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Short Communication
Genetics

Accounting for the nuclear and mito genome in dairy cattle breeding—A simulation study

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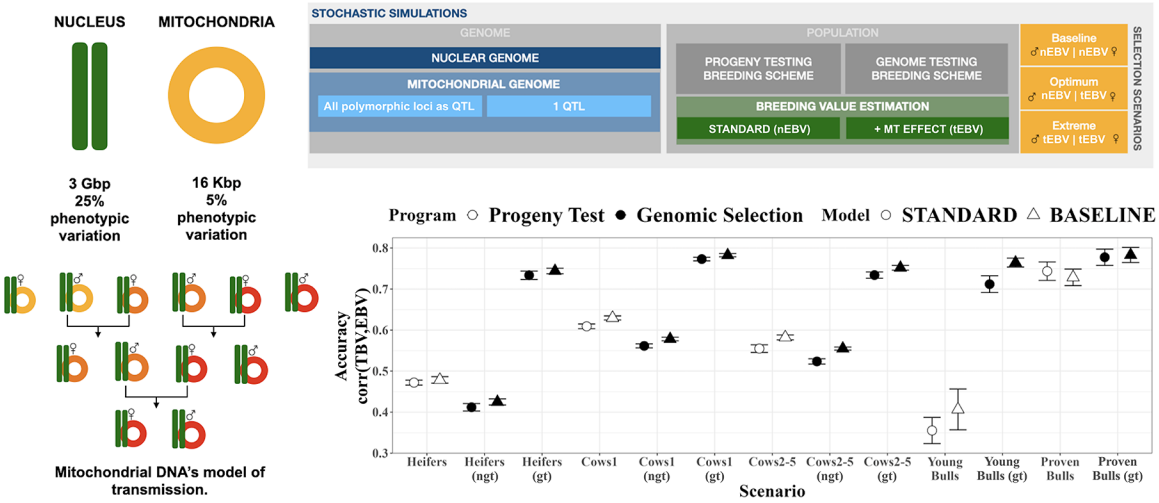
Graphical Abstract



Summary

Despite studies suggesting an association between mitochondrial DNA (mDNA) and phenotypic variation in dairy cattle, breeders have overlooked the impact of the cytoplasmic genome. To determine the effect of mDNA in dairy breeding practices, we redefine breeding value as composed of both mitochondrial and nuclear components and demonstrate how it should be used in selection, as mDNA is only transmitted by females. We used simulations to test different scenarios regarding the use of mDNA in dairy breeding. Our results suggest a benefit in accounting for mDNA. The magnitude of the benefit depends on the definition of breeding value, selection strategy, and animal category.

Highlights

- mDNA variation explains sizable phenotypic variance per nucleotide.
- mDNA variation is often ignored in most breeding operations.
- We defined breeding values with both nuclear DNA (nDNA) and mDNA components.
- Females should be selected on both nDNA and mDNA, whereas males only on nDNA.
- Our simulations show accounting for mDNA improves genetic evaluations and genetic gain.

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The list of standard abbreviations for JDSC is available at adsa.org/jdsc-abbreviations-24. Nonstandard abbreviations are available in the Notes.

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Accounting for the nuclear and mito genome in dairy cattle breeding—A simulation study

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Abstract: Mitochondria play a significant role in numerous cellular processes through proteins encoded by both the nuclear genome (nDNA) and mito genome (mDNA), and increasing evidence shows that traits of interest might be affected by mito-nuclear interactions. Whereas the variation in nDNA is influenced by mutations and recombination of parental genomes, the variation in mDNA is solely driven by mutations. In addition, mDNA is inherited in a haploid form, from the dam. Cattle populations show substantial variation in mDNA between and within breeds. Past research suggests that variation in mDNA accounts for 1% to 5% of the phenotypic variation in dairy traits. Here we simulated a dairy cattle breeding program to assess the impact of accounting for mDNA variation in pedigree-based and genome-based genetic evaluations on the accuracy of EBVs for mDNA and nDNA components. We also examined the impact of alternative definitions of breeding values on genetic gain, including nDNA and mDNA components that both affect phenotype expression, but mDNA is inherited only maternally. We found that accounting for mDNA variation increased accuracy between +0.01 and +0.03 for different categories of animals, especially for young bulls (+0.03) and females without genotype data (between +0.01 and +0.03). Different scenarios of modeling and breeding value definition affected genetic gain. The standard approach of ignoring mDNA variation achieved competitive genetic gain. Modeling but not selecting on mDNA expectedly reduced genetic gain, whereas optimal use of mDNA variation recovered the genetic gain.

Most breeding research and applications focus on how variation between and within nuclear genomes (**nDNA**) affects economically important traits. However, other genomic elements, such as mitochondrial genomes (**mDNA**), may also affect response to selection (Bell et al., 1985). In dairy cattle, ~30% of the phenotypic variation for milk yield is associated with variation in the nDNA (e.g., García-Ruiz et al., 2016), which is a molecule of ~3 Gb (e.g., Srirattana and St. John, 2017). In contrast, variation in the mDNA, which spans only ~16 kbp (e.g., Srirattana and St. John, 2017), is associated with 1% to 5% of the phenotypic variation (Bell et al., 1985; Schutz et al., 1992; Brajkovic et al., 2023). These proportions indicate that dairy breeding could benefit from accounting for mDNA variation. With the advances in SNP array technologies and the increasing accessibility of whole-genome sequencing, it will soon be possible to routinely include the variation in nDNA and mDNA in genetic evaluations and practical breeding programs. Mitochondria have critical roles in cellular processes. They generate energy, synthesize ATP, contribute to metabolic homeostasis, and so on. Their evolution from an autonomous prokaryote involved gene loss and transfer, leading to close integration with the host's nDNA (Ladoukakis and Zouros, 2017). Recent research is unveiling the extent of such integration and the effects of mito-nuclear interactions in the expression of many traits (St. John, 2021; Ward et al., 2022; Rosenberg et al., 2023). Unlike nDNA, mDNA is transmitted between generations via maternal lineages without recombination (Sato and Sato, 2013; Roger et al., 2017). This mechanism is thought to avert conflicts and safeguard the genome from selfish genes and the consequential reduction in fitness (Hastings, 1992). In addition, mDNA is thought to have a higher mutation rate compared with nDNA, which may result from the intramitochondrial environment (Ladoukakis and Zouros, 2017). Mitochondrial DNA is categorized into haplogroups, reflecting interpopulation variation. However, variation within populations (breeds) is also observed (Dorji et al., 2022). This diversity is associated with various traits. In humans, mDNA polymorphisms are associated with genetic disorders and variations in quantitative traits (Stewart and Chinnery, 2015). In dairy cows, mDNA plays a role in milk yield and composition (Bell et al., 1985; Schutz et al., 1992; Spehar et al., 2017), possibly due to the energy-intensive lactation process. All this suggests that mDNA variation should be accounted for in breeding programs. Gibson et al. (1997) demonstrated that even small contributions from mDNA to the total variation of a trait can drive differences in performance between maternal lineages. The maternal inheritance of mDNA enables tracking maternal lineages from founders via pedigrees (Schutz et al., 1992; Brajkovic et al., 2023). Spehar et al. (2017) estimated that variation between pedigree maternal lineages accounted for 2% to 3% of the phenotypic variance for milk yield in the Croatian Holstein population, whereas a genomic analysis in the same population accounted for up to 5% of the phenotypic variance (Brajkovic et al., 2023). An earlier simulation study accounting for variation between maternal lineages suggested an increase in the accuracy of EBV for cows by 0.01 when the maternal lineages accounted for 2.5% of the phenotypic variance and 0.04 when they accounted for 10% (Boettcher et al., 1996). Gibson et al., (1997) also highlighted that accounting for maternal lineages reduces the bias of EBV for cows

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because they transmit both nDNA and mDNA components of their breeding value to their offspring. Considering the limited number of studies and the ongoing questions, this work aims to expand the past research by evaluating (1) the impact of accounting for the mDNA variation on the accuracy of genetic evaluation and (2) the impact of alternative breeding value definitions (including nDNA and mDNA components) on genetic gain in a simulated dairy cattle breeding program.

A dairy cattle breeding scheme was simulated with the R package AlphaSimR (Gaynor et al., 2021). All the simulation scripts are available at https://github.com/HighlanderLab/gfortuna_mtdna_breed. We simulated nDNA and mDNA independently. To simulate nDNA chromosome haplotypes, we used the coalescent simulator MaCS (Chen et al., 2009) as implemented in AlphaSimR with the "CATTLE" parameters for 10 diploid chromosomes (to reduce computation time) with 10^8 bp each, mutation rate of 2.5×10^{-8}, recombination rate of 1×10^{-8}, and historical effective population sizes ($\mathbf{N_e}$) as described in MacLeod et al. (2013). We chose 1,000 loci per chromosome as SNP markers and another 1,000 as QTL. For the mDNA haplotypes, we considered 1 haploid chromosome with 16,202 bp, mutation rate of 2.5×10^{-7}, and no recombination. We set mDNA N_e to 1,000 in the most recent generation. We increased the historical N_e from MacLeod et al. (2013; see GitHub) to obtain over 1,000 polymorphic loci in line with literature (Xia et al., 2019; Dorji et al., 2022; Brajkovic et al., 2023). We chose all polymorphic loci (on average 1,084 across 100 replicates) in the mDNA as SNP markers. We evaluated a scenario where all or only one randomly chosen SNP were/was a QTL. Both simulated nDNA and mDNA haplotypes were randomly allocated to nuclear and mito genomes of 1,000 founding individuals. The nDNA was then passed between generations with recombination in diploid form, whereas mDNA was passed only from mothers to their progeny without recombination in haploid form. We defined one polygenic trait with a heritability of 0.3, partitioned between nDNA $\left(\sigma^2_{a_n} = 0.25\right)$ and mDNA $\left(\sigma^2_{a_m} = 0.05\right)$ components in the base population. The QTL allele substitution effects for nDNA and mDNA were sampled from a Gaussian distribution that generated targeted genetic variances and heritability after environmental variation from Gaussian distribution was added. The trait was expressed only in cows and was generated as

$$y_{ij} = \alpha_i + a_{n,j} + a_{m,j} + p_j + e_{ij}, \quad [1]$$

where y_{ij} is the phenotype of animal j in lactation i, μ_i is the population mean for lactation i (6,733 kg for first lactation and 7,440, 7,344, 7,482, and 7,168 kg for the following lactations), $a_{n,j}$ is the nDNA breeding value for animal j (nTBV), $a_{m,j}$ is the mDNA breeding value for animal j (**mTBV**, which was the same as for its mother, maternal grandmother, and so on), p_j is the permanent environment effect of animal j sampled from $N\left(0, 0.1\sigma^2_y\right)$, and e_{ij} is the environmental effect sampled from $N\left(0, 0.6\sigma^2_y\right)$. Therefore, in the base population the simulated phenotypic variance was $\sigma^2_y = \sigma^2_{a_n} + \sigma^2_{a_m} + \sigma^2_p + \sigma^2_e = 0.25 + 0.05 + 0.10 + 0.60 = 1.00$.

We defined an individual j's breeding value in 2 ways: (1) as nDNA breeding value (**nTBV**) and (2) as the sum of nDNA and mDNA breeding values (**tTBV** = nTBV + mTBV). Definition (2) is correct for phenotype expression in males and females because both sexes have nDNA and mDNA, and for inheritance in females because only they transmit nDNA and mDNA to the next generation. Hence, for females, definition (2) should always be used, whereas for males, definition (1) should be used for selection and definition (2) should be used for modeling their own phenotype data. However, male phenotypes are seldom modeled in dairy breeding.

We analyzed the phenotype data to estimate breeding values (EBV) using the generative model (1) with pedigree- and genome-based information and accounting for the mDNA variation or not. In the pedigree-based model, we assumed $\boldsymbol{a}_n \sim N\left(0, \mathbf{A}\sigma^2_{a_n}\right)$ with $\mathbf{A}$ being the pedigree relationship matrix for the nuclear genome of dimension equal to the number of animals in the pedigree, and $\boldsymbol{a}_m \sim N\left(0, \mathbf{I}\sigma^2_{a_m}\right)$ with $\mathbf{I}$ being an identity matrix of dimension equal to the number of distinct maternal founder lineages/haplotypes. In the genome-based model, we assumed $\boldsymbol{a}_n \sim N\left(0, \mathbf{H}_n\sigma^2_{a_n}\right)$ with $\mathbf{H}_n$ being the "single-step" joint pedigree- and genome-based relationship matrix for nDNA with dimension equal to the number of animals in the pedigree (Aguilar et al., 2010), and $\boldsymbol{a}_m \sim N\left(0, \mathbf{G}_m\sigma^2_{a_m}\right)$ with $\mathbf{G}_m$ being the genome-based relationship matrix for mDNA with dimension equal to the number of distinct mDNA in the data, n_m. Note that n_m was smaller than the number of distinct maternal founder lineages/haplotypes in pedigree. We calculated the mDNA genomic relationship matrix as $\mathbf{G}_m = \mathbf{M}_m\mathbf{M}_m{}^{\mathrm{T}} / k$, where $\mathbf{M}_m = \mathbf{W}_m - \mathbf{P}_m$ with $\mathbf{W}_m$ an $n_m \times n_s$ matrix of mDNA haplotypes encoded as 0s (for ancestral allele) and 1s (for mutation) for n_m distinct mDNA and n_s polymorphic loci (we assume we know all these loci by sequencing mDNA within pedigrees; Brajkovic et al., 2023), $\mathbf{P}_m$ a matrix of mutation frequencies, $k = \sum_{l=1}^{n_s} p_l\left(1 - p_l\right)$, and p_l the mutation frequency at locus l. To speed up simulations, we fixed variance components to simulated values during the burn-in phase (see the next paragraphs). After the burn-in phase, we estimated the variance components and used these new estimates for the remainder of the simulation. We fitted all the models with the BLUPF90 suite (Misztal et al., 2018).

We evaluated 16 scenarios driven by 3 factors across 100 replicates. All scenarios included a burn-in step of 10 years of progeny testing-based selection. The first factor was the breeding scheme: (1) progeny testing-based selection (**PT**) and (2) genomic selection (**GS**). We simulated a 20-year breeding program considering overlapping generations, generating 35,179 animals annually. This population size was determined to produce 5 Elite Sires every year with a selection intensity of 0.9. In the PT scenarios, the male selection pathway had a generation interval of 6 years, with 4 years for the progeny test. This time was reduced to 2 years in the GS scenarios. To ensure accurate genetic evaluations, each Waiting Bull was required to have at least 100 phenotyped daughters at the time of testing. The female selection pathway involved 5 lactations over a 7-year generation interval. We categorized the animals into 6 groups: Elite Dams (top 250 first-lactation cows), Commercial (best 70% first-lactation cows after Elite Dams selection), Heifers (7,110 females without lactation record), Young Bulls (97% male offspring from Elite categories—nucleus population), Waiting Bulls (top 50 Young Bulls based on breeding values), and Elite Sires (5 highest-

Table 1. Accuracy (average ± SD across replicates) of EBV for different animal categories in the model with nDNA breeding value (Standard) or with nDNA and mDNA breeding value (Baseline) with the pedigree-based model in progeny testing-based selection (PT) or with genome-based model in genomic selection (GS) scenarios

Scenario	Category[1]	Standard	Baseline	Difference
PT	Heifers	0.47 ± 0.03	0.48 ± 0.03	0.01 ± 0.03
	Cows1	0.61 ± 0.03	0.63 ± 0.02	0.02 ± 0.03
	Cows2–5	0.55 ± 0.03	0.58 ± 0.02	0.03 ± 0.04
	Young bulls	0.40 ± 0.08	0.40 ± 0.10	0.00 ± 0.10
	Proven bulls	0.74 ± 0.06	0.73 ± 0.06	0.00 ± 0.10
GS	Heifers (ngt)	0.41 ± 0.02	0.42 ± 0.02	0.01 ± 0.03
	Heifers (gt)	0.73 ± 0.03	0.75 ± 0.02	0.02 ± 0.03
	Cows1 (ngt)	0.56 ± 0.02	0.58 ± 0.01	0.02 ± 0.02
	Cows1 (gt)	0.77 ± 0.03	0.78 ± 0.02	0.02 ± 0.03
	Cows2–5 (ngt)	0.52 ± 0.03	0.55 ± 0.01	0.03 ± 0.03
	Cows2–5 (gt)	0.73 ± 0.03	0.75 ± 0.01	0.02 ± 0.03
	Young bulls (gt)	0.72 ± 0.05	0.75 ± 0.03	0.03 ± 0.06
	Proven bulls (gt)	0.75 ± 0.06	0.76 ± 0.06	0.00 ± 0.08

[1]gt = genotyped; ngt = nongenotyped.

rated males based on breeding values). Elite Dams and Commercial females were replaced at a 30% rate/year and 100% after their fifth lactation, whereas all Elite Sires were replaced after 5 years in the category. In GS scenarios, 10,200 genotypes were generated each year. The reference population began with 8,944 genotyped females. New genotypes, 613 males and 2,461 females, were added every year. All genotyped animals were from the nucleus. Old records were removed to keep the number of genotyped animals within the 25,000 limit of the free version of BLUPF90.

The second factor was a statistical model accounting for mDNA variation or not and selection on different definitions of breeding value: (1) using a standard model (without mDNA) and selecting both females and males on their nDNA EBV (Standard), (2) using a model with mDNA and selecting both females and males on their nDNA EBV (Baseline), (3) using a model with mDNA and selecting females on their nDNA plus mDNA EBV and selecting males on their nDNA EBV (Optimum), and (4) using a model with mDNA and selecting both females and males on their nDNA plus mDNA EBV (Extreme). We consider the Optimum scenario to be the correct strategy to be used, hence the name.

The third factor was the assumption that all or just one polymorphic locus in mDNA is a QTL.

We evaluated all the scenarios with (1) accuracy of the last year of genetic evaluation as the correlation between true and estimated breeding value for Standard and Baseline scenarios because accuracy does not change with the Optimum and Extreme scenarios and (2) genetic gain for mTBV, nTBV, and tTBV = mTBV + mTBV (in units of tTBV standard deviation from year 10) as the mean after 20 years of selection for scenarios Standard, Baseline, Optimum, and Extreme.

We present results separately for the following 5 categories: (1) heifers, (2) first-lactation cows (**Cows1**), (3) cows with 2 to 5 lactation records (**Cows2–5**), (4) young bulls, males without progeny; and (5) proven bulls, progeny-tested males. For the GS scenarios, the female categories were split to show the difference between genotyped and nongenotyped animals. We present only the scenario where all mDNA polymorphic loci were QTL (the other scenario with a single QTL was qualitatively the same).

In both PT and GS cases, accounting for mDNA variation increased the accuracy of nDNA EBV between 0.01 and 0.03, depending on the animal category (Table 1). In the PT case, the highest increase was observed for the young bulls (+0.03) and Cows2–5 (+0.03). The same was observed in the GS; accuracy of nDNA increased 0.03 in young bulls and 0.03 for nongenotyped Cows2–5, whereas for genotyped Cows2–5 the increase was 0.02. The accuracy of mDNA EBV in both PT and GS was close to one for all animal categories (results not shown), which is expected given the lack of recombination in mDNA. However, variation between simulation replicates was substantial and larger than differences.

Genetic gain for mTBV, nTBV, and tTBV after 20 years of breeding with different estimation and selection scenarios is shown in Figure 1. Modeling but not selecting on mDNA variation (Baseline) reduced genetic gain for tTBV compared with not modeling it (Standard). This was due to the lack of genetic gain for mTBV with the Baseline scenario, whereas the Standard scenario partially captured the mTBV variation even without direct modeling and selection, via "mTBV-biased" estimation of nTBV. Modeling and selecting on mDNA variation recovered genetic gain for tTBV in Optimum and Extreme scenarios. There was an indication of increased gain for mTBV with the Optimum and Extreme scenarios, though variation between simulation replicates was substantial, particularly for the Extreme scenario. These trends were similar for the PT and GS breeding scheme.

This study shows that considering mDNA variation can improve dairy breeding by increasing accuracy of selection, but genetic gain depends on how mDNA variation is modeled and selected upon. In the following, we discuss: (1) mDNA causal sites, (2) mDNA demography, (3) mDNA heteroplasmy, and (4) interactions between mDNA and nDNA.

We simulated scenarios with one mDNA segregating site as QTL as well as all segregating sites as QTL, which made no qualitative difference to results. When simulating one QTL, we assumed this site was the source of all observed phenotypic variation due to mDNA. However, when considering all sites, the effect of individual QTL was reduced. The absence of recombination creates strong linkage between loci along the mDNA, making the sum of several small-effect QTLs effectively equal to that of a single large-effect QTL. This also explains why the mDNA EBV had almost perfect accuracy, which in turn explains differences between the tested

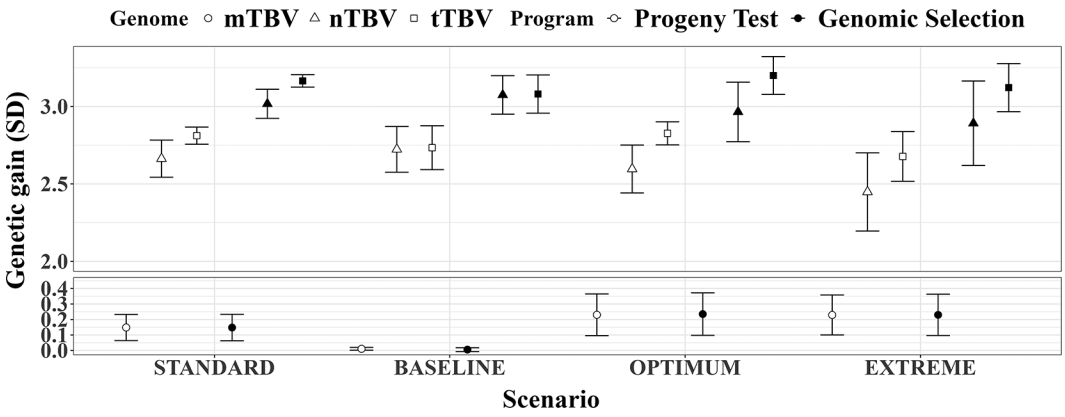

Figure 1. Standardized genetic gain (average ± SD across replicates) after 20 generations of selection. Circles indicate results for mito true breeding values (mTBV), triangles for nuclear (nTBV), and squares for total true breeding value (nTBV + mTBV); the definition of breeding value in estimation and selection varied according to the simulation scenario (see the main text). Empty symbols indicate results with progeny testing-based selection, and full symbols indicate results with genomic selection.

scenarios for modeling and selecting on mDNA variation. Future studies with collected data will give more information about the QTL, realized accuracies, and genetic gain.

Our initial simulations of mDNA indicated that we need larger N_e for mDNA than for nDNA (despite an order of magnitude larger mutation rate in mDNA) to obtain several segregating sites in mDNA in line with the observed variation both within and across cattle populations (Dorji et al., 2022; Brajkovic et al., 2023). As expected, we noticed that the lower the diversity among the mDNA, the smaller the impact of accounting for mDNA in breeding value estimation, in line with Boettcher et al. (1996). Theoretically, N_e for mDNA equals the number of females or a quarter of the nDNA N_e, though these relationships depend on the sex ratio (Birky et al., 1983). In a recent study, Cubric-Curik et al. (2022) inferred the demographic trend in N_e for mDNA in cattle. They found that mDNA N_e is increasing over time, which is opposite to results for nDNA in dairy cattle (MacLeod et al., 2013), but in line with the large diversity observed in mDNA (~1,000 polymorphic sites out of 16,202 bp). The limited effect of accounting for mDNA observed in this study could be an underestimation due to the mismatched demographic parameters for the mDNA in our simulation. More research is needed to estimate demographic trends in nDNA and mDNA jointly and to understand how inheritance of these 2 DNA molecules interplays with modeling and selection.

We did not consider the presence of multiple mDNA copies with possible differences in mitochondria, known as heteroplasmy (Stewart and Chinnery, 2015). Future research should consider this additional variation, which is challenging because heteroplasmy varies between cells, tissues, and time points.

We did not consider interactions between mDNA and nDNA. Studies suggest that incompatibility between the 2 DNA can lead to mitochondrial malfunction, decreasing energy production efficiency and increasing oxidative damage (Pozzi and Dowling, 2022; Ward et al., 2022). This factor could be relevant, and therefore, additional research is required, especially in the context of taurine-indicine crossbreeding systems (Ward et al., 2022).

In conclusion, the results show that accounting for mDNA variation can affect the success of dairy breeding. This study provides a genomic update of Boettcher et al. (1996) with additional results. With the increasing relevance of selection among females, especially for use in egg-transfer schemes, accounting for the mDNA will improve the accuracy of selecting more productive cows.

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Notes

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Nonstandard abbreviations used: Cows1 = first-lactation cows; Cows2–5 = cows with 2 to 5 lactation records; MABG = European Masters in Animal Breeding and Genetics; GS = genomic selection; gt = genotyped animals; mDNA = mitochondrial DNA; mTBV = mitochondrial true breeding value; nDNA = nuclear DNA; N_e = effective population size; ngt = nongenotyped animals; nTBV = nuclear true breeding value; PT = progeny testing; tTBV = sum of nDNA and mDNA breeding values.