HERITABILITY AND REPEATABILITY OF PATERNAL HAPLOTYPE RECOMBINATION RATE IN BEEF CATTLE AUTOSOMES

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SUMMARY

Recombination and de novo mutations generate genetic diversity in a population, which is the key element for evolution and selective breeding. The variation in recombination rate across the genome and the recombination hotspots can be estimated by haplotype analysis. However, the crossing-over rate is not uniform across different individuals. In this research, we estimated the recombination rate across the autosomal chromosomes of 4 Australian beef cattle breeds. Further, we estimated variance components, heritability and repeatability of recombination rate within each breed.

INTRODUCTION

During meiosis, haplotypes exchange Deoxyribonucleic acid (DNA) strands as a result of recombination processes, which contribute to the genetic diversity of the next generation. Genetic diversity is an essential element for natural and artificial selection. The change in genetic diversity across generations mainly depends on selection, the reduction in genetic variation due to genetic drift and inbreeding, and the amount of generated variation as a result of de novo mutations and recombination events (REs). In humans, recombination rates vary by gender and on average there are 1.65 times more autosomal crossing-over events in maternal than paternal haplotypes. In addition, recombination rate is higher near centromeres in females and near telomeres in males (Kong *et al.* 2002). In male beef cattle, mutations in REC8 (Sandor *et al.* 2012), CLPX1, (Ma *et al.* 2015) and RNF212 (Kong *et al.* 2002; Sandor *et al.* 2012) genes have been reported to affect genome-wide recombination rates. Progeny of sires with high recombination rates may have higher genetic diversity at each chromosome. Hence, depending on the selection criteria, the recombination rate of paternal chromosomes can be considered in selecting superior individuals to produce the next generations.

Based on phased data generated by Beagle (Browning and Browning 2007) and DAGPHASE2 (Druet and Georges 2010), Weng *et al.* (2014) estimated the recombination rates in Angus and Limousin cattle breeds. They tried to minimise the effect of wrong phasing in their results by removing anomalies in the phased genotypes like double crossover at short intervals, more than three crossovers per chromosome, and haplotype mismatch. These factors could substantially affect the ability to identify the number of REs correctly. Ferdosi *et al.* (2016) developed a maximum likelihood algorithm to identify paternal haplotype REs. This method was an extension to hsphase (Ferdosi *et al.* 2014) to identify REs in the paternal strand of half-sib families. It is robust to genotyping errors and does not require phased genotypes to identify REs. Our aim in this study was to estimate the heritability and variation of genome-wide recombination numbers in paternal haplotypes (GRNP) of Brahman, Hereford, Santa Gertrudis, and Wagyu without phasing their genotypes.

[*] A joint venture of NSW Department of Primary Industries and University of New England

MATERIALS AND METHODS

Genomic Data and estimation of recombination rate. The genomic data for this study was extracted from the BREEDPLAN genomic pipeline (Connors *et al.* 2017). The BREEDPLAN genomic pipeline was developed at the Animal Genetics and Breeding Unit (AGBU) and is commercialised by the Agricultural Business Research Institute (ABRI). This pipeline performs several quality control steps and consolidates several marker densities together. For example, the individuals were removed if they failed parent verification due to Mendelian inconsistency or other issues, had less than 79% calls with GC score less than 0.6, less than 80% call rate, average GC less than 0.6 or had more than 80% homozygosity rate (for more details, please refer to (Connors *et al.* 2017). To be able to estimate the paternal chromosomal REs accurately, the sires with more than eleven genotyped progenies were used in our study (Table 1). The pedigree was also extracted from the BREEDPLAN genomic pipeline for the selected individuals up to 3 generations. The GRNP was estimated in each offspring using hsphase 2 (Ferdosi *et al*. 2016).

Table 1. Number of sires and genotyped progeny and range of half-sib family size in different beef breeds after quality control and removing half-sib families with less than 12 progenies

Breed	Number of Sires	Range of Half-sib family size (mean ± s.d.)	Number of Individuals
Brahman	789	12 to 288 (33.65 ± 26.54)	26,491
Hereford	1,125	12 to 584 (34.32 ± 37.96)	38,609
Santa Gertrudis	164	12 to 145 (34.28 ± 23.88)	5,622
Wagyu	1,760	12 to 3245 (61.23 ± 148.22)	107,763

Variance components – repeatability model. The heritability and repeatability of recombination rate for each breed were estimated using the following model: $\mathbf{y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{Wp} + \mathbf{e}$, where **X, Z** and **W** are design matrices that relate observations to their corresponding effects, and **y**, **b**, **u**, **p**, and **e** are the vectors containing the number of REs of paternal autosomal chromosomes in progeny, fixed effects (mean), predicted breeding values, sire permanent environment effects (PE) and random residual terms, respectively. The variance of EBVs, PE and residual effects were assumed to be normally distributed with $u \sim N(0, \mathbf{A}\sigma 2u)$, $p \sim N(0, \mathbf{I}\sigma 2pe)$, and $e \sim N(0, \mathbf{I}\sigma 2e)$, respectively, where **A** is the Numerator Relationship Matrix (NRM) built using pedigree and **I** is an identity matrix. ASReml-R was used to estimate the variance components, heritability and repeatability of GRNP (Gilmour *et al*. 2015).

RESULTS AND DISCUSSION

The estimated GRNP in four cattle breeds using hsphase 2 in Santa Gertrudis, Wagyu, Hereford, and Brahman had on average 28, 27, 25, and 25 REs in autosomes, respectively. The normal distributions of estimates and the range of GRNP were in line with the previously published articles (Chowdhury *et al.* 2009; Weng *et al.* 2014). Weng *et al.* (2014) reported GRNP of 27.4 and 26.9 for Angus and Limousin, respectively. The number of genome wide REs ranged from 0 (Brahman and Hereford) to 59 (Wagyu). Figure 1 shows the median, first quartile and third quartile of REs in each half-sib group. There was large variation in GRNP across half-sib groups, which could be partially explained genetically (Table 2).

The boxplot of the number of REs by chromosome is shown in Figure 2. The average number of REs in chromosomes 1 to 20 was higher (close to 1) than other autosomal chromosomes (close to 0). Weng *et al*. (2014) removed the individuals with more than three REs in each chromosome from their study. However, the individuals which had high GRNP in Figure 2 were not removed in our

study due to the high reliability of the hsphase 2 algorithm in detecting crossing-over events.

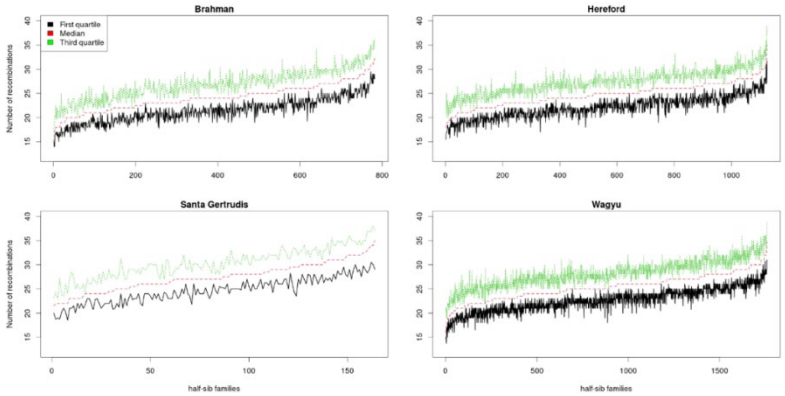

Figure 1. First quartile, median and third quartile of number of recombination events in different half-sib families sorted by median of number of genome-wide recombination numbers in paternal haplotypes

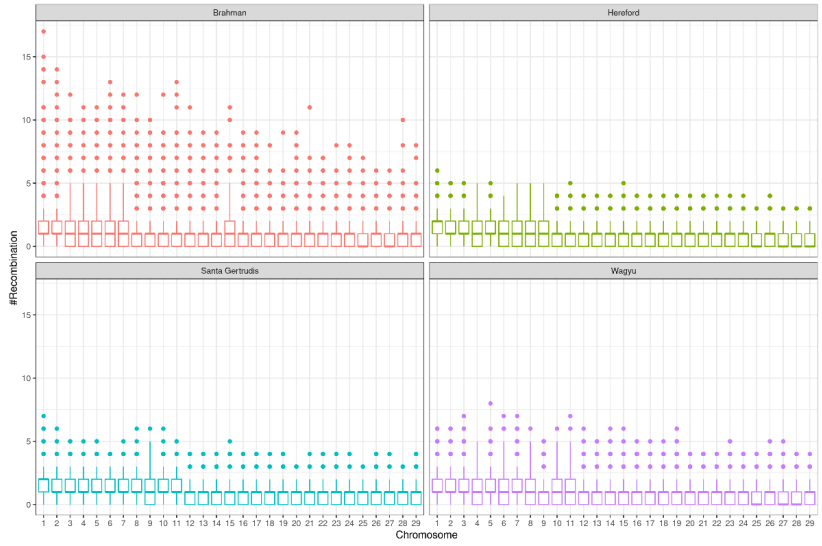

Figure 2. Boxplot of number of recombination events in 29 autosomal chromosomes in different breeds

The GRNP in some Brahman individuals was higher than our expectations. These individuals must be investigated further to identify the possible reason behind their strangely high recombination number estimates. This issue may be caused by the *Bos Taurus* map assemblies, as this map may not be adequate for mapping SNPs in the *Bos Indicus* cattle genome. However, removing these individuals had a negligible effect on the variance component estimation.

Variance components, heritability and repeatability of the number of REs are shown in Table 2. Weng *et al.* (2014) have reported heritability of 0.26 ± 0.030 and 0.23 ± 0.042 for recombination rate in Angus and Limousin sires, respectively, which were higher than our estimates. The rate of chromosome recombination is proportional to chromosome length and also varies between individuals. However, the identification of crossing-overs can be influenced by the level of

heterozygosity in the parents (Weng et al. 2014). Assuming the sire is completely homozygous, no REs can be detectable in the progeny. High homozygosity caused by low quality genotypes was not a concern in our study, as the BREEDPLAN genetic data passed the stringent quality control pipeline, and any individual with greater than 80% homozygosity was eliminated from the dataset. For example, although Australian Wagyu had very low haplotype diversity (Ferdosi *et al.* 2021), the number of detected REs in Wagyu was very similar to other breeds in our study.

Table 2. Additive genetic (σ^2_u), permanent environment (σ^2_{pe}) and residual (σ^2_e) variances, and the estimated heritability (h^2) ± s.e., and repeatability (r) ± s.e. of genome-wide recombination numbers in paternal autosomal chromosomes of different beef breeds

Breed	σ^2_u	σ^2_{pe}	σ^2_e	h^2	r
Brahman	1.57 ± 0.68	4.80 ± 0.67	19.10 ± 0.17	0.06 ± 0.03	0.25 ± 0.01
Hereford	3.08 ± 0.43	1.21 ± 0.31	17.90 ± 0.13	0.14 ± 0.02	0.19 ± 0.01
Santa Gertrudis	3.84 ± 2.03	3.56 ± 1.77	21.86 ± 0.42	0.13 ± 0.08	0.25 ± 0.09
Wagyu	2.97 ± 0.38	2.30 ± 0.25	20.33 ± 0.09	0.12 ± 0.02	0.21 ± 0.02

CONCLUSIONS

There was a large variation in the frequency of GRNP across individuals. The heritability of the number of REs was similar in different beef cattle breeds in our study, except Brahman, which was lower and could be a result of the *Bos Taurus* genome assembly used. A high GRNP in sires may contribute to an increase in population diversity. However, the underlying mechanisms and consequences of variation in REs in different individuals need to be investigated in future studies.

ACKNOWLEDGEMENTS

This study was supported by Meat and Livestock Australia project L.GEN.1704 and L.GEN 2204. The authors want to thank ABRI, the Australian beef societies and their members for providing the data for this study.

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