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Supplemental information

A revamped rat reference genome improves the discovery of genetic diversity in laboratory rats

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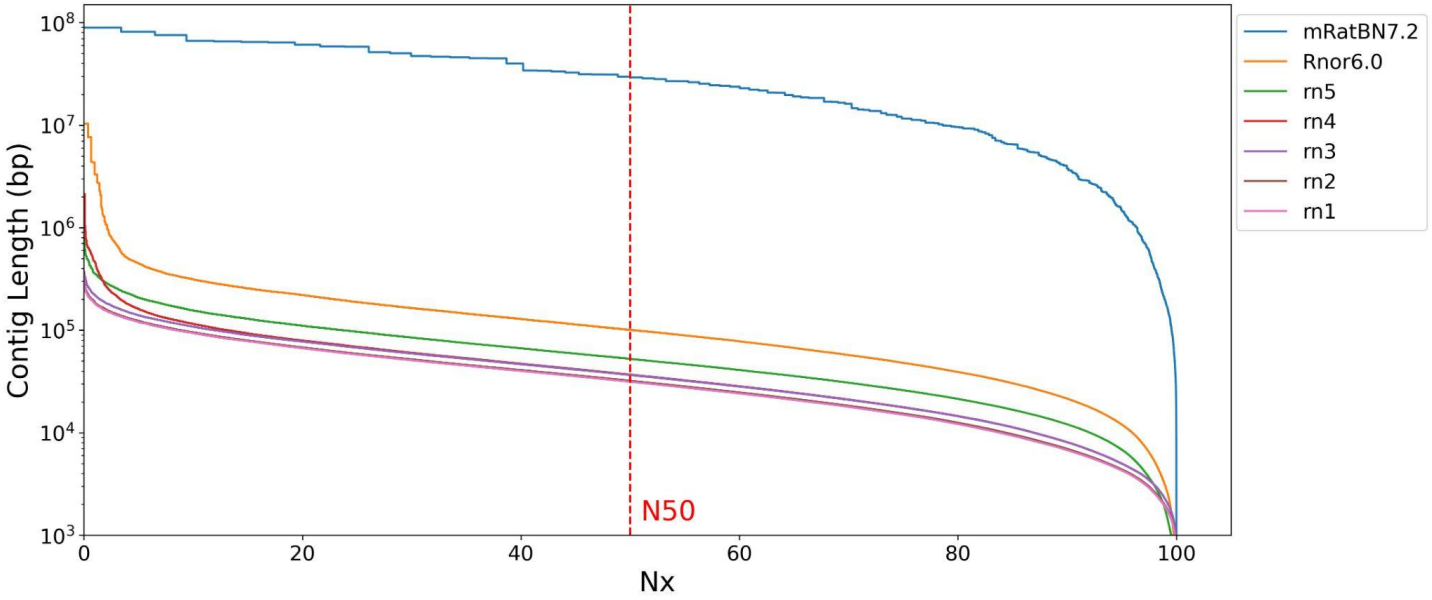

Figure S1 (related to Figure 1). The Contig Nx plot for mRatBN7.2 and 6 prior rat reference genomes. The red dashed line indicates the contig N50 values. Small improvements in contig continuity are observed for the previous updates, with the most significant improvement (~290X) coming from mRatBN7.2

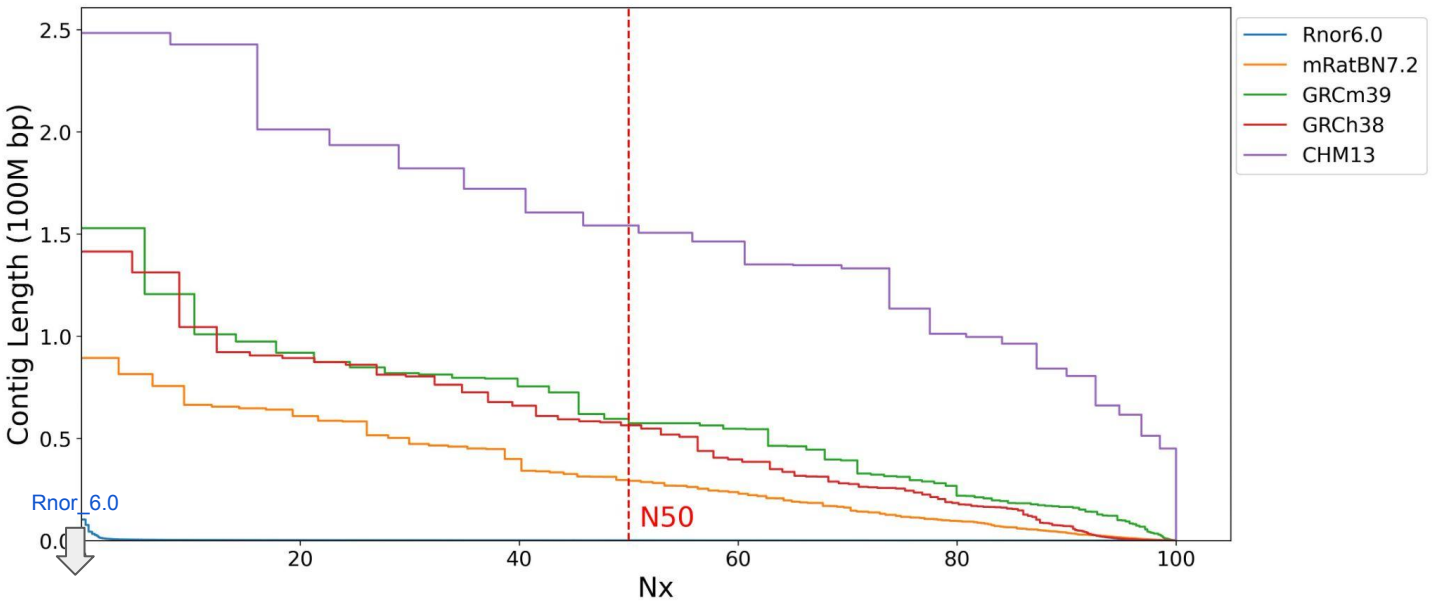

Figure S2 (related to Figure 1). The Contig Nx plot for the Rat, Mouse, and Human reference genomes. The red dashed line indicates the contig N50 values. The Nx curve for Rnor6.0 is very low and partially overlapping with the X axis. The CHM13, being the first truly gapless human genome, is in its own tier in terms of assembly continuity. The GRCh38 released in 2014 and the GRCm39 released in 2020 have similar continuity. Although mRatBN7.2 is still lagging behind in continuity compared to the current human and mouse reference genomes, it represent a very significant improvement over the current rat reference genome Rnor_6.0 (Orange vs. Cyan line).

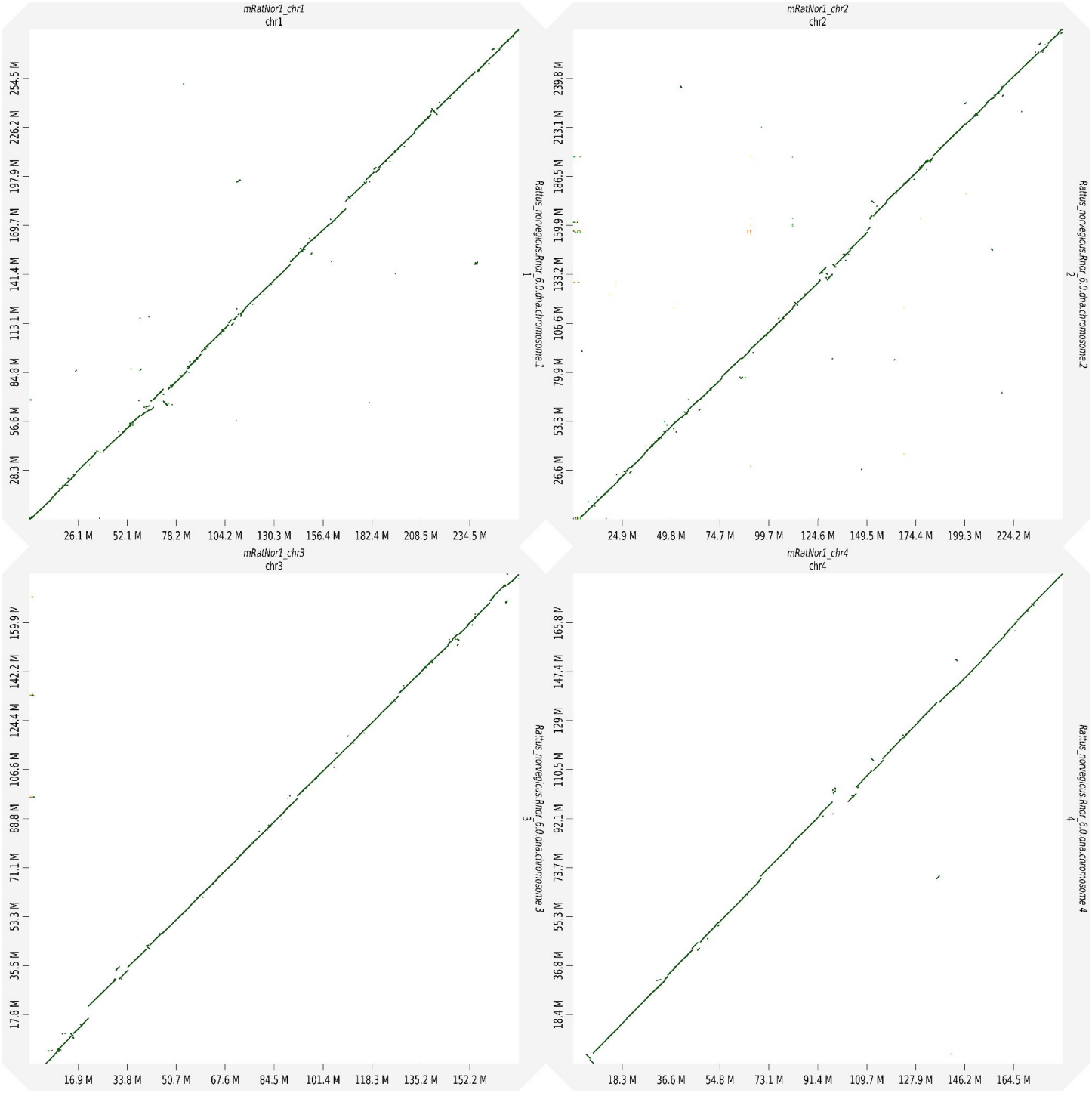

Figure S3 (related to Figure 1). Chromosomal dot plots between Rnor_6.0 and mRatBN7.2. mRatBN7.2 is on the x-axis and Rnor_6.0 is on the y-axis. mRatNor1 is the initial name of the assembly released by the Darwin Tree of Life/Vertebrate Genome Project. chr1-chr4 are shown here. To see the complete set, see the Key Resources Table “Chromosomal dot plots between Rnor_6.0 and mRatBN7.2” https://doi.org/10.5281/zenodo.10515796

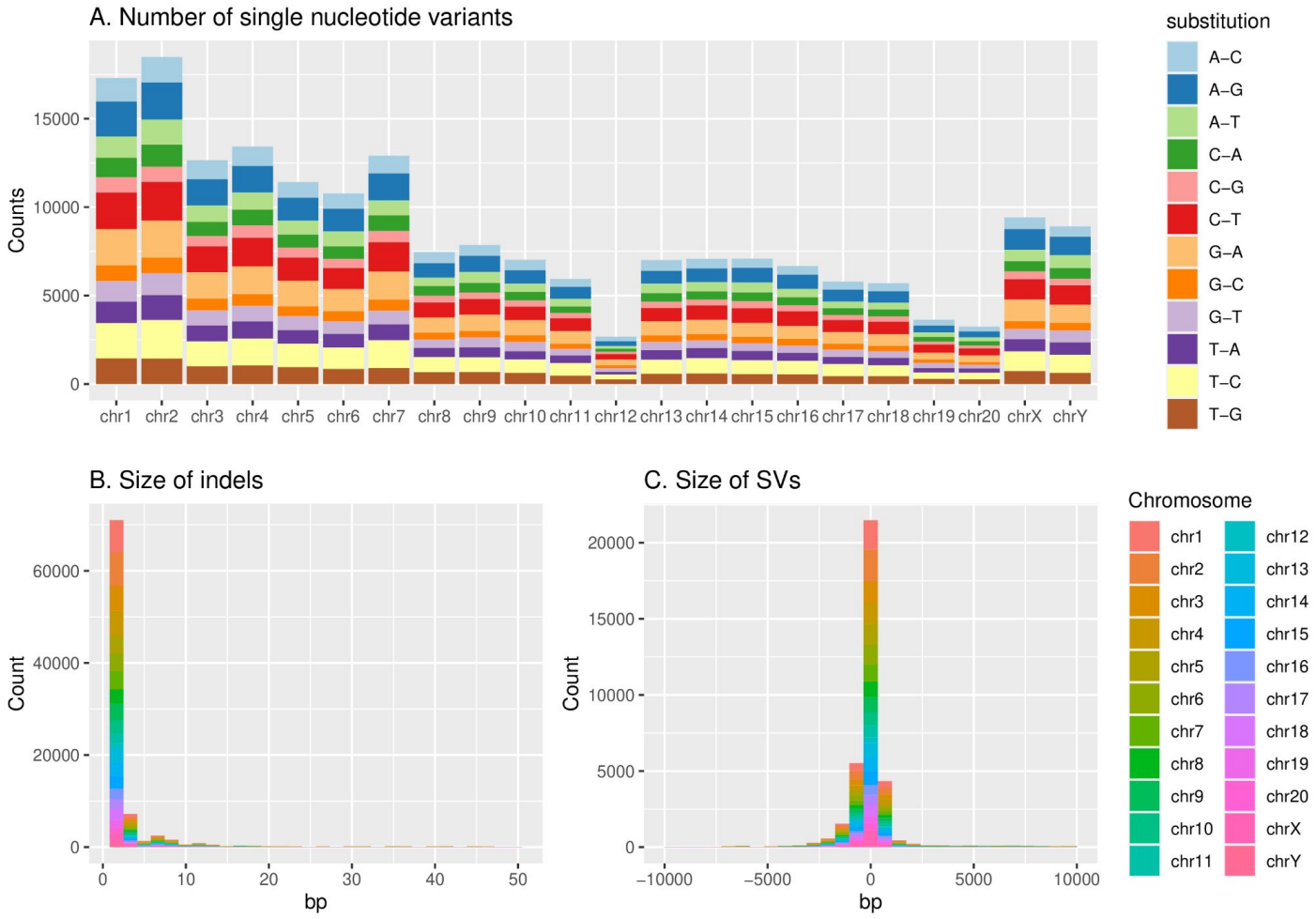

Figure S4 (related to Figure 1). SNP and structural variants between Rnor_6.0 and mRatBN7.2. A) The substitution frequency per chromosome for Rnor_6.0 and mRatBN7.2. **B)** The size of indels between Rnor 6.0 and mRatBN7.2. **C)** The size of SVs between Rnor6.0 and mRatBN7.2.

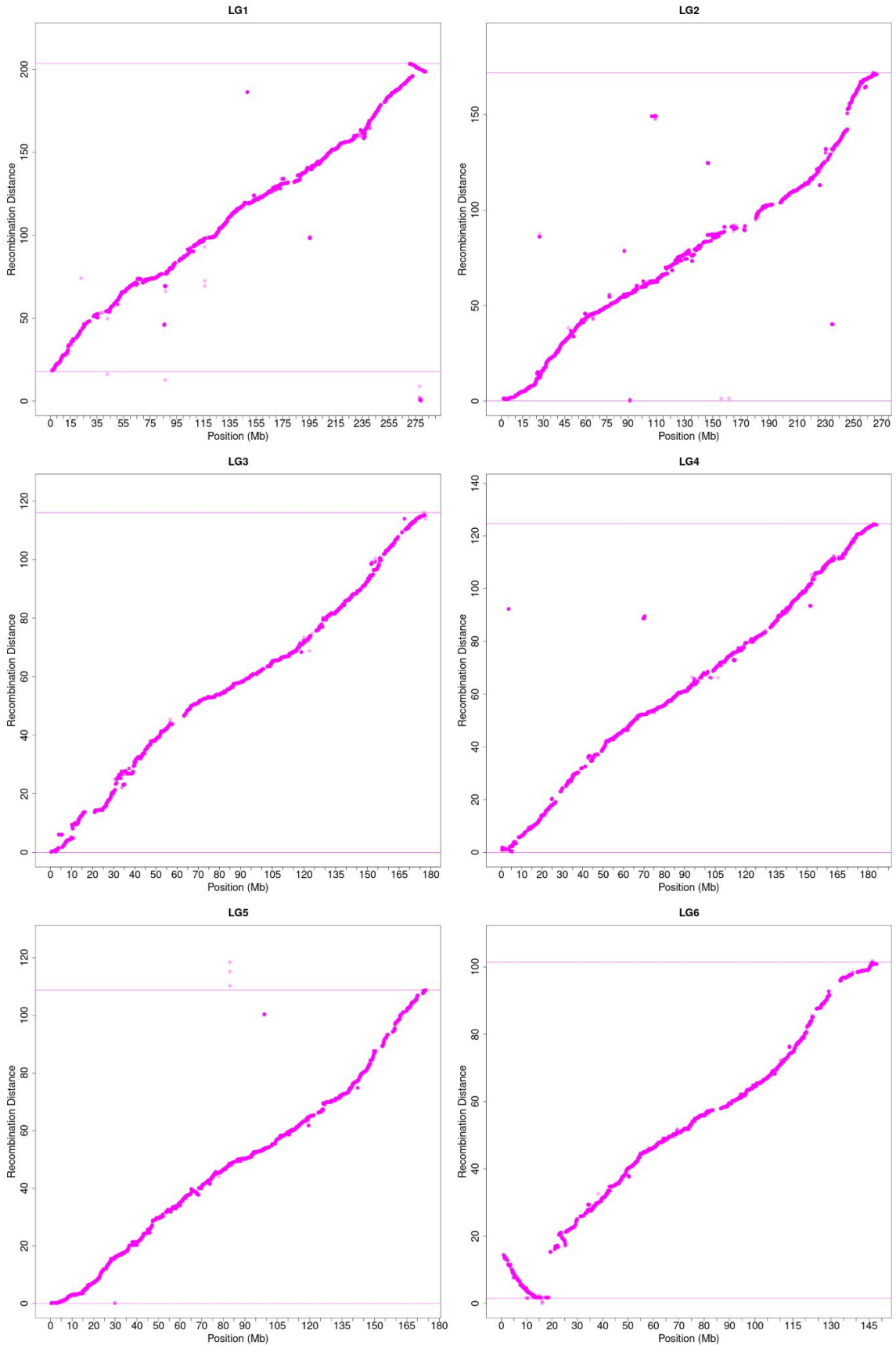

Figure S5 (related to Figure 1). The order of genetic markers and the distances from a rat genetic map compared to their locations in Rnor_6.0. Note the large inversion at proximal Chr 6. chr1-chr6 are shown here. To see the complete set, see the Key Resources Table "The order of genetic markers and the distances from a rat genetic map compared to their locations in Rnor_6.0" https://doi.org/10.5281/zenodo.10520087

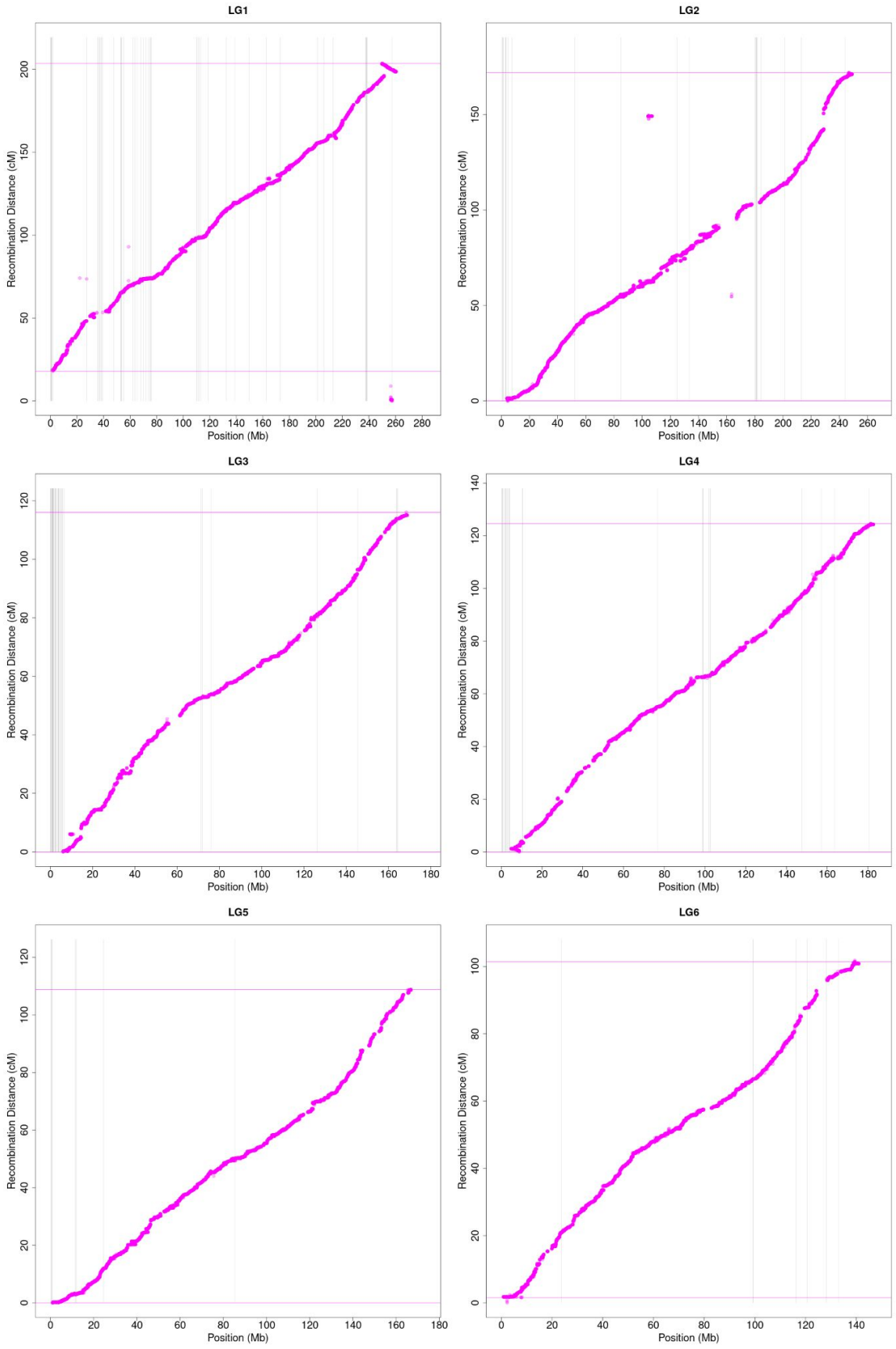

Figure S6 (related to Figure 1). The order of genetic markers and the distances from a rat genetic map compared to their locations in mRatBN7.2 chr1-chr6 are shown here. To see the complete set, see the Key Resources Table "The order of genetic markers and the distances from a rat genetic map compared to their locations in mRatBN7.2" https://doi.org/10.5281/zenodo.10520119

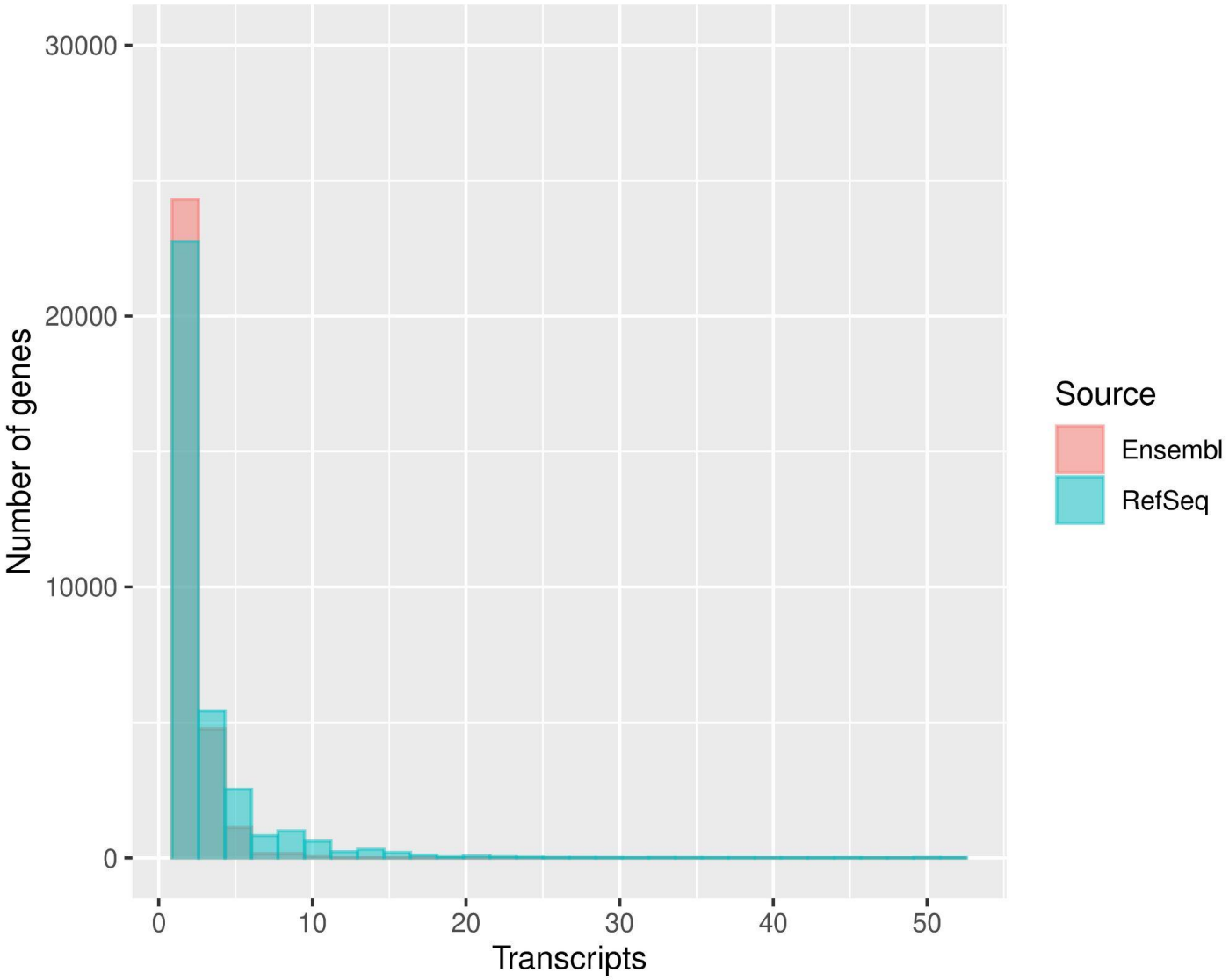

Figure S7 (related to Figure 1). The number of transcripts annotated by Ensembl and RefSeq. Refseq annotated a greater number of genes with multiple transcripts than Ensembl. The average number of transcripts per gene was 2.9 for RefSeq and 1.8 for Ensembl.

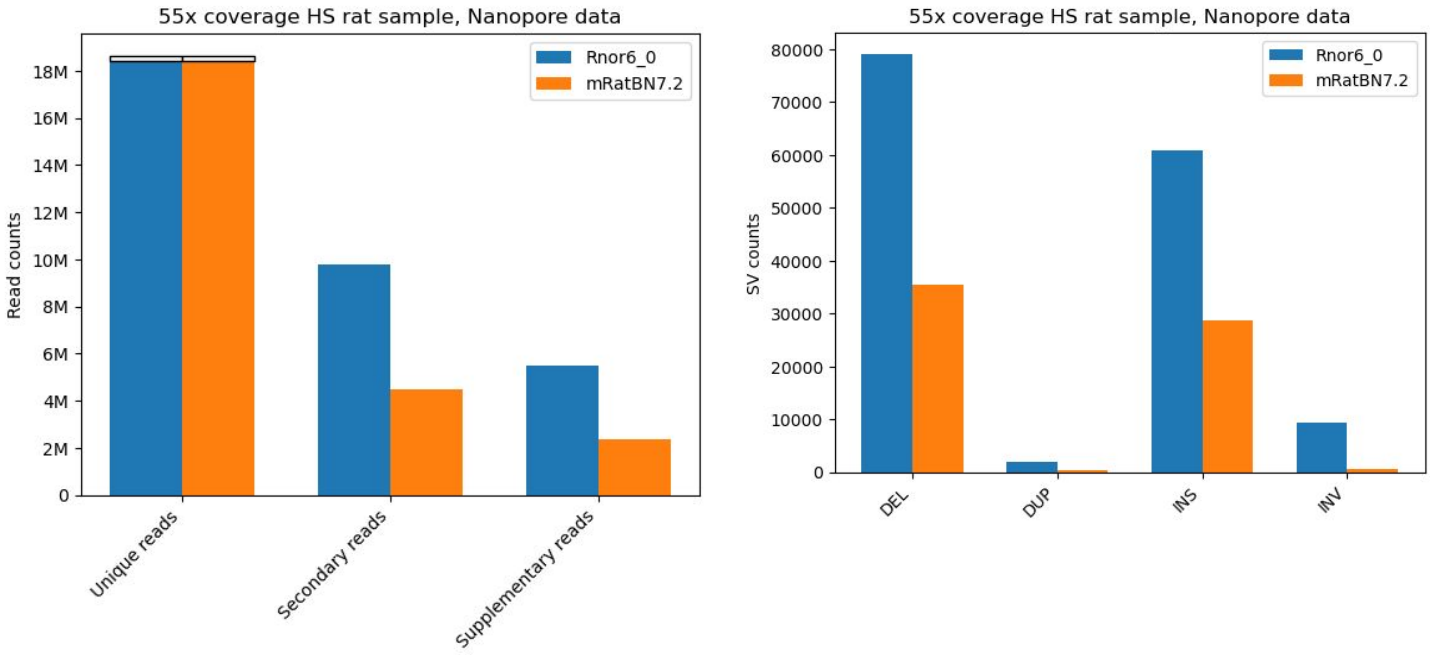

Figure S8 (related to Figure 2). Mapping results of nanopore data of one HS rat with 55x coverage. Using mRatBN7.2 as the reference decreased the number of structural variants compared to using Rnor_6.0 as the reference. In the context of our other findings, this is likely due to the improved quality of the reference genome.

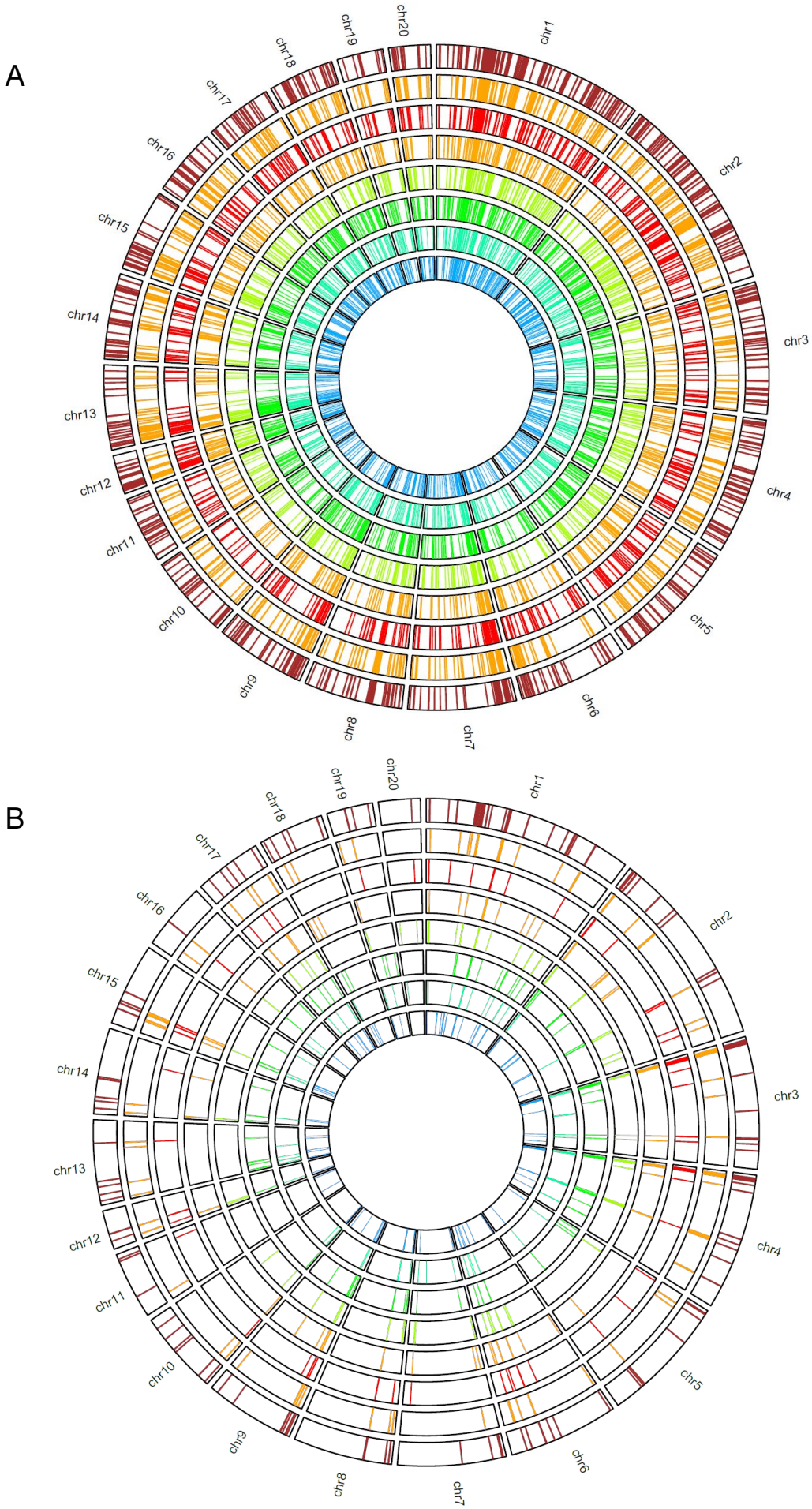

Figure S9 (related to Figure 2). Locations of large deletions from multiple linked-read samples. A) Rnor_6.0 B) mRatBN7.2. From outer circle to inner circle are the following strains: BN, SHR/Olalpcv, BXH10, BXH8, BXH2, HXB17, HXB2, and HXB21.

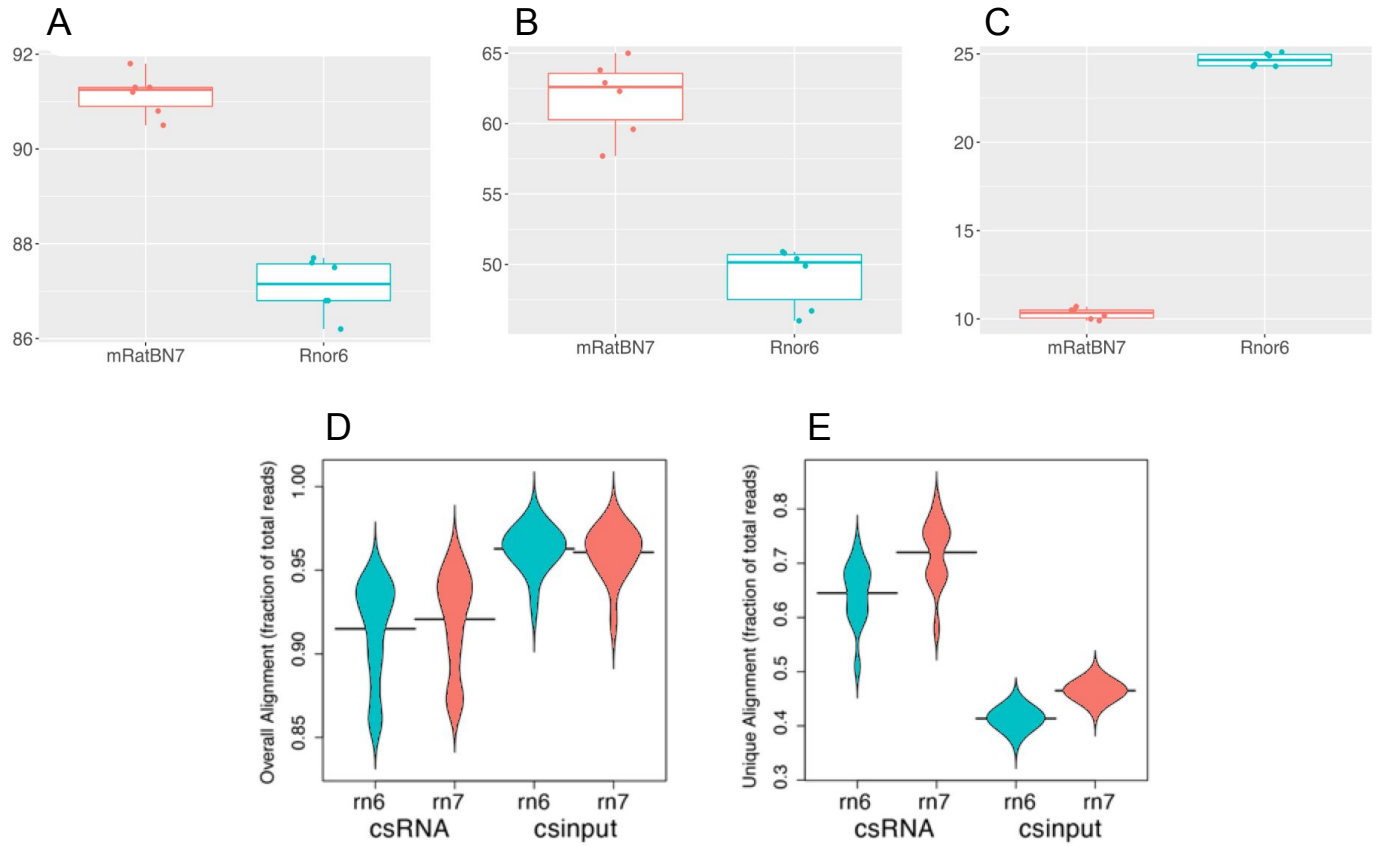

Figure S10 (related to Figure 2). Mapping metrics of single nuclei RNA-seq and small capped RNA-seq data generated using rat brain tissues. Percentage of snRNA-seq reads mapped to A) the genome, B) the transcriptome, and C) an intergenic region of the genome for mRatBN7.2 and Rnor_6.0. D) Overall mapping rates of csRNA-seq data to two reference genomes. E) Unique alignment of csRNA-seq data to two reference genomes.

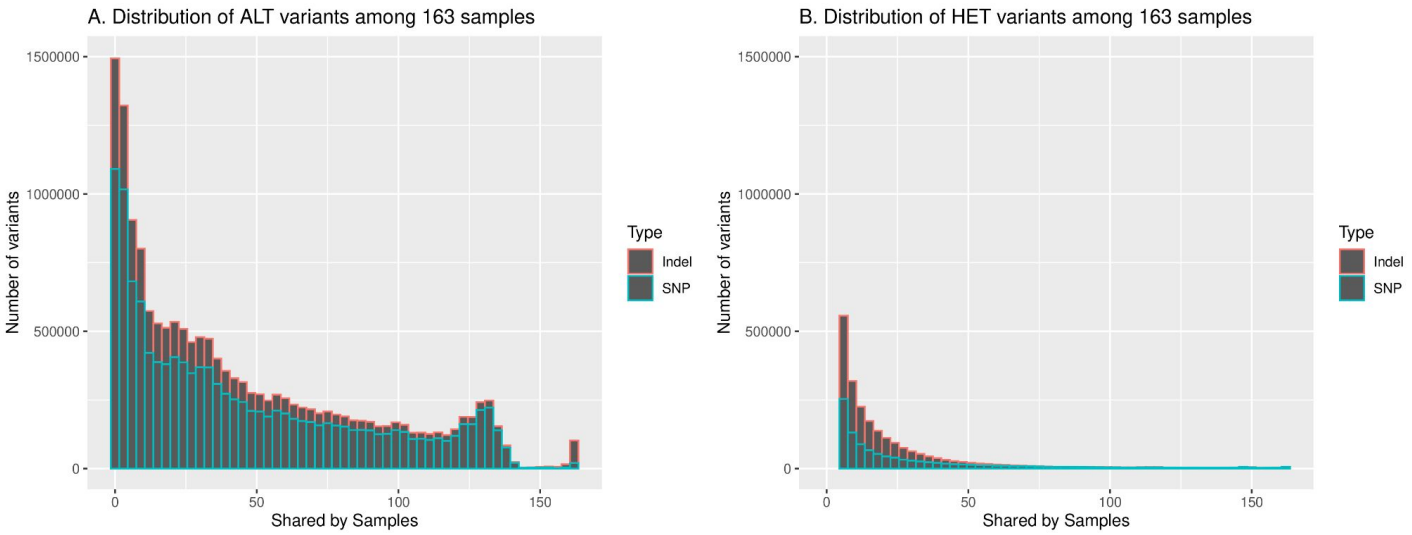

Figure S11 (related to Figure 6). Distribution of the total number of variants shared by 1 or more samples across all 163 samples for A) Homozygous alternative SNPs/Indels. The lack of variants shared by approximately 140-155 samples and the distinct peak after 155 samples indicate variants shared by more than 156 samples are likely caused by errors in the reference genome. B) Heterozygous SNPs/Indels. Similar pattern as A can be observed.

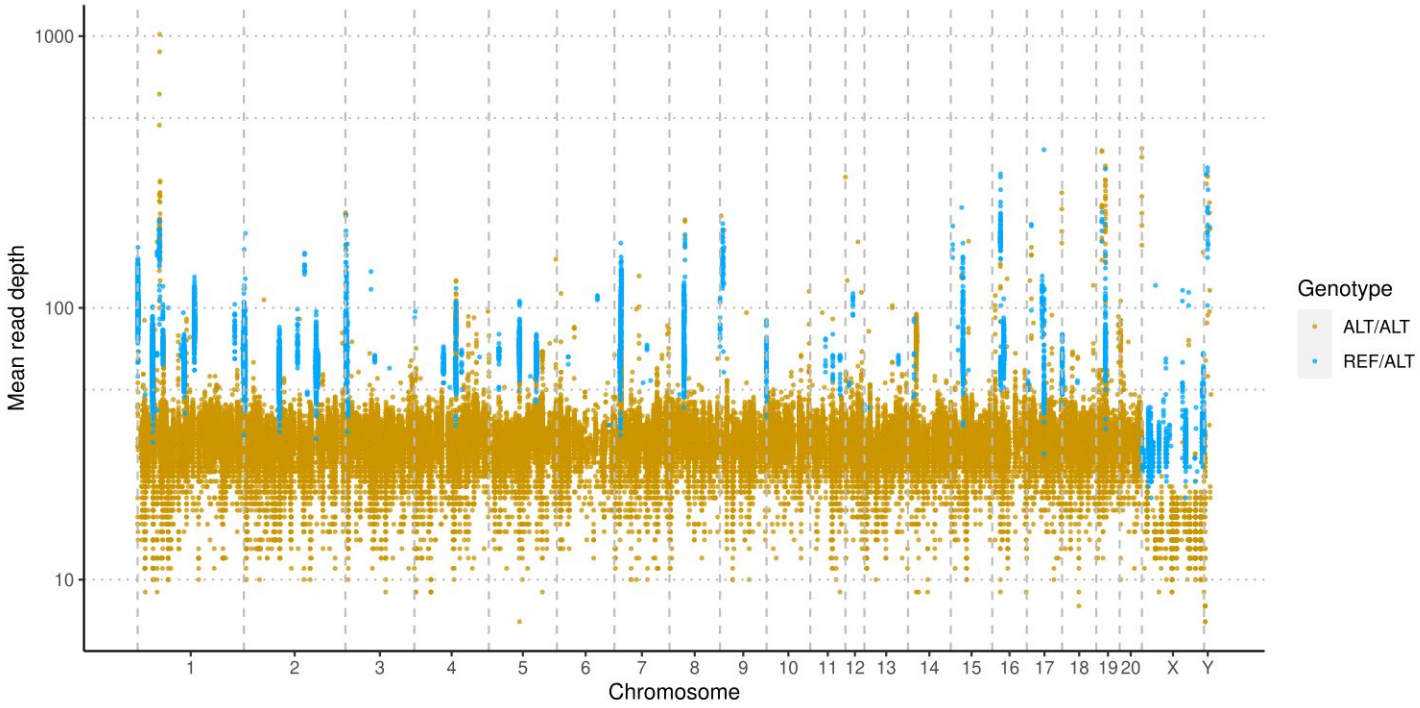

Figure S12 (related to Figure 6). SNPs and indels indicate remaining errors in mRatBN7.2. Base-level errors are indicated by homozygous variants that are shared by the majority (i.e. more than 153 out of 163) of samples, including all seven BN/NHsdMcwi rats, one of them is part of the data used to assemble mRatBN7.2. Variants that are heterozygous for the majority of the samples are clustered in a few regions and have significantly higher read-depth. This suggests that they originated from collapsed repeats in mRatBN7.2.

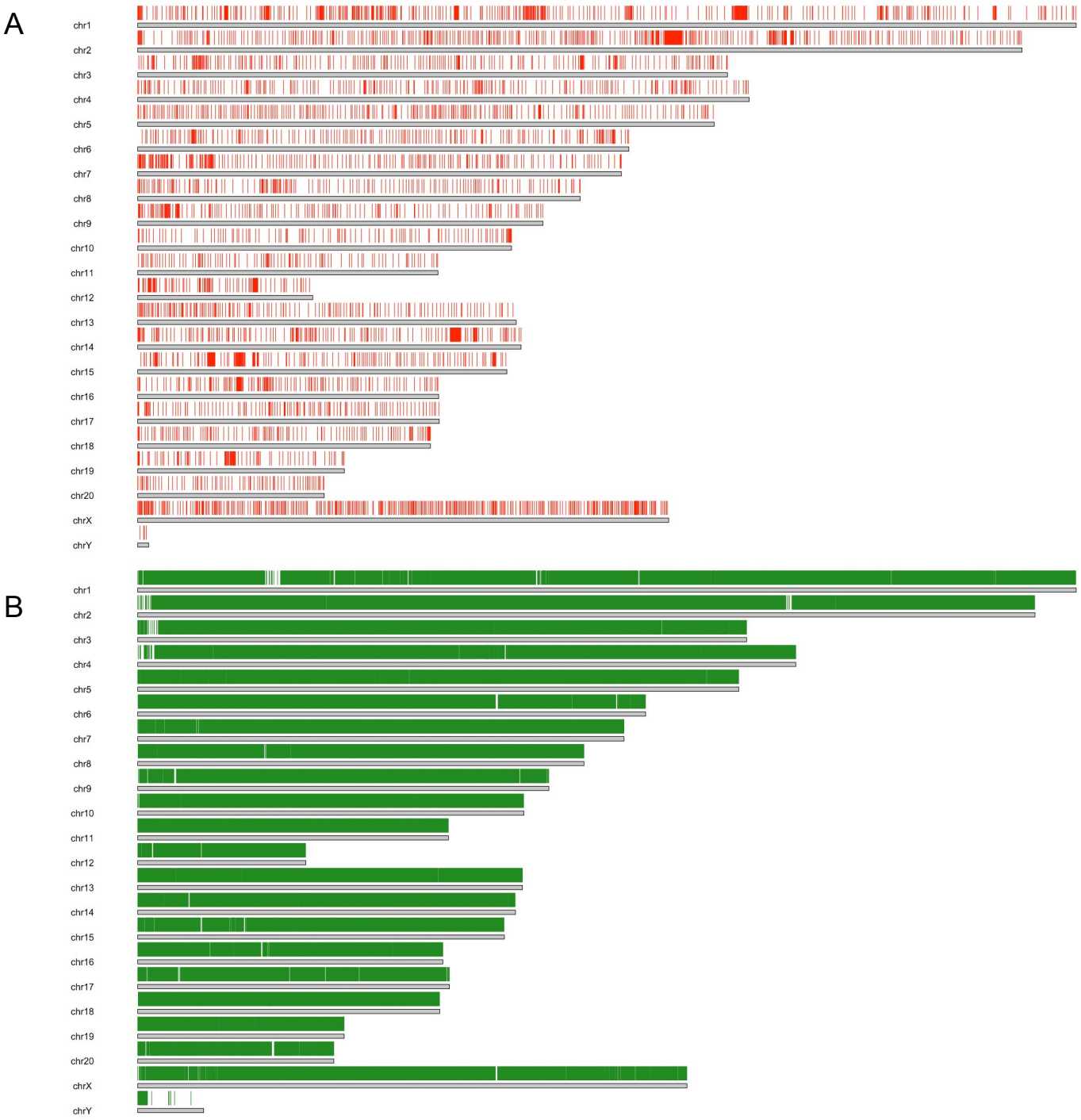

Figure S13 (related to Figure 4). Simulated liftover analysis: unliftable and lifted site distribution. An evenly 1000 bp spaced bed file covering Rnor_6.0 is generated and then lifted to mRatBN7.2. Out of the 2,782,023 sites, 92.04% are liftable, 7.96% are not liftable. A) The distribution of the unliftable sites are plotted on Rnor_6.0. B) The distribution of the lifted sites are plotted on mRatBN7.2. The data are subsampled by 50 for better visualization.

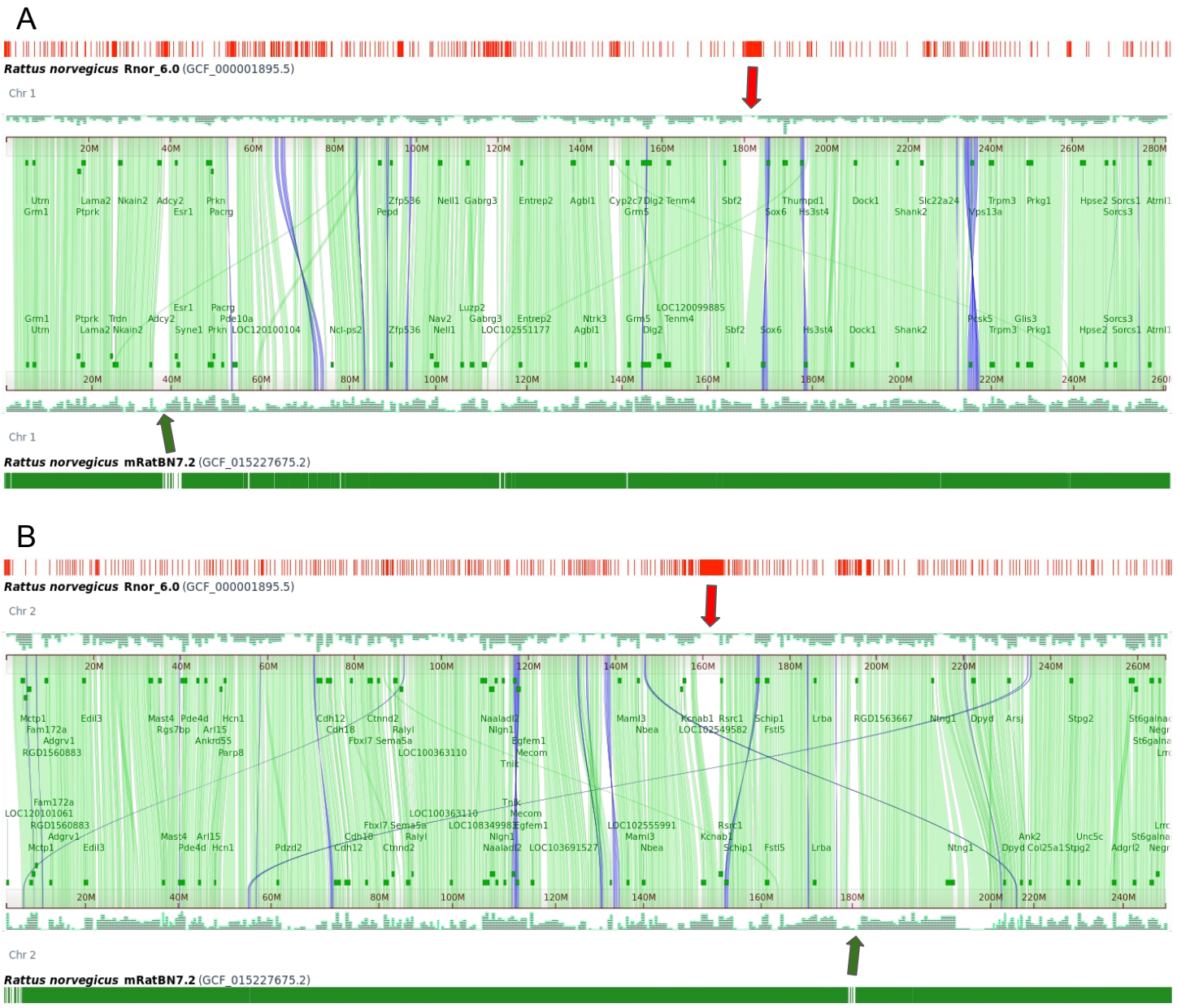

Figure S14 (related to Figure 4). Simulated liftover analysis and comparative genome view. Top red track is the unliftable sites distributed on the Rnor_6.0. Bottom green track is the lifted sites distributed on the mRatBN7.2. The middle is the NCBI comparative genome viewer between chr1 of Rnor_6.0 and mRatBN7.2. The red arrow highlights a region that's not liftable in Rnor_6.0. According to the comparative genome view, the region has no corresponding region in mRatBN7.2 (not just chr1). The green arrow highlights a regiono in mRatBN7.2 that has no lifted sites from Rnor_6.0. According to the comparative genome view, this region has matching region in Rnor_6.0. A) Chromosome 1. B) Chromosome 2.

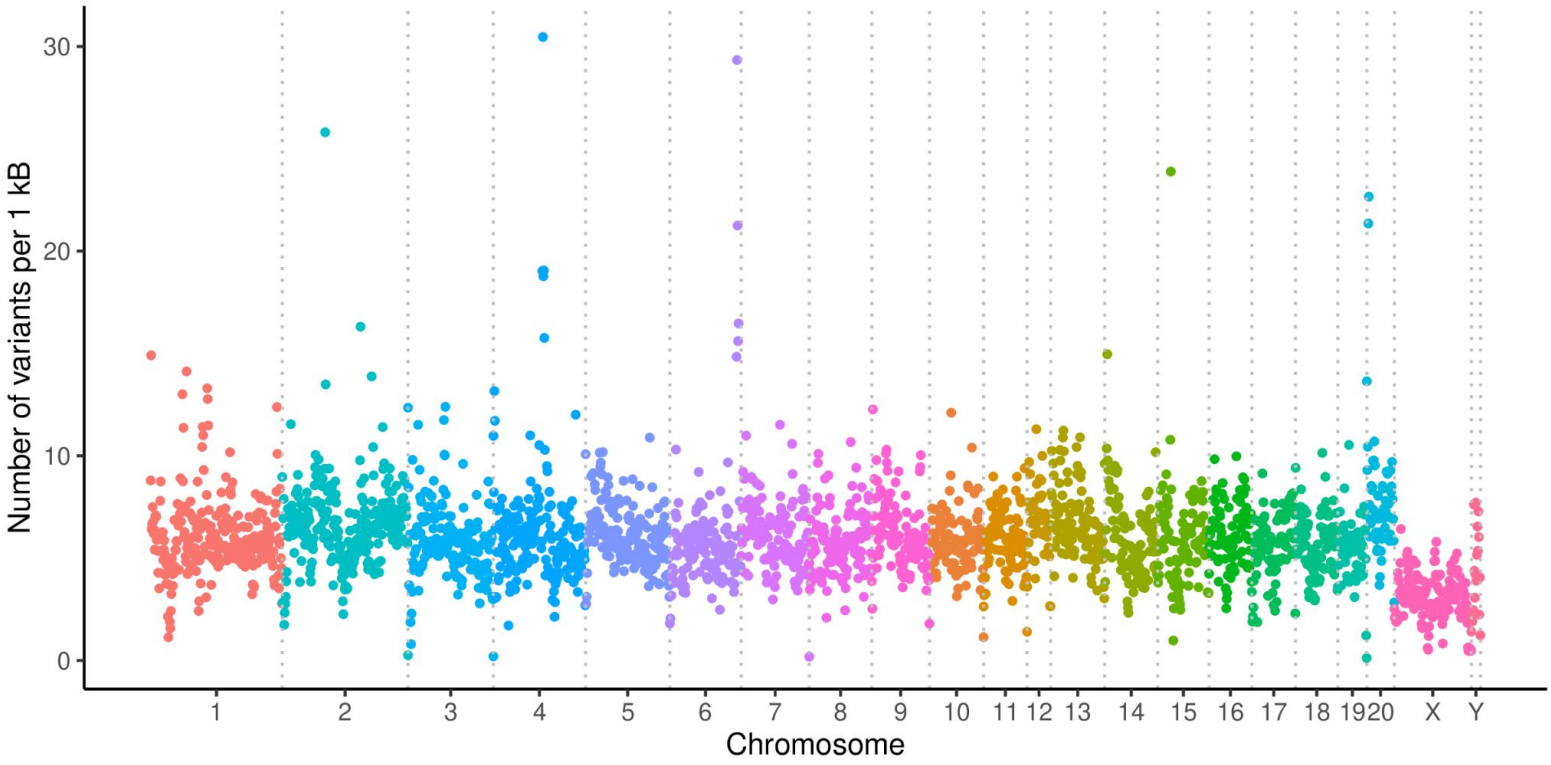

Figure S15 (related to Figure 5). Density of variants across the genome in a collection of 163 rat WGS samples. The mean variant density was 5.96 ± 2.20/Kb (mean ± SD). The highest variant density of 30.5/Kb was found on Chr 4 at 98 Mb.

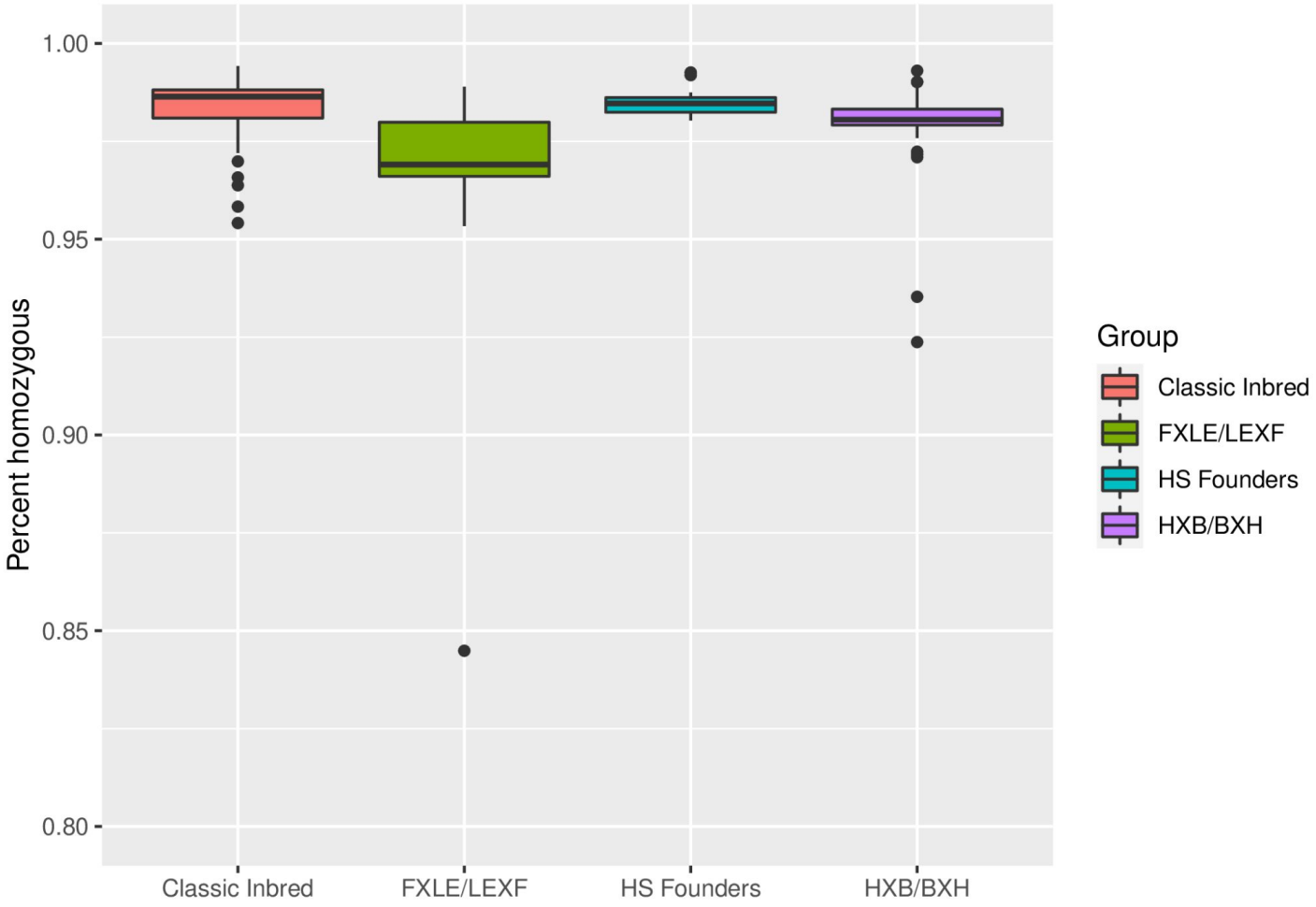

Figure S16 (related to Figure 5). Homozygosity of inbred strains. Variants in most sample were homozygous, confirming the inbred nature of most strains. A few exceptions were noted. For example, 15.6% of the variants from FXLE24 were heterozygous. Additionally, BXH2, which we sequenced two samples, has ~7.7% heterozygous variants.

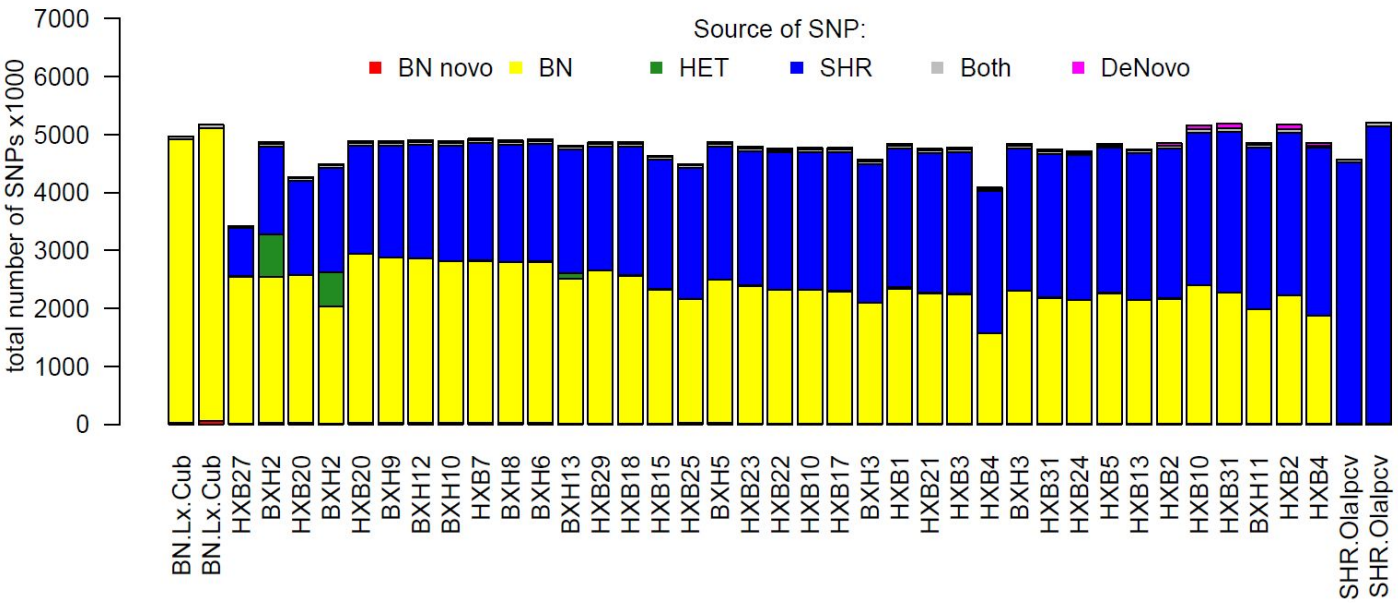

Figure S17 (related to Figure 5). The majority of the variants in HXB/BXH RI panel are inherited from the parental strains. De Novo Mutations on BN.Lx (Red) Mutations originating from BN (Yellow), Heterozygous (Green), Mutations originating from SHR (Blue), SNPs found on both BN and SHR (Grey), De Novo SNPs from neither parental strains (Pink).

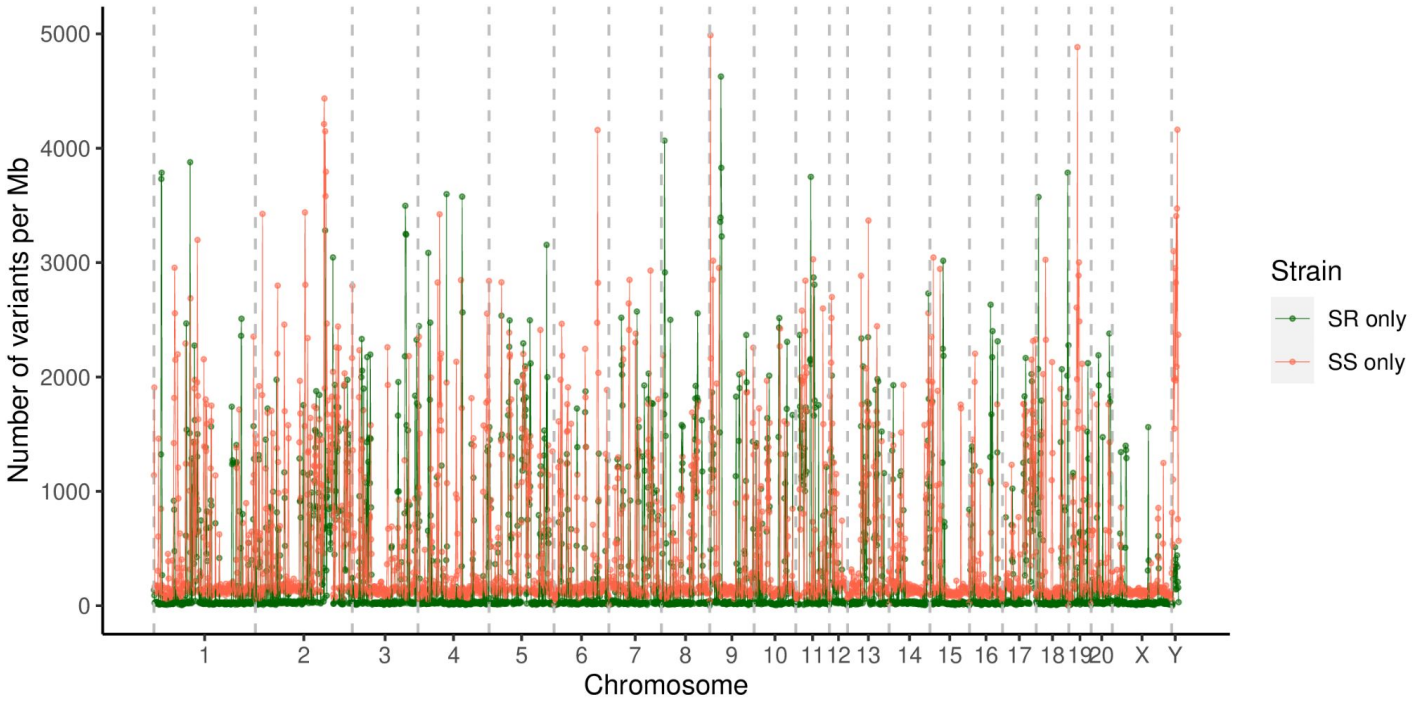

Figure S18 (related to Figure 5). Distribution of variants different between SS and SR rats. Total number of variants unique to either SS or SR rats across the genome. The SS strain contains more unique variants than SR.

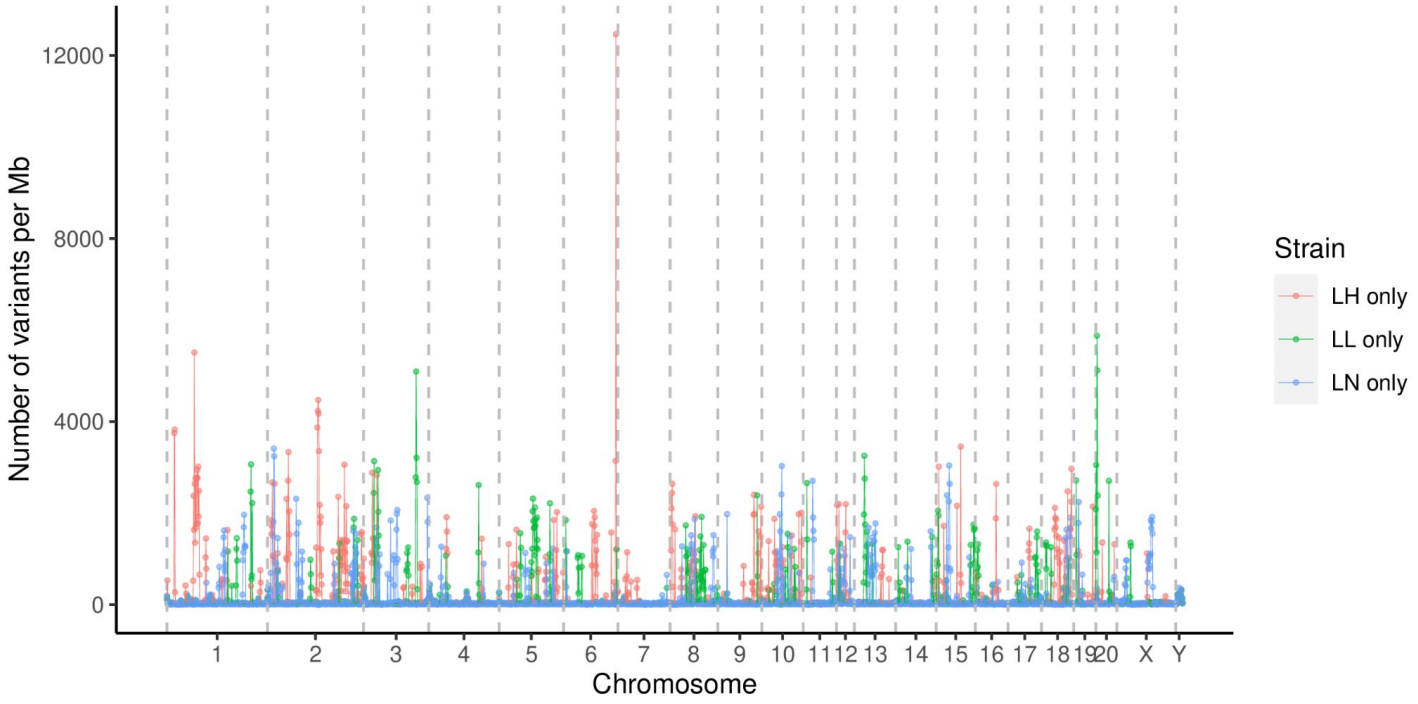

Figure S19 (related to Figure 5). Distribution of variants unique to LL/LH/LN rats. Strain-specific variants tend to cluster by strain.

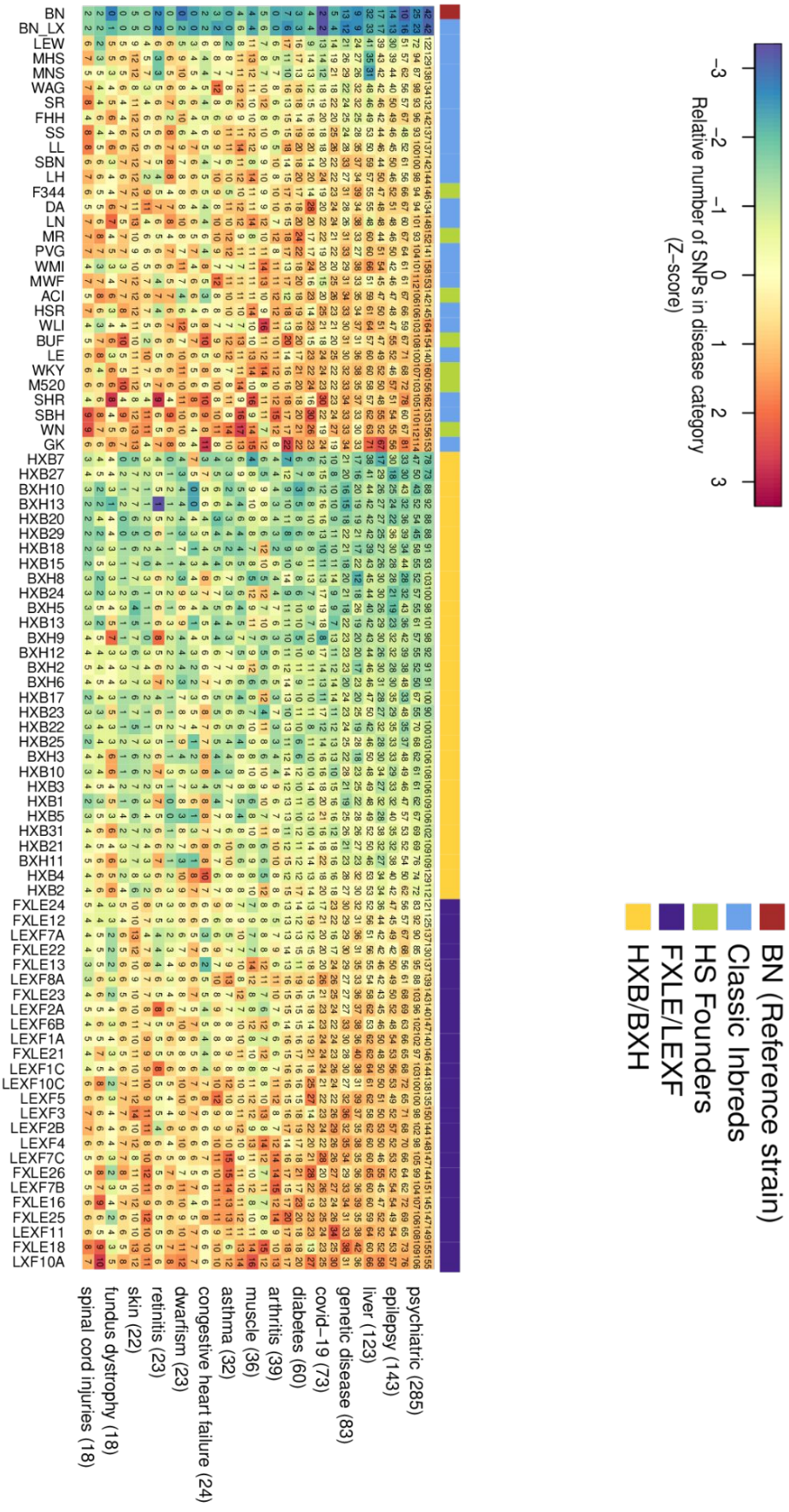

Figure S20 (related to Figure 5). Overview of disease ontology annotation of variants in RatCollection. Heat maps shows relative number of SNPs in proximity of genes associated per disease category within the reference, classic inbreds, HS progenitors and recombinant inbred panels.

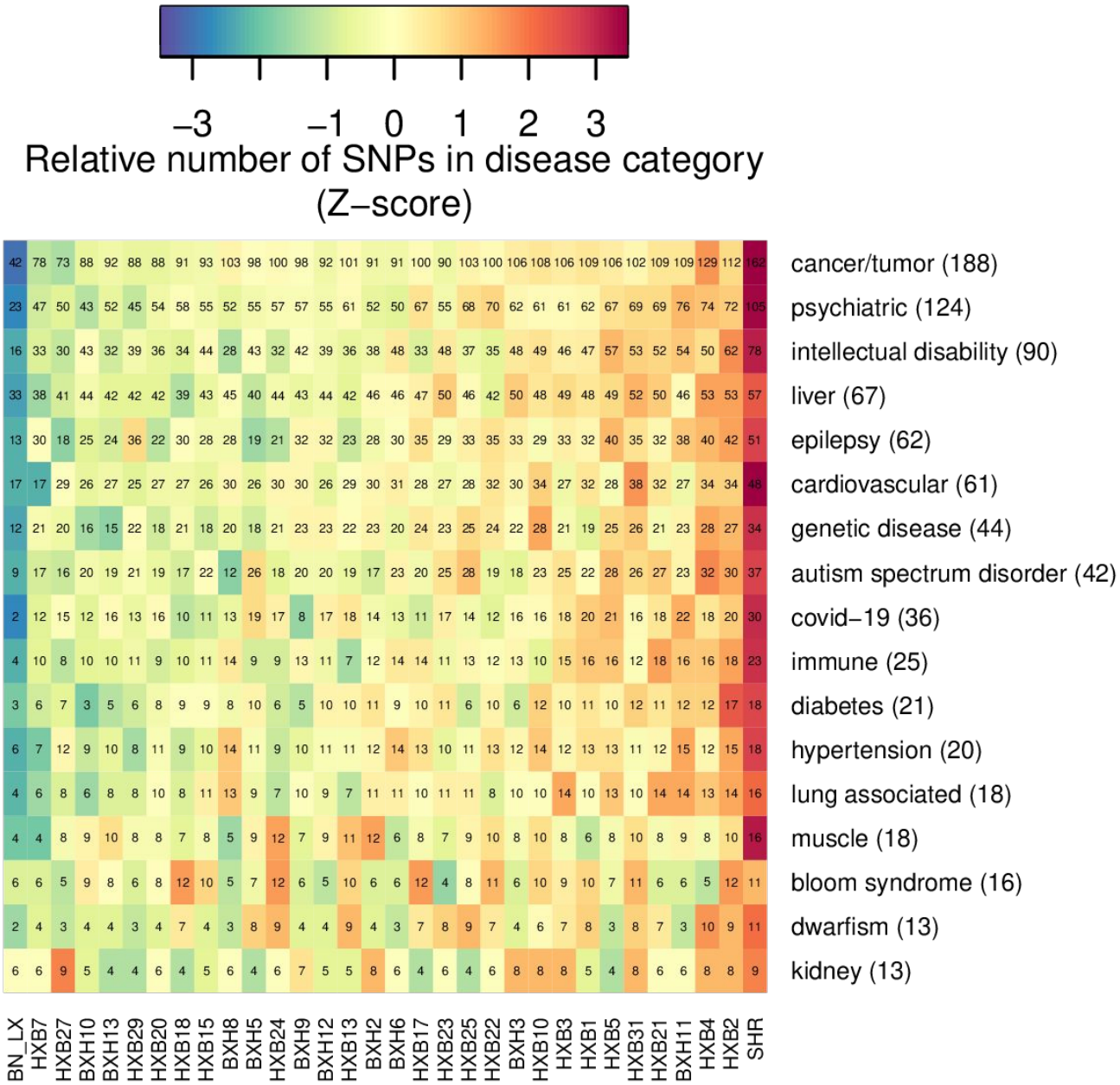

Figure S21 (related to Figure 5). Disease ontology of genetic variants found in the HXB/BXH RI panel. Numbers within the grid show the absolute number of SNPs with high impact on genes within the disease annotation. Numbers following the disease name shows the total number of annotated genes with at least 1 high impact variant within the panel.

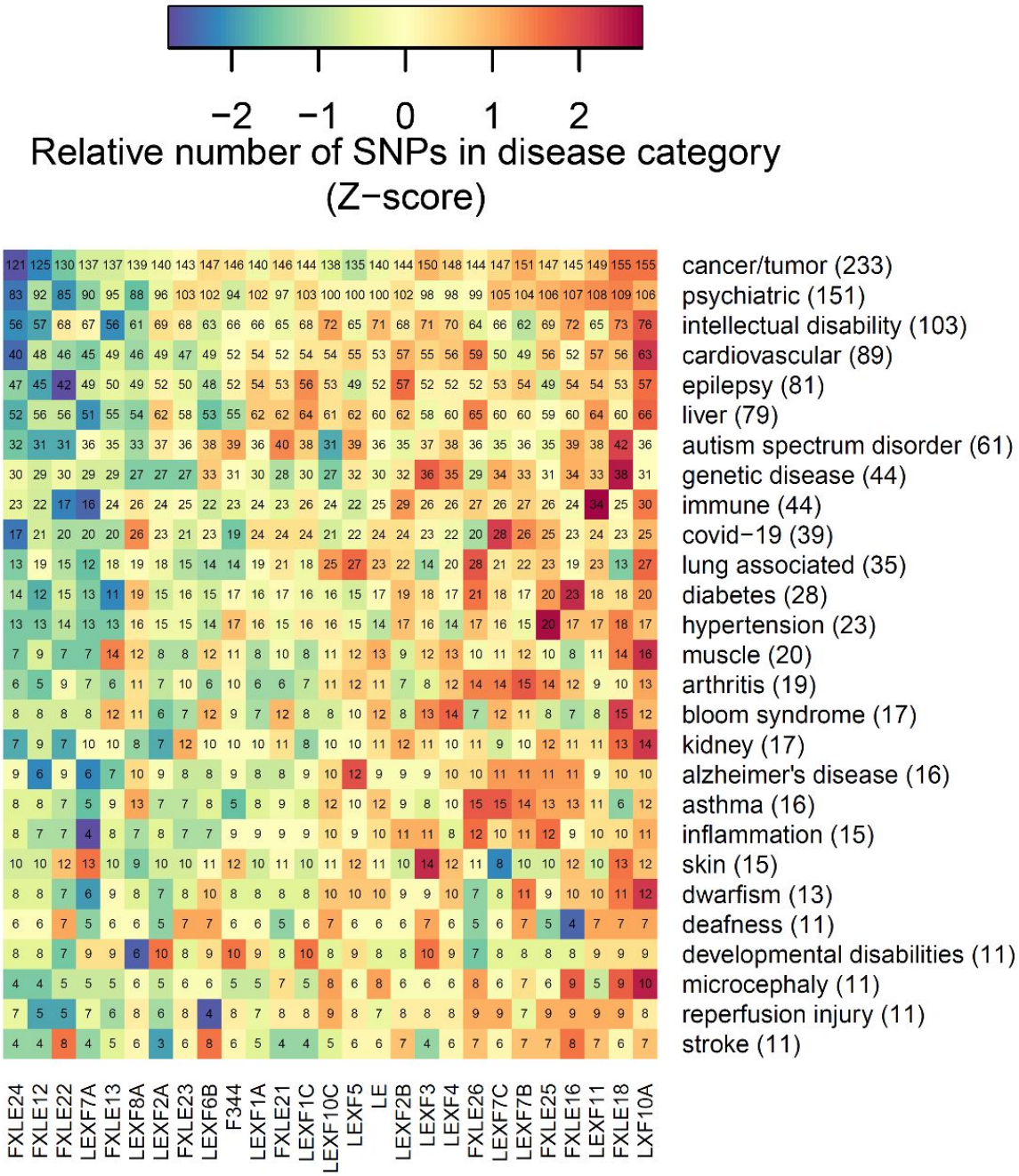

Figure S22 (related to Figure 5). Disease ontology annotation of variants in the LEXF/FXLE RI panel. Numbers within the grid show the absolute number of SNPs with high impact on genes within the disease annotation. Numbers following the disease name shows the total number of annotated genes with at least 1 high impact variant within the panel.

Supplemental references in Excel files

[1] L. Wu, W. Shi, J. Long, X. Guo, K. Michailidou, J. Beesley, MK. Bolla, XO. Shu, Y. Lu, Q. Cai, F. Al-Ejeh, E. Rozali, Q. Wang, J. Dennis, B. Li, C. Zeng, H. Feng, A. Gusev, RT. Barfield, IL. Andrulis, H. Anton-Culver, V. Arndt, KJ. Aronson, PL. Auer, M. Barrdahl, C. Baynes, MW. Beckmann, J. Benitez, M. Bermisheva, C. Blomqvist, NV. Bogdanova, SE. Bojesen, H. Brauch, H. Brenner, L. Brinton, P. Broberg, SY. Brucker, B. Burwinkel, T. Caldés, F. Canzian, BD. Carter, JE. Castelao, J. Chang-Claude, X. Chen, TD. Cheng, H. Christiansen, CL. Clarke, M. Collée, S. Cornelissen, FJ. Couch, D. Cox, A. Cox, SS. Cross, JM. Cunningham, K. Czene, MB. Daly, P. Devilee, KF. Doheny, T. Dörk, I. Dos-Santos-Silva, M. Dumont, M. Dwek, DM. Eccles, U. Eilber, AH. Eliassen, C. Engel, M. Eriksson, L. Fachal, PA. Fasching, J. Figueroa, D. Flesch-Janys, O. Fletcher, H. Flyger, L. Fritschi, M. Gabrielson, M. Gago-Dominguez, SM. Gapstur, M. García-Closas, MM. Gaudet, M. Ghoussaini, GG. Giles, MS. Goldberg, DE. Goldgar, A. González-Neira, P. Guénel, E. Hahnen, CA. Haiman, N. Håkansson, P. Hall, E. Hallberg, U. Hamann, P. Harrington, A. Hein, B. Hicks, P. Hillemanns, A. Hollestelle, RN. Hoover, JL. Hopper, G. Huang, K. Humphreys, DJ. Hunter, A. Jakubowska, W. Janni, EM. John, N. Johnson, K. Jones, ME. Jones, A. Jung, R. Kaaks, MJ. Kerin, E. Khusnutdinova, VM. Kosma, VN. Kristensen, D. Lambrechts, L. Le Marchand, J. Li, S. Lindström, J. Lissowska, WY. Lo, S. Loibl, J. Lubinski, C. Luccarini, MP. Lux, RJ. MacInnis, T. Maishman, IM. Kostovska, A. Mannermaa, JE. Manson, S. Margolin, D. Mavroudis, H. Meijers-Heijboer, A. Meindl, U. Menon, J. Meyer, AM. Mulligan, SL. Neuhausen, H. Nevanlinna, P. Neven, SF. Nielsen, BG. Nordestgaard, OI. Olopade, JE. Olson, H. Olsson, P. Peterlongo, J. Peto, D. Plaseska-Karanfilska, R. Prentice, N. Presneau, K. Pylkäs, B. Rack, P. Radice, N. Rahman, G. Rennert, HS. Rennert, V. Rhenius, A. Romero, J. Romm, A. Rudolph, E. Saloustros, DP. Sandler, EJ. Sawyer, MK. Schmidt, RK. Schmutzler, A. Schneeweiss, RJ. Scott, CG. Scott, S. Seal, M. Shah, MJ. Shrubsole, A. Smeets, MC. Southey, JJ. Spinelli, J. Stone, H. Surowy, AJ. Swerdlow, RM. Tamimi, W. Tapper, JA. Taylor, MB. Terry, DC. Tessier, A. Thomas, K. Thöne, RAEM. Tollenaar, D. Torres, T. Truong, M. Untch, C. Vachon, D. Van Den Berg, D. Vincent, Q. Waisfisz, CR. Weinberg, C. Wendt, AS. Whittemore, H. Wildiers, WC. Willett, R. Winqvist, A. Wolk, L. Xia, XR. Yang, A. Ziogas, E. Ziv, AM. Dunning, PDP. Pharoah, J. Simard, RL. Milne, SL. Edwards, P. Kraft, DF. Easton, G. Chenevix-Trench, and W. Zheng. A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer. Nat Genet, 50(7):968–978, 2018. PMCID: PMC6314198, PMID: 29915430.

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