



Validation of software for calculating the likelihood ratio for parentage and kinship

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ABSTRACT

Although the likelihood ratio is a well-known statistical technique, commercial off-the-shelf (COTS) software products for its calculation are not sufficiently validated to suit general requirements for the competence of testing and calibration laboratories (EN/ISO/IEC 17025:2005 norm) *per se*. The software in question can be considered critical as it directly weighs the forensic evidence allowing judges to decide on guilt or innocence or to identify person or kin (i.e.: in mass fatalities). For these reasons, accredited laboratories shall validate likelihood ratio software in accordance with the above norm.

To validate software for calculating the likelihood ratio in parentage/kinship scenarios I assessed available vendors, chose two programs (Paternity Index and *familias*) for testing, and finally validated them using tests derived from elaboration of the available guidelines for the field of forensics, biomedicine, and software engineering. MS Excel calculation using known likelihood ratio formulas or peer-reviewed results of difficult paternity cases were used as a reference.

Using seven testing cases, it was found that both programs satisfied the requirements for basic paternity cases. However, only a combination of two software programs fulfills the criteria needed for our purpose in the whole spectrum of functions under validation with the exceptions of providing algebraic formulas in cases of mutation and/or silent allele.

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1. Introduction

Forensic laboratories utilise a number of software programs as aids in the provision of basic and advanced forensic tests in DNA laboratories: typing, printing expert reports, databasing DNA profiles, communicating with machines and networking. Quality-control and assurance in an EN/ISO/IEC 17025 accredited laboratory should govern all aspects of the laboratory work critical for customer service, software included (paragraphs 5.4.7.2 and 5.5.2). While calculating the likelihood ratio or paternity index can be done by hand [1], in more complicated cases it is a tedious task prone to human error and dedicated software is necessary. The impact of the likelihood ratio calculating software on the quality of the expert witness report is critical as the wrong calculation and data interpretation can invalidate the DNA profiling. In extreme cases it may lead to judicial error.

According to the wording of EN/ISO/IEC 17025, validation is the confirmation by examination and provision of objective evidence

that the particular requirements for a specific intended use are fulfilled (paragraph 5.4.5.1). For software, this means that computer systems must be documented and properly maintained.

COTS software like MS Excel is considered sufficiently validated if used within the designed application range. Forensic genetics specific recommendations for validation are provided in guidelines published by the Scientific Working Group on DNA Analysis Methods (SWGDM) [2] and DNA Advisory Board (DAB) Quality Assurance Standards [3].

These recommendations are not aimed primarily at software validation. Rather, they are general in nature and considered rather vague guidance by some authors [4]. Software in comparison with machines and instruments, has several specific features [5]:

- Software problems are traceable to design and development, not to manufacture.
- Even short programs can be complex due to branching-executing alternative series of commands based on differing inputs.
- Unlike hardware, software may improve with age, if new defects are not introduced during updates when seemingly insignificant

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changes in software code can create problems elsewhere in the program.

- Software failures may occur without warning.
- Thorough documentation is also needed because of the mobility of software personnel.
- Testing alone cannot verify the completeness and correctness of software. In addition to testing, a structured and documented development process is needed.

In this paper, software validation requirements and tasks are defined, based on applying the available guidelines for the field of forensics [6], biomedicine [7], and software engineering [8–10] to the current needs of our laboratory. Two likelihood ratio calculating software (Paternity Index and *familias*) programs were then chosen and subjected to validation (Fig. 1).

2. Methods

2.1. Review: why, who, what, where, and how much

Generally, validation of calculating software is done to ensure that the same accurate result is obtained each time the calculation is performed. Such software validation leads to more adequate output and greater confidence in the results.

The possibility of software error is not negligible: 7.7% of medicinal device recalls to FDA between 1992 and 1998 were attributable to software failures [5]. Although such statistics do not exist for software used for forensic purposes, similar values may be expected based on anecdotal evidence (i.e.: http://www.corbettlifescience.net/public/software/rotor-gene/history/VersionHistory_6_1_Build93.html). Generally, a successful

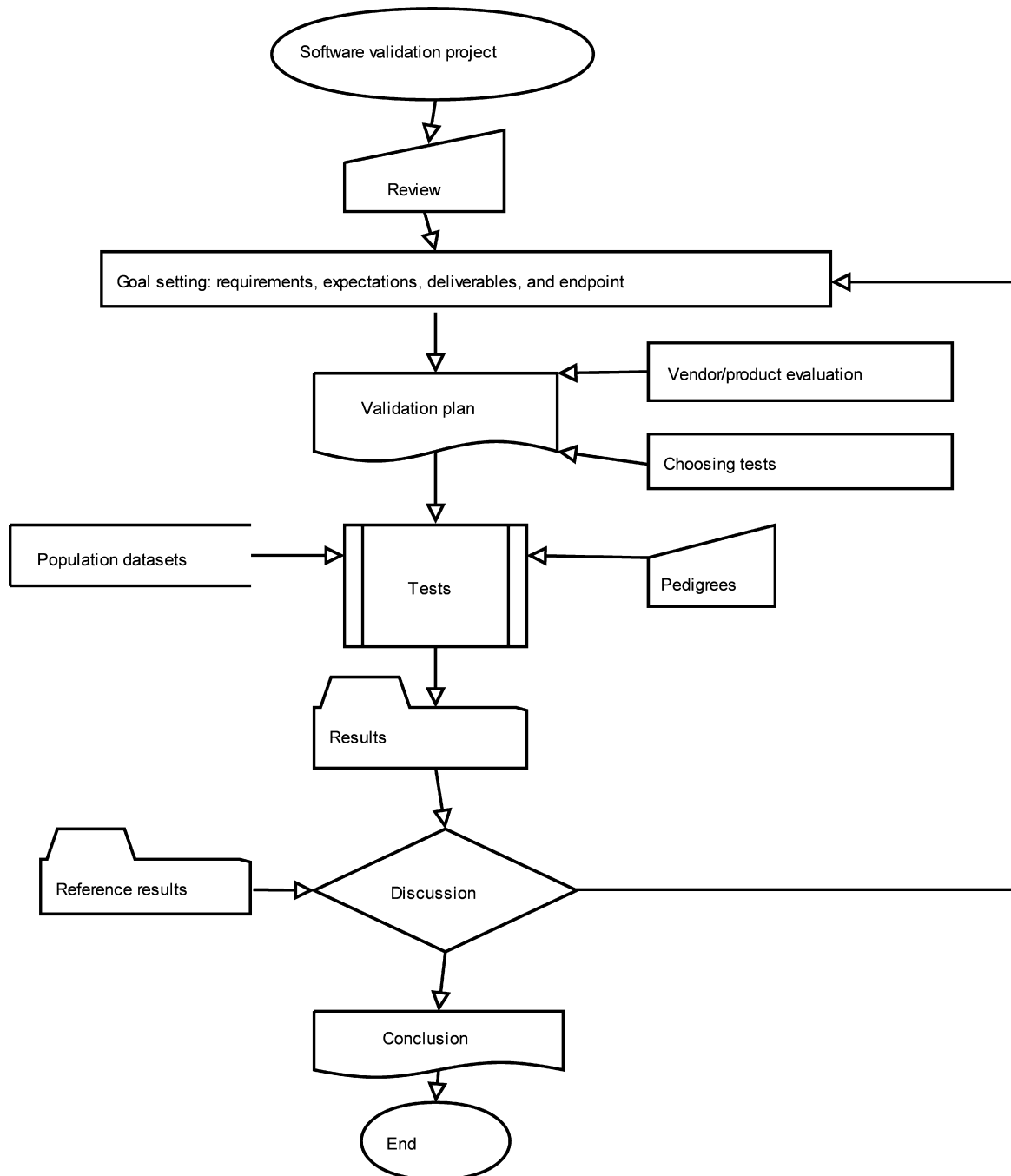


Fig. 1. Outline of software validation plan.

business model of providing unfinished software and developing it in realtime, relying on constant feedback from customers to identify bugs, costs less in the long-run.

The main responsibility for such software validation lies with the end user although some parts may be delegated to software suppliers who can more efficiently track errors that emanate from early software development stages than end users [8]. In this paper, the software is validated by the person who actually uses the software and confirms the final results.

The scope of the validation tests will be based on the intended use of the program functions, complexity and risk assessment of the software. Likelihood ratio calculating software does not reach a large number of linearly-independent paths through a program module [11] in comparison with other programs [12]. According to Good Automated Manufacturing Practises, it belongs to category GAMP4. For this reason, validation efforts resemble performance qualification of the 4Q model of software lifecycle [9] with expected specific technical outcomes relating to: mathematics, population genetics, special cases, and non-paternity [6].

Software will be tested and used in the laboratory where humidity, temperature, power feed line voltage fluctuations, dust and electromagnetic interference are within sanitary limits using a laptop Acer Aspire 5100 with a Windows XP operating system. The currently installed programs will be assessed by WinAudit 2.27 (<http://www.pxserver.com/>, data not shown).

2.2. Goal setting: requirements, expectations, deliverables, and endpoint

Based on published biostatistics recommendations [6], encountered cases to date, and expected case scenarios during testing in the population of the Czech Republic, software should be able to calculate the correct likelihood ratio using a Windows XP computer with Czech regional settings in:

- (1) basic cases (mother–child–alleged man trio);
- (2) deficiency cases (i.e.: missing mother);
- (3) kinship (i.e.: incest, monozygotic vs dizygotic twins);
- (4) complicated pedigrees (i.e.: ranging from deficiency cases with relatives to disaster victim identification),

while it should be able to incorporate:

- (5) population substructure (coancestry/kinship coefficient F_{ST} (θ));
- (6) null (silent) alleles;
- (7) mutations using at least two mutation models and provide;
- (8) housekeeping/trivial software functions (add, import, edit, and remove sample, profile, locus, allele, population, and pedigree);
- (9) algebraic notation for likelihood ratio;
- (10) simulation of the expected likelihood ratio for paternity according to input pedigree while being;
- (11) user friendly (installation and user interface following Windows standard instead of command prompt style);
- (12) priced under 2500 euros.

This is a list of the necessary software features compiled in order to be feasible, accurate, unambiguous, specific, testable, and uniquely identifiable. The list is incomplete owing to potential advances in DNA testing that cannot be predicted and will be reflected in future requirements. The first eight requirements are mandatory, while the other four ones may be modified based on vendor assessment and results of testing.

Knowing that most software errors occur around the boundary limits, the worst case testing concept (grey box testing) was

applied for validation instead of a statistically feasible number of tests. Interim deliverables are calculated numbers–likelihood ratios for different scenarios.

The universal acceptance criteria were set as likelihood ratio matches with reference (<http://dna-view.com/> [13,14]) within 1% error ($100 \times (\text{true_value} - \text{programme_value})/\text{true_value}$) while stress inputs will not damage data or disrupt system operation, and the system will recover after producing error message [15]. The end point is defined as meeting all (re)defined acceptance criteria either by one program or by a combination of programs.

2.3. Testing case 1: classical trio

To test basic functions (requirements 1, 8, 9, and 11), artificial mother–child–alleged father trio data with all possible allelic paternity situations were input into software. The results were compared to the output of MS Excel that is considered sufficiently validated by the norm. Algebraic notations for likelihood ratio were input into MS Excel using “IF” and “INDIRECT” functions (Suppl. 1).

Concomitantly, stress testing (alphabetic characters instead of numeric ones, inappropriate character length, Czech diacritics, and confusing character composition during input) was performed.

2.4. Testing case 2: motherless

To test handling of deficiency cases (requirements 2, 8, 9, and 11), likelihood ratio for missing mother case was calculated. In particular, the common error (a motherless likelihood ratio calculated the same way as the one for the trio case obtained by introducing a fictitious mother identical to the child) was checked (Suppl. 2).

2.5. Testing case 3: complicated pedigree

To test handling of complicated cases (requirements 4, 9, and 11), HLA-DQA low-resolution genotypes for a Japanese cousin case were input (Suppl. 3).

2.6. Testing case 4: mutation

To test including possibility of mutations in cases of paternity inconsistency (requirements 7, 9, and 11), handling of trio profiles: mother 12, 14; child 14, 16; alleged man 17, 18 was assessed. Since there is not consensus among biostatisticians as to which model for mutation and parameter values in paternity and kinship are the best, any reasonable and well-documented method of modifying likelihood ratio is accepted (Suppl. 4).

2.7. Testing case 5: null allele

To test incorporation of null alleles (requirements 6, 9, and 11), handling of trio profiles: mother 12, 14; child 14, -; alleged man 18, - was assessed (Suppl. 5).

2.8. Testing case 6: simulation

To test simulations of possible likelihood ratio based on paternity pedigree (requirements 7, 9, and 11), 100 simulating repeats without null alleles and mutations were performed for sixteen pedigrees [16] supplied with FBI Caucasian frequencies of CODIS loci taken from OmniPop 200.1 (<http://www.cstl.nist.gov/div831/strbase/population/OmniPop200.1.xls>).

Acceptance criteria: if graph of 16 geometrical means agrees with Ref. [16], then simulation function of validated software is accepted (Suppl. 6).

2.9. Testing case 7: kinship

To test requirements for sibship (3, 5, 9, and 11), formulas from <http://dna-view.com/sibfmla.htm> and Ayres [14] for two persons were installed and compared to outputs of Paternity Index and *familias* for full sibs, half sibs, and unrelated persons. Moreover, incorporating population substructure was tested using $F_{ST} = 0.03$ (Suppl. 7).

3. Results

3.1. Vendor/product evaluation

Three hundred and eighteen papers were found on the Web of Science (<http://apps.isiknowledge.com>) using the combination of keywords (paternity OR parentage OR kinship) AND (software OR program) in the “topic” field. From these, 13 references to likelihood ratio software were located on the Internet (Table 1) and their vendors were assessed (Table 2). Other free programs found that were too narrow in scope or aimed primarily at nonhuman population studies [17], i.e.: Cervus [18], PyPedal [19], FaMoz [20], Identity [21], Kingroup [22], MLTR [23], and PAE [24] were not included in primary vendor consideration. The same holds for programs without positive response from authors/distributors after contacting them by email (i.e.: FSS-ibd or FINEX [25]).

The vendor BJ-Diagnostik GmbH (Paternity Index) and distributor Norwegian Computing Center (*familias*) were chosen for software validation because in combination they were predicted to fulfill Requirements 1 to 12 (Table 2). These subjects were chosen despite the missing formal proof of software validation (i.e.: ITQS or TickIt) [8] during development in accordance with system of quality assurance because their competitors had no such proof. Rather, publications in peer-reviewed journals [26–28] were considered sufficient proof of scientific and programmatic consistency. Moreover, both programs use up-to-date programming language and both vendors expressed willingness to continue work on future versions. Another combination of programs, theoretically fulfilling requirements was Hugin and Calculation of the pedigree probability. However, a comparatively large manual input is required while working with Hugin [29] and development of Calculation of the pedigree probability came to standstill.

As product risk was assessed as comparatively low, just one license for the Paternity Index software will be purchased (*familias* is free) and product customization/networking are not required. The software was mature: it was successfully used for complicated cases (Paternity Index for 2004 ISFG Paper Challenge while *familias* was used for the Romanov tsar family identification [26]). User documentation and training was found to be adequate, through

manuals, tutorials and video. Any future impact on our business is low as in the worst case (complete software failure or deleterious registry change), MS Windows XP can be reinstalled on the laptop used and golden standard software DNA-View [30] can be purchased. To minimize the second worst case (software producing wrong likelihood ratio), programs can be used side by side in cases where probability of paternity reaches a value close to the judicial threshold.

For this reason, direct vendor audits or 3rd party audits were not performed and validation was centred on the seven cases.

Paternity Index v0.77 was downloaded from <http://www.paternityindex.com/>, driver WIBU-KEY v5.20b from http://www.wibu.com/download_user.php#wk, *familias* v1.8 software from <http://www.math.chalmers.se/~mostad/familias/>. Software was found virus-free by Jotti (<http://virusscan.jotti.org/>) and installed.

Paternity Index and *familias* passed all tests with the following exceptions:

3.2. Paternity Index

Major bugs or omissions (failed):

- Mutation models are confusingly documented and cannot be linked to papers referred to in the manual [37–39].
- For null allele, algebraic formula agrees with computed result; however, result is different from golden standard without sufficient documentation.
- Coancestry option is not offered.

Minor bugs (passed):

- To allow allele unobserved in the database, the whole frequency database must be modified instead of applying corrected frequency formula (i.e.: $(k + 1)/(N + 1)$ or $5/N$).
- “Force null alleles” function has no effect and Numerical results for LR equals 0. Result from “Comparison of hypotheses” is nulled when “Force null alleles” and “Recompute” is clicked.
- Population frequency data cannot be edited within the program.
- Some steps in “Save” function are superfluous (i.e.: questions: “Do you want to close this dialog?” after clicking “Close” or “Do you want to save previous scenario before loading a new one?”, appearing after restart of program), while other steps are imperfect (saving data in different folder than inside Paternity Index program folder is not fully supported).
- Communication between different parts is not smooth (so far Scenario must be saved before enabling to add DNA profiles to persons; sometimes, saved scenario cannot be open for unknown reasons).
- Calculating likelihood ratio for complicated pedigree takes significantly more time (10 times) than for *familias*.

Table 1

List of software providing likelihood ratio for parentage and kinship.

Name	Author/company, country	Contact	Reference
DNASat	Jaroslav Berent, Poland	http://www.umed.lodz.pl/ou/zms/	[31]
DNA-View	Charles Brenner, USA	http://dna-view.com/index.html	[32]
EasyDNA	Wing Kam Fung, Hong Kong	http://www.hku.hk/statistics/EasyDNA/	[33]
EasyPat	Michael Krawczak, Germany	http://www.uni-kiel.de/medinfo/mitarbeiter/krawczak/download/	
<i>familias</i>	Petter Mostad, Norway	http://www.math.chalmers.se/~mostad/familias/	[26]
GenoProof	Qualitytype, Germany	http://qualitytype.de/genoproof/index.jsp?lang=en	
Genotype	Kvant s.r.o., Slovakia	http://www.dip.sk/typo3/dip.sk/index.php?id=9&no_cache=1&L=1	
Hugin	Hugin Expert, Denmark	http://www.hugin.com/Products_Services/Products/Demo/Lite/	[29]
PatCan	Jose Antonio Riancho, Spain	jose.riancho@unican.es	[34]
Patern	Michael Krawczak, Germany	http://www.uni-kiel.de/medinfo/mitarbeiter/krawczak/download/	[35]
Paternity Index	Michael Jung, Germany	http://www.paternityindex.com/	[27]
PatPCR	Juan Antonio Luque, Spain	vestad@telepolis.com	
[Calculation of the pedigree probability]	Petr Linhart, Czech Republic	http://library.fpf.slu.cz/cgi-bin/k6	[36]

Table 2
Tabular evaluation of stated program functions against specified requirements.

Software name	Last update	Price (Euro)	Trio	Motherless	Grandparents	Complicated	Kinship	Mutation	Null allele	Simulation	Fst	Likelihood ratio formula	User friendliness	Restrictions	Extras
DNASat	2007	free	■	■				■	■		■		instructions in Polish language	database and forensic module	
DNA-View	2008	4500	■	■	■	■	■	■	■	■	■			X chromosome, Y chromosome, and mixture modules	
EasyDNA	2008	2500	■	■	■	■	■						only abridged (academic) version with Hong Kong frequencies is for free	mixture module	
EasyPat	2000	free	■	■			■								
<i>familias</i>	2006	free	■	■	■	■	■	■	■		■			generates hypotheses	
GenoProof	2008	3500	■	■	■		■	■						X and Y chromosome (partial solution), mixture, forensic modules; GeneMapper substitute	
Genotype	2008	3900	■	■	■	■	■	■	■					forensic module	
Hugin	2004	2500	■	■	■	■	■	■	■	■	■		only Lite version is for free	broad applicability	
PatCan	2003	free	■	■	■		■						described error in the calculation of likelihood ratio		
Patern	1996	free	■												
Paternity Index	2007	2000	■	■	■	■	■	■	■	■	■				
PatPCR	2003	free	■	■	■								MS Excel sheets locked for Spanish frequencies		
[Calculation of the pedigree probability]	2004	free	■	■	■	■	■						instructions in Czech language		

- Copying the generated formula is not possible and the function “Print to .pdf” yields unintelligible result. Algebraic formula could be simplified before installment of frequencies. So far, simplification requires manual transcription of monitor and sending to online program Simplify <http://www.hostsrv.com/>

- [webmab/app1/MSP/quickmath/02/pageGenerate?site=quick-math&s1=algebra&s2=simplify&s3=advanced](http://www.hostsrv.com/webmab/app1/MSP/quickmath/02/pageGenerate?site=quick-math&s1=algebra&s2=simplify&s3=advanced).
- The method of calculating LR in the case of mutation can be set independently in two places: “File – Scenario properties – Mutation” and “Calculations – Evaluate numerically – Evaluate

Table 3Tabular results for *familias* and Paternity Index software validation.

Software	Trio	Trio formula	Deficiency	Deficiency formula	Complicated	Complicated formula	Kinship	Kinship formula	Mutation	Null allele	Simulation	Population substructure	Editing of results
<i>familias</i>	■		■		■		■		■	■		■	■
Paternity Index	■	■	■	■	■	■	■	■			■		

likelihood ratio” while it is not clear which model is finally applied.

- “Force null allele” and “Recompute all” functions behave differently than stated in manual.

3.3. *familias*

Major bugs and omissions (failed):

- simulation function is not offered;
- algebraic formula is not offered.

Minor bugs (passed):

- to allow allele unobserved in the database, the whole frequency database must be modified instead of applying corrected frequency formula (i.e.: $(k + 1)/(N + 1)$ or $5/N$);
- single digit alleles must be preceded by zero (i.e.: allele 7 must be named 07) to allow application of stepwise mutation model (as is correctly stated in manual);
- mutation model data are not saved together with saving scenario;
- “Allele System” window shows just six decimal places of allele frequencies, while actually it calculates likelihood ratio using 16 decimal places;
- active windows cannot be spread over the whole monitor to fill the main *familias* window.

It is planned that yearly review of validation results (verification) will be performed by regression testing—reprocessing of data files and comparing the results with previous result unless verification needs to be performed earlier due to software upgrade [5].

4. Discussion

In this paper, the seven testing cases chosen proved to be sufficiently thorough and revealed some likelihood ratio software failures, especially in the Paternity Index software.

In contrast to laboratory methods, the duration of the preparatory phase exceeded the execution phase of validation in the case of software. ISO 17025 expectant laboratories may find timesaving the availability of pedigree data in supplementary material for evaluation of their likelihood ratio software.

There are a variety of opinions on balancing the potential software risk emanating from the limitations of the software

validation on the one hand and doing superfluous testing on the other hand. While consensus is unlikely, this paper aims to be the expressed opinion of its author with the distant objective of assisting the standardization of validation.

It may be argued that improper use of software is more frequent cause of error than software itself. However, even the best-qualified personnel can get an incorrect likelihood ratio using unvalidated software function.

5. Conclusion

The following statement is issued for the software validation: executed program and data files are loaded correctly on the hard disk. The actual computer hardware is compatible with the software. The actual version of the operating system and user interface software is compatible with the application software. The actual version of the application software works correctly for the following tested functions (Table 3):

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.fsigen.2008.11.005.

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