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Multiple mutations, covert mutations and false exclusions in paternity casework

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Abstract. The universal practice, up to now, is to make the judgement "paternity excluded" whenever there are more than some established number—such as two—of loci in which the genetic pattern, barring mutation, is inconsistent with paternity. Such a rule is founded on the implicit assumption that the probability of two mutations is vanishingly small. However, the ideal procedure would of course be to evaluate the paternity index (PI) over all loci, taking possible mutation into account. With STRs, unlike with RFLPs, a reasonably accurate mathematical model of mutation exists and hence the ideal procedure is finally possible. What happens when it is applied is somewhat surprising. Notwithstanding two or even three inconsistent loci, the posterior probability of paternity (assuming 50% prior probability) can easily be 20%. Unless the inconsistencies are particularly implausible as mutations (i.e. multiple repeat units), the posterior probability is not vanishingly small. The old rule causes bad decisions; it excludes fathers. Instead, we should compute the proper paternity index across all loci, considering the possibility of multiple mutations, and evaluate the result. The computing part is easy. The evaluation part brings a new difficulty, for it forces us to confront a question that the inaccurate policy of the past hid from view: How unlikely must paternity be in order to justify the decision "paternity excluded"? An incidental discovery is the heretofore overlooked implication that the existence of "covert mutations" imply that most STR mutation estimates from paternity studies are wrong.

Keywords: Mutation; Covert mutation; Stepwise; Paternity index; Exclusion

1. Introduction

Dealing with possible mutations in paternity casework has always been awkward. In recent years, the use of STR systems have nearly supplanted RFLPs. It is time to reconsider the outmoded policies as well. The mutation rate among STR markers appears to average about 1/400 [1–3 and unpublished data]. Assuming a 13-marker paternity test and binomial model, the expectations are shown in Table 1. Clearly, two inconsistencies is the critical case. Prima facie it supports non-paternity by a likelihood

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Table 1
Paternity inference based on counting inconsistencies

Inconsistencies	Rate among false trios	Rate among true trios	LR supporting paternity
0	1/210,000	1/1	200,000
1	1/10,000	1/49	210
2	1/1100	1/5100	1/4.7
3	1/190	1/860,000	1/4600

ratio of 4.7, which is inconclusive. This paper examines more closely the case of two inconsistencies.

2. Materials and methods

Four hundred paternity trios, half true and half false trios but all with two inconsistent loci, were generated by an accelerated Monte Carlo method. For the true trios, mutations are generated according to a modified stepwise mutation model [4], that most mutations (μ = locus-specific rate of one-step paternal mutations) are by plus or minus one repeat unit (factor by which $|s+1|$ step mutations are rarer than $|s|$ step mutations $\cong$ 20) and are paternal (factor by which maternal mutations are rarer than paternal ones $\cong$ 3.5). The PI was then computed for each of the 400 cases using the model.

3. Results

3.1. Covert mutations

Analyzing the results of the true-trio simulations revealed an obvious phenomenon which we might call "covert mutations" (Fig. 1) whose significance has not been previously noted. The fraction of mutations that are covert can be quite large–over 25% at some loci.

3.2. Two inconsistencies

As Table 1 shows, two inconsistencies is modest prima facie favoring non-paternity. Table 2 shows that taking into account the rarity of shared alleles and the plausibility as

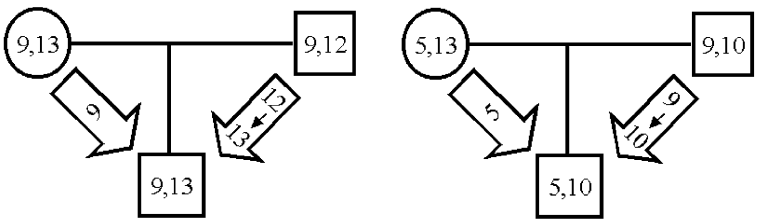

Fig. 1. Ways that a mutation can be covert.

Table 2
Distribution of PIs among simulated two inconsistency cases

x	% false trios with PI>x	% true trios with PI>x
1000	0	4.5
100	0	19
10	0.5	43
1	3	78
1/10	20	95.5
1/100	47	99.5

mutations of inconsistencies—i.e. computing the PI—somewhat distinguishes true from false trios.

4. Discussion

The significance of covert mutations is that since mutation rates are estimated from paternity studies, all published mutation rates for autosomal loci are too low by a possibly significant amount. The rate of apparent mutations is the right number to use to calculate Table 1, but for case calculations—Table 2—the covert-adjusted μ must be used. For example, in CSF1PO apparent $\mu = 3/1000$ but the true $\mu = 4/1000$. Failure to account for covert mutations thus inflates paternity indices, so is anti-conservative. There may also be an implication in evolutionary studies when a mutational clock is considered.

Taking into account the predominance of true over false trios in paternity laboratories, cases with two inconsistencies are false trios by a margin of only 2:1. Routinely excluding paternity based on two inconsistencies is thus a very poor policy. Computing a likelihood ratio is the proper course. Interpreting it, though, can be problematic when it is small.

Once the untenable policy of the past—pretending in effect that PI = 0 whenever some target number of inconsistencies are observed—is abandoned, one is confronted with making a policy based on interpreting the true PI. For example, if PI = 1/10 000, reporting "paternity excluded" may be acceptable, notwithstanding the paradox that in the symmetrically opposite case that PI = 10 000, no one would report "paternity certain". But what of less extreme cases, such as $1/100 < PI < 1/10$? Science and judicial custom collide; there is no obvious and acceptable answer. Fortunately, the situation is infrequent (Table 1).

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