Sex differences in recombination maps are associated with differential hotspot usage in sheep

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Abstract

Recombination is a fundamental biological process for the reproduction and evolution of species. Recombination phenotypes have been shown to exhibit large inter-individual variation with a significant genetic determinism. Here we make use of large genotyping datasets in the Sheep to: (1) study the distribution of recombinations along the genome (recombination maps); and (2) evaluate its inter-individual variation using a phenotype termed *hotspot usage* (HSU). We precisely estimated sex specific recombination maps and found that sex differences in recombination rates are concentrated in 16% of the genome, mostly at chromosome extremities. Individual variation in HSU is dominated by a large difference between sexes: males are found to preferentially use recombination hotspots contrary to females. This difference is most pronounced in regions with large sex differences in recombination rate. This suggests that sex difference in recombination maps in Sheep could be due to different crossover determination processes in male and female meioses.

Introduction

Recombination is a fundamental biological process that exhibits variation among species, populations and individuals. Two main recombination phenotypes have been studied at the individual level: recombination rate and recombination localisation. Individual recombination rates can be measured by counting the number of crossovers per meiosis (using pedigree or cytogenetic approaches). However, individual variation in crossover localisation is more difficult to measure as it requires data from a large number of meioses per individual and/or a very precise localisation of individual crossovers. One of the individual phenotypes that can be measured to evaluate variation in recombination maps is *hotspot usage (HSU)*. It is the propension for an individual to recombine in small genomic regions of high average historical recombination rate called hotspots. In this study we used a new dataset of precisely localised crossovers in sheep families to estimate HSU in multiple individuals and investigate its variation between the sexes.

Materials & methods

Datasets. This study exploits three datasets. First, two previously published datasets of medium density genotypes (~50K SNPs) in large pedigrees in Lacaune (Petit *et al.* 2017) and Soay (a primitive breed of domestic sheep; Johnston *et al.* 2016) sheep populations to build sex-specific recombination maps. Second, a new dataset of small nuclear families in a Romane population genotyped for a high-density SNP array (HD; ~600K SNPs) and used to study HSU variation. Datasets were phased and crossover positions identified using the software yapp (https://yapp-doc.netlify.app/).

Sex specific recombination maps. Recombination maps were estimated for each sex using poisson regression on crossover (CO) counts observed in non-overlapping 1 Mb intervals along the genome using the glm procedure in R. Sex-specific recombination maps were estimated considering each population by sex as a group in a Poisson-Log-Normal Model framework using the PLNmodels R package (Chiquet, Mariadassou, and Robin 2021). An extension of the model allowing for a mixture of poisson distributions assigned each 1 Mb interval to a specific mixture component and identified intervals with clear differences in recombination rates between sexes.

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Hotspot usage estimation. Hotspot usage was estimated in individuals from the HD Romane dataset and hotspots identified in Petit *et al.* (2017) using the procedure described in Coop *et al.* (2008). Briefly, this method estimates HSU in a collection of crossovers as the proportion that use a hotspot, adjusted for the size of the crossover localisation interval and the local hotspot density. First the probability that each crossover overlaps a hotspot by chance is estimated by randomly shifting its position locally. This allows to account for the size of the localisation interval (crossovers with large intervals have a higher probability of overlap by chance) and the local recombination rate (crossovers located in regions of high hotspot density have higher probability of overlap by chance). Then given a set of crossovers (for an individual, a sex …), the HSU is estimated by maximizing the likelihood that depends on these overlap probabilities (see Coop *et al.* (2008) for details).

Results

Table 1 summarises the crossover data for the three datasets. The two medium density datasets identify a large number of crossovers and can be used to precisely estimate average recombination rates. The HD dataset resolves crossovers in intervals roughly 10 times smaller and allows estimation of HSU.

Sexes differ in their recombination maps in few genomic intervals. Statistical analysis of crossover counts in the two MD datasets reveals that genomic intervals can be separated into 2 components in terms of recombination rate variation between groups. The majority component I (84% of the genome, green on Figure 1) exhibits essentially the same recombination rate in males and females. The minority component II (16% of the genome, purple on Figure 1) corresponds to intervals with large between sex variation, most of them located at the extremities. In both classes, the Soay and Lacaune populations have essentially the same recombination rates in males and females, despite their large genetic distance.

Hotspot usage exhibits strong sex differences and within sex variation. Pooling all crossovers from the Romane dataset, the HSU estimate is 59% with 95% confidence interval [57-61]. Males had significantly higher HSU (72%, CI [70-75]) than females (29%, CI [24-34]) (LRT=207.67 (1 df), P=4.5×10^{-47}). Figure 2 left shows that there is a large variation in individual estimates of HSU but mostly due to the large difference between sexes. However, a few outliers can be identified (two females with HSU>75 and 3 males with HSU<60) and the likelihood ratio tests on individual variation within each sex are significant (for females LRT=57.34 (27 df) P=5.8×10^{-4}, for males LRT=52.36 (28 df) P=3.5×10^{-3}).

Sex difference in hotspot usage and recombination rate are associated. Estimating hotspot usage in component II vs component I intervals reveals that females have an extremely low hotspot usage in intervals of class II while males have the same high hotspot usage in both components (Figure 2 right).

Table 1. Crossover data used in this study.

Population	Sex	# Parents	# Meioses	# CO	CO localization size (kb)[1]
Lacaune	Female	286	483	13,789	715 (249-4,168)
Lacaune	Male	542	8,991	325,487	687 (202-6,311)
Soay	Female	1,001	4,471	123,852	1,204 (266-9,614)
Soay	Male	631	4,157	144,237	829 (160-8,129)
Romane	Female	28	59	2,665	82.3 (18-2,605)
Romane	Male	29	166	6,433	91.7 (17-4,012)

[1] Median size (lower – upper 5% quantiles)

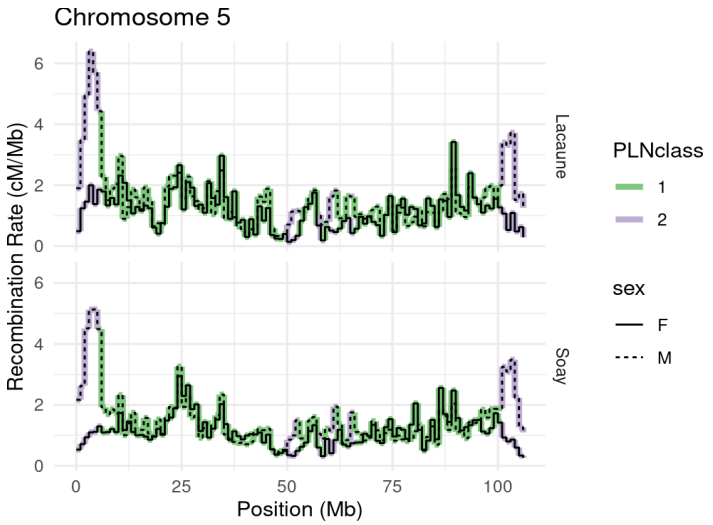

Figure 1. Example of recombination maps along chromosome 5 in two sheep populations and two sexes. Genomic intervals are coloured according to their mixture component (PLNclass).

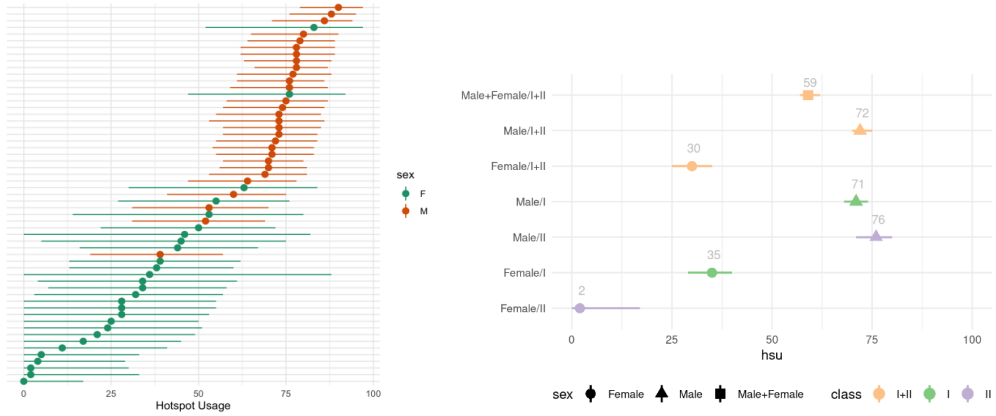

Figure 2. Hotspot Usage in the Romane population. Left panel: individual estimates of HSU Right panel: HSU in different genomic interval components and sex.

Discussion

We have established precise recombination maps in males and females in two highly differentiated populations of sheep. While sex differences in the recombination landscape are large, within sex between population variation is mostly negligible at the megabase scale so maps established here can be generally useful in many sheep populations. However, our results suggest that genetic analysis of segregation in pedigrees or genomic selection methods exploiting gametic variance, e.g. Bijma *et al.* (2020), should take account of between sex variation in recombination.

The sex difference in recombination rate between males and females in sheep is characterized by females recombining less than males due to a lower recombination rate in a small part of the genome mostly located at chromosome extremities. This is consistent with previous results in many mammals including cattle

(Ma *et al.* 2015), mouse (Peterson and Payseur 2021) and human (Broman *et al.* 1998) but different from red deer (Johnston *et al.* 2017) or pig (Tortereau *et al.* 2012) where females rather than males tend to have elevated recombination rates at chromosome ends.

Analysis of inter-individual variation in recombination localisation (HSU) show that the sex-difference in the recombination landscape in sheep is associated with a lower overall hotspot usage in females, particularly in the genomic intervals that exhibit large sex-differences in recombination rates. These differences could be due to differential use of crossover resolution pathways as was shown recently in the mouse (Brick *et al.* 2018; Powers *et al.* 2020).

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