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How often have X- and autosomal-STRs mutations equivocal parental origin been assigned?

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ABSTRACT

Short tandem repeat markers (STRs) are widely applied in population, evolutionary, and forensic genetics, due to extensive polymorphism in the number of repetitive motifs. The primary mutational mechanism leading to changes in the length of STRs is thought to be polymerase template slippage. Mutation rates in STRs and corresponding parental assignment are usually assessed through the number of Mendelian incompatibilities observed in one-generational, parent(s)-child, pedigrees, and paternal mutations have been assumed to be preponderant over maternal ones. Notwithstanding, diploid and haplodiploid modes of genetic transmission may not allow for the unequivocal assigning of the mutation to the correct parental origin (either paternal or maternal), especially when genotyping methodologies of fragment length determination are employed. In this work, the frequency under which a mutation might be assigned to the wrong parental origin or be interpreted as having an ambiguous origin is analyzed for both diploid and haplodiploid modes of genetic transmission. Genotypic configurations were generated with Python™ programming language, considering parents-child trios for autosomal transmission, and parents-daughter trios for the X chromosomal one. One single-, one two- or one three-step mutation was simulated in each familial constellation, and the resulting genotypic configuration was analyzed regarding the parental assignment of the mutation. When considering autosomal transmission, the meiosis suffering mutation was randomly selected. Contrarily, differential analyses were performed for paternal and maternal mutations for X-chromosomal transmission. In this work, we show that the biases in the rates between paternal and maternal mutations differ for autosomal and X-chromosomal modes of transmission. In the differential analysis performed for the X-chromosomal STRs, it is possible to ascertain that the maternal and paternal meioses are subject to different biases, the latter being better estimated than the first. This work shows that simulated data, along with reliable and properly communicated real one, may be crucial for the correct modeling of biological processes, such as the mutation in STRs.

1. Introduction

Short tandem repeats (STRs) or microsatellites are highly mutating repetitive stretches of DNA of usually 2–6 base pairs. The elevated polymorphism resulting from the high mutation rate of these genetic markers makes them extremely useful in several contexts, such as forensic, evolutionary, and population genetics [1–3]. The understanding of the mutational dynamics is, thus, crucial for the quantification of the data. The polymerase template slippage is thought to be the main mechanism behind length mutations where one or several repeats – single- and multistep mutations, respectively, are gained or lost in the derived sequence [4,5]. Mutation rates are usually estimated through the simple counting of Mendelian incompatibilities in one generation pedigrees, parents-child trios or parent-child duos, comparative to the number of genetic transmissions observed. This implies, for both the autosomal and X-chromosomal modes of transmission, the possibility of

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Table 1
Rates of mutations that resulted in Mendelian incompatibilities, in which parental meiosis would be ambiguous or wrongly assigned, when either autosomal-STRs were analysed in parents-child trios or X-STR mutations were analysed in parents-daughter trios.

Autosomal mode of transmission										
Mutation change	**One-step**		**Two-steps**				**Three-steps**			
Parental origin observed	**Hidden**	**Ambiguous**	**Hidden**	**Ambiguous**		**Wrong parent (one-step)**	**Hidden**	**Ambiguous**		**Wrong parent (one- or two-steps)**
				Two-step	**One-step**			**Three-steps**	**One- or two-steps**	
Random mutation	16.5%	17.8%	11.1%	12.1%	4.7%	3.1%	7.3%	11.5%	5.1%	4.6%

X-chromosomal mode of transmission										
Mutation change	**One-step**		**Two-steps**				**Three-steps**			
Parental origin observed	**Hidden**	**Ambiguous**	**Hidden**	**Ambiguous**		**Wrong parent (one-step)**	**Hidden**	**Ambiguous**		**Wrong parent (one- or two-steps)**
				Two-step	**One-step**			**Three-steps**	**One- or two-steps**	
Maternal mutation	14.4%	17.4%	8.9%	13.6%	4.1%	–	4.9%	13.0%	5.4%	–
Paternal mutation	3.4%	15.7%	1.6%	13.3%	–	4.1%	0.7%	16.7%	–	8.2%

erroneous mutation assignment, either in the number of repeats or the parental origin, especially when genotyping methodologies of fragment length determination are used.

For all nuclear modes of genetic transmission (autosomal, X-chromosomal, and Y-chromosomal), it has been generally accepted for STRs that: i. single-step mutations are much more frequent than multistep ones [6]; ii. longer alleles are more mutable than shorter ones; iii. the paternal genetic transmission is more prone to mutation than the maternal one (with the obvious exception for the Y chromosome, with exclusive patrilineal inheritance) [7]; and iv. the paternal age is positively correlated with the occurrence of mutations [8]. To assess the strength of these assumptions, biological, reliable, and properly reported data are needed. However, simulated data is also critical for the understanding and modeling of these phenomena. In this work, we focus our attention on the assumption that paternal mutations are more common than the maternal ones, showing how the mode of transmission considered, or even the interpretation of the expert based on priors may bias this conclusion.

2. Material and methods

Genotypic configurations were generated with Python™ programming language, considering parents-child trios for autosomes, and parents-daughter trios for the X chromosome. One single-, one two-, or one three-step mutation was simulated in each familial constellation. For autosomal transmission, the meiosis suffering mutation was randomly selected, but when considering X-chromosomal transmission, differential analyses were performed for paternal and maternal mutations. For each case, 1,000,000 genotypic trios were simulated. The frequency under which a mutation might be assigned to the wrong parental origin or interpreted as having ambiguous parental origin was computed and analyzed.

3. Results and conclusions

When a single-step mutation was simulated in mother-father-child trios under the scope of autosomal transmission, 83.5% of mutations were detected (not hidden), and out of these 17.8% would be interpreted as having an ambiguous parental origin. When a two-step mutation was simulated, 88.9% of mutations were detected and 16.8% of these would be interpreted as having an ambiguous parental origin, and 3.1% would be interpreted as single-step paternal mutations (see Table 1).

When a single-step maternal mutation was simulated in mother-father-daughter trios assuming the X-chromosomal transmission, 85.6% of the mutations were detected, and 17.4% out of these would be interpreted as having ambiguous parental origin. In the case of a paternal mutation simulated, 96.6% were detected and 13.3% would be interpreted as having ambiguous parental origin (see Table 1).

The biases in the rates between paternal and maternal mutations differ for autosomal and X-chromosomal modes of transmission. For autosomal transmission, biases in the evaluation of paternal and maternal mutation rates may occur due to the expert's interpretation based on priors.

On the other hand, considering haplodiploid markers, biases associated with the different paternal and maternal modes of genetic transmission should also be considered as the level of detection of maternal and paternal mutations differs. Indeed, regardless of the interpretation of the expert, maternal hidden mutations showed to be 4.2 times more frequent than the paternal ones (in the case of single-step mutation, 5.6 for two-steps and 7 for three-steps). This can bring to the discussion the true ratio between paternal and maternal mutations. Indeed, since X chromosomal paternal mutations are more detectable than maternal ones, as shown in this work, the differential between the two rates might be overestimated.

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Conflict of interests

The authors declare no conflict of interest.

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