Journal of Animal Breeding and Genetics

WILEY

Journal of Animal Breeding and Genetics

ORIGINAL ARTICLE OPEN ACCESS

An Increase in Male Recombination Rate With Age in Dairy Cattle Is Heritable and Polygenic

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Received: 24 April 2025 | **Revised:** 5 May 2025 | **Accepted:** 30 May 2025

Funding: Evelyn Jade was supported by a University of Auckland Summer Research Scholarship.

Keywords: age-related change | *Bos taurus* | crossing over | meiosis | recombination rate

ABSTRACT

Meiotic recombination is an essential process for shuffling genetic diversity in sexually reproducing organisms, can vary within and between individuals in response to intrinsic and extrinsic factors, and can be heritable. Interestingly, recombination rate has been found to vary with age in some species, but to date, there have been no assessments of the heritability and genetic architecture of this age effect. Here, we leverage a large pedigree of SNP chip-genotyped Aotearoa New Zealand Holstein-Friesian and Jersey dairy cattle to test for an effect of age on male recombination rate, the heritability of recombination rate and of any such age effect on recombination, and the genetic architecture underlying these two phenotypes. We found a significant, albeit small, increase in the average number of male autosomal recombinations with age. Consistent with previous studies, we found moderate heritability ($h^2 \approx 0.15$) of sire recombination rate and detected association with several regions on chromosome 10 encompassing genes such as *REC8*, *REC114*, *RNF212B* and *NEK9*. Further, we found novel evidence of some heritability ($h^2 \approx 0.05$) in the rate of change in recombination with age in sires. Variation in the rate of change with age is likely also polygenic, but there is a region on chromosome 1 that is weakly associated with the rate of change. It is unclear whether the heritability of age-related recombination rate change is widespread across species, and we encourage studies in other taxa to assess its prevalence and evolutionary significance.

1 | Introduction

Recombination, also called crossing over, is the exchange of genetic material between maternally and paternally inherited homologous chromosomes during meiosis, resulting in hybrid 'recombinant' chromosomes containing a mixture of maternal and paternal alleles (Zickler and Kleckner 2023). In many taxa, recombination is required for the accurate segregation of chromosomes during meiosis (Sherratt et al. 2004). Recombination is important evolutionarily because it creates new combinations of alleles along a chromosome, facilitating the formation of new beneficial haplotypes or the breakup of deleterious haplotypes, which can in turn increase the rate of evolutionary change in both natural and artificial selection contexts (McDonald et al. 2016; Otto and Barton 2001). However, recombination can also break up beneficial haplotypes and decrease progeny fitness, as well as allowing deleterious alleles to 'hitchhike' and spread through the population

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during a selective sweep (Hartfield and Otto 2011). Further, recombination is itself a mutagenic process (Halldorsson et al. 2019). Therefore, while higher recombination rates increase the efficacy of selection at a population level, increased mutation and the dissociation of beneficial haplotypes mean that high-recombining individuals may suffer from lower fitness (Henderson and Bomblies 2021). As a consequence, there is some evolutionary constraint on recombination rate, with empirical studies suggesting approximately one- to twofold variation within a species (Ritz et al. 2017).

Recombination rates are known to vary between individuals, sexes, populations and species (Stapley et al. 2017) and variation in genome-wide recombination rate is heritable in many species (Brekke et al. 2023; Johnsson et al. 2021; Kawakami et al. 2019; Shen et al. 2018; Stapley et al. 2017). Genome-wide association study (GWAS) analyses have revealed associations to genes involved in modulating and resolving crossovers (Henderson and Bomblies 2021; Johnston 2024). Recombination can resolve the double-strand breaks that arise at the base of chromatin loops that are anchored along the chromosome axis, and recombination rates are therefore mechanistically correlated with the formation of the axis and the length of the loops (Johnston 2024; Ruiz-Herrera et al. 2017). Genome-wide association analyses of recombination rates have therefore also found associations to genes that regulate the formation of chromatin loops (Henderson and Bomblies 2021; Johnston 2024).

Recombination rate can also vary plastically within individuals, such as in response to extreme temperature, pathogens or other stress, and has been observed to change as individuals age in some species (Shen et al. 2021; Stapley et al. 2017; Zhong and Priest 2011). Human studies have found recombination to increase with female but not male age (Hussin et al. 2011; Kong et al. 2004; Sun et al. 2005). Conversely, spermatocyte analysis in mice found that both the mean and variance in recombination rate increased with male age (Vrooman et al. 2014). There was no effect of male age on autosomal recombination count in other mammals including Swedish Trotter and North-Swedish Trotter horses (Andersson and Sandberg 1984), Norwegian Red cattle (Brekke et al. 2023), red deer (Johnston et al. 2018) and Landrace and Large White swine (Lozada-Soto et al. 2021). Current evidence is therefore mixed regarding the effect of age on recombination. When detected, age-related changes in recombination rate are often hypothesised to be functional outcomes of physical changes to genome packaging and organisation. For example, in human studies, an observed increase in female but not male recombination rate with age has been linked to the age-related deterioration of sister chromatid cohesion in females (Tsutsumi et al. 2014). In mice, older male mice had a higher rate of meiotic errors leading to germ cell loss and eventually decreased sperm count (Vrooman et al. 2014). To date, there has been no investigation of whether age-related changes in recombination, if present, are themselves heritable, which would suggest that some individuals are more resilient to these age-related changes to the genome.

Agricultural datasets offer a unique ability to study recombination because large numbers of individuals within breeding programmes with known ancestry have been genotyped and phenotyped (Brekke et al. 2025; Wiggans and Carrillo 2022). Furthermore, artificial insemination technologies in many agricultural species can result in many offspring from a single sire, allowing estimation of recombination rate at many points over the lifetime of the animal. This makes agricultural mammals such as dairy cattle an ideal model organism for studying recombination (especially in males) due to the substantial volumes of genetic/genomic information and large half-sibling family structures. The history of artificial selection in these species also makes them interesting candidates to explore whether bottlenecking combined with strong selection on production traits has had an impact on increasing rates of recombination (Otto and Barton 1997; Ross-Ibarra 2004). This increase is predicted in scenarios where bottlenecking or genetic drift leads to beneficial alleles being dispersed amongst individuals in a population; co-inheritance of these beneficial alleles requires recombination between parental haplotypes, and hence recombination can be indirectly selected for during strong selection (Otto and Barton 1997).

Although there is mixed evidence for an increase in recombination in other domesticated species (Muñoz-Fuentes et al. 2015), cattle (*Bos taurus*) have high levels of recombination compared to other bovid species (Ruiz-Herrera et al. 2017; Vozdova et al. 2013). Previous work on cattle recombination has shown the genome-wide recombination rate to be heritable, though estimates of male narrow-sense heritability (h^2) vary across different studies and cattle breeds, from 0.04 in Norwegian Red (Brekke et al. 2023) and 0.14 in a combined Holstein-Friesian and Jersey dataset (Zhang et al. 2020), up to around 0.2 in Angus, Limousin and Holstein-Friesian (Sandor et al. 2012; Weng et al. 2014). GWAS analyses have implicated a range of loci that contribute to variation in cattle recombination rate, with multiple studies highlighting a region near the end of chromosome 6 (containing *CPLX1* and *RNF212*) and several regions on chromosome 10 (containing *REC8*, *REC114*, *RNF212B*, *PABPN1*, *FMN1* and *NEK9*) (Kadri et al. 2016; Ma et al. 2015; Sandor et al. 2012; Shen et al. 2018).

Here, using an Aotearoa New Zealand dairy cattle dataset from Livestock Improvement Corporation (LIC) with 93,592 sire-offspring pairs genotyped at 31,732 single nucleotide polymorphism (SNP) markers, we estimate the effect of male age on recombination rate, the heritability of recombination rate and the heritability of the age effect on recombination, as well as the genetic architecture underlying recombination rate and the age effect.

2 | Methods

2.1 | Data Processing

2.1.1 | Data Sources and Quality Control (Individual/SNP-Level)

Our genetic dataset was subset from a large LIC database of >150,000 Aotearoa New Zealand dairy cattle physically genotyped or imputed to the Illumina BovineSNP50k SNP chip (Reynolds et al. 2021). A list of focal males was first identified from this database by extracting those that had information on their date of birth, breed and location and had at least one

genetically verified parent and at least one genetically verified progeny also in the database. The list of focal males was further filtered to exclude sires who had no progeny with a known sperm collection date. All focal males, along with their genotyped parents, genotyped progeny with a known sperm collection date and genotyped dams of these progeny were extracted into a dataset. The data represent 121,685 dairy cattle, including 3151 focal sires, and form part of a 260,306-individual pedigree, with family relationships but not genotypes known for the remainder of individuals. Our genetic dataset of 121,685 New Zealand dairy cattle overlaps with a smaller subset of 58,474 individuals previously analysed alongside two other populations to detect loci associated with recombination rate variation (Kadri et al. 2016).

Genotypes were available for 34,738 SNP markers from the BovineSNP50k panel, representing a subset of variants that had been quality-filtered as previously described (Jivanji et al. 2019; Reynolds et al. 2021). We further filtered this genotype data using *PLINK* v1.9 (Chang et al. 2015), ensuring that cattle and SNPs had < 1% missing genotypes and Mendel error rate, that SNPs had minor allele frequency > 1%, but that we kept all 3151 sires of interest in the data. This gave us a final dataset of 118,976 cattle genotyped at 31,732 SNPs. Full details of data quality control and filtering are available in Table S1. We then zeroed out' (set genotype to 0) 1,386,629 remaining Mendel errors via –set-me-missing so that they would not interfere with phasing.

2.1.2 | Phasing and Crossover Inference

We used the LIC genotype data in conjunction with a linkage map generated in a previous study (Data S1; Shen et al. 2018) to phase alleles and infer crossover events passed from sires to their progeny. The Shen linkage map provided male and female SNP-to-SNP genetic distances for Holstein, Jersey, Brown Swiss and Ayrshire cattle. We chose to average the Holstein and Jersey male distances, as this study investigates male recombination and our sires were a fairly even mix of Holstein-Friesian and Jersey (42.3% Jersey and 56.7% Holstein average ancestry across the 3151 sires of interest; the remainder were Ayrshire but were later excluded during filtering). We then summed the SNP-to-SNP distances along each chromosome to calculate cumulative genetic locations for each of the 58,981 Shen SNPs. We integrated these distances into the LIC data, removing the 2481 LIC SNPs not present in the Shen data and the 469 remaining LIC SNPs with a non-unique ID. This left us with 31,732 SNPs with known genetic distances and a total genetic distance of 24.275 Morgans across the 29 autosomes.

Using a hidden Markov model via *LINKPHASE3* (Druet and Georges 2015), we estimated the number and location of crossovers for each genotyped parent-offspring pair in the pedigree separately for each autosome. Each parent–offspring pair represented one meiosis (Figure 1), as *LINKPHASE3* estimates the recombinations passed from that single parent to the gamete that formed the offspring. From the *LINKPHASE3* output, we extracted the per-chromosome crossover count, informative marker count, parent sex, half-sibling family size and, if there

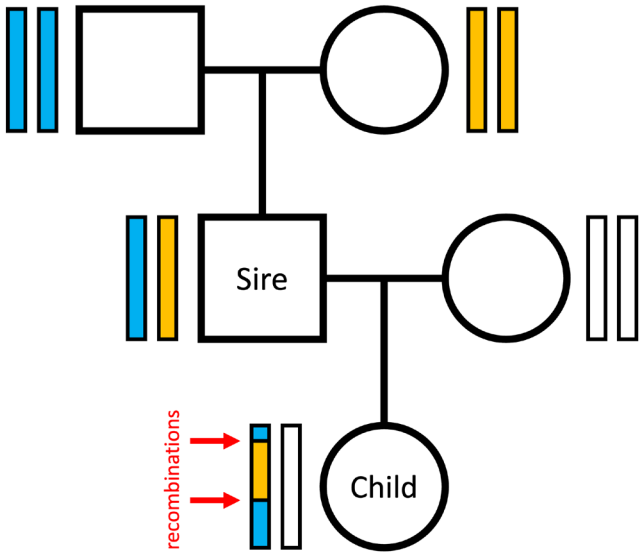

FIGURE 1 | Graphical representation of phasing process to determine number of recombinations passed from sire to offspring. The sire inherits one chromosome from each parent (blue and orange) and passes one chromosome to his offspring. Phasing allows the determination of the number of crossover points ('recombinations') there have been between the sire's paternally- and maternally inherited chromosomes (red arrows). Figure adapted from Johnston et al. (2016). [Colour figure can be viewed at wileyonlinelibrary.com]

were multiple crossovers on the chromosome, minimum distance between crossover locations for each parent–offspring pair. We then combined this with the LIC data on sire date of birth, breed and location.

2.1.3 | Data Filtering (Meiosis/Chromosome-Level)

LINKPHASE3 phasing identified 151,995 parent-offspring pairs and the number of recombinations for each of them, with 118,563 of these with a male parent. Due to earlier filtering to remove offspring and parents with poor genotyping success, 82 focal sires had no genotyped first-degree relatives, so 3069 of the focal sires remained. We then performed a series of filtering steps for further quality control on the individuals and their metadata, including only parent–offspring pairs where the focal parent was one of the 3069 sires of interest, excluding all pairs where the sire's breed was Ayrshire or unknown (generally because there was some non-Jersey/Holstein ancestry), the sire's date of birth or the offspring's date of sperm collection was unknown or unclear (i.e., the sire's age at time of sperm collection was unknown), or the date of sperm collection preceded the date of birth (i.e., the inferred sire age at collection was negative). Within each parent–offspring pair, we also filtered chromosomes to exclude chromosomes that had two crossovers within 3 centimorgans (cM) of each other and chromosomes with the lowest 2.5% of informative markers for each chromosome number (i.e., not all parent–offspring pairs had recombination data for all chromosomes). We then excluded parent–offspring pairs where fewer than 20 chromosomes remained, there were more than 70 total recombinations, there were more than two crossovers per Morgan genome-wide, or there were fewer than 10 remaining

offspring in the half-sibling family. Full filtering details are available in Table S2.

After chromosomes were excluded, we calculated the recombination rate as crossovers per Morgan for each parent-offspring pair by dividing the number of crossovers on the remaining chromosomes by the total genetic distance across all remaining chromosomes. This step aimed to normalise the data for the variable number of remaining chromosomes, which would otherwise affect the total number of crossovers for each pair. Recombination rate is the main response variable we used throughout the study. We also calculated the breeding window for each sire (time between his first and last sperm collection dates). Our final dataset after filtering consisted of 93,592 offspring from 1976 sires, with an average recombination rate of 1.04 crossovers per Morgan.

2.2 | Data Analysis

2.2.1 | Global Age Effect Estimation

We used the *lme4* v1.1–34 package in *R* v4.2.1 (Bates et al. 2015; R Core Team 2023) to fit a linear mixed model examining the effect of male age on recombination rate. To choose which covariates to include, we fitted a large model including sire age, breed, birth date and breeding window as fixed effects, as well as all first-order interactions therebetween, and a quadratic term for age, and used sire identity (ID), location and birth year as random effects. We then used the *MuMIn* v1.47.5 package (Bartoń 2023) to do a complete submodel search on the fixed effects, ranked by corrected Akaike information criterion (AICc) (Sugiura 1978). The best-performing submodel included only age and breed as fixed effects (no interactions or quadratic term). To choose the best combination of random effects, we then fitted models with the eight possible combinations of ID, location and birth year (with age and breed as fixed effects) and chose the best of these, again ranked by AICc. The best-performing model had age and breed as fixed effects and ID and birth year as random effects. *gglm* v1.0.2 diagnostics (White 2023) suggested the model was a good fit to the data (Figure S1); therefore, this model was used for estimation of the global age effect. The *car* v3.1–2 and *effects* v4.2–2 packages (Fox and Weisberg 2019) were used to extract *p*-values from the *lme4* model via a Type II Wald chi-square test, and to isolate the effect of age for plotting in *ggplot2* v3.4.2 (Wickham et al. 2019). The same model was also fitted to near-pure Holstein sires only ($\leq 1/16$ Jersey) and near-pure Jersey sires only ($\geq 15/16$ Jersey). The model originally estimated change in recombination rate per day, but results were scaled by 24.275 Morgans and 365 days to present a more interpretable change in inferred autosome-wide crossover count per year.

The final model we fitted was:

$$y = X\beta + Rr + \varepsilon$$

where: y is the recombination rate for each sire-offspring pair,

X is the design matrix for fixed effects, including:

- Sire age at time of sperm collection
- Sire breed (proportion Jersey ancestry, as opposed to Holstein, out of 16 at the great-great-grandparent level),

R is the design matrix for random effects, including:

- Sire ID (unique to each sire).
- Sire birth year (from 1986 to 2014).β and r are the estimated coefficient vectors for fixed and random effects, respectively, and ε is the residual vector.

2.2.2 | Heritability Analysis

To investigate the heritability of a sire's mean recombination rate ('mean') and the rate of change in recombination rate with age ('slope'), we first calculated each sire's overall mean recombination rate as a simple mean of the rates observed in each of his meioses/progeny. The approach of calculating a mean recombination rate per sire allows consistency in the analyses of recombination rate and the age effect, which is also a single value per sire. To find the per-sire age effect slope, we fitted a linear model regressing recombination rate against age for each sire individually and recorded the coefficient of the age effect. To avoid double-correcting for any covariates, we did not fit any covariates at this stage, instead fitting them in the downstream heritability model only.

To choose a method for heritability estimation, we used our pedigree with simulated phenotype data across a range of 'true' heritabilities (simulations performed in *R* via *hibayes*) to compare four methods: *GCTA* v1.94.1 (Yang, Lee, et al. 2011), *GCTB* v2.05beta (Zeng et al. 2018), *LDAK* v5.2 (Berrandou et al. 2023), and the 9 different Bayesian methods ('BayesA', 'BayesB', 'BayesBpi', 'BayesC', 'BayesCpi', 'BayesL', 'BayesR', 'BayesRR', and 'BSLMM') provided in the *R* package *hibayes* v3.0.1 (Yin et al. 2022). Comparisons of true versus estimated heritability across methods suggested that *GCTB* and the BayesCpi method in *hibayes* performed similarly well and consistently across heritability values (Figure S2). Given that *hibayes* has the advantage of allowing covariate fitting in *R*, we chose to use *hibayes* BayesCpi to estimate heritability.

To estimate the heritability, we recoded the *PLINK* per-allele genotypes (1/2) as per-SNP genotypes (0/1/2), and imputed missing genotypes (~1% of genotypes) as the mean genotype for that SNP. We then fitted a BayesCpi *hibayes* model with either overall sire recombination rate or rate of change in recombination as the response/phenotype variable, with sire breed (% Jersey), total number of half-siblings and breeding window as fixed covariates; sire location and year of birth as random environmental effects; and genotypes as explanatory terms. We used 10,000 total MCMC iterations with 2000 burn-in, and no thinning. This gave a posterior h^2 distribution from the 8000 remaining MCMC iterations, the mean of which was our estimated heritability for each trait and the 2.5%/97.5% quantiles of which provided our credible intervals. This analysis was performed with a sliding filter on sire breeding window (number of days between first and last sperm collection from each sire) from 0 to 500 days, as a more stringent

filter (e.g., requiring a minimum of 365 days between the first and last sperm collection for the sire) reduces the sample size but increases the quality of slope estimates (because slope estimates for sires with offspring over a shorter period will be less reliable). It was done once for all cattle, once for near-pure Holstein cattle only (≤1/16 or less Jersey heritage) and once for near-pure Jersey cattle only (≥15/16 Jersey heritage).

To test whether any differences we saw across the breeding window were statistical artefacts of diminishing sample size versus a biological difference, we fitted the same model with a sliding filter on breeding window from 0 to 365 days, but took a random subsample without replacement of the data each iteration with sample size 444 (the number of sires present with the filter at 365), and fitted the same *hibayes* model as before to the subsampled data. This was done only for all cattle (no breed subsetting), as the sample sizes at filter = 365 for the breed subsets would have been too small.

The model we fitted each time in *hibayes* was:

$$y = X\beta + Rr + M\alpha + \varepsilon$$

where:

y is the phenotype, either sire mean recombination rate or sire rate of change in recombination rate per day,

X is the design matrix for fixed effects, including:

- Sire breed (proportion Jersey ancestry, as opposed to Holstein, out of 16 at the great-great-grandparent level)
- Total number of phased offspring from the sire (immediately post-*LINKPHASE*, including those later removed during filtering)
- Sire breeding window (days between first and last date of sperm collection resulting in an offspring remaining in the data),

R is the design matrix for random effects, including:

- Sire birth year (from 1986 to 2014)
- Sire region (out of Bay of Plenty, Canterbury, Central Auckland, Central Plateau, Hawkes Bay, Nelson/Marlborough, Northland, Otago, South Auckland, South Canterbury, Southland, Taranaki, Wairarapa, Wellington, West Coast),

β and r are estimated coefficient vectors for fixed and random effects, respectively,

M is the genotype matrix, with one row per sire and one column per SNP, genotypes coded as 0/1/2,

α is the estimated SNP effect size vector, and ε is the residual vector.

These results were cross-checked against the same models fitted in *MCMCglmm* v2.36 (Hadfield 2010), with 10,000 iterations, no thinning and 2000 burn-in. Furthermore, overall heritability with one measure per offspring (a repeated measures model per sire) was estimated with the same *MCMCglmm* model, except with a random effect of sire ID added (to account for nonindependence between offspring from the same sire) and the fixed effect of number of phased offspring removed (as all offspring are included individually in the repeated measures model). This allowed comparison with other studies that report the heritability of recombination rate after accounting for permanent environment effects.

The relationship between heritability estimates and the sire breeding window was visualised in ggplot2 v3.4.2, with a loess smooth line with a span of 0.5 fitted via geom_smooth().

2.2.3 | Genetic Architecture

Finally, we explored the genetic architecture underlying the mean and slope phenotypes by testing each SNP marker for association with the phenotype, and partitioning the amount of variance explained by each chromosome. Multiple associated loci in the genome indicate support for a non- monogenic trait, while multiple chromosomes contributing to variance and/or a significant relationship between chromosome size and variance explained indicates a polygenic trait (Santure and Garant 2018; Yang, Manolio, et al. 2011b). To make sure we continued correcting for the fixed and random covariates, we extracted the residuals and the genetic variation components from the *hibayes* heritability model, i.e., extracted $M\alpha + \varepsilon$ (by multiplying the genotype matrix M by the SNP effect vector α, and adding the result to the residual vector ε). This gave the per-sire phenotypes against which we partitioned per-chromosome variance and tested for per-SNP association.

For per-chromosome variation partitioning, we used *GCTA* to construct a genetic relatedness matrix (GRM) for each chromosome individually, then used *LDAK* to estimate the proportion of phenotypic variance explained jointly by loci on each chromosome (fitting all chromosomes simultaneously). We then used *GCTA* to perform a SNP-level genome-wide association study (GWAS), accounting for genetic relatedness and estimating the effect and significance of each SNP. These analyses were done separately for both phenotypes and the three breed groups (all/near-pure Holstein/near-pure Jersey) and were repeated with breeding window filters of 0 or 365 days. All model settings were left as defaults. SNPs with <1% minor allele frequency were removed on a per-breed basis when generating the GRMs. A Bonferroni correction was performed for the 0.05 significance threshold to determine the adjusted genome-wide significance threshold. Due to the per-test minor allele frequency threshold resulting in different numbers of remaining SNPs, the corrected threshold was slightly different for each combination of breed and filter. With no breeding window filter, the corrected thresholds for all cattle, Holstein and Jersey were 1.577×10^{-6}, 1.582×10^{-6} and 1.685×10^{-6}, respectively, based on 31,714, 31,609 and 29,673 SNPs (equivalent to $-\log_{10}(p)$ scores of 5.802, 5.801 and 5.773). With the 365 days filter, the corrected thresholds for all cattle, Holstein and Jersey were 1.578×10^{-6}, 1.586×10^{-6} and 1.694×10^{-6}, respectively, based on 31,695, 31,526 and 29,517 SNPs (equivalent to $-\log_{10}(p)$ scores of 5.802, 5.800 and 5.771).

Once we had the SNP-wise GWAS results, we then used their genomic coordinates together with the UCSC genome browser

tool (Kent et al. 2002) and the ARS-UCD1.2/bosTau9 reference genome (Rosen et al. 2020) to identify genes within 250 kb of the genomic locations of strongly associated SNPs. This distance was chosen as LD decays to background levels of approximately $r^2 = 0.05$ at around 250 kb in both breeds (de Roos et al. 2008). Results were visualised via the *R* package *topr* v2.0.2 (Juliusdottir 2023) with further modification in *ggplot2*.

3 | Results

3.1 | Global Age Effect

From the *lme4* mixed model, we found a significant positive relationship between recombination rate and age ($p = 1.82 \times 10^{-18}$; Table 1, Figure 2). We estimate that for every year older a sire gets, the expected autosomal recombination rate in his meioses

TABLE 1 | Summary of final global age effect model output, from linear mixed model of autosomal recombination rate against sire age at time of sperm collection (in days) and sire breed (proportion Jersey ancestry, as opposed to Holstein), with random effect of sire ID and sire birth year.

Breed	*n*	Variable	Estimate (95% credible interval)	*p*
All sires	93,592	Intercept	1.047 (1.036, 1.057)	N/A
		Sire age at collection (days)	1.626×10^{-5} (1.256×10^{-5}, 1.989×10^{-5})	$\mathbf{1.824 \times 10^{-18}}$
		Sire breed (Jersey proportion)	−0.063 (−0.072, −0.055)	$\mathbf{1.389 \times 10^{-48}}$
Near-pure Holstein only (≤1/16 Jersey)	42,583	Intercept	1.056 (1.045, 1.067)	N/A
		Sire age at collection (days)	1.075×10^{-5} (5.551×10^{-6}, 1.587×10^{-5})	$\mathbf{4.372 \times 10^{-5}}$
		Sire breed (Jersey proportion)	−0.236 (−0.517, +0.048)	0.102
Near-pure Jersey only (≥15/16 Jersey)	27,232	Intercept	1.103 (0.711, 1.501)	N/A
		Sire age at collection (days)	2.133×10^{-5} (1.462×10^{-5}, 2.787×10^{-5})	$\mathbf{1.269 \times 10^{-10}}$
		Sire breed (Jersey proportion)	−0.128 (−0.526, +0.264)	0.524

Note: n represents the total number of sire-offspring pairs from which recombination rate is estimated. $p < 0.05$ bolded. Values for the estimate are in recombinations per Morgan.

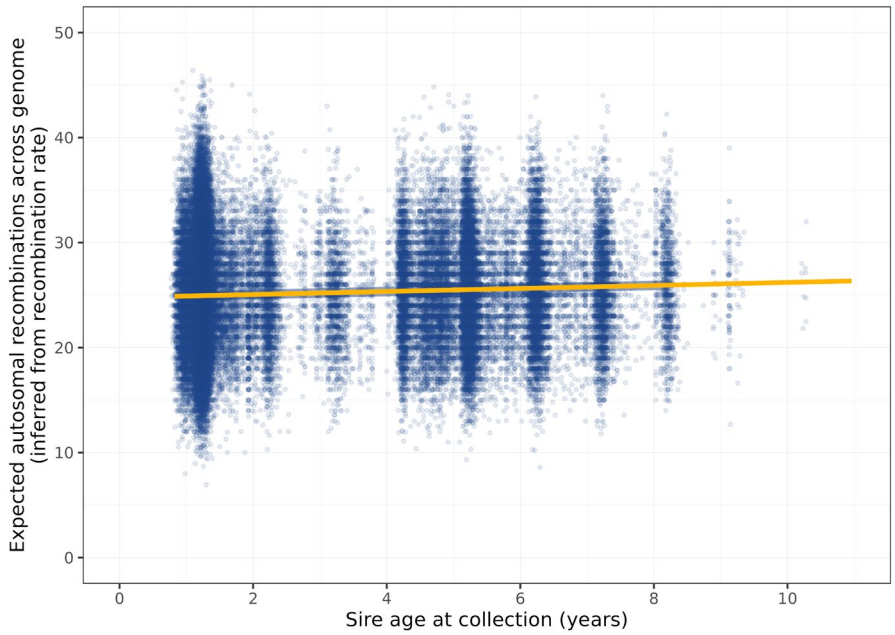

FIGURE 2 | Autosomal recombination rate in male Holstein-Friesian and Jersey dairy cattle is positively associated with the age of the sire at the time of sperm collection. The per sire-offspring pair recombination rate (crossovers per Morgan) was used to infer the expected total autosomal recombinations by multiplying by the total genetic distance across the genome (24.275 Morgan). A linear mixed model of recombination rate against sire age and breed, with a random effect of ID and birth year, was fitted with age in days (the graph axis has been scaled by 365 for interpretability); isolated effect of age is shown with the orange line. [Colour figure can be viewed at wileyonlinelibrary.com]

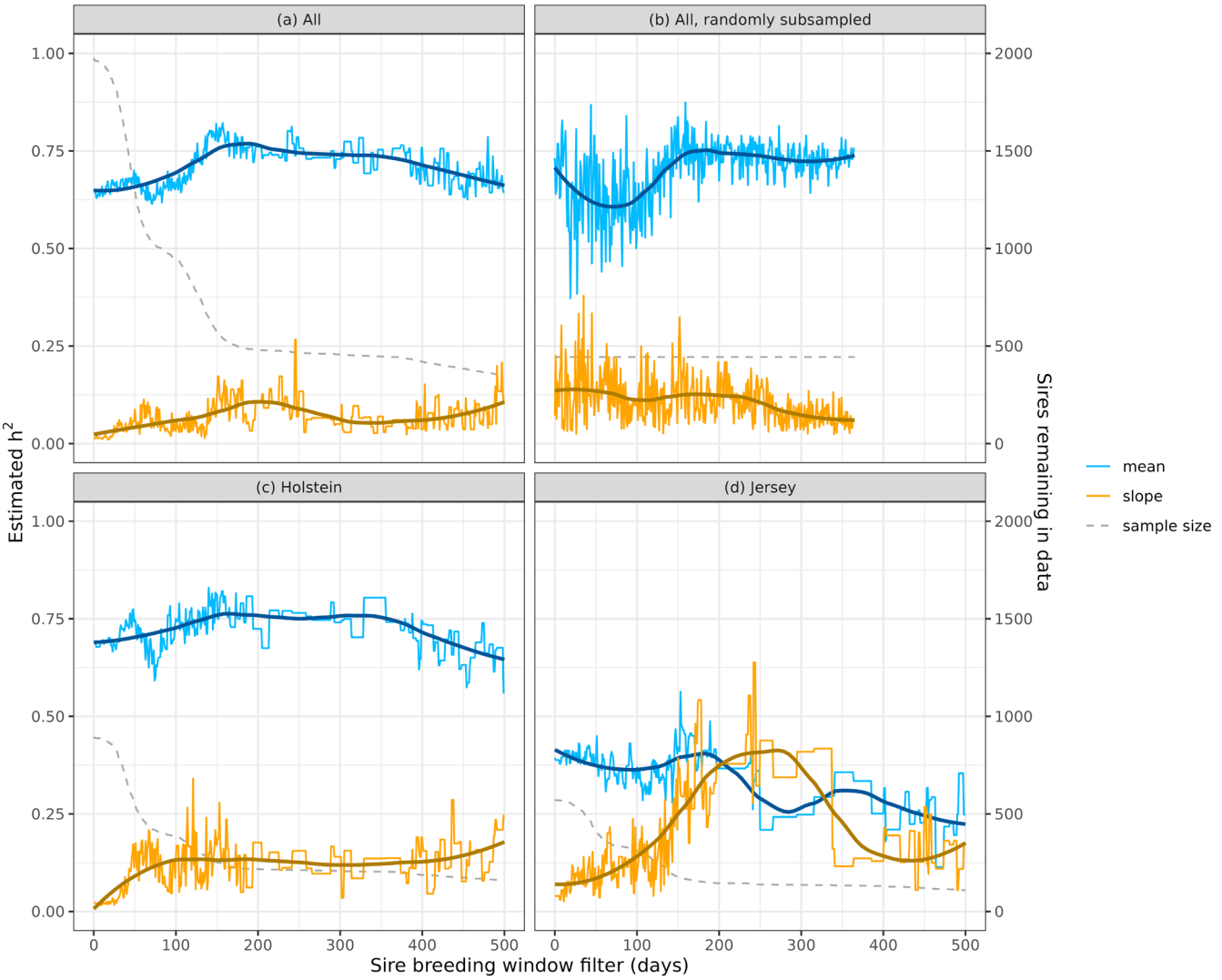

FIGURE 3 | Hibayes heritability estimates for mean recombination rate ('mean', blue) and rate of change of recombination rate with age ('slope', orange) in male Holstein-Friesian and Jersey dairy cattle, across different values of a filter keeping only sires that had sperm collected over a period of at least × days. Estimates presented for (a) all cattle, (b) all cattle randomly subsampled to $n = 444$ (the sample size remaining with filter at 365 days), (c) near-pure Holstein only (≤ 1/16 Jersey) and (d) near-pure Jersey only (≥ 15/16 Jersey). Sample size at each filter value shown in grey via alternative right-hand axis. [Colour figure can be viewed at wileyonlinelibrary.com]

increases by between 0.00458 and 0.00726 recombinations per Morgan. This corresponds to between 0.111 and 0.176 additional autosomal crossovers passed to each of his offspring on average.

Fitting the model to offspring of near pure-bred sires only, we still find a positive relationship with age ($p = 4.37 \times 10^{-5}$ for ≤ 1/16 sire Jersey ancestry; $p = 1.27 \times 10^{-10}$ for ≥ 15/16 sire Jersey ancestry; Table 1). Breed effects were predictably no longer significant when subsetting to near-purebreds only. We estimate that for every year older a near-pure Holstein sire gets, there will be between 0.049 and 0.141 additional autosomal crossovers passed to each of his offspring on average; for Jersey sires, we estimate an average of 0.130 to 0.247 additional autosomal crossovers per year.

3.2 | Heritability

Our estimates for heritability were quite sensitive to different values of the breeding window filter (different minimum amounts of time between first and last sperm collection for each sire) (Figure 3). Including all cattle, the *hibayes* method estimated a narrow-sense heritability (h^2) of 0.643 (95% credible interval [95% CI]: 0.554, 0.757) for mean recombination rate ('mean') and 0.0155 (0.000644, 0.0483) for the rate of change with age ('slope'). However, including only cattle that had sperm collected over the course of at least a year (breeding window ≥ 365 days), *hibayes* estimated a higher heritability of 0.765 (0.581, 0.920) for mean and 0.0410 (0.00114, 0.128) for slope (Figure 3a). *MCMCglmm* estimates for heritability of mean and slope (Figure S3) were consistent with the *hibayes* estimates shown in Figure 3, though with a

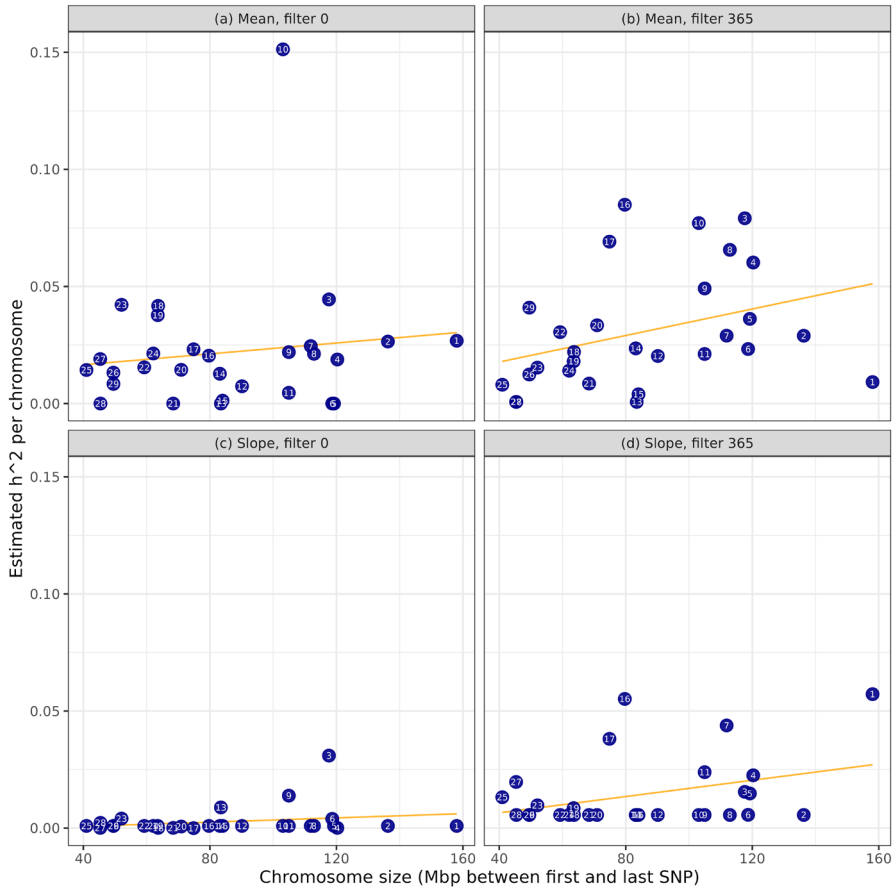

FIGURE 4 | Chromosomal associations with mean recombination rate ('mean') and rate of change in recombination with age ('slope') in male Holstein-Friesian and Jersey dairy cattle, filtering either to all sires or to only those that had offspring at least 365 days apart. Restricted maximum likelihood model was fitted to all chromosomes simultaneously in LDAK v5.2 (Berrandou et al. 2023), allowing estimation of narrow-sense heritability h^2 per chromosome. Linear best fit shown in orange; points labelled with chromosome number in white. Chromosome sizes here are the distance between the first and last SNP in our data for each chromosome, so they exclude telomeric regions and similar and are thus not always in the same length order as the chromosome numbers indicate. [Colour figure can be viewed at wileyonlinelibrary.com]

higher degree of noise and some missing data where *MCMCglmm* models failed to converge. The *MCMCglmm* repeated measures per sire model estimated an overall heritability of recombination rate of 0.116 (0.0987, 0.132) for all cattle and 0.149 (0.109, 0.188) for cattle with a breeding window of at least 365 days.

Subsetting by breed, the near-pure Holstein heritability estimates were quite similar to the overall estimates for mean and slightly higher for slope (Figure 3c,d). Conversely, the near-pure Jersey estimates were much lower for mean and very inconsistent for slope. For both breed subsets, but particularly Jersey, the small sample sizes led to erratic estimates, especially at the more stringent filter values. This was again consistent with the *MCMCglmm* estimates (Figure S3c,d).

Rerunning the all-cattle analysis with random subsampling without replacement at each filter level (meaning the sample size was fixed at $n = 444$, the sample size with breeding window ≥ 365), we saw that while there was considerable variation in the estimates, the increase in heritability from around 0.65 at filter 0 days to around 0.75 past filter 150 days was still present (Figure 3b, compared to 3a). This indicated a true biological increase rather than a statistical artefact of sample size, and was also true of the *MCMCglmm* estimates for both mean and repeated-measures overall heritability (Figure S3a,b).

3.3 | Genetic Architecture

Chromosome partitioning indicated an overall polygenic architecture for both the mean and slope of recombination rate, with multiple chromosomes contributing to variance, and an increase in variance explained as chromosome size increased (Figure 4a–d). However, there was evidence of a large effect locus contributing to mean recombination rate, with a strong contribution of chromosome 10 to variation in overall recombination rate, with a per-chromosome h^2 of 0.151 when considering all cattle (Figure 4a). The chromosome 10 contribution was not present when filtering to only cattle with a breeding window of at least 365 days (Figure 4b), likely because of the greatly reduced sample size without any change in the quality of the phenotype estimates (Figure 3a).

The SNP-level genome-wide association showed similar results. Using the 'mean' phenotype with filter 0 days on all cattle, we see two significant peaks on chromosome 10, with peak

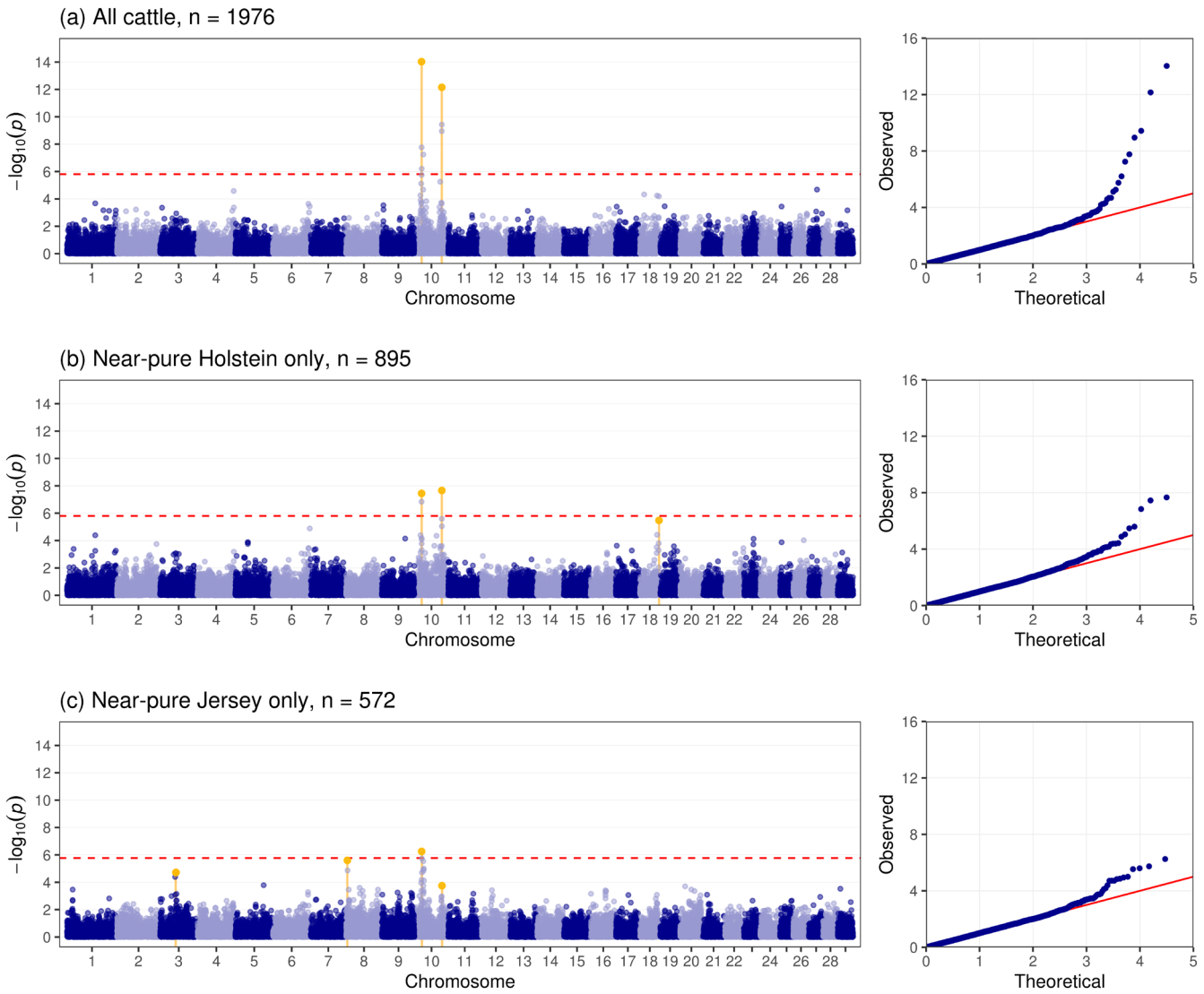

FIGURE 5 | Genome-wide association of mean recombination rate in male Holstein-Friesian and Jersey dairy cattle, looking at (a) all sires, (b) only sires with ≤1/16 Jersey heritage, or (c) only sires with ≥15/16 Jersey heritage. Manhattan plots showing the association of each SNP to mean recombination rate are on the left; QQ plots showing observed versus expected $-\log_{10}(p)$ values are on the right; Bonferroni genome-wide significance is shown in red. Significant or suggestive loci are highlighted in orange. [Colour figure can be viewed at wileyonlinelibrary.com]

associations at 'rs110890764' and 'rs43640523' markers, at positions 21,225,382 and 86,717,378, respectively (Figure 5a). Although not the closest genes, the first peak notably includes *REC8*, a meiotic chromatid binding protein which has previously been implicated in recombination (Sandor et al. 2012) and *REC114* and *RNF212B*, which are also involved in meiosis and may influence recombination (Kadri et al. 2016; Shen et al. 2018). Marker rs43640523 is within an intron of the *BATF* gene (basic leucine zipper ATF-like transcription factor). Further, around 350 kb from rs43640523 is *NEK9*, a spindle organisation and meiotic progression gene that has likewise previously been identified in cattle recombination GWAS analyses (Ma et al. 2015; S.-W. Yang et al. 2012). These chromosome 10 peaks are therefore in line with previous GWAS findings, and there were no other obvious peaks for all cattle. All GWAS results for SNPs with $p < 10^{-4}$ are provided in Table S3; all NCBI GenBank Reference Sequence IDs and gene locations of genes within 250 kb up- or down-stream of those SNPs with $p < 10^{-4}$ are provided in Table S4.

Subsetting to near-pure Holstein only, both chromosome 10 peaks were still significant, but there was a new peak on chromosome 18 that nearly reached Bonferroni significance (Figure 5b). The chromosome 18 SNP with the highest $-\log_{10}(p)$ (5.47) was 'rs109311845' at position 63,037,062. The nearest characterised gene is *CDC42EP5* (CDC42 effector protein 5).

Subsetting to near-pure Jersey only, the second peak on chromosome 10 was no longer significant, though it was still visible below the Bonferroni threshold for this breed/filter combination, and this may be a consequence of the smaller sample size (Figure 5c). There was no signal on chromosome 18, but there was an almost-significant peak on chromosome 8 and a weaker association on chromosome 3. The SNP with the highest $-\log_{10}(p)$ (5.60) on chromosome 8 was 'rs42403123' at position 4,069,868. This occurs within an intron of the large *GALNTL6* gene (polypeptide N-acetylgalactosaminyltransferase like 6). At the possible peak on chromosome 3, the 'rs41624964' and 'rs109736324' SNPs are close together (positions 51,245,024

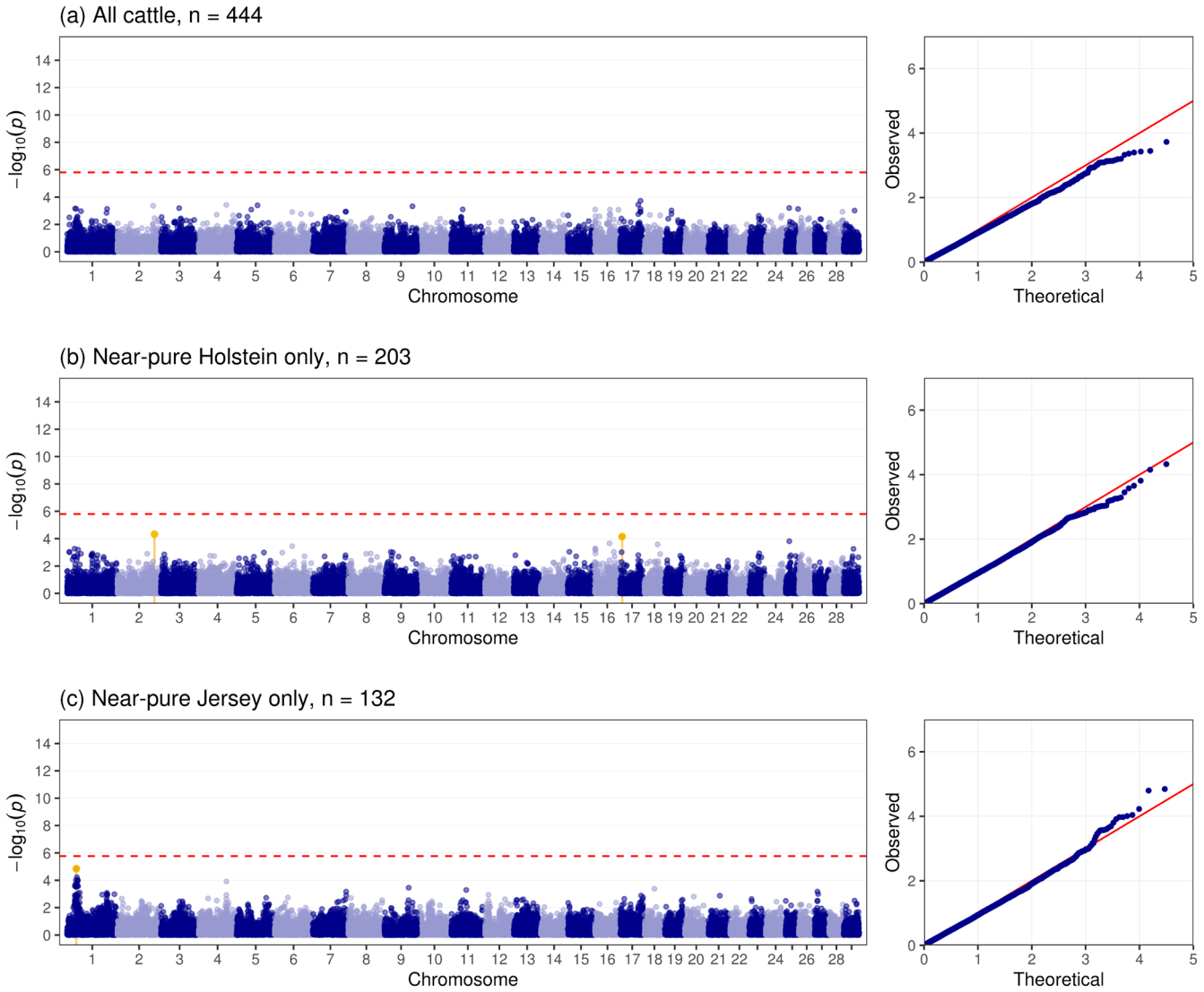

FIGURE 6 | Genome-wide association of rate of change in recombination rate with age in male Holstein-Friesian and Jersey dairy cattle, looking at (a) all sires, (b) only sires with ≤1/16 Jersey heritage, or (c) only sires with ≥15/16 Jersey heritage. Manhattan plots showing association of each SNP are on the left; QQ plots showing observed versus expected −log10(p) values are on the right; Bonferroni genome-wide significance is shown in red. All sires in this analysis had at least 365 days between their first and last date of sperm collection that resulted in an offspring in the data. Suggestive loci are highlighted in orange. [Colour figure can be viewed at wileyonlinelibrary.com]

and 51,399,357, respectively) and are in complete linkage disequilibrium, thus were equally the most associated with the trait ($\log_{10}(p) = 4.72$). The former occurs just upstream (possibly within an intron, depending on annotation/splice variant) of the *BTBD8* gene (BTB/POZ-domain containing 8) while the latter is within an intron of the *BRDT* gene (bromodomain testis-specific protein).

Using the 'slope' phenotype with filter 365 days on all cattle, there were no obvious or even suggestive peaks, with the largest $\log_{10}(p)$ value being 3.73, well below the threshold of 5.80 (Figure 6a). Subsetting to near-pure Holstein only, there were two SNPs with a $-\log_{10}(p)$ score above 4, namely 'rs41646050' ($-\log_{10}(p) = 4.33$, chr2:118,824,462) and 'rs110477203' ($-\log_{10}(p) = 4.15$, chr17:6,348,852), though they were again well below the threshold of 5.80 (Figure 6b). rs41646050 lies within an intron of the *SPATA3* gene (spermatogenesis-associated protein 3) while rs110477203 is within an intron of the *FHIP1A* gene (FHF complex subunit HOOK interacting protein 1A). Conversely, subsetting to near-pure Jersey only showed a suggestive peak on chromosome 1 composed of many SNPs (Figure 6c). While it did not reach the Bonferroni threshold of 5.77, having many somewhat associated SNPs in the same location gives some support for true association in this region. The SNP with the highest $-\log_{10}(p)$ (4.84) was 'rs29010795' at position 29,524,658. The closest gene is *GBE1* (1,4-alpha-glucan branching enzyme 1).

Using the 'mean' phenotype with filter 365 days and the 'slope' phenotype with all sires, we did not find any noteworthy associations (likely because the filter reduces sample size but does not benefit phenotype estimation for mean, whereas the filter is necessary for slope because slope cannot be properly estimated without the sire having had offspring over a long period of time), so they are not presented here but are available as Figures S4 and S5.

4 | Discussion

4.1 | Global Age Effect

We found that the recombination rate was positively associated with sire age in cattle, and that this pattern was consistent across both Holstein-Friesian and Jersey breeds. This is contrary to most previous studies in mammals, including other cattle studies, which have found no effect of age on male recombination (Andersson and Sandberg 1984; Brekke et al. 2023; Hussin et al. 2011; Johnston et al. 2018; Kong et al. 2004; Lozada-Soto et al. 2021; Sun et al. 2005). It is likely that we were able to detect a relationship between age and recombination because of the large number of sire-offspring pairs in our study. Sample sizes in previous studies ranged from as low as 34 in humans (Hussin et al. 2011) to 28,652 in horses (Andersson and Sandberg 1984), which are considerably smaller than our sample of 93,592 offspring (including 42,583 from near-pure Holstein and 27,232 from near-pure Jersey sires). We note that our estimated effect size was very small, with an average increase on the order of 0.1–0.2 additional crossovers autosome-wide per year. Therefore, in many cases it seems plausible that the previous studies did not have the power to detect such a small effect—highlighting the effectiveness of agricultural species as models for studying recombination. A full comparison of sample sizes is available in Table S5. It is also possible that the age effect we detected is specific to cattle, or even the specific Holstein and Jersey breeds in our data.

4.2 | Heritability

We found high heritability of mean recombination rate per sire, with an h^2 of around 0.65–0.75 (depending on the breeding window required for sires to be included in the model, Figure 3), but lower heritability of overall recombination rate when fitting a model with multiple measures per sire (i.e., one measure per offspring), with an h^2 of 0.10–0.15. The latter was broadly consistent with previous repeated-measure estimates in cattle, which have been as low as 0.04 in Norwegian Red (Brekke et al. 2023), 0.14 in comparable Holstein-Friesian and Jersey breeds (Zhang et al. 2020), 0.22 in Holstein-Friesian (Sandor et al. 2012), up to 0.23 and 0.26 in Limousin and Angus, respectively (Weng et al. 2014). Male heritability estimates in other mammals likewise tend to be low to moderate, such as 0.06 in domestic pigs (with an estimate of 0.86 for the per-sire mean heritability) (Brekke et al. 2025), 0.07 (not significant) in red deer (Johnston et al. 2018), 0.12 in Soay sheep (Johnston et al. 2016), 0.14 in humans (Fledel-Alon et al. 2011) and 0.46 (both sexes) in mice (Dumont et al. 2009). These studies typically use repeated-measures rather than per-sire mean models, so the *MCMCglmm* repeated-measures model was comparable in both methodology and results. Nonetheless, our single-measures mean model was important for within-study consistency and comparison. The slope phenotype necessitated a single-measures approach as the rate of change in recombination over each sire's lifetime cannot be calculated per-offspring and is inherently a single value per sire. We are confident that none of the heritability estimates were confounded by breed differences, as we accounted for breed in the *hibayes* heritability estimation model and fitted breed-specific models. Although there were some breed differences, with near-pure Holsteins heritability higher than for near-pure Jerseys, this was likely due to lower sample size for the near-pure Jerseys.

An interesting result was that heritability of mean recombination rate, and to a lesser extent repeated-measures recombination rate, changed when increasing the minimum breeding window (the time in days between first and last sperm collection that produced an offspring in the data). The breeding window filter choice represents a trade-off between including all sires and including only individuals who had sired offspring from sperm sampled across a number of collection events. In the all-cattle model, both *hibayes* and *MCMCglmm* estimates for mean recombination rate rose from around 0.65 with no filter up to 0.75 when keeping only sires that had sperm collected over the course of at least 150 days, while *MCMCglmm* repeated-measures estimates rose from around 0.10 to 0.15. Rerunning the analysis with a fixed sample size (achieved via random subsampling without replacement) showed that this was not an artefact of decreasing sample size, suggesting it represents an actual biological difference between sires that were only used briefly and those that continued to be bred over long periods of time. Dairy sires in artificial breeding programmes are carefully selected to optimise offspring for beneficial milk production traits (Berry et al. 2020; Hinks 1972; Schmitt et al. 2019), so those that are kept for longer will be the ones that are considered genetically 'better'. It may be the case that increased heritability of recombination rate is a side effect that happens to coincide with beneficial traits for which breeders select, or it may itself be beneficial and selected for (intentionally or otherwise). Alternatively, it is possible that the sires chosen for long-term breeding may have some shared environmental features that are not shared between all sires, leading to comparatively decreased phenotypic variance and therefore a greater proportion of variance attributable to genotype, i.e., heritability.

The heritability of the rate of change in recombination rate with age has not been studied previously, and our results suggest that it is heritable to some extent, though much less so than overall recombination rate. There is again a change with filter stringency, but in this case, the estimates start at near-zero and then stabilise at 0.05–0.1 for the all-cattle and Holstein groups (they vary a lot more in Jersey, likely due to very small sample size). The change here is most likely because of poor estimation of the slope phenotype in sires with a narrow breeding window, as attempting to estimate the rate of change for a sire that had offspring only days or weeks apart is extremely unreliable. Therefore, using only sires that had offspring over a significant period of time allows for more robust estimation of the rate of change. This presents an inherent limitation of studying the rate of change in recombination on a per-sire basis, as relatively few sires are kept and bred for a long time.

4.3 | Genetic Architecture

The variance partitioning analysis indicated a polygenic trait architecture for both traits, with contributions to overall heritability coming from several chromosomes. For mean

recombination rate, chromosome 10 contributed far more to overall heritability than did other chromosomes, whereas for the rate of change in recombination with age, there was no single chromosome explaining a large amount of variance. GWAS results largely aligned with variance partitioning, identifying two locations on chromosome 10 that were strongly associated with the mean phenotype, as well as some breed-specific differences.

Our results for overall recombination rate largely correspond with previous studies in cattle that implicated two clusters of chromosome 10 genes including *REC8*, *REC114*, *RNF212B* and *NEK9* (Ma et al. 2015; Sandor et al. 2012; Shen et al. 2018). In particular, our results are concordant with a previous analysis of a subset of this New Zealand data alongside two other dairy cattle populations that tested for association with recombination rate in both males and females and found significant association for both sexes in these two regions on chromosome 10 (Kadri et al. 2016). *REC8*- and *RNF212B*-containing regions have also been associated with recombination in other mammals such as sheep and deer (Johnston et al. 2016, 2018), and even in plants such as barley (Dreissig et al. 2020). These genes all have well-characterised roles in meiosis, such as *REC8* facilitating segregation and *REC114* influencing double-strand break formation (Kumar et al. 2018; Sakuno and Hiraoka 2022). However, an important location we did not find a strong association with was the *RNF212/CPLX1* region on chromosome 6, which regulates crossing over (Reynolds et al. 2013) and has been implicated in recombination rate in many species including cattle (Kadri et al. 2016; Le et al. 2021; Sandor et al. 2012; Shen et al. 2018), humans (Fledel-Alon et al. 2011; Kong et al. 2008) and pigs (Brekke et al. 2025; Johnsson et al. 2021). Furthermore, chromosome 6 explained near-zero heritability in the variance partitioning analysis. This region has occasionally been found to have female-specific effects (Brekke et al. 2025; Johnston et al. 2016), which may have explained its lack of detection in our sire-only dataset, but both Shen et al. (2018) and Kadri et al. (2016), that examined a subset of the same Holstein-Friesian and Jersey sires we analyse here along with Holstein animals from France and the Netherlands, detected association in this region in male cattle. It is possible that the *RNF212/CPLX1* association signal detected in Kadri et al. (2016) was driven by these two other populations, and our New Zealand cattle have low frequencies of the quantitative trait loci variants in this region.

While we did not find any loci significantly associated with the rate of change in recombination with age ('slope'), there was a cluster of moderately associated SNPs on chromosome 1 in the Jersey group. We have not identified any strong candidate genes in the region, but given the interplay between chromosome packaging and organisation with recombination rate (Johnston 2024; Ruiz-Herrera et al. 2017), it seems likely that both meiotic genes and ageing-related genes are likely to play a role in the way that recombination changes with age. We note low power in this analysis, both because reliable rate-of-change phenotype estimates necessitate reducing the sample size (as discussed for heritability), and because the Bonferroni approach to multiple testing is conservative and does not account for nonindependence between SNPs. With this in mind, we believe chromosome 1 merits further investigation for potentially influencing how recombination rate changes with age, ideally with much more power than the 132 sires we had left for this analysis.

4.4 | Evolutionary Implications

The high heritability of recombination rate suggests that there is considerable genetic variation being maintained at loci that contribute to modulating and resolving crossovers, as well as those that regulate chromatin packaging. Given the history of strong artificial selection and bottlenecking in these dairy cattle populations, the maintenance of this variation may reflect the balance between artificial selection acting both to preserve favourable haplotypes present in the high-value dairy sires and to improve the efficacy of selection. In contrast, we identified a small change to recombination rate as sires age, and that this trait had detectable albeit low heritability. It is unclear if these characteristics are a feature of artificial selection or if they occur more broadly across taxa. It is possible that artificial selection may have acted to optimise the ability of individuals to buffer age-related changes to genome packaging and organisation; however, more data in this and other species are needed. Future work could focus on gene expression and methylation assays, currently predominantly focused on female dairy cattle (Prowse-Wilkins et al. 2022), to explore male age-related changes in gene regulation.

5 | Conclusions

Overall, this study found that there is a small but significant increase in the male recombination rate with age in Aotearoa New Zealand dairy cattle (0.11 to 0.18 additional autosomal recombinations per year on average). We found that the mean recombination rate per sire was highly heritable ($h^2 \approx 0.7$), the rate of change with age per sire was somewhat heritable ($h^2 \approx 0.05$), and the overall recombination rate with multiple records per sire was moderately heritable ($h^2 \approx 0.15$), though all varied when changing the minimum breeding window for sires to be included in the analyses. Loci on chromosome 10 were strongly associated with the mean recombination rate, consistent with the literature, and there was suggestive evidence that a locus on chromosome 1 might be associated with the rate of change with age, meriting further investigation with greater power.

Author Contributions

J.S. and A.W.S. conceived this study. J.S. contributed to methods and data curation and analyses. E.J. designed and performed data filtering and bioinformatic and statistical analyses with input from A.W.S. and J.S. K.E. designed and completed the extraction of genotype and metadata. M.D.L. and R.J.S. contributed important resources to the analyses. E.J. wrote the manuscript with input from A.W.S., J.S. and M.D.L. All authors contributed to the interpretation of the results and the final draft.

Acknowledgements

We acknowledge the use of New Zealand eScience Infrastructure (NeSI) high-performance computing facilities and Genetic Diversity Center (GDC) Zurich for computational support. Open access publishing is

facilitated by The University of Auckland, as organised by the Council of Australian University Librarians and its Member Institutions. We extend many thanks to Laura Duntsch and Susan Johnston for discussions that shaped the final manuscript. Our thanks to the reviewers for their helpful suggestions and feedback. Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Full code for all data filtering and analyses, and code to generate all graphs and outputs, along with sire metadata including breed, age at time of sperm collection and birth year is available at https://github.com/ejade42/Cattle-Recombination. The SNP genotype data used in this study are the sole property of Livestock Improvement Corporation (LIC) (Hamilton, New Zealand). Restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of LIC. A request to LIC for accessing the SNP data may be sent to Mathew Littlejohn (mathew.littlejohn@lic.co.nz).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.