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Genetic Contributions of Genes on Sex Chromosomes and Mitochondrial DNA in a Pedigreed Population

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Abstract: The genetic contribution with respect to autosomal genes has been widely used to evaluate the genetic diversity of a target population. Here, we developed a method to calculate the genetic contribution with respect to genes on sex chromosomes and mitochondrial DNA through pedigree analysis. To demonstrate the performance, we applied the methods for calculating genetic contributions to example pedigree data. To verify the results of genetic contribution calculations, we performed gene-dropping simulations mimicking flows of genes on autosomes, X and Y chromosomes, and mitochondrial DNA, and then compared the results from the simulation with the corresponding genetic contributions. To investigate the effect of pedigree error, we compared the results of genetic contribution calculations using pedigree data with and without errors. The results of gene-dropping simulation showed good agreement with the results of the genetic contribution calculation. The effect of pedigree errors on the calculation of genetic contribution depended on the error rate. Since the patterns of the genetic contributions of such genes might be different from those on autosomes, the novel approach could provide new information on the genetic composition of populations. The results are expected to contribute to the development of methods for sustainable breeding and population management.

Keywords: autosome; genetic contribution; mitochondrial DNA; pedigree analysis; sex chromosomes

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1. Introduction

In livestock breeding, production traits have been the main targets of genetic improvement, such as milk yield of dairy cattle, carcass weight of beef cattle, and growth rate of pigs [1]. Heritabilities estimated from many phenotypic records and pedigree information under the infinitesimal model, which generally targets quantitative trait loci on autosomes (e.g., [2–4]), are often moderate to high (e.g., [5–7]), and genetic improvements have made steady progress (e.g., [8–10]). On the other hand, there is growing concern about the decline in genetic diversity within given populations, which might be further boosted by introducing a genomic selection scheme (e.g., [11–13]). Therefore, developing a tool to effectively manage and secure genetic diversity is an urgent need (e.g., [14–16]). Existing theories assume the use of 100% accurate pedigree data, although low but non-zero pedigree error rates, partly due to human errors, have been reported (e.g., [17–19]). This indicates the importance of investigating the effect of pedigree error on evaluation of genetic diversity (e.g., [20–22]).

Recent studies have investigated genetic improvement of novel traits, including fertility and disease resistance (e.g., [23–25]), with lower estimated heritabilities than those of production traits (e.g., [5,26,27]). An increasing number of studies have examined the relationships of sex chromosomes and mitochondria with gametogenesis, embryogenesis, immune function, feed efficiency, and heat stress (e.g., [28–33]). These facts suggest the importance of non-autosomal genetic materials (e.g., [34–36]), although the sex chromosomes and mitochondrial DNA have fewer genes than autosomes.

The use of conserved genetic resources, such as cryopreserved semen, oocytes, embryos, and even primordial germ cells, seems important in securing genetic variability within a population to improve based on revised breeding objectives, occasionally adding novel traits (e.g., [37–39]). Furthermore, for example, domestic pig breeders occasionally introduce foreign genes into their populations by using imported frozen semen. On the other hand, introduction of external genes to increase genetic variance could have risk of genetic contamination or pollution of a population (e.g., [40–42]). Genetic pollution is also a problem in managing the genetic diversity of wild animal populations, such as the case of wild boars in Japan reported after the Fukushima Daiichi Nuclear Power Plant accident in 2011 (e.g., [42–44]). Thus, providing a proper methodology to manage the genetic composition in a target population is always essential.

The genetic contribution of a particular individual can be used as an indicator to monitor the pattern of gene transmission in a population with pedigree information (e.g., [45–47]). In Japan, the genetic contribution has been used for line maintenance and brand identification in pigs and for genetic diversity management in Wagyu cattle populations (e.g., [48–51]). For example, different pig strains have been developed through closed-line breeding with widely collecting animals and semen as a base population and strict selection of several generations (e.g., [8,52,53]), and the coefficient of variation (CV) of genetic contribution has been used to keep the genetic composition of the population after approving it as a distinct strain (e.g., [51,54,55]). Nishida et al. [54] proposed a goodness-of-fit test using the CV of genetic contribution to evaluate the degree to which the genetic contributions deviate from equal. However, the classical genetic contribution generally targets only autosomal genes.

Here, we developed a method for calculating the genetic contribution with respect to genes on the sex chromosomes and mitochondrial DNA, as an extension of the method for calculating that with respect to autosomal genes. We assessed the performance using the toy example obtained from Fernando and Grossman [56] and the pedigree data of laboratory mice of Ogawa and Satoh [57]. To verify the results of genetic contributions calculated using the mouse pedigree data, we performed a gene-dropping simulation [58] and compared the results from the simulation with the calculated genetic contributions. To assess the effect of pedigree errors, we compared results with and without introduced errors in the pedigree data.

2. Materials and Methods

2.1. Genetic Contribution of an Individual with Respect to Autosomal Genes

First, we will introduce the genetic contribution of individual I to individual A with respect to autosomal genes, $GCA_{I,A}$, which is calculated as [45,58]:

$$GCA_{I,A} = \sum_{t=0}^{n} \frac{a_t}{2^t}, \quad (1)$$

where n is the maximum difference between the generations of I and A ($n \geq t$) in a given pedigree structure, and at is the total number of appearances of I. For instance, $GCA_{I,A} = 0.5$ when I is the parent of A, $GCA_{I,A} = 0.25$ when I is the grandparent of A, $GCA_{I,A} = 0$ when I is the sib of A, and $GCA_{I,A} = 1$ when I and A are identical. Note that it is assumed that individual I has two unique alleles for autosomal genes and that the contribution of one of the I's two alleles to individual A can be calculated as the half of $GCA_{I,A}$, whereas the contribution of individual I to one of the A's two alleles can be the same as $GCA_{I,A}$.

Next, when A is the direct descendant of I, denoting A's sire and dam as S and D, the following equation holds [51,54]:

$$GCA_{I,A} = \frac{GCA_{I,S}}{2} + \frac{GCA_{I,D}}{2}. \quad (2)$$

By extending this approach, we devised a method of calculating the genetic contribution with respect to genes on sex chromosomes and mitochondrial DNA.

2.2. Genetic Contribution with Respect to Genes on Sex Chromosomes and Mitochondrial DNA

We will consider the genetic contribution of individual I with respect to genes on sex chromosomes to individual A of each sex. Note that here we considered genes on X-specific and Y-specific regions because sex chromosomes contain pseudoautosomal regions (e.g., [59–61]). Here, it is assumed that individual I has a unique one allele and two alleles for genes on X chromosome, and a unique one allele and no allele for genes on Y chromosome when I is male (XY) and female (XX), respectively, as well as a unique one allele for genes on mitochondrial DNA regardless of the sex of I. When A is male (XY), the genetic contributions with respect to genes on X and Y chromosomes, denoted respectively as $GCX_{I,A}$ and $GCY_{I,A}$, are:

$$GCX_{I,A} = 0GCX_{I,S} + 1GCX_{I,D} = GCX_{I,D} \text{ and } GCY_{I,A} = 1GCY_{I,S} + 0GCY_{I,D} = GCY_{I,S}. \quad (3)$$

When I and A are identical, $GCX_{I,A} = GCY_{I,A} = 1$. When A is female (XX):

$$GCX_{I,A} = \frac{GCX_{I,S}}{2} + \frac{GCX_{I,D}}{2} \text{ and } GCY_{I,A} = 0GCY_{I,S} + 0GCY_{I,D} = 0. \quad (4)$$

When I and A are identical, $GCX_{I,A} = 1$ but $GCY_{I,A} = 0$ because I does not have her Y chromosome.

The genetic contribution with respect to genes on mitochondrial DNA, regardless of the sex of A, is calculated as:

$$GCM_{I,A} = 0GCM_{I,S} + 1GCM_{I,D} = GCM_{I,D}. \quad (5)$$

When I and A are identical, $GCM_{I,A} = 1$.

2.3. Average Genetic Contribution of an Individual to a Target Population

Now we can consider the average genetic contribution of individual I to a target population, denoted as population B (Figure 1). We assume that population B consists of m males and f females, and each is denoted as individual A_k ($k = 1, \ldots, m, m+1, \ldots, m+f$). Thus, we can calculate the average genetic contribution of individual I to target population B with respective to autosomal genes, $GCA_{I,popB}$, as [51,54,55]:

$$GCA_{I,popB} = \frac{\sum_{k=1}^{m} 2GCA_{I,A_k} + \sum_{k=m+1}^{m+f} 2GCA_{I,A_k}}{2m+2f} = \frac{\sum_{k=1}^{m} GCA_{I,A_k} + \sum_{k=m+1}^{m+f} GCA_{I,A_k}}{m+f}. \quad (6)$$

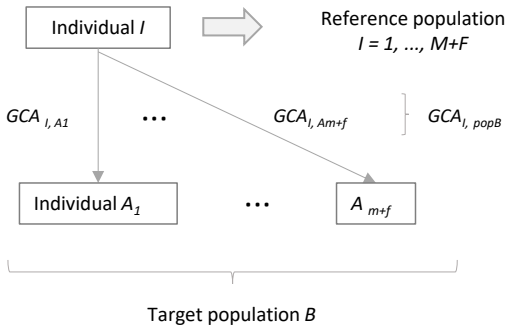

Figure 1. Concept of calculating average genetic contribution of individual I to a target population B, showing GCA as an example.

Here, multiplying by 2 reflects that each A_k has two alleles for autosomal genes. Following this, the average genetic contributions with respect to genes on X chromosome ($GCX_{I,popB}$), Y chromosome ($GCY_{I,popB}$), and mitochondrial DNA ($GCM_{I,popB}$) can be calculated as:

$$GCX_{I,popB} = \frac{\sum_{k=1}^{m} 1GCX_{I,A_k} + \sum_{k=m+1}^{m+f} 2GCX_{I,A_k}}{1m+2f} = \frac{\sum_{k=1}^{m} GCX_{I,A_k} + \sum_{k=m+1}^{m+f} 2GCX_{I,A_k}}{m+2f}, \quad (7)$$

$$GCY_{I,popB} = \frac{\sum_{k=1}^{m} 1GCY_{I,A_k} + \sum_{k=m+1}^{m+f} 0GCY_{I,A_k}}{1m + 0f} = \frac{\sum_{k=1}^{m} GCY_{I,A_k}}{m}, \text{ and} \quad (8)$$

$$GCM_{I,popB} = \frac{\sum_{k=1}^{m} 1GCM_{I,A_k} + \sum_{k=m+1}^{m+f} 1GCM_{I,A_k}}{1m+1f} = \frac{\sum_{k=1}^{m} GCM_{I,A_k} + \sum_{k=m+1}^{m+f} GCM_{I,A_k}}{m+f}. \quad (9)$$

2.4. Coefficient of Variation of Genetic Contribution

Here, we assume that a population, denoted as reference population in this study and being different from target population B, consists of M males and F females, including individual I ($I = 1, \ldots, M, M + 1, \ldots, M + F$). We also assume the situation that a new offspring is obtained from target population B and want to evaluate the degree of heterogeneity in genetic contributions to a virtual offspring from population B (Figure 2). The sum of the genetic contributions of males in the reference population to a virtual offspring from population B is expected to be 1/2, 1/3, 1, and 0 for genes on autosomes, the X chromosome, the Y chromosome, and mitochondrial DNA, respectively, while that of females in the reference population is expected to be 1/2, 2/3, 0, and 1, respectively. Based on these, weighted averages of the genetic contributions of individual I in to population B with respect to genes on autosomes ($GCA^*_{I,popB}$), the X chromosome ($GCX^*_{I,popB}$), the Y chromosome ($GCY^*_{I,popB}$), and mitochondrial DNA ($GCM^*_{I,popB}$), with weights based on the number of males and females in a target population, can be calculated as:

$$GCA^*_{I,popB} = \frac{2\frac{\sum_{k=1}^{m} GCA_{I,A_k}}{m} + 2\frac{\sum_{k=m+1}^{m+f} GCA_{I,A_k}}{f}}{4} = \frac{\sum_{k=1}^{m} GCA_{I,A_k}}{2m} + \frac{\sum_{k=m+1}^{m+f} GCA_{I,A_k}}{2f}, \quad (10)$$

$$GCX^*_{I,popB} = \frac{\frac{\sum_{k=1}^{m} GCX_{I,A_k}}{m} + 2\frac{\sum_{k=m+1}^{m+f} GCX_{I,A_k}}{f}}{3} = \frac{\sum_{k=1}^{m} GCX_{I,A_k}}{3m} + 2\frac{\sum_{k=m+1}^{m+f} GCX_{I,A_k}}{3f}, \quad (11)$$

$$GCY^*_{I,popB} = \frac{1\frac{\sum_{k=1}^{m} GCY_{I,A_k}}{m}}{1} = GCY_{I,popB}, \text{ and} \quad (12)$$

$$GCM^*_{I,popB} = \frac{1\frac{\sum_{k=m+1}^{m+f} GCM_{I,A_k}}{f}}{1} = \frac{\sum_{k=m+1}^{m+f} GCM_{I,A_k}}{f} \quad (13)$$

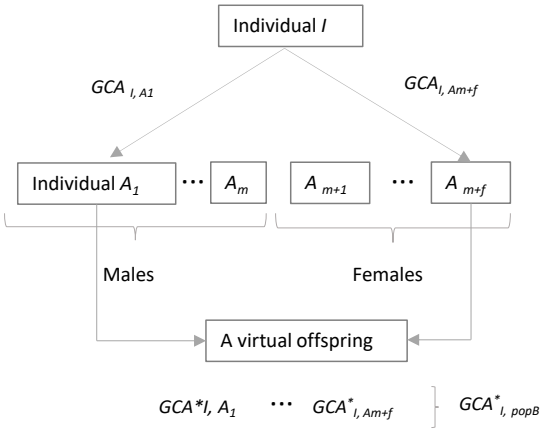

Figure 2. Concept of calculating weighted average of genetic contribution of individual I to a target population B, showing GCA^* as an example.

Finally, the CV of the genetic contribution to population B with respective to autosomal genes (CVA) is calculated as [51,54]:

$$CVA = \sum_{I=1}^{M} \frac{\left(GCA^{*}_{I,popB} - \frac{1}{2M}\right)^2}{\frac{1}{2M}} + \sum_{I=M+1}^{M+F} \frac{\left(GCA^{*}_{I,popB} - \frac{1}{2F}\right)^2}{\frac{1}{2F}} \quad (14)$$

Here, the values of $1/2M$ and $1/2F$ are used as the expected values of $GCA^{*}_{I,popB}$ for males and females in a reference population, respectively [51,54]. Similarly, CV of the genetic contribution with respect to genes on X chromosome (CVX), Y chromosome (CVY), and mitochondrial DNA (CVM) to population B, were calculated as:

$$CVX = \sum_{I=1}^{M} \frac{\left(GCX^{*}_{I,popB} - \frac{1}{3M}\right)^2}{\frac{1}{3M}} + \sum_{I=M+1}^{M+F} \frac{\left(GCX^{*}_{I,popB} - \frac{2}{3F}\right)^2}{\frac{2}{3F}}, \quad (15)$$

$$CVY = \sum_{I=1}^{M} \frac{\left(GCY^{*}_{I,popB} - \frac{1}{M}\right)^2}{\frac{1}{M}}, \text{ and } CVM = \sum_{I=M+1}^{M+F} \frac{\left(GCM^{*}_{I,popB} - \frac{1}{F}\right)^2}{\frac{1}{F}}. \quad (16)$$

2.5. Example Pedigree Data

To investigate the performance of the approach we devised, two pedigree data were used as examples. Table 1 shows the toy sample obtained from Fernando and Grossman [56]. Table S1 is the pedigree data of a mouse population [57], an experiment was carried out over 2 years from 2018 to 2020, under the Regulations for Animal Experiments and Related Activities at Tohoku University (http://www.clar.med.tohoku.ac.jp/en.html) (lastly accessed on 1 October 2021). All mice were reared and handled according to the protocols approved by the Institutional Animal Care and Use Committee of Tohoku University [57]. For breeding scheme, see Figure 1 in Ogawa and Satoh [57]. The mouse population was a total of non-overlapping 8 generations from G1 to G8 (Table 2). Parent information on 100 G1 mice (50 male and 50 female mice) was unknown, and the 92 G1 mice (46 male and 46 female mice) had their offspring in G2. Nishida et al. [54] proposed a goodness-of-fit test using the following values as chi-square statistics, to test whether the genetic contributions with respect to autosomal genes to a virtual offspring obtained from target population B are equal:

$$\chi^2_{df=M+F-1} = \sum_{I=1}^{M} \frac{\left\{(m+f)GCA^{*}_{I,popB} - \frac{m+f}{2M}\right\}^2}{\frac{m+f}{2M}} + \sum_{I=M+1}^{M+F} \frac{\left\{(m+f)GCA^{*}_{I,popB} - \frac{m+f}{2F}\right\}^2}{\frac{m+f}{2F}} = (m+f)CVA. \quad (17)$$

Table 1. Pedigree data from Fernando and Grossman [56].

Individual	Sex	Sire	Dam
1	Male	Unknown	Unknown
2	Female	Unknown	Unknown
3	Male	1	Unknown
4	Female	1	2
5	Male	3	4
6	Female	1	4
7	Male	5	6
8	Female	5	6

Table 2. Numbers of male and female mice in pedigree data from Ogawa and Satoh [57].

Generation	No. of Males	No. of Females	No. of Known Sires	No. of Known Dams
G1	50	50	0	0
G2	186	173	46	46
G3	248	249	124	124
G4	149	146	95	95
G5	174	171	112	112
G6	158	154	103	103
G7	151	156	100	100
G8	151	152	101	101
Total	1267	1251	681	681

A previous study [57] conducted this test for the contribution of the 92 G1 mice ($M = F = 46$) to the parents of each generation and confirmed that p-value was always >0.05.

2.6. Data Analysis

To demonstrate the performance, we applied the rules for determining $GCA_{I,A}$, $GCX_{I,A}$, $GCY_{I,A}$, and $GCM_{I,A}$ to the pedigree data from Fernando and Grossman [56] (Table 1). We also applied the same rules to mouse pedigree data from Ogawa and Satoh [57] (Table S1) in order to obtain $GCA_{I,A}$, $GCX_{I,A}$, $GCY_{I,A}$, and $GCM_{I,A}$ of each of the G1 mice (50 males and 50 females) to each of the G8 mice (151 males and 152 females) (Table 2), and then we calculated the average genetic contributions, $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$, of each G1 mouse to the population of 303 G8 mice.

To verify the results of calculating $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ in the mouse population, we performed a gene-dropping simulation [58]. In the case of autosomal genes, every mouse in G1 has two unique alleles, giving a total of 200 unique alleles in G1. In the case of genes on X chromosome, each of the 50 males has one unique allele and each of the 50 females has two unique alleles, giving a total of 150 unique alleles in G1. In the case of genes on Y chromosome, each male has one unique allele, giving a total of 50 unique alleles in G1. In the case of mitochondrial DNA, every mouse has one unique allele, giving a total of 100 unique alleles in G1. Simulated alleles in G1 were then dropped progressively to descendants in G8 according to each mode of inheritance, and then we determined the frequency of each allele in G8 population. These frequencies were converted to the frequency of all alleles each G1 mouse uniquely had, that is, the frequencies were summed when a G1 mouse had two alleles. We ran this simulation for 10,000 iterations to obtain the averages of the proportions through the iterations, and then compared the results to the average genetic contributions, $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$.

To assess the effect of pedigree error on calculated genetic contributions, errors were introduced into parent information on G2 to G8 mice by randomly replacing the original parents with others used as parents in the same generation. $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ of each G1 mouse to G8 population were calculated using pedigree information with errors. According to estimated pedigree error rates by previous studies (e.g., [17–19]), the error size was set to 1%, 2%, 4%, 8%, and 16% of the total number of known parents (Table 2). Within the same error rate, we ran this simulation for 10,000 iterations to obtain the root mean squared error (RMSE) of the average genetic contributions calculated with and without pedigree errors. Note that only 50 G1 males were considered in calculating RMSE for $GCY_{I,popB}$ and 50 G1 female mice were considered for $GCM_{I,popB}$.

We calculated CVA, CVX, CVY, and CVM using mouse pedigree data, changing the target population from G1 to G8 while retaining the reference population as G1.

3. Results and Discussion

3.1. Calculated Genetic Contribution

Table 3 shows the results of the calculation of $GCA_{I,A}$, $GCX_{I,A}$, $GCY_{I,A}$, and $GCM_{I,A}$ using the pedigree data shown as Table 1. No pairs completely matched the distribution of the calculated genetic contributions. As expected, the results were real numbers ranging from 0 to 1 for $GCA_{I,A}$ and $GCX_{I,A}$, and either 0 or 1 for $GCY_{I,A}$ and $GCM_{I,A}$. The sums of $GCA_{I,A}$ of individuals 1 and 2 to individuals 3, 5, 7, and 8 were <1, because the dam of individual 3 was unknown in the pedigree data. This problem might be manageable by introducing the concept of a phantom parent group and a meta-founder [62,63]. In this example, all the Y chromosomes and mitochondrial DNA of the individuals 4 to 8 were derived from individuals 1 and 2, respectively.

Table 3. Values of genetic contributions of individual *I* to individual *A* ($GCA_{I,A}$, $GCX_{I,A}$, $GCY_{I,A}$, and $GCM_{I,A}$) in Table 1.

I	A															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	Autosomes ($GCA_{I,A}$)								*X chromosome* ($GCX_{I,A}$)							
1	1	0	0.5	0.5	0.5	0.75	0.625	0.625	1	0	0	0.5	0.5	0.75	0.75	0.625
2	0	1	0	0.5	0.25	0.25	0.25	0.25	0	1	0	0.5	0.5	0.25	0.25	0.375
3	0	0	1	0	0.5	0	0.25	0.25	0	0	1	0	0	0	0	0
4	0	0	0	1	0.5	0.5	0.5	0.5	0	0	0	1	1	0.5	0.5	0.75
5	0	0	0	0	1	0	0.5	0.5	0	0	0	0	1	0	0	0.5
6	0	0	0	0	0	1	0.5	0.5	0	0	0	0	0	1	1	0.5
7	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
8	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
	Y chromosome ($GCY_{I,A}$)								*Mitochondrial DNA* ($GCM_{I,A}$)							
1	1	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1
3	0	0	1	0	1	0	1	0	0	0	1	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1
5	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
7	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

3.2. Comparing with Gene-Dropping Simulation Results

Figure 3 compares $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ of each G1 mouse to G8 with the total frequencies of all unique alleles of each G1 mouse, which were determined by the gene-dropping simulation performed with mouse pedigree data. Coefficients of determinations between them were all >0.999, the single regression coefficients were almost 1, and the intercepts were almost 0, indicating very high consistency. The results indicate the validity of using $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ as indicators of "expected" contributions of individual *I* to target population *B*.

Figure 4 shows histograms of the total numbers of all unique alleles of four mice with the highest $GCA_{I,popB}$ and $GCX_{I,popB}$. As shown by Figure 4, the gene-dropping simulation could provide results like the interval estimation, although the performing would be time-consuming. In all cases, the histograms are asymmetric, and therefore, average and mode values seemed inconsistent. There were iterations showing the number of their unique alleles inherited to G8 of 0, suggesting the possibility that even the four mice did not actually transmit their alleles on autosomes and the X chromosome to G8, although their $GCA_{I,popB}$ and $GCX_{I,popB}$ were >0. This possibility would be higher when the difference in the generation number between populations is greater, owing to Mendelian segregation events, or genetic drift. Therefore, a gene-dropping simulation for genes

on the X chromosome could provide information, including the expected proportion of surviving alleles (what is called allele retention) as in the case of autosomal genes [58]. Such results cannot be obtained from the calculation of $GCA_{I,popB}$ and $GCX_{I,popB}$ because these are expected contributions. For genes on the Y chromosome and mitochondrial DNA, there was no variation in the number of alleles dropped to G8 among the iterations. This means that individuals with non-zero $GCY_{I,popB}$ and $GCM_{I,popB}$ are expected to transmit their genes without uncertainty.

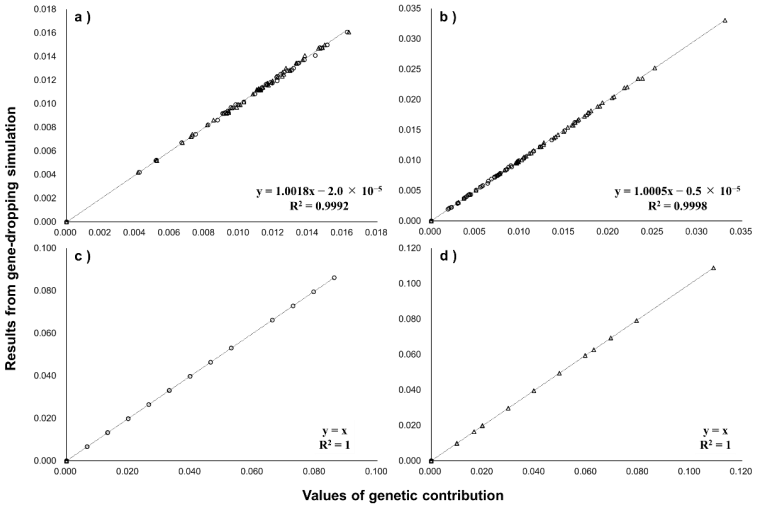

Figure 3. Comparison of average genetic contribution of 100 G1 mice to G8 (horizontal axis) and results of gene-dropping simulation (vertical axis) for genes on autosomes (**a**), X chromosome (**b**), Y chromosome (**c**), and mitochondrial DNA (**d**). Circle: 50 G1 male mice; triangle: 50 G1 female mice.

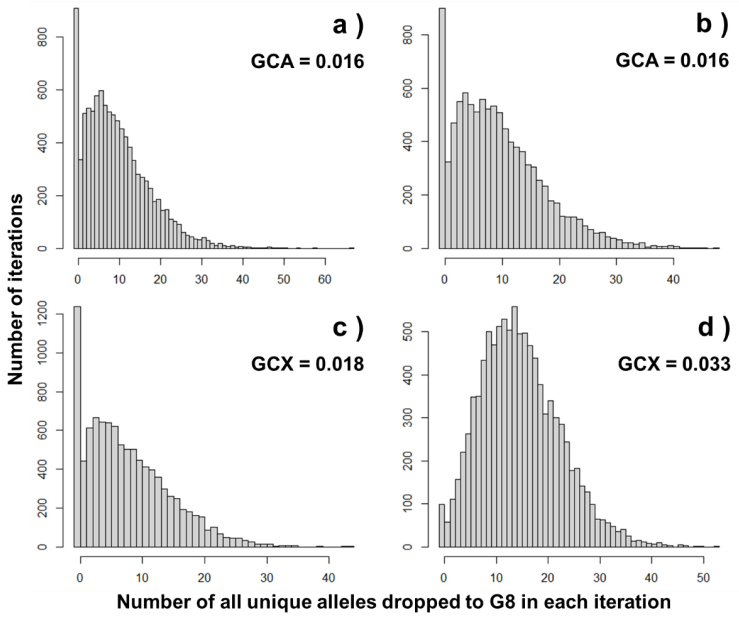

Figure 4. Distribution of the number of alleles of G1 mice inherited to G8 in gene-dropping simulation: (**a**) shows the histogram of the number of dropped alleles of autosomal genes of the G1 male with the highest $GCA_{I,popB}$ to G8, (**b**) shows the histogram of the number of dropped alleles of the G1 female with the highest $GCA_{I,popB}$ to G8, (**c**) shows the histogram of the number of dropped gene alleles on the X chromosome of the G1 male with the highest $GCX_{I,popB}$ to G8, and (**d**) shows the histogram of the number of dropped gene alleles on the X chromosome of the G1 female with the highest $GCX_{I,popB}$ to G8.

3.3. Effect of Pedigree Errors on Genetic Contribution Calculation

Table 4 summarizes the results of $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ of G1 mice to G8 calculated using pedigree data with errors. As expected, the higher the error rate, the larger the RMSE. On the other hand, the range of RMSE was substantial within the same pedigree error rate. For instance, the maximum value of RMSE for $GCA_{I,popB}$ was 2.20 when the error rate was 1%, which is greater than the mean value of 2.14 when the error rate was 4%, and even the minimum value of 1.87 when the error rate was 8%. When the error rate was 1%, the minimum value of RMSE was >0 for $GCA_{I,popB}$ and $GCX_{I,popB}$ but 0 for $GCY_{I,popB}$ and $GCM_{I,popB}$. It was expected that there was no effect on calculating $GCM_{I,A}$ when sires were replaced because mitochondrial DNA is assumed to be maternally inherited, and that replacement of dams did not affect $GCY_{I,A}$ because females do not have the Y chromosome. These results indicate that pedigree errors could affect the results of genetic contribution calculations, and the effect might depend on error rate and the kinds of errors. Pedigree errors could have effects not only on genetic diversity evaluation but also on genetic parameter estimation, breeding value prediction, evaluating the degree of inbreeding and inferring inbreeding depression, and so on (e.g., [20,21,64]). Thus, efforts should be still paid to collect and accumulate accurate pedigree information (e.g., [19,65,66]).

Table 4. Effects of pedigree errors (RMSE $\times 10^3$) on calculating the average genetic contributions to G8 [1].

Error Rate	$GCA_{I,popB}$				$GCX_{I,popB}$				$GCY_{I,popB}$				$GCM_{I,popB}$			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
1%	1.07	0.23	0.37	2.20	1.57	0.40	0.47	3.18	6.74	2.95	0	19.06	6.58	3.34	0	24.27
2%	1.53	0.24	0.74	2.56	2.25	0.42	0.89	4.07	9.88	3.09	1.87	23.80	9.79	3.62	1.14	27.40
4%	2.14	0.27	1.16	3.27	3.17	0.46	1.61	5.04	14.00	3.18	3.50	26.85	14.07	3.81	3.85	30.88
8%	2.97	0.31	1.87	4.31	4.41	0.50	2.81	6.60	19.53	3.36	7.25	34.08	19.73	3.90	8.08	36.12
16%	4.02	0.36	2.69	5.39	5.97	0.59	3.98	8.31	26.23	3.66	13.64	42.57	26.69	3.95	13.32	42.15

[1] $GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ average genetic contribution of individual I to target population B with respect to genes on autosomes, X chromosome, Y chromosome, and mitochondrial DNA, respectively. SD: standard deviation; Min: minimum value; Max: maximum value.

3.4. Calculating Coefficient of Variation of Genetic Contribution

Figure 5 shows the changes in *CVA*, *CVX*, *CVY*, and *CVM* through generations. As expected, *CVA*, *CVX*, *CVY*, and *CVM* were all zero in G1. Increases in values from G1 to G2 and G2 and G3 were similar among the CVs, while those from G3 to G4 and after seem different. For this population, the way to produce offspring was slightly different between G1 and G2 and during G3 and G8 [57], which might affect the results of calculating *CVA*, *CVX*, *CVY*, and *CVM*. Values of *CVY* and *CVM* were higher than *CVA* and *CVX* in G8, which agreed with greater variances of $GCY_{I,popB}$ and $GCM_{I,popB}$ than $GCA_{I,popB}$ and $GCX_{I,popB}$, shown in Figures 4 and 6.

3.5. General Discussion

The proposed method for calculating the genetic contribution with respect to genes on sex chromosomes is based on the XX–XY-type sex-determination mechanism found in many mammals, including mice, cattle, and pigs. The similar concept used in this study could also be applicable to the ZZ–ZW-type mechanism found in birds, such as chickens and Japanese crested ibises, and in silkworms. For example, briefly, genetic contribution with respect to genes on Z and W chromosomes might be calculated in a similar way to calculate that with respect to genes on X and Y chromosomes, respectively, although the difference in inheritance patterns between sexes must be considered. In recent years, population genetic analysis using genomic information, such as genome-wide single nucleotide polymorphism markers, has become available (e.g., [67–69]). However, in livestock populations where selection based on pedigree information has been conducted for many years, it is often more difficult to use genotype information closer to the base population, and thus approaches based on pedigree data are still useful. It should be noted that the indicators proposed do

not consider mutations, recombination, or mitochondrial DNA heteroplasmy, as is the case with the genetic contribution with respect to autosomal genes [48–51].

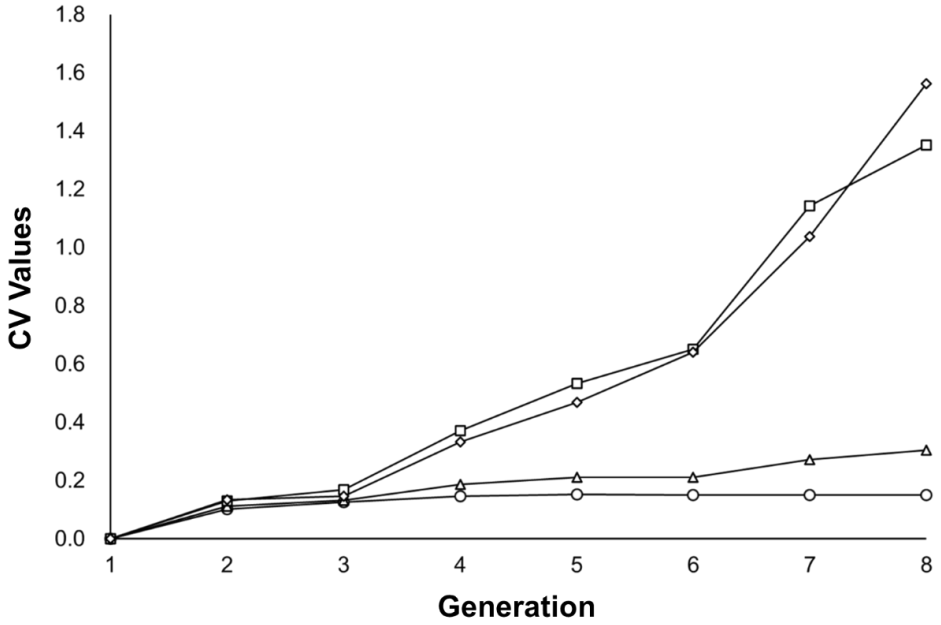

Figure 5. Changes in values of coefficient of variation of the genetic contribution (CV). Circle: autosomes (*CVA*); triangle: X chromosome (*CVX*); square: Y chromosome (*CVY*); rhombus: mitochondrial DNA (*CVM*).

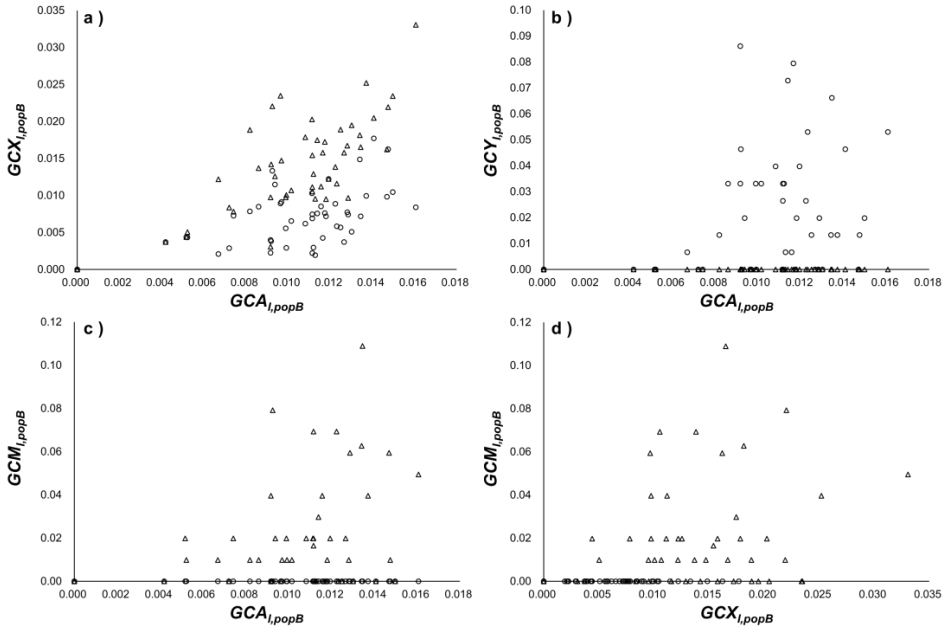

Figure 6. Comparison of average genetic contributions of 100 G1 mice to G8: (**a**) shows the relationship between $GCA_{I,popB}$ and $GCX_{I,popB}$, (**b**) shows the relationship between $GCA_{I,popB}$ and $GCY_{I,popB}$, (**c**) shows the relationship between $GCA_{I,popB}$ and $GCM_{I,popB}$, and (**d**) shows the relationship between $GCX_{I,popB}$ and $GCM_{I,popB}$. Circle: average genetic contributions of 50 G1 male mice to G8; triangle: average genetic contributions of 50 G1 female mice to G8.

This study developed the novel method to calculate the genetic contributions with respect to genes on sex chromosomes and mitochondrial DNA. The results of gene-dripping simulation support the validity of our method (Figure 4). The distributions of values for

$GCA_{I,popB}$, $GCX_{I,popB}$, $GCY_{I,popB}$, and $GCM_{I,popB}$ were different (Table 3, Figure 6), implying that the degree of genetic composition (diversity) in a target population and its change through time could be different, as shown in Figure 5, depending on what genes are focused on. Therefore, when genes on sex chromosomes and mitochondrial DNA become more important, it will be required to use indicators for sex chromosomes and mitochondrial DNA, as well as autosomal genes. An extreme example would be the case when a genetic disease risk allele is located on sex chromosomes and mitochondrial DNA. Male fertility traits might also be a possible example to utilize *GCY* and *GCM* (e.g., [70–72]). Genetic evaluation using an animal model in considering the effects of X chromosome inheritance has been proposed [56,73]. Several studies have used this model to estimate the X-linked additive genetic effects using real data (e.g., [74–76]), while Meyer [77], with computer simulation, showed the difficulty in accurate estimation of X-linked effects. Wittenburg et al. [78] used the statistical model in considering autosomal and gonosomal (X and Y chromosomes) effects to estimate genetic parameters of piglet birth weight. Effects for Y chromosome and mitochondrial DNA inheritances could be considered as paternal and maternal lineage effects, respectively, based on the calculated *GCY* and *GCM*, and then, a statistical model for genetic evaluation simultaneously considering effects for genes on autosomes, sex chromosomes, and mitochondrial DNA might be available. Using this model could provide information on the relative importance of each kind of inheritance (autosomes, X chromosome, Y chromosome, and mitochondrial DNA), which might be available as weighting factors to take all components into account.

Pedigree error could affect the results of calculating genetic contributions (Table 4), which might introduce inappropriate population management. Errors in pedigree data occurred by different reasons, including human errors, and thus, continued efforts should be paid to confirm the accuracy of pedigree data. On the other hand, the values of genetic contributions obtained through pedigree analysis are "expected" values, and "actual" contributions might be different for genes on autosomes and X chromosome due to Mendelian segregation events (genetic drift) (Figure 4). This might be more crucial in the case that a long-term closed-line breeding with smaller population size has been practiced, such as maintaining a pig population after approving as a distinct strain in Japan.

Our primary objective was to develop the method to calculate genetic contributions with respect to genes on sex chromosomes and mitochondrial DNA, and as a further challenge, we extended the concept of CV of genetic contribution with respect to autosomal genes to those with respect to sex chromosomes and mitochondrial DNA. Our method developed in this study might also contribute the expansion of other indicators for genetic diversity, such as the number of founder alleles [48,50]. Further study would be valuable to develop an indicator to monitor the genetic diversity with respect to genes on sex chromosomes and mitochondrial DNA.

In the mouse study population [57], the sex ratio at mating was 1:1, the population has been closed, and there was no generation overlap (Table S1). We used this data as the example because such a pedigree structure seems easier to interpret the obtained results. On the other hand, livestock populations often feature generation overlap and sex ratio bias at mating, as shown in the pedigree data of Fernando and Grossman [56] (Table 1). As a result, for example, limited Y chromosome diversity has been reported in horse and cattle populations (e.g., [35,79,80]). Recent studies have examined the genetic improvement of superovulatory responses in cattle (e.g., [25,81,82]), in connection with the idea of preimplantation genomic selection (e.g., [83–85]). This kind of production might increase the frequency of full-sibs and reduce genetic diversity, especially with respect to the X chromosome and mitochondrial DNA. In the future, the behavior of genetic contribution under different pedigree structures should be investigated in detail using computer simulations.

Storage facilities, such as gene banks, are used to preserve gametes and embryos (e.g., [86–88]), and as a response to epidemics, such as recent outbreaks of classical swine fever in Japan [89–91]. Previous studies have examined the use of conserved genetic

resources for autosomal genes (e.g., [92–94]), while genetic diversity of genes on sex chromosomes and mitochondrial DNA should also be monitored. Therefore, in the future, the performance of the results of a genetic contribution calculation in tracing the gene flow should be assessed in detail. Moreover, genetic improvement by selection while considering genetic diversity for autosomal genes has been studied (e.g., [95–97]), and it might be possible to consider genes other than autosomes by using the indicators developed here.

4. Conclusions

We developed novel methods for calculating the genetic contribution for genes on sex chromosomes and mitochondrial DNA by extending the method for calculating the genetic contribution of autosomal genes. Using real pedigree data of a mouse population [57] (Table S1), the calculated genetic contributions were in excellent agreement with the results of the gene-dropping simulation (Figure 3). The consistency among the calculated genetic contributions for genes on different types of DNA was not consistently high (Figure 6). The effect of pedigree errors on the calculated genetic contribution depended on the error rate and when errors were introduced (Table 4). We believe that the proposed methodology could contribute to future sustainable breeding strategies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/d14020142/s1, Table S1: Pedigree data of mice population in Ogawa and Satoh [57].

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