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A template for quality control and reporting of genetic data used in management

Phillip A. Morin[1], Karen K. Martien[1], Frederick I. Archer[1], Frank Cipriano[2], Barbara L. Taylor[1]

[1]Southwest Fisheries Science Center, National Marine Fisheries Service, La Jolla, CA, USA

[2]San Francisco State University, San Francisco, CA, USA

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Abstract

Genetic data are often critical for defining populations for management, and recent IWC policies have dictated sharing of data so that all interested parties can critically review and analyze them. Genetic data quality standards have been discussed, but guidelines have not yet been agreed to. We present a template for quality control and quality analysis (QC/QA), outlining the major steps that we apply to two of the most common types of genetic data, mitochondrial DNA sequences and microsatellite genotypes. These steps can serve both as guides to conservation geneticists, and as an initial protocol to be used by managers and others to evaluate genetics studies to determine whether they may hold up against legal and scientific challenges.

Introduction

Genetics studies are playing a substantial role in delimiting units to conserve in marine animals. These decisions in turn affect conservation and management with significant impacts on not only the animals but also the human enterprises that depend upon the animal populations. There have recently been full or partial fisheries closures resulting from such decisions, and debates of the merits and uses of genetic data used to define conservation units (King et al. 2006, Ramey II et al. 2007). Efficient use of genetic data when sample sizes are expected to increase through time also requires planning to allow tracking of additions, changes and corrections, careful documentation of laboratory protocols to ensure that current datasets will be compatible with expected future data, and mechanisms to ensure access to the most up-to-date results by all researchers engaged in the analysis. For these reasons, the methodology used for collecting genetic data and their application in management decisions should be as transparent as possible, and methods for assessment of data quality and the results of such assessments should also be clearly described and controlled.

As a potential template for quality control and quality analysis (QC/QA), we outline the major steps that we apply to two of the most common types of genetic data, mitochondrial DNA sequences and microsatellite genotypes. Many of these steps can and should also be applied to any type of genetic data used to make management decisions. These steps can serve both as guides to conservation geneticists, and as an initial protocol to be used by managers and others to evaluate genetics studies to determine whether they may hold up against legal and scientific challenges. A summary of the steps in a genetics study, with types of quality control that can be implemented to maximize data quality and transparency, is shown in Table 1.

Establishment of the biological question is critical, as it will affect the choice and number of markers (loci) used, analytical methods, decision criteria, and interpretation of data, all of which play different roles in the detection of population structure. (Taylor & Dizon 1996, Taylor et al. 1997, Taylor & Dizon 1999, Palsboll et al. 2007, Morin et al. 2008, Morin & Dizon in press, Taylor et al. submitted). For the purposes of this paper, we will focus on the effects of data quality on the interpretation of data under the assumption that the focus of the study has been determined and appropriate markers have been selected, and that those markers include (but are not necessarily limited to) mitochondrial DNA sequences and nuclear microsatellite genotypes.

We structure the paper to follow, step-by-step, the process from receiving samples to making data available that are ready for analysis. We begin with steps to quantify the quality of the DNA, and then separately treat mtDNA sequencing and microsatellite genotyping and the relevant laboratory and data

quality checks.

Quality Control/Quality Analysis Considerations at each Step of Genetic Analysis

Step 1: Assessing sample quality prior to genetic analysis

For all genetic studies, variation in sample quality will be a consideration (e.g., degraded samples from stranded animals, non-invasively collected samples such as faeces and sloughed skin, samples degraded from long-term storage or improper handling, etc.). Few studies can claim that sample quality is equal for all samples, and that variation in quality has not affected the researchers' ability to generate accurate data. There are many publications discussing methods to assure data accuracy for samples known to be of poor quality, (e.g., Navidi et al. 1992, Taberlet et al. 1996, Morin et al. 2001, Paetkau 2003, McKelvey & Schwartz 2004), and the need to estimate error rates (Bonin et al. 2004, Broquet & Petit 2004, Morin et al. 2007b).

Sample quality variation can be quantified prior to attempting to generate genetic data, resulting in cost and time savings as well as higher quality data. Although not strictly necessary, DNA sample quality analysis prior to genetic data generation can ensure, for example, that low quality (and therefore highly error prone) samples are either removed from the study, or replicated sufficiently to ensure accuracy. This is particularly important for studies involving sample types that are very likely to be of poor quality (e.g., non-invasive and historical samples; Taberlet et al. 1996, Morin et al. 2001, Paetkau 2003, McKelvey & Schwartz 2004, Morin & McCarthy 2007), but can also be important for any study, as sample quality can vary significantly even when samples appear be of relatively high and uniform quality. Indeed, the presence of even a single poor quality sample in a small population sample can result in false inference of population structure (Morin & LeDuc 2004, Morin et al. 2007b).

For these reasons, we strongly recommend that samples be pre-screened for at least DNA concentration prior to beginning a study with nuclear markers. When samples are expected to meet a minimum threshold level of DNA (e.g., 20ng per PCR), quantification by absorbance or fluorescence spectrophotometry (e.g., Pico Green) can be rapid and inexpensive, allowing sample concentrations to be normalized to produce consistent results. When samples are expected to be of low quality or concentration, more sensitive methods such as quantitative PCR (qPCR) can provide highly accurate data on DNA concentration, and even on relative abundance of DNA at multiple fragment sizes, to optimize sample selection and data replication criteria (Morin et al. 2001, Morin et al. 2007a, Morin & McCarthy 2007).

Step 2: Data Generation

Sample controls:

To estimate error rates once data have been generated, replicated blind controls that can be used to compare genotypes generated throughout the data generation process are required, and should be specified in the initial study design. These controls serve several purposes:

1. Random sample replication to identify random and systematic errors. A subset of samples (a few percent of the total) scattered throughout the samples and genotyped/sequenced at all loci will help to identify errors that have to do with both sample handling and raw data interpretation.
2. Control samples (2-3) replicated in every genotyping experiment (PCR and electrophoresis) serve to verify alleles and normalize sizes across time, laboratories and technologies.
3. Targeted replication of samples after the majority of data are generated will allow verification of data quality and can also detect sample handling errors (e.g., reversal of a sample plate). This should involve some samples from every sample group run together, and result in ≥10% replication of the data set (in combination with the controls from (1) and (2)).

Double blind genotype scoring:

In addition to controls, genotype scoring can be prone to biases and common error types. At least 10% of microsatellite genotypes (across all loci) should be scored (blind to the original scores) by a second experienced genotyper. This serves to identify particular loci that may be difficult to score consistently, and biases in the way one genotyper interprets raw data.

Electronic capture of raw and scored genotypes:

Most genotyping now makes use of fluorescently labelled PCR products detected by automated detection systems (e.g. capillary electrophoresis), followed by automated or semi-automated allele size scoring. The data that can be captured automatically from the software include sample names, raw allele sizes, fluorescence peak heights, scored genotypes, fluorophore, run date, instrument type, capillary length, polymer, etc. When data may be compared across time or laboratories, these ancillary data can be critical for proper allele binning and data quality checking. Electronic capture of the data in a simple database (e.g., Microsoft Access) can reduce errors due to manual transcription of genotypes to spreadsheets, and has the added benefit of easily capturing all experimental results, including those that failed to be scored. Failed genotypes can be indicative of both sample and marker quality problems, so provide important information for quality analysis. An example of some of the data that can be automatically captured for storage in a database is shown in Table 2. This type of database storage of genotype data simplifies analysis of replicates and calculation of error rates, as well as facilitating more sophisticated queries of the data for QC, data analysis, and data reporting.

Allele size binning:

One of the biggest technical difficulties for microsatellites is the variability in allele size that can be introduced because of variation in chemical and physical conditions. Electrophoretic migration can be affected by both size and nucleotide composition of the alleles, plus the addition of fluorescent molecules for detection. Inferred allele size is, therefore, not always perfectly correlated with the actual size of the amplified alleles; allele sizes can differ by more or less than the size of the microsatellite repeat unit (e.g., a CA repeat can have alleles that differ on average by 1.8-2.2bp; Amos *et al.* 2007). In addition, electrophoresis is itself variable, and can cause allelic size differences of up to 7bp across time, technologies, and instruments (LaHood et al. 2002, Davison & Chiba 2003). Several methods have been introduced to facilitate normalization of alleles, but all require that controls or allelic ladders (LaHood *et al.* 2002) are included with each run to verify that alleles are correctly assigned to bins (Amos et al. 2007, Morin et al. in prep).

Step 3: Assessing sample-specific data quality

The other source of error is sample-dependent, and needs to be evaluated on a per-sample basis. Several methods can be used to investigate data quality for individual samples (Table 3), ranging from simple calculations, like the number of homozygous genotypes per individual, to more complicated analysis of the effects of individual genotypes on deviations from Hardy-Weinberg Equilibrium (HWE). Indeed, if genomic DNA quantity and/or quality is assayed, the correlation of DNA concentration (or other qualitative or quantitative quality measures) with error rates can be used to predict which samples might require additional replication or error checking to ensure correct genotypes and low error rates (Morin et al. 2001, Morin & McCarthy 2007).

With or without such DNA characterization, individual samples with unusual characteristics warrant extra scrutiny to verify genotypes and sequences, as these samples are both more likely to contain errors and more likely to bias analytical results. For microsatellite data, a simple analysis of the number or percentage of homozygous genotypes per individual can rapidly identify individuals likely to have experienced high levels of "allelic dropout" (failure to amplify one of the alleles in a heterozygote). Plotting the values indicates which samples are outliers from the general population (figure 1), so that genotypes can be replicated to correct seemingly homozygous genotypes that are due to allelic dropout. In some cases it might be better to simply exclude the samples from further analysis rather than spend the time and money to replicate a poor quality sample if exclusion doesn't significantly impact sample size in the strata or introduce bias (e.g., poor quality samples disproportionately present in one stratum).

Mitochondrial sequence data should also be carefully scrutinized for sample-specific errors. Simply calculating haplotype frequencies and the nucleotide frequency at each position across sequences can reveal anomalous data. If a sample is found to have a unique haplotype sequence (i.e., a haplotype not found in any other sample), then the trace file should be checked to ensure that all nucleotides were called correctly. If there is uncertainty about any of the nucleotides, the sequence should be replicated. This is especially true if the haplotype differs from other haplotypes by only a single nucleotide. Similarly, any nucleotide substitution that is unique to a single haplotype should be checked. Finally, unique haplotypes containing transversion substitutions should be checked and replicated.

Although it is not practical to detect and correct every error, some errors have potentially greater impact on analysis than others. One example of this is the presence of erroneous homozygous genotypes at rare

alleles. Presence of a single rare homozygous genotype in a stratum has been shown to cause significant deviations from Hardy-Weinberg equilibrium, resulting in false inference of population structure (Morin *et al.* 2007b). Jackknife analysis of genotypic data (repeated analysis with the removal of one sample at a time) can reveal which samples have the greatest effect on HWE, so that they can be re-checked to verify the genotypes (Morin *et al.* 2007b).

Finally, sample replication can include both intentional and unintentional replicates, e.g., samples included multiple times in the data generation process specifically to control for variability across sample runs, time, laboratories etc., and samples unknowingly replicated because animals were sampled multiple times or because of sample handling errors. These replications can be identified by using software that identifies genotypes that match at more loci than is typical for unrelated individuals (e.g., DropOut; McKelvey & Schwartz 2004). When no genotyping errors are present in the replicated samples, these are easy to identify because of perfect genotype matches at all loci. Genotyping errors introduce uncertainty, however, and software that identifies near matches can help to identify potential replicates to be re-checked. It is important to note that even with low error rates, the chances that replicated samples will not match at all loci increases with the number of loci. For example, an error rate of 1% per genotype, which is typical of microsatellite studies, would result in a 40% probability that the same sample genotyped twice for 20 microsatellites wouldn't match at all alleles.

Step 4: assessing data set quality

Mitochondrial DNA sequence data are rarely evaluated for error rates or types, as it is generally assumed that, especially for current data sets, sequencing technologies have advanced to the point where sequencing is routine and generally of high quality. Nevertheless, there can be systematic errors in mtDNA sequencing that should be checked and reported. Replication of a portion of the samples is important to identify random and systematic sequencing errors. In addition, a potential error that is often ignored and difficult to detect is the presence of nuclear copies of mitochondrial sequences, or NuMts (Lopez et al. 1994, Bensasson et al. 2001). NuMts are pervasive in some species (e.g. Tursiops sp; Dunshea *et al.* 2008), and can easily be mistaken for actual mitochondrial haplotypes, potentially leading to false inference of population structure or other analysis errors. Several methods have been described that can in most cases help to identify NuMts (Bensasson et al. 2001, Dunshea et al. 2008).

For microsatellite data, the use of a set of replicated controls results in an estimate of the overall, averaged error rate for the whole data set, under the assumption that the control samples reflect the quality of the overall data set. In reality, however, the control samples rarely reflect average quality. This is because controls are often chosen because they represent samples that have yielded high quantity and/or high quality DNA that won't be exhausted during the data generation period, and which will yield data that can be used for inter-experiment normalization and validation as well as estimates of error rates due to experimental factors (sample handling, variation in experimental conditions, systematic errors) and genetic marker characteristics (e.g., short-allele dominance, allelic stutter, PCR product adenylation; reviewed in van Oosterhout et al. 2004, Morin et al. 2007b).

Finally, genetic marker characteristics, especially for microsatellites, can be highly variable. Microsatellite data quality can be affected by repeat complexity, the number of alleles, the size range of alleles, tendency of microsatellite PCR products to "stutter" (van Oosterhout *et al.* 2004) or be adenylated (also called "plus-A"), and variation in experimental conditions (LaHood et al. 2002, Davison & Chiba 2003). Many papers have been published describing these issues and suggesting methods to deal with them, but every dataset differs, so it is up to individual researchers to decide which markers can be genotyped reliably and accurately. There are some analytical ways to assess marker quality, however, that can be used to decide whether markers should ultimately be included or excluded from analysis (Givens *et al.* 2007). This has been the subject of intense debate for some data sets at previous IWC meetings, and ultimately the decision to exclude a marker must be justified by objective description of marker issues (such as identification of null alleles, high failure rates, inconsistent genotypes, binning problems, etc.). Significant deviation from Hardy-Weinberg expectations within a population can be indicative of marker problems, but should not in itself be considered reason to exclude a marker from analysis. For this reason, it is imperative that researchers routinely assess and report marker quality control issues thoroughly enough to justify exclusion of data from analysis. Reasons for marker exclusion include (but are not limited to) evidence of systematic errors or unusually high error rates, high-frequency null alleles, or high frequency of PCR failure or failure to score genotypes (relative to other markers). When marker quality is questionable but not obviously poor, analysis of data with and without a marker can help to determine whether a single marker is causing a particular result.

Step 5: reporting data

For management decisions based on genetic data, transparency in analysis and data quality will be critical, as the survival of species and populations is at stake, and economic and personal impacts can be substantial. Scientific and legal challenges can be costly and delay implementation of management decisions. For these and other reasons, we advocate standards for genetic data reporting that go far beyond what is typical for academic research reporting, summarized in Table 4. Specifically, raw data need to be made available for replication of the analysis and quality evaluation by independent researchers. We do not advocate that scientists simply post all data for anyone to use as they see fit, but rather that data be made available on request, and under legally binding limits on their use by those requesting the data. This protects the scientific investment of those generating the data while creating necessary transparency for management. In addition to raw data, a thorough presentation of the quality control methods and results as discussed above will provide scientists evaluating the results with appropriate context to judge the data quality, and can be used by managers to determine whether to request additional analyses or opinions on data quality. As an example of how samples and genetic markers have been checked, and QA/QC steps documented, we have provided a summary of data QA/QC for a sperm whale genetic project currently in progress at the SWFSC (Table 5).

Table 1: Application of quality control steps in each phase of a conservation genetics study.

Project stage	Quality control	References
Study design	Determine level of differentiation that is relevant to conservation	(Moritz 1994, Taylor & Dizon 1999, Palsboll et al. 2007, Taylor et al. submitted)
	Selection of samples and genetic markers and statistical power analysis	(Taylor & Dizon 1996, Ryman & Palm 2006, Morin et al. 2007b, Narum et al. 2008)
Data generation	Marker quality check (allele binning, allelic stutter, null alleles, NuMts, etc.)	(van Oosterhout et al. 2004, Dunshea et al. 2008)
	Replication controls for estimation of error rates and detection of systematic errors	(Taberlet et al. 1996, Morin et al. 2001, Miller et al. 2002, Bonin et al. 2004, Broquet & Petit 2004, McKelvey & Schwartz 2004, Morin et al. 2007b)
	Checks for sample-specific variation in data quality	(Morin et al. 2001, Morin & LeDuc 2004, Morin et al. 2007a, Morin & McCarthy 2007)
Data presentation	Publication of raw/normalized allele sizes; Sequences in public databases; samples used in each stratum, description of sample exclusion procedures/policies	

Table 2: Some of the data captured by the software “GeneMapper” (Applied Biosystems) that can be exported from the software and stored in a database.

Sample File	Marker	Dye	Sample ID	Allele 1	Allele 2	Size 1	Size 2	height1	height2	polymer	capillary length	run_date
51485-D17_B11_003.fsa	D17	B	51485	144	214	143.52	213.99	7589	2217	pop4	50	20-Nov-06
51486-D17_C11_005.fsa	D17	B	51486	144	144	143.67	143.67	6469	6469	pop4	50	20-Nov-06
51487-D17_D11_007.fsa	D17	B	51487	144	144	143.67	143.67	7580	7580	pop4	50	20-Nov-06
51488-D17_E11_009.fsa	D17	B	51488	140	196	139.22	196.33	4070	1682	pop4	50	20-Nov-06
37775-D17_B01_003.fsa	D17	B	37775	144	144	143.67	143.67	4072	4072	pop4	50	28-Nov-06
42271-D17_F01_011.fsa	D17	B	42271			116.98	116.98	40	40	pop4	50	28-Nov-06
42273-D17_G01_013.fsa	D17	B	42273			190.9	190.9	32	32	pop4	50	28-Nov-06

Table 3: sample-dependent error checking methods

Method	**Application**	**References**
DNA quantification	Identifies samples likely to produce poor quality data (allelic dropout, spurious alleles, short-allele dominance)	(Morin et al. 2001, Morin & LeDuc 2004, Morin et al. 2007a, Morin & McCarthy 2007)
Excess homozygosity	Identifies samples with unusual (outlier) levels of homozygosity that could be due to allelic dropout.	(Taberlet et al. 1996, Miller et al. 2002, Morin & LeDuc 2004, Johnson & Haydon 2007)
Genetic identity or similarity	Identifies known and unknown sample duplicates, and types of genotyping errors found in duplicates that don't match perfectly.	(McKelvey & Schwartz 2004)
Effect on HWE (Jackknife analysis)	Jackknife analysis of microsatellite data for the effect of individual samples on significant deviations from HWE. Identifies rare homozygous genotypes and influential samples	(Morin et al. 2007b)

Table 4: Reporting of genetic and quality control data.

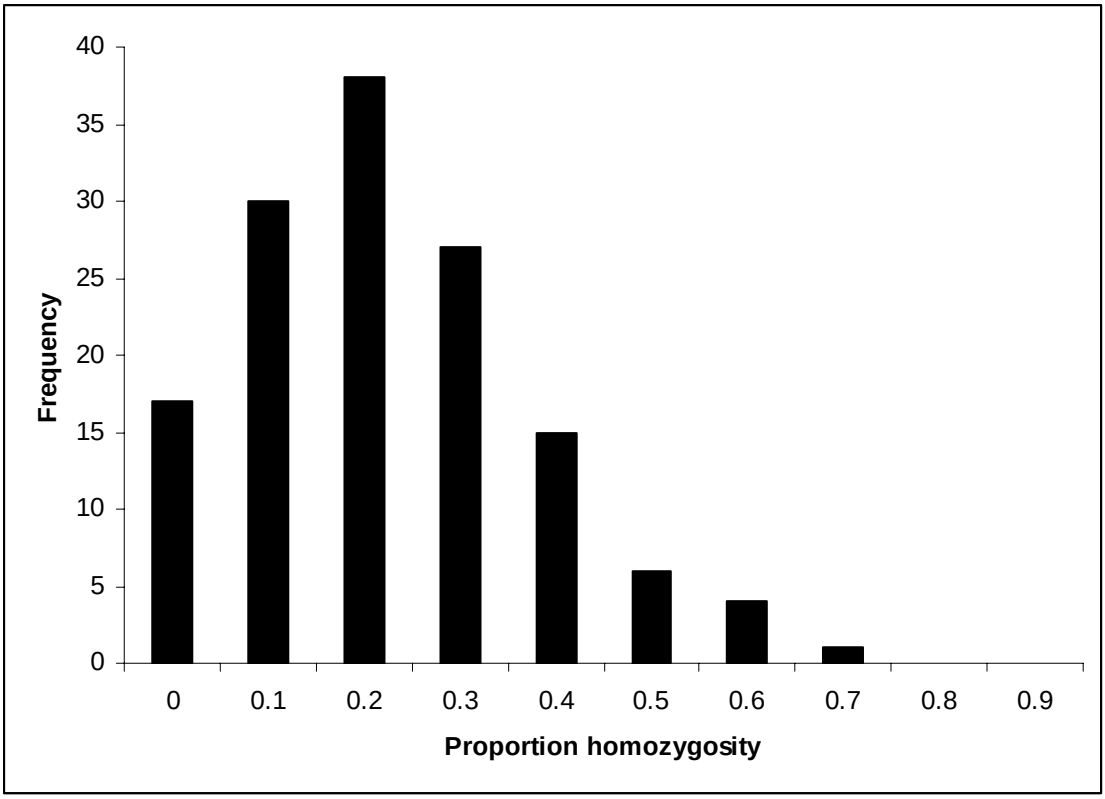
Microsatellites	
Genotype data	Uncorrected raw allele sizes, normalized allele sizes, scored genotypes
Summary statistics	Deviation from HWE, number of alleles, allele size range, repeat size, heterozygosity, results of MicroChecker or other error detection software
Error rates	Per marker and whole data set error and PCR failure rates
Analysis exclusion	Justification for exclusion of markers and samples from all or some analyses
QA/QC	Description of all quality control and quality analysis methods used and their results (if not included above, e.g. in estimating error rates)
mtDNA	
Haplotype sequences	Submitted to public sequence databases (e.g. Genbank), with haplotype designations
Summary statistics	Haplotypic diversity, number of haplotypes
Error rates	Whole data set, based on replication and double checking of novel haplotypes differing by 1 nucleotide
QA/QC	Description of all quality control and quality analysis methods used and their results (if not included above, e.g. in estimating error rates)

Table 5: Sperm whale microsatellite genotyping QC/QA summary for genotyping project with 8 microsatellite markers and 320 samples.

QC/QA step	Results	Sample No.
Checked allele binning for all experiments using control samples	Could not bin alleles for loci EV37, EV30; excluded loci from further analysis	320
Checked for genotype mismatches between replicated samples	16 out of 1849 replicated genotypes (0.9%) didn't match; most were resolved by looking at the raw data, and others were re-genotyped to verify the genotype	320
Checked for samples with ≤50% completed genotypes	28 samples had 3 or fewer completed genotypes. All had been attempted multiple times from ≥2 extractions, so they were excluded from further analysis.	292
Calculated % homozygosity for all samples	6 samples had >50% homozygosity across 6 loci; re-genotyped homozygous loci. 5 were excluded due to high failure rate and evidence of allelic dropout at several loci.	287
Used MicroChecker to analyse all remaining data	Two loci have potential null alleles, but effect is limited; all loci retained for analysis.	287
Jackknife analysis of deviations from Hardy-Weinberg equilibrium	6 samples caused two markers to deviate from HWE because of homozygous rare alleles (odds ratio > 2). 4 were re-genotyped; 2 had been previously replicated. After re-genotyping, no samples had odds ratios >2.	287
Checked for duplicate samples using program "Dropout" to find multi-locus genotype matches and near-matches among samples	Identified 27 perfect matches* across 6 loci, plus 10 potential matches (1 or two differences, usually where one genotype was homozygous for an allele for which the other individual was heterozygous). After re-genotyping homozygotes, all were confirmed to be perfect matches. (mtDNA haplotypes also verified to match). One sample of each matched set was retained and the rest were excluded from further analysis.	250
Final data set released for population structure analysis	Six microsatellite loci completed for 250 samples, quality checked for common genotyping problems, with >97% completion of genotypes for all loci, and an estimated error rate of 0.9%. Duplicate and poorest quality samples removed.	250

*most duplicated samples were from animals biopsied from the same group, so represent accidental double sampling of the same individual. At least one duplication represents genetic re-sampling identification of the same individual at different locations in the migratory route.

Figure 1: Proportion homozygosity for 138 bottlenose dolphin samples genotyped for 11 microsatellites. The proportion is the number of homozygous genotypes divided by the number of completed genotypes.



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