciardi F (2013) Estimation of mutation probabilities for autosomal STR markers. Forensic Sci Int Genet 7(3): 337–344
14. Stuhlmiller GM, Maha GC, Koester RP, Ladd MA, Mikhail FM, Hurst AC(2016) Maternal uniparental isodisomy at chromosome 6 discovered in parentage testing case. ISHI 27 (Promega) 96 (https://www.promega.com/-/media/files/products-and-services/genetic-identity/ishi-27-poster-abstracts/96-gary-stuhlmiller.pdf)
15. Bein G, Driller B, Schürmann M, Schneider PM, Kirchner H (1998) Pseudo-exclusion from paternity due to maternal uniparental isodisomy 16. Int J Legal Med 111(6):328–330

16. Mansuet-Lupo A, Henke J, Henke L, Blank C, Ernsting A, Kozlowski P, Rouger P, Van Huffel V (2009) A paternity case with three genetic incompatibilities between father and child due to maternal uniparental isodisomy 21 and a mutation at the Y chromosome. Forensic Sci Int Genet 3:141–143
17. Heide E, Heide KG, Rodewald A (2000) Maternal uniparental isodisomy (UPD) for chromosome 2 discovered by exclusion of paternity. Am J Med Genet 92(4):260–263
18. Ou X, Liu C, Chen S, Yu J, Zhang Y, Liu S, Sun H (2013) Complete paternal uniparental isodisomy for chromosome 2 revealed in a parentage testing case. Transfusion 53(6):1266–1269
19. Xiao P, Liu P, Weber JL, Papasian CJ, Recker RR, Deng HW (2006) Paternal uniparental isodisomy of the entire chromosome 3 revealed in a person with no apparent phenotypic disorders. Hum Mutat. 27(2):133–137