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Forensic Science International: Genetics Supplement Series 1 (2008) 638–639
www.elsevier.com/locate/FSIGSS

Research article

The impact of silent alleles in kinship probability calculations

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Received 10 August 2007; accepted 7 October 2007

Abstract

A silent gene formally designates a rare (non-polymorphic, with frequency below 1%) recessive allele. Therefore, its presence can be unnoticed, even in large samples. The currently used routines in kinship expertise are based on the analysis of autosomal short tandem repeat (STR) loci, which are treated as harbouring just codominant alleles. Only when incompatible results are obtained (like apparent opposite homozygosity), the silent allele is invoked. The main purpose of this work is to quantify the impact of silent alleles in paternity testing in ''non-exclusion'' situations. We demonstrate that silent alleles can non-negligibly lower the paternity index in trios where opposite homozygosity is observed and we provide some examples in real cases.

Keywords: Silent allele; Kinship probability; Paternity index

1. Introduction

A silent gene (a preferable designation to null allele [1]) formally designates any rare (<1%) recessive allele escaping detection by the typing method employed (whatever the underlying molecular basis). The silent allele frequency constitutes therefore a purely empirical parameter, (i) for which no expected theoretical values can be calculated, (ii) that can display extensive variation across populations and (iii) between different typing methods for the same locus [2,3] and, finally, being by definition simultaneously recessive and rare, (iv) difficult to estimate accurately. In fact, an autosomal silent gene as frequent as 1% is expected to show up phenotypically only once in 10,000 random individuals and Hardy–Weinberg equilibrium tests are not sensitive enough. Even when extensive family data are available, such as a large number of mother/child pairs, incompatibilities due to apparent opposite homozygosity are extremely rare (although, in this case, upper bounds or maximum frequencies can be safely estimated).

The task of genetically evaluating a kinship likelihood can be defined as comparing the probability of the genetic evidence assuming true kinship and the probability of the same observations under the alternative (and mutually exclusive) hypothesis. Traditionally a dichotomous approach is however used, treating ''exclusions'' separately [4,5] and neglecting that an ''exclusion'' is, in fact, a result that contradicts either the formal genetic model or the hypothesis of true kinship. This paradigm has slowly being changing, due to the relatively high mutation rate of the commonly used STR loci [6] but the impact of silent genes has been considered to be of ''small effect'' [7].

In this work, we demonstrate that silent alleles can non-negligibly lower the paternity index in duos and trios and we provide some examples in real cases.

2. Materials and methods

We derived the formulas for the calculation of paternity indexes in cases for which the mother is analysed (''trios'') or not (''duos''). Due to space limitations, we do not present them here, but they are available upon request. The ratio between the PI calculated invoking a silent gene with a frequency >0, and the PI computing without it was named ''correcting factor''.

From the paternity cases analysed at our lab with both Promega and Applied Biosystems kits (involving a total of 17 STR loci), 70 true trios and 85 true duos ($PI > 10^5$) were randomly selected.

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doi:10.1016/j.fsigss.2007.10.024

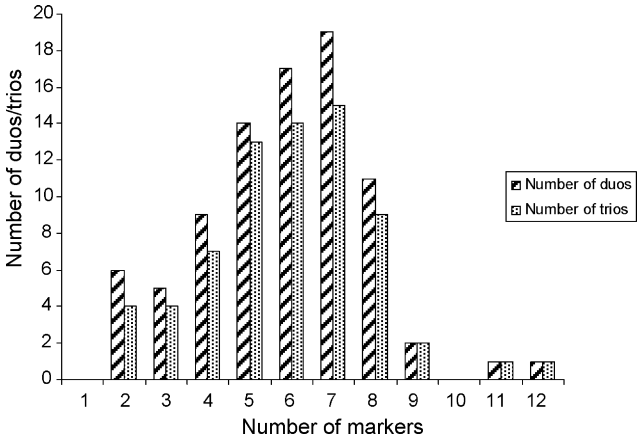

Fig. 1. Distribution of genetic constellations possibly involving a silent allele among 85 true duos and 70 true trios.

3. Results and discussion

Depending on the postulated values for the frequencies of the silent (always below 1%) and codominant (between 1% and 50%) alleles, the discrepancy between paternity indexes computed with (PIs) or without (PI) the consideration of the recessive gene varies greatly. As expected, when the codominant allele is too common (∼50%, a very unlikely situation with commonly used STRs, the effect of introducing the silent is negligible (PIs > 99% of PI). However, when facing situations in which the codominant frequency approaches the polymorphic borderline (1%), a rather usual circumstance with highly polymorphic forensic STR loci, the ratio can drop to 67%, even with modest silent allele frequencies.

Using the random sample of true duos and trios, we then estimated the frequency of occurrence of genetic constellations in which a silent gene could possibly be present (Fig. 1). It turns out that both among duos and trios no single instance of a paternity case where no correction is needed was found, whereas situations with up to 12 loci requiring correction were detected. Using a crude 'average correcting factor' of 0.83, we can predict that the consideration of a silent gene can substantially reduce the PI calculated without it in most cases, and for the extreme situation (12 loci) it can diminish it by an order of magnitude (cumulative correcting factor = 0.83^{12} = 0.107).

4. Conclusions

The assumption of the absence of silent when no incompatibility is present leads to non-negligible differences in paternity index values (systematically biased towards the prosecution hypothesis).

Since the unbiased, formally coherent, treatment of silent genes is feasible, all routine kinship probability calculations (and software packages) should consider inclusion of silent genes in the employed algorithms (even in the absence of 'exclusions') and without previous demonstration of silent genes at the locus with the typing method used.

Acknowledgements

IPATIMUP was funded by Fundação para a Ciência e Tecnologia, through POCI (Programa Operacional Ciência e Inovação 2010).

Funding source

The work was partially funded by Fundação para a Ciência e Tecnologia, through POCI (Progama Operacional Ciência e Inovação 2010). The study sponsors had no involvement in the study design; collection, analysis and interpretation of data.

Conflict of interest

None.

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