Domestication shapes recombination patterns in tomato

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Meiotic recombination is a biological process of key importance in breeding, to generate genetic diversity and develop novel or agronomically relevant haplotypes. In crop tomato, recombination is curtailed as manifested by linkage disequilibrium decay over a longer distance and reduced diversity compared to wild relatives. Here we compare domesticated and wild populations of tomato and find an overall conserved recombination landscape, with local changes in effective recombination rate in specific genomic regions. We also study the dynamics of recombination hotspots resulting from domestication and found that loss of such hotspots is associated with selective sweeps, most notably in the pericentromeric heterochromatin. We found footprints of genetic changes and structural variants, among them associated with transposable elements, linked with hotspot divergence during domestication, likely causing fine-scale alterations to recombination patterns and resulting in linkage drag.
Introduction

Generation of genetic diversity through meiotic recombination has been an integral subject of breeding and genome research following Mendel’s work on patterns of inheritance and Morgan’s theory of gene linkage and crossing-over (Hunter 2015). Studies on meiotic recombination have indicated that one crossover (CO) per chromosome is obligatory and essential for proper chromosome segregation during prophase I (Jones and Franklin 2006). COs are non-uniformly distributed across plant genomes, mostly located in distal chromosome regions and clustering in hotspots (Lambing et al. 2017; Mercier et al. 2015; Wang and Copenhaver 2018). Characterizing the pattern of recombination has both practical and fundamental relevance, as it enables identification of informative markers, building of genetic maps and genome assemblies, reconstruction of evolutionary histories, association studies on important alleles and profiling linkage drags (Cardon and Abecasis 2003; Dutta et al. 2017; Fransz et al. 2016; Marand et al. 2019; Wang et al. 2010; Yang et al. 2011).

Different methods have been developed to detect recombination events between specific parents, such as chiasmata and recombination nodule counting (Anderson et al. 2003; Stack et al. 1989), pollen genotyping (Drouaud et al. 2013), SNP-array-based profiling or sequencing of recombinant inbred line (RIL) populations (Demirci et al. 2017; Huang et al. 2009; Qi et al. 2009; Wijnker et al. 2013), and image analysis of meiotic tetrads (Francis et al. 2007; Lim et al. 2020). These approaches revealed useful information about the recombination landscape of gametes and offspring populations. Still, detection of recombination between all members of a population is impractical and often infeasible, especially for long-generation species. However, analysis of resequencing data of natural populations allows detection of historical recombination rates and associated genomic features, revealing their evolutionary histories. Here, historical recombination refers to the reciprocal exchange of chromosomal segments that has successively occurred between ancestral individuals over multiple generations, in various environments and under changing selective pressures and genetic backgrounds. Recombination rate landscapes and historical crossover hotspots in populations of different plants (Choi et al. 2013; Dreissig et al. 2019; Marand et al. 2019; Schwarzkopf et al. 2020), fungi (Stukenbrock and Dutheil 2018), insects (Chan et al. 2012) and mammals (Brunschwig et al. 2012; Guo et al. 2018; Stevison et al. 2016) have previously been subjected to coalescent-based analysis of genetic variation.

Studying historical recombination can help to explain the changes that domestication enforced on recombination patterns. Domestication is a process of human-imposed evolution by selection of favorable phenotypes, resulting in genetic modification of wild progenitors to create new forms that meet human needs (Doebley et al. 2006; Yang et al. 2019). In this process, an initial stage of cultivating wild species with desirable traits is followed by a second stage of improvement, further
targeting specific traits through selective breeding (Gross and Olsen 2010; Meyer and Purugganan 2013). Strong selection during domestication is accompanied by increased recombination rate in many species (Moyers et al. 2018; Ross-Ibarra 2004). For example, the domesticated population of cacao was reported to have a higher recombination rate compared to wild populations (Schwarzkopf et al. 2020). In addition, the recombination landscape in barley is highly conserved throughout domestication, with fine-scale changes in recombination rate that have been linked to different environmental conditions and with defense response genes (Dreissig et al. 2019). However, currently, for most plants information on how domestication shaped the recombination landscape is still scarce.

Given that several genomic features like promoter regions, repeat motifs, nucleosome occupancy, chromatin accessibility, structural variations (SVs), transposable elements (TEs) and nucleotide diversity have been found linked to crossover incidence, changes to their patterns due to evolution of a species may have influenced the recombination profiles (Choi and Henderson 2015; Dluzewska et al. 2018; Lambing et al. 2017; Petes 2001; Termolino et al. 2016). Population-level patterns of recombination in different species revealed substantial divergence of hotspots across populations of the same species. Distinct crossovers hotspots, associated with lineage-specific variation in SV and TE profiles, have been implicated as major drivers in population dynamics (Marand et al. 2019). In rice, potato and Arabidopsis thaliana, specific superfamilies of DNA transposons are abundantly located in recombination-prone regions, which may be explained by nucleosome depletion in DNA transposons (Choi et al. 2018; Marand et al. 2017; Marand et al. 2019).

Domesticated in South America, wild tomato species S. pimpinellifolium (SP) gave rise to the cherry tomato (S. lycopersicum var. cerasiforme; SLC), which was later improved into the big-fruited tomato (S. lycopersicum var. lycopersicum; SLL) in Mesoamerica (Blanca et al. 2015; Lin et al. 2014; Razifard et al. 2020). Due to domestication and continued selection, current tomato cultivars have lost 95% of the genetic diversity of their wild relatives, pushing breeders to introgress alleles from compatible wild relatives underlying disease resistance, stress tolerance, adaptation to diverse environments, higher yield and fruit quality (Bai and Lindhout 2007). However, there are some reproductive barriers such as SVs (Soyk et al. 2019) that limit the applications of introgressive hybridization breeding. It was observed that linkage disequilibrium decays over a longer distance in domesticated tomato compared to its wild relatives, implying changes into the recombination patterns (Lin et al. 2014; Zhu et al. 2018). In this study, we address how domestication shaped the recombination patterns specifically for tomato and its related wild species. We investigate crossover profiles in tomato populations and its wild relative S. pimpinellifolium, using resequencing data assigned into three taxonomic groups: wild tomato (SP), early domesticated types (SLC), and vintage or heirloom cultivars (SLL). We generated recombination landscapes, identified recombination
hotspots and analyzed genomic features that are associated with the differing recombination patterns between the populations. This provided insights into the factors that contributed to or are associated with the changes in local recombination patterns during tomato domestication, revealing how domestication has severely constrained the ability of recombination to generate diversity, both for inbred and hybrid crosses. This new data may help the selection of targets for inducing meiotic recombination, cross checking hotspots in hybrids, identifying tightly-linked genes, and defining recombination barriers in hybridization.

Results
Conserved recombination landscape between wild and vintage tomato
After the domestication of tomato from its wild progenitor, its genetic diversity has dramatically reduced and linkage disequilibrium decay over a longer distance, indicating changes in recombination patterns (Aflitos et al. 2014; Lin et al. 2014; Razifard et al. 2020; Tieman et al. 2017). Furthermore, there are structural rearrangements between wild and domesticated plants that hamper recombination, manifested by the phenomenon of co-segregation of specific alleles linked to a desired trait (linkage drag). To get more insight into how domestication influences recombination patterns, we profiled the recombination landscape of tomato and wild relatives based on existing resequencing data of 75 accessions from each of the wild (SP), early domesticated (SLC) and vintage (SLL) populations (Figure 1a; Supplementary Figure 1; Supplementary Table 1).

Consistent with available crossover data from recombinant-inbred lines (referred to from here on as COD1; Demirci et al. 2017) and pollen gametes of an interspecific cross (COD2; Fuentes et al. 2020) in tomato, and data from other species (Kianian et al. 2018; Wijnker et al. 2013), the majority of historical recombination in both wild and domesticated tomato occurred in the distal gene-rich euchromatic regions of the chromosomes. More in detail, the recombination landscape of each population correlates with both COD1 (Spearman’s rank correlation; euchromatin, ρ = 0.32 - 0.44; P < 2.2 x 10^{-11}; heterochromatin, ρ = 0.64 - 0.67; P < 2.2 x 10^{-16}) and COD2 (Spearman’s rank correlation; euchromatin, ρ = 0.31 - 0.55; P < 2.2 x 10^{-10}; heterochromatin, ρ = 0.38 - 0.51; P < 2.2 x 10^{-16}). To further verify the consistency of the recombination rates with available data, the population-scaled recombination rate computed using LDhat was converted from ρ/kb to cM/Mb, and compared against the EXPIM2012 genetic map generated from a cross between S. lycopersicum and S. pimpinellifolium (Sim et al. 2012). The correlation between the genetic map and recombination rate estimates of each population is approximately 0.9 (Spearman’s rank correlation; P < 2.2 x 10^{-16}), supporting the concordance of population-scaled recombination rates with the genetic map.
To compare the recombination landscapes of the three populations in our study, we calculated multi-scale correlations, i.e. in varying window sizes (Supplementary Figure 2), and selected a 1-Mb window size. We found correlations in the range 0.6 - 0.7, indicating conservation of the genome-wide recombination landscape despite the differing selection and domestication processes (Spearman’s rank correlation; P < 2.2 x 10^{-16}, Supplementary Figure 3). The higher correlation coefficient between genetic distances and population-scaled recombination rate is influenced by the low marker density in the genetic map, limiting the comparison to the overall landscape. On the other hand, the use of shorter windows when comparing rates between populations or against COD1 and COD2 accounts for local changes in the recombination rates (Supplementary Figure 2).

Local increase of recombination rate in early-domesticated tomato

Although the general landscape of recombination is conserved, there are also clear local changes between populations (Supplementary Figure 1). Using the \( \rho \) value calculated by LDhat, we computed the effective recombination rate \( (r_e) \) to account for the difference in effective population size \( (N_e) \) of the three groups. We found that the median recombination rate in the SLC population \( (r_e = 9.3 \times 10^{-10}) \) is higher than the median in both SP \( (r_e = 5.6 \times 10^{-10}) \) and SLL \( (r_e = 6.8 \times 10^{-11}) \). Given that the heterochromatin regions have a low recombination rate, we separately analyzed \( r_e \) for euchromatic and heterochromatic regions. We determined the borders between euchromatin and heterochromatin by computing the euchromatin length (\( \mu m \)) from the average length of pachytene chromosome, multiplying it by the euchromatin DNA density (1.54 \( \mu m^3/\mu m \)), and using the length of each euchromatin to identify the heterochromatin boundary. In euchromatin, SP has a significantly higher \( r_e \) of 1.8 \( \times 10^{-8} \) compared to 9.4 \( \times 10^{-9} \) for SLC and 2.6 \( \times 10^{-9} \) for SLL. But in the heterochromatin, SLC has a higher median \( r_e \) of 6.3 \( \times 10^{-10} \) compared to 3.5 \( \times 10^{-10} \) and 4.8 \( \times 10^{-11} \) of SP and SLL, respectively (Figure 1b; Supplementary Table 2).

We plotted the change in \( r_e \) during the domestication (from SP to SLC) and improvement (from SLC to SP) stages to detect localized changes of recombination rates (Figure 1c). In the majority of cases where there is an increase of \( r_e \) through domestication (SLC \( r_e - SP r_e > 0 \)) across the whole genome, they are followed by a proportional decrease in \( r_e \) during improvement (SLL \( r_e - SLC r_e < 0 \)). The reduction of \( r_e \) through domestication is confined mostly to the euchromatic region (Figure 1d; Supplementary Figure 4). Although 65% of euchromatin regions have reduced \( r_e \) during domestication, over the entire genome more regions (54%) have an increased rate. On the other hand, during the improvement stage the effective recombination rate in 76% of the genome was reduced, in both euchromatin and heterochromatin.
The local increase of \( r_e \) from SP to SLC is consistent with the fact that domestication increases the actual recombination rate in many species, as was demonstrated previously by counting chiasmata per bivalent (Moyers et al. 2018; Ross-Ibarra 2004). This increased recombination is favored during periods of rapid evolutionary change and specifically during domestication (Burt and Bell 1987; Otto and Barton 1997; Rees and Dale 1974; Ross-Ibarra 2004). On the other hand, the significant reduction of effective recombination rate during improvement may be explained by increased inbreeding and homozygosity in the vintage accessions (Moyers et al. 2018); SP and SLC are known to have higher outcrossing rates than SLL (Rick and Holle 1990; Rick et al. 1978). As previously reported, inbreeding results in reduced heterozygosity and effective population size, and longer distance for linkage-disequilibrium decay (Allard 1999; Kovach et al. 2007; Morrell et al. 2003). The estimated effective recombination rate may be reduced in inbred species if the homologous chromosomes are identical and no appreciable exchange of alleles is observed after recombination (Moyers et al. 2018). The decreased effective recombination rate has actually been observed in maize improved lines, with an estimated 82.3% reduction compared to the wild progenitors (Hufford et al. 2012).

To check for the genetic diversity in each population, we first computed the number of single nucleotide polymorphisms (SNPs). The average SNP count per kilobase for SP, SLC and SLL accessions was 0.097, 0.075 and 0.021, respectively, which indicates a reduction of genetic diversity from wild to heirloom tomato (pairwise Wilcoxon rank sum test; \( P < 8.5 \times 10^{-3} \); Supplementary Figure 5). At the individual sample level SP accessions have more SNPs than SLC accessions, but SLC has more unique SNP sites in the overall whole population. The mean nucleotide diversity measured for SLL \( (4.4 \times 10^{-4}) \) and SLC \( (2.2 \times 10^{-3}) \) populations is lower than for SP \( (3.8 \times 10^{-3}) \), which is typically associated with domestication syndrome, the distinguishing characteristics between domesticated crop and wild ancestors (Bai and Lindhout 2007; Doebley et al. 2006; Sauvage et al. 2017). Both increased homozygosity and inbreeding contributed to the reduced effectiveness of recombination in the vintage population.

**Divergent hotspots between populations**

Visual inspection of the landscape (Supplementary Figure 1, Figure 1a) reveals local peaks of recombination rates throughout the genome of each population. To further investigate this, we detected historical recombination hotspots for each population using sequenceLDhot, reporting 1,784, 2,899 and 667 hotspots for SP, SLC and SLL, respectively (Figure 2a; Supplementary Table 2 & 3) and a total of 5,082 unique hotspots with a median size of 2 kb. Pairs of the three populations have 4-10% of hotspots in common, significantly higher than expected by chance (pairwise Fisher’s exact test; \( P < 1.9 \times 10^{-5} \); Figure 2b). However, of 181 hotspots shared between SP and SLC, only 4 are
retained in SLL. This low overlap in hotspots between populations of the same or closely related species was also reported in rice and cocoa (Marand et al. 2019; Schwarzkopf et al. 2020). SLC has 62.5% more unique hotspots than SP, in concordance with its increased recombination rate. Out of all the identified hotspots, 84 (1.6%) and 96 (1.8%) overlapped with empirical crossovers in COD1 (Fisher’s exact test; \( P = 6.3 \times 10^{-24} \)) and COD2 (Fisher’s exact test; \( P = 1.2 \times 10^{-26} \)), respectively. Furthermore, 3 of the 23 reported hotspots in Fuentes et al. (2020) match hotspots in SP and SLC. The limited overlap between historical hotspots and crossovers found in these previous studies is in line with the relatively modest correlation between the population-scaled recombination rate and crossovers from COD1 and COD2 reported above. These observations may be explained by the inclusion of different genotypes in the different dataset, by the possibly differing crossover patterns between the RIL/pollen populations and the natural tomato population, or by the inability of experimental studies to exhaustively sample possible recombination sites. The hotspots mentioned in the succeeding sections refers to recombination hotspots, except for those that explicitly refer to hotspots from previous studies.

Recombination in the pericentromeric heterochromatin

Aside from divergent hotspots, another distinct difference between the recombination landscapes of wild and domesticated tomato is the presence of hotspots in the pericentromeric regions. Previous studies in plants mostly report suppression of recombination in pericentromeric regions, which is largely heterochromatic, and high recombination rates in the distal chromosome regions. However, we observed that hotspots are not confined to the terminal chromosome ends, but also are scattered over the pericentrome. Compared with both SP (51.8%) and SLC (61.5%), only 32.7% of the genome-wide hotspots in vintage tomato (SLL) are located in the pericentromeric regions, which covers 75% of the genome. This rate is comparable to the 39.1% of hotspots distributed in the pericentromere of maize (Pan et al. 2017). Sherman and Stack (1995) actually reported cases of recombination nodules in the pericentromeric heterochromatin of tomato, but these are 20-50x less frequent per unit length of the synaptonemal complex than in euchromatin. This frequency, though, may be different for historical hotspots. Additionally, hotspots in the heterochromatin have generally lower recombination rates than those located in the euchromatin (Wilcoxon rank sum test; SP, \( P < 2 \times 10^{-16} \); SLC, \( P < 2 \times 10^{-16} \); SLL, \( P = 6.2 \times 10^{-12} \); Figure 2c). To determine whether the observed recombination rates in the heterochromatin are due to the use of a domesticated tomato as reference genome for wild accessions which contains genomic rearrangements, we recomputed recombination rates for the wild population using the S. pimpinellifolium genome assembly (Wang et al. 2020) as reference. As shown in Supplementary Figure 6, the pericentromeres still exhibits presence of historical crossovers.
also important to emphasize that SNPs located in the repeat or TE regions were excluded in the estimation of recombination rates to avoid issues due to misaligned reads or false positive SNPs.

To give an example of recombination occurring in the pericentromeric heterochromatin, we show the landscape for chromosome 2 in Figure 2d, where both SP and SLC show presence of historical recombination in the heterochromatin. However, the same region is almost devoid of recombination in SLL; hotspots are clustering mostly at the ends of the chromosome, consistent with population data, the genetic map (Sim et al. 2012), RILs (Demirci et al. 2017) and pollen gametes from interspecific crosses (Fuentes et al. 2020). Around 55% and 42% of SP and SLC hotspots in chromosome 2, respectively, are located in the pericentromeric regions, in contrast to 9% of SLL, but the number of hotspots per megabase of euchromatin is still higher than in heterochromatin for both SP and SLC. We further examined these heterochromatic hotspots and found that they are close to or within genes (Fisher’s exact test; P = 4.9 x 10^{-12}), which suggests that these hotspots may be located in euchromatin islands or accessible regions in the heterochromatin.

**Crossover hotspots in selective sweep genes**

The results above confirm that historical crossovers are non-uniformly distributed over the genome and occur mostly in the distal part of the chromosome. This raises the question how the changing patterns of recombination hotspots may be linked to specific genomic features that evolve during domestication. To test the association of recombination hotspots with gene features, for each population, a permutation test of crossover hotspots with sizes below 5 kb was applied. This shows a significant enrichment in promoter regions, defined as 1-kb regions upstream of the transcriptional start sites (TSS), and in gene bodies. Moreover, hotspots are depleted in intergenic regions, further supporting previous reports of recombination mostly occurring near genes. To account for the significant difference of crossover distribution in the euchromatin and heterochromatin, we performed enrichment analysis for euchromatin regions only and still found an excess in promoters and gene bodies (Figure 3a). The promoter regions exhibit a 3 to 13-fold increase in crossovers over the background, which was computed based on a set of 10,000 permutations. Despite the reduction of hotspots in vintage tomato (Supplementary Table 2), the enrichment in both gene bodies and promoters persists. An excess of crossovers in promoter and UTR regions of tomato was previously reported in RILs and pollen data (de Haas et al. 2017; Demirci et al. 2017; Fuentes et al. 2020) and is consistent with observations in other species (Choi et al. 2018; Demirci et al. 2018; Kianian et al. 2018; Marand et al. 2017; Pan et al. 2017; Wijnker et al. 2013). The overrepresentation in the 5’ and 3’ UTRs may be related to epigenetic modifications such as DNA and histone methylation, contrasting open chromatin that may be accessible for the recombination machinery (Eichten et al. 2011; Pan et al.
With the preference of crossovers to occur near genes, the significant reduction of genes in domesticated tomatoes compared to wild relatives consequently limits the possible sites for recombination (Gao et al. 2019).

Knowing that crossovers preferentially occur near genes and that specific genes are affected by domestication, we examined the relation between recombination hotspots and genes. In detecting association, we included the 2-kb regions flanking both sides of the genes. First, we compared hotspots against R genes, which are known to reside in recombination hotspots (Andolfo et al. 2021; Nieri et al. 2017), and observed a significant overlap (Fisher’s exact test, $P = 3.38 \times 10^{-17}$). Afterwards, we computed the overlap between hotspots and the selective sweeps or regions with reduced nucleotide diversity previously reported by Lin et al. (2014). We refer to genes in these selective sweeps as domestication (DSG) and improvement (ISG) sweep genes. For heterochromatic DSGs/ISGs, a significant enrichment in both SP and SLC hotspots is observed, while there is no association with SLL hotspots (Supplementary Table 4). Conversely, in the euchromatin, there is a difference between DSGs and ISGs. Euchromatic SP hotspots significantly overlap with both DSGs and ISGs, while euchromatic SLC hotspots only show enrichment in ISGs, which implies that many DSGs have lost hotspots after domestication. Lastly, SLL hotspots in the euchromatin overlapped DSGs and ISGs significantly less than expected by chance, indicating that most SLL hotspots are outside selective sweeps.

Many of the hotspots in SP and SLC sweep genes are lost in the SLL population. Nevertheless, it might be that sweep genes still undergo recombination even after hotspots are lost during domestication. To investigate this, we examined the changes in recombination rates of both sweep and non-sweep genes across these three populations. We computed the effective recombination rates in DSG and ISG genes across the different populations and compared them against the remaining genes (Figure 3b; Supplementary Figure 7). Genes with hotspots clearly exhibited an elevated effective recombination rate, with even higher rates for sweep genes (DSGs/ISGs) than non-sweep genes. However, the loss of these hotspots during the domestication or improvement process resulted in $r_e$ being reduced to almost the same level as the non-hotspot genes. Interestingly, sweep genes show more reduction in $r_e$ than non-sweep genes, which may reflect how sweep genes were directly affected by tomato domestication. Altogether, Supplementary Figure 7 underlines the severity of the decrease in $r_e$ between wild and domesticated tomato genes, which resulted in reduced genetic diversity and forces breeders to introgress alleles from the wild relatives to recover desired traits.

Aside from increasing the frequency of alleles in specific genes, domestication of tomato also resulted in lost or negatively-selected promoters during both domestication and improvement stages (Gao et al. 2019). These promoters are considered unfavorable because of their significantly lower...
frequency in SLC than SP or in SLL than SLC. Given that above it was demonstrated that recombination is associated with promoters, the question is how the loss of these promoters influence recombination. We found that the upstream region (<1kb) of the genes with promoters under selection during domestication have reduced effective recombination rate in SLC compared to SP (Wilcoxon rank sum test, $P < 2 \times 10^{-16}$ (Figure 3c). Similarly, the upstream region of the genes with promoters under selection during improvement have reduced $r_e$ in SLL compared to SLC (Wilcoxon rank sum test, $P < 2 \times 10^{-16}$) (Figure 3d). This analysis reveals that loss of promoters due to domestication affected the recombination rate in the genomic regions from which these promoters were lost, highlighting a specific way in which domestication reduces recombination.

**TE and SV-associated hotspots**

Domestication and improvement not only influence gene content but have a broader effect on genomic variants (Alonge et al. 2020; Gao et al. 2019). Hence, we finally analyzed the association between hotspots and transposable elements (TEs) as well as structural variants (SVs). Certain transposable element families show strong association with hotspots (Figure 4a). Both hAT-Tip100 and Stowaway show enrichment while Tag1, L1, Copia and Gypsy show strong depletion, based on a permutation test. Most class I TE or retrotransposons are under-represented in hotspots, except for ERV1 in the SLL population and SINE in all three populations. Moreover, regions with low complexity and simple repeats have an excess of recombination hotspots. Similar to potato, rice and maize, Stowaway and SINE are significantly overrepresented, whereas Gypsy and Copia are depleted in hotspots (Marand et al. 2017; Marand et al. 2019; Pan et al. 2017). In Arabidopsis, DSBs overlapped Gypsy and Copia elements significantly less than expected by chance (Choi et al. 2018); however, in maize, most DSBs are formed in repetitive regions, predominantly Gypsy retrotransposons, but only genic DSBs contribute to crossover formation (He et al. 2017). Schwarzkopf et al. (2020) reported that hotspots shared by both domesticated and wild cocoa populations appear to be associated with DNA transposons. Furthermore, Marand et al. (2019) found that the presence of Stowaway and Harbinger elements in crossover hotspots is associated with increased recombination rates, augmented chromatin accessibility and reduced DNA methylation. Our result is also consistent with the findings on differentially accessible chromatin regions between meiotic cells and somatic cells of tomato (Chouaref J, Tark-Dame M, Koes R, Fransz P, Stam M, unpublished data), corroborating that TE families with an excess of hotspots are accessible in meiotic cells while those with depletion of hotspots are inaccessible. TE families enriched with hotspots are known to be preferentially located in genic regions, but the retrotransposon LTR/ERV1 is particularly interesting because it was also reported to be one of the most transcriptionally active TE families due to its abundance in exonic regions (Mehra...
et al. 2015). The insertion of retrotransposons in a promoter region or UTR can both regulate gene expression (Alonge et al. 2020; Dominguez et al. 2020) and negatively affect the chance of crossover incidence. Similarly, the accumulation of certain DNA transposons that are known to be accessible in meiotic cells may provide new sites for DSBs that can resolve to crossovers. Our results suggest that TE activities during domestication also influenced the landscape of meiotic recombination (Choi et al. 2018; He et al. 2017; Kent et al. 2017; Underwood and Choi 2019).

Alonge et al. (2020) reported that, compared to SLL and SLC, SP has significantly more SVs relative to the Heinz 1706 reference genome and that the majority of insertions and deletions are associated with Gypsy and Copia elements. To determine if SVs influence meiotic recombination, we compared the SVs between S. pimpinellifolium and S. lycopersicum reported in Wang et al. (2020) against the effective recombination rate and hotspots. We found that the length of deletions correlates with recombination rate, specifically deletions longer than 500 bp (Figure 4b), and that recombination hotspots are suppressed in long deletions in the wild population (Fisher’s exact test, P = 2.1 x 10^-6). Hotspot suppression is less prominent in deletions with lower allele frequency (Supplementary Figure 8). As a specific example, we found a 4-fold reduction of SP hotspots in large deletions (> 500 bp) with allele frequency above 0.5 (Figure 4c). Interestingly, the same set of large deletions have low allele frequency and lack hotspot suppression in both SLC and SLL populations, which may be explained by the increased inbreeding and lower heterozygosity of SV regions in domesticated varieties compared to the wild relatives. Knowing the wild ancestral alleles, we can instead look at these regions of low frequency deletions (relative to Heinz reference) as insertion sites for alleles that fixated in the vintage accessions. Lye and Purugganan (2019) reported that SVs associated with domestication traits have an increased allele frequency in the population due to selection or have become fixated in the population. This suggests that in natural populations, suppression of recombination hotspots in SVs occurs more in outcrossing populations with a certain level of heterozygosity of SVs between compatible individuals (Dluzewska et al. 2018; Wang and Copenhaver 2018). To put this result in a broader perspective, we analyzed the crossovers detected from the interspecific hybrid between S. pimpinellifolium and S. lycopersicum (COD2) and found crossover suppression in the large deletions segregating between SP and SLL populations (Fisher’s exact test, P = 1.4 x 10^-5; Figure 4d). This suppression of crossovers in deletions segregating between the parents of hybrid crosses is consistent with results obtained from the natural populations with high levels of outcrossing.

Interestingly, the shorter deletions (< 500 bp) overlap recombination hotspots in each population significantly more than expected by chance (Fisher’s exact test, SP P = 1.1 x 10^-6; SLC P = 4.9 x 10^-12; SLL P = 6.4 x 10^-13; Supplementary Figure 9). These regions with short deletions and
hotspots have high homology and are enriched with simple repeats (z-score > 11.1) and hAT-Tip100 (z-score > 3.1) elements. These small deletions have significant allele frequency differences between the wild and domesticated populations based on Wang et al. (2020), mostly have low frequency in the vintage population. Moreover, we found that the fixed SLL alleles in these deletion sites are causal mutations in domestication syndrome genes, like OVATE (Solyc02g085500), Lin5 (Solyc09g010080) and YABBY (Solyc11g071810) and other genes controlling horticulture traits in tomato (Wang et al. 2020).

As we reported above, we identified some TE families that associate with hotspots and we speculated that TE activities during domestication affects recombination patterns. Comparing TE to deletions, we selected TE elements that show a significant difference in frequency between the wild and domesticated populations, mostly Gypsy, Copia and L1 elements. As shown in Figure 4e, the frequencies of these TE elements increased during domestication (fewer deletion alleles), while recombination rates in these elements significantly declined. This is consistent with the suppression of hotspots in these specific TE families that became fixed in the vintage population (Figure 4a). The result indicates that despite the lower deletion frequency or lower heterozygosity in a region, genomic content such as presence of specific TEs can influence whether recombination is suppressed or not.

Discussion

Throughout domestication, the general recombination landscape of both wild and domesticated tomato remains conserved, consistent with the known phenomenon in tomato and other plant species that recombination rates are significantly higher in distal parts of chromosomes (Lamberg et al. 2017; Mercier et al. 2015; Wang and Copenhaver 2018). Effective recombination rates are in agreement with empirical crossover data derived from RILs and pollen gametes, and with genetic distances from the EXPIM2012 linkage map. Despite the conservation of the recombination landscape, we observed local increases in recombination rates across the chromosomes of early-domesticated tomato (SLC), which reflects the expected increase of recombination due to domestication (Moyers et al. 2018; Ross-Ibarra 2004). Concomitantly, some regions of the gene-rich euchromatin showed a reduction of recombination. After the domestication stage, further reduction of effective recombination rates is observed in vintage (SLL) tomato. This might either be due to low diversity in highly homozygous regions limiting the detection of actual recombination, or because the recombination has actually decreased during the improvement stage (Moyers et al. 2018; Otto and Barton 1997). Nevertheless, the effective recombination rates reported here, allowed us to identify genomic regions that still recombine and generate diversity in vintage tomato.

We also identified recombination hotspots and found a small but significant overlap between the three populations, representing conserved recombination sites apparently not affected by
domestication. The number of hotspots in vintage tomato is four times less than in its progenitor, revealing genomic sites in domesticated tomato preferentially maintained with lower if not completely suppressed recombination. Previous studies have reported that the pericentromeric heterochromatin of tomato displays extremely low recombination compared to the distal chromosome regions (Demirci et al. 2017; Fuentes et al. 2020), but we identified historical recombination hotspots near or within genes located in the heterochromatin, hinting on their accessibility as possible euchromatin islands within heterochromatin. These heterochromatin hotspots have a lower recombination rate than those located in euchromatin, which could explain why it can be hard to observe them in previous studies. Furthermore, compared to SP and SLC, the majority of SLL hotspots are located in the euchromatin. Our results on the divergence of hotspots between tomato populations suggests highly dynamic recombination patterns, likely as a result of the intense selection in domestication (Otto and Barton 1997; Schwarzkopf et al. 2020). Despite the use of interspecific tomato crosses in several studies, genetic shuffling through meiosis still remains strongly confined to the ends of the chromosomes (Demirci et al. 2017; Fuentes et al. 2020). Interestingly, Dreissig et al. (2019) reported an increase in pericentromeric crossovers, although they have been observed for crosses of domesticated and wild barley accessions. The low recombination rate in 75% of the tomato genome limits possibilities of generating diversity or breaking fixed haplotype blocks in either or both wild and domesticated tomato. However, despite the very limited sites for recombination in the domesticated tomato, detecting recombination hotspots in the wild genomes may help reveal factors that led to their divergence and ways to restore hotspots and genetic diversity in tomato.

The recombination hotspots found in wild and domesticated tomatoes are enriched in gene bodies and promoter regions and depleted in intergenic regions, which agrees with previous reports on tomato crossovers (Demirci et al. 2017; Fuentes et al. 2020). This implies that the reduction in the number of genes and promoters from wild to vintage tomato limits possible hotspot locations. Gao et al. (2019) reported hundreds of genes and promoters excised as a result of domestication and improvement, reducing recombination rate in specific genomic regions of vintage tomato and increasing the spans of haplotype blocks. The profile of recombination hotspots in the wild population reveals genomic regions that provide candidate targets for inducing meiotic recombination or loss-of-function mutations to domesticate wild plants or re-introduce desirable traits, or serve as guide for cross checking hotspots from experimental populations (Li et al. 2018; Zsogon et al. 2018).

Comparing with the known selective sweep genes, we discovered that they overlap with recombination hotspots in both the wild and early-domesticated tomato significantly more than expected by chance. The hotspot-associated selective sweep genes in the SLC population indicated
selection for increased recombination rate during domestication, which was then followed by a loss of hotspots after subsequent improvement. Otto and Barton (1997) proposed that higher recombination rates during domestication were favored to elevate the fixation rate of adaptive or beneficial alleles. These manifested as reduced nucleotide diversity in sweep regions of the SLL population that historically comprised hotspots. The increased recombination rate and number of hotspots in SLC may also relate to adaptive evolution in response to changing environments during domestication. Similar observations have been made for rice genes that showed higher recombination in response to stresses (Si et al. 2015). In addition, Razifard et al. (2020) identified an overrepresentation of defense-response genes in the selective sweeps of an SLC population, which agrees with our observation of excess recombination hotspots in R genes. Unlike SP and SLC hotspots which significantly overlap selective sweeps, SLL hotspots are mostly located outside the sweeps, showing the divergence of SLL hotspots from regions under selection during tomato domestication and improvement. The reduced genetic diversity in sweep regions of the highly inbred SLL population could have resulted from the loss of hotspots or reduced recombination incidence. Alternatively, the low diversity, possibly due to a selection bottleneck, may have led to the low effectivity of recombination in these sweep regions. Our results support an evolution of effective recombination related to the fixation of alleles in selective sweeps genes.

In all three populations, recombination hotspots were found to be positively (e.g. Stowaway, SINE) and negatively (e.g. Gypsy, Copia) associated with specific families of transposable elements. TE families with excess recombination hotspots were preferentially located in genic regions (Mehra et al. 2015). During meiosis, these specific TEs probably are accessible to recombination complexes, whereas most retrotransposons have closed chromatin status (Chouaref J, Tark-Dame M, Koes R, Fransz P, Stam M, unpublished data). Aside from TEs, we also identified association of hotspots with structural variations. We showed that large deletions suppress recombination in SP populations, but this depends on the frequency of the deletion variant in the population. Since most large deletions have lower frequency in both SLC and SLL populations, we do not observe hotspot suppression by deletions in these populations. Reduced recombination in SVs combined with geographic isolation can lead to the development of alleles that are incompatible with distantly-related haplotypes (Bomblies and Weigel 2007; Jiao and Schneeberger 2020). As an example, crossover suppression is observed in a hybrid cross between SP and SLL parental accessions, implying that SVs can cause linkage drag that constrains introgression of specific alleles from the wild relatives while excluding unwanted alleles (Taagen et al. 2020). Rowan et al. (2019) provided several hypotheses as to why crossovers are suppressed in SV regions, such as absence of repair template, COs in SVs creating inviable gametes,
DSB in SVs preferentially resolving to NCOs, constrained interaction with the central element and homologous chromosomes and lastly the DNA methylation in SVs.

On the other hand, we found enrichment of hotspots in short deletions across all populations, which we hypothesize is not due to mutations inducing hotspots but more likely due to mutations formed by non-allelic homologous recombination in the hotspot regions with tracts of homology (Balachandran and Beck 2020; Escaramís et al. 2015). These small causal mutations, that are located in many horticulture trait genes, may have originated from the wild progenitor and may confer adaptive domestication traits that promote their fixation in the vintage population (Lye and Purugganan 2019). Previous studies already reported recurrent SVs in regions with high recombination rate (Badet et al. 2021; Liu et al. 2012; McVean 2010; Rowan et al. 2019), although there are other mechanisms that generate more SVs (Escaramís et al. 2015). SVs are reported to have key roles in the evolution of domesticated species and are associated with post-domestication traits (Lye and Purugganan 2019). Thus, the divergence of TEs and SVs, both associated with recombination rates and hotspots, also contributes to the differing patterns of recombination during domestication. Identifying these divergent sequences between populations can allow us to determine genomic regions that are unlikely to recombine, or alleles that remain tightly linked in the hybrid crosses. Our results further confirm that domestication influenced local genomic contents, which in turn affected the recombination patterns in tomato.

Methods

Computing recombination rates and detecting hotspots

We collected resequencing data from previous studies under accession numbers PRJEB5235 (Aflitos et al. 2014), PRJNA454805 (Razifard et al. 2020), PRJNA353161 (Tieman et al. 2017) and PRJNA259308 (Lin et al. 2014) and based on previous population analyses (Alonge et al. 2020; Gao et al. 2019; Razifard et al. 2020; Tieman et al. 2017; Zhu et al. 2018) we selected accessions that were unanimously assigned to the S. pimpinellifolium (SP), S. lycopersicum var. cerasiforme (SLC) or S. lycopersicum var. lycopersicum (SLL) taxonomic groups. Most accessions were sequenced using Illumina HiSeq2000 except those from Razifard which utilized Illumina NextSeq. Modern processing cultivars and hybrids were excluded to avoid obscuring the recombination patterns in each of these three major groups. From the combined list of accessions, we selected 81 SPs, 140 SLCs, and 136 SLLs.

Reads were trimmed using Trimmomatic (Bolger et al. 2014) and aligned against the tomato Heinz 1706 (SL4.0) reference genome (Hosmani et al. 2019) using bwa mem (Li 2013). Accessions with read and physical coverage below 5x and 70%, respectively, were discarded. Filtering left 75 SP, 122 SLC and 117 SLL samples. SNPs were identified per accession using GATK HaplotypeCaller (Poplin et
al. 2017) with default parameters and then we randomly selected 75 accessions per population for GATK joint-genotyping and hard-filtering. Using bedtools (Quinlan and Hall 2010) and bcftools (Danecek et al. 2011), we selected bi-allelic SNPs located outside repeat or transposable element regions, with a minimum allele frequency of 0.05, less than 10% missing data, and consisting of at most one heterozygous genotype. Heterozygous genotypes were then converted to missing data. All missing calls were imputed and phased using Beagle v. 5.1 (window = 5, overlap = 2, iterations = 30, err = 0.001, burnin = 10 ) (Browning et al. 2018).

A widely used method to infer historical recombination rate is LDhat (Auton and McVean 2007), which implements coalescent resampling with a Bayesian reversible-jump Markov Chain Monte Carlo (rjMCMC) algorithm to estimate population-scaled recombination rates ($\rho = 4N_e r_e$) from pairs of SNPs. We estimated recombination rate using the LDhat v2.2 interval program per window of 5000 SNPs, overlapping by 500 SNPs. LDhat was run with 20 million iterations, sampling every 2000 iterations, using a mutation rate of 0.001 and the first 2000 samples for burn-in. We subsequently detected recombination hotspots using sequenceLDhot (Fearnhead 2006) with non-overlapping 1-kb windows, a 500-bp step size, and background recombination rate set as the median rate in a 50-kb window centered at each 1-kb window. Hotspots with rates greater than 10 times and less than 200 times the background and with likelihood ratio (LR) above the 95th percentile are reported. We merged hotspots within 500 bp of each other and used the highest LR and recombination rate for merged intervals. Only hotspots with at least a 10 times increase in recombination rate, based on the ratio of LDhat-computed $\rho$ and the background $\rho$, were reported as the final set of crossover hotspots.

To compare recombination rates between populations and account for potential differences in effective population sizes ($N_e$), we first computed the nucleotide diversity ($\Theta_w$, Watterson’s theta), using LDhat convert and used the neutral mutation rate ($\mu$) of $1 \times 10^{-9}$ (Baer et al. 2007; Lin et al. 2014; Moyers et al. 2018) to estimate the $4N_e$ ($4N_e = \Theta_w/\mu$). The estimated $4N_e$ was then used to calculate the effective recombination rate per generation ($r_e = \rho/4N_e$) for each population.

**Comparison with genetic maps**

For validating the recombination map, we compared median recombination rates against the crossover frequencies from tomato RILs (Demirci et al. 2017) and pollen gametes (Fuentes et al. 2020) using a 50-kb sliding window and performed Spearman’s rank correlation test. Further correlation testing was done by comparing against EXPIM2012 genetic map (Sim et al. 2012), using the method from Choi et al. (2013). Between every pair of adjacent SNPs in the genetic map, the population-scaled recombination rate ($\rho/kb$) was converted to cM/Mb. We also compared the recombination landscapes between populations using multi-scale correlations by calculating the average recombination rates in
varying window sizes, by randomly sampling these windows 10,000 times, and subsequently calculating Spearman’s correlation coefficients.

**Compute euchromatin regions**

The border between euchromatin and heterochromatin in each chromosome was computed according to Stack et al. (2009) and Demirci et al. (2017). Using Table 1 of Sherman and Stack (1992), we calculated the average length and heterochromatin length (μm) of each pachytene chromosome. Euchromatin length was calculated by subtracting heterochromatin length from each arm length and multiplying by the euchromatin DNA density (1.54 Mb/μm). Then, we determined the euchromatin-heterochromatin boundary based on the length of each euchromatic region. We also computed the heterochromatic region boundaries per chromosome relative to the Heinz 1706 (SL4.0) reference genome.

**Supplemental Material**

Supplemental data and figures are available at *Molecular Biology and Evolution* online. Scripts are available at https://github.com/rrfuentes/histo-recom.git.

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Figure 1. Recombination landscape and transformation from wild to domesticated tomato. (A) Recombination landscape in chromosome 1 of wild (SP), early-domesticated (SLC), and vintage (SLL) tomato. This $\rho$/kb landscape is intended to show overall landscape only; $r_e$ is used to compare populations in other analyses. Gray vertical lines mark heterochromatin boundaries. (B) Effective recombination rate ($r_e$) in 1-Mb windows of both wild and domesticated tomato. (C) Change in effective recombination rate in 50-kb regions during domestication (SLC $r_e$ – SP $r_e$) and improvement (SLL $r_e$ – SLC $r_e$). (D) Resulting change in $r_e$ for chromosome 1 after the domestication process or between the wild and vintage population. Gray vertical lines mark the heterochromatin boundaries and the colors correspond to the colors in (C).
Figure 2. **Historical recombination hotspots.** (A) Number of hotspots in each chromosome of the wild and domesticated populations. (B) Small but significant numbers of hotspots are shared between populations. (C) Effective recombination rates of hotspots in euchromatic and heterochromatic regions. (D) Recombination hotspots in the upper heterochromatic arm of chromosome 2. Gray lines mark the heterochromatin boundaries.
Figure 3. **Recombination hotspots in genes.** (A) Enrichment of euchromatin hotspots in UTRs and promoter regions (1-kb upstream of genes) in all three populations. (B) Recombination rates of domestication (DSG) and non-domestication (nDSG) sweep genes overlapping and not overlapping *S. pimpinellifolium* hotspots. *h* and *nh* mean hotspots and non-hotspots, respectively. (C-D) Recombination rate upstream (<1kb) of genes with excised promoters due to (C) domestication and (D) improvement.
Figure 4. **Recombination and genomic variants.** Using permutation tests, we identified (A) specific TE families with an excess or depletion of recombination hotspots. TE families are grouped into repeat elements (gray), retrotransposons (brown), and DNA transposons (yellow). (B) Scatter plots of effective recombination rate and deletion size (n=1255) per population. (C-D) Significance of overlap between (C) hotspots and deletions in SP and (D) empirical crossovers and deletions segregating between SP and SLL. The black and red vertical lines indicate the average number of overlaps found in 10,000 permutation sets and the number of overlaps at $P = 0.05$, respectively. The green vertical line indicates the observed number of overlaps. (E) Recombination rates (violin) and allele frequencies (red boxplot) of Gypsy, Copia and L1 elements.