Optical mapping compendium of structural variants across global cattle breeds

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Abstract

Structural variants (SV) have been linked to important bovine disease phenotypes, but due to the difficulty of their accurate detection with standard sequencing approaches, their role in shaping important traits across cattle breeds is largely unexplored. Optical mapping is an alternative approach for mapping SVs that has been shown to have higher sensitivity than DNA sequencing approaches. The aim of this project was to use optical mapping to develop a high-quality database of structural variation across cattle breeds from different geographical regions, to enable further study of SVs in cattle.

To do this we generated 100X Bionano optical mapping data for 18 cattle of nine different ancestries, three continents and both cattle sub-species. In total we identified 13,457 SVs, of which 1,200 putatively overlap coding regions. This resource provides a high-quality set of optical mapping-based SV calls that can be used across studies, from validating DNA sequencing-based SV calls to prioritising candidate functional variants in genetic association studies and expanding our understanding of the role of SVs in cattle evolution.

50 # Background & Summary

51 Structural variants (SV) are a heterogeneous class of genetic variants involving large
52 fragments of the genome (>50bp)[1]. These variants include genomic insertions and deletions
53 (InDels), inversions, duplications, translocations and more complex rearrangements[2]. Single
54 nucleotide polymorphisms (SNPs) have been the primary focus of studies trying to map
55 genetic loci underlying important cattle phenotypes. However, there are multiple lines of
56 evidence suggesting SVs likely underlie many important cattle traits. As many as 25-29% of all
57 protein truncating events are thought to be caused by an SV in humans[1] and notably, despite
58 being less well studied, SVs have already been tied to key livestock phenotypes. For example,
59 a duplication of the CIITA class II major histocompatibility complex transactivator gene in
60 cattle has been tied to resistance to intestinal nematodes[3] and a 12Kb copy number variant
61 has been linked to mastitis in cattle[4]. Chromosomal translocations and duplications have been
62 linked to skin pigmentation, a phenotype closely tied to environmental adaptation, and SVs
63 across livestock species have been linked to phenotypes such as olfaction or resistance to
64 adenocarcinoma-causing viruses[5]. Importantly SVs are responsible for approximately 5-10
65 times as many heritable nucleotide sequence differences between individuals than SNPs[6].
66 Unlike SNPs, that only effect a single basepair, and most often far from coding regions, SVs
67 effect large regions and potentially multiple genes. Consequently, although smaller in
68 number, any given novel SV event is more likely to have a phenotypic consequence.
69 The two most popular methods used to detect SVs are high-throughput sequencing (HTS) and
70 array comparative genomic hybridisation (aCGH), both of which have been applied to
71 European cattle[7–9], but with few studies performed in other cattle breeds[10–12]. Each
72 technology has advantages and limitations. aCGH, for example, involves measuring binding
73 to probes covering the reference genome, and therefore it can only detect relative copy
74 number changes between sample pairs and cannot for example detect novel insertions.
75 Resolution is also limited. A major advantage of HTS approaches is that theoretically they can
76 detect SVs at base-pair resolution. However, accurate calling of SVs from HTS data has proven
77 to be difficult for a number of reasons including poor reference assemblies, chimeric reads,
78 aligners penalising reads that don't match the reference and the difficulties of sequencing
79 and mapping to repetitive regions. This is exemplified by the generally poor agreement
80 between SV callers even when run across the same samples[13,14]. Approaches using long reads

and *de novo* assembly can still have true positive rates as low as 77%, even when using simulated data[15].

Optical mapping (OM), a light microscope-based method that labels and physically locates specific motifs in the genome[16], offers an alternative protocol to accurately detect large SVs. OM molecules can be consistently hundreds of Kb long, allowing for the detection of complex rearrangements undetectable using HTS. Despite the limitation of not being able to detect the actual sequence of the identified SVs, as well as missing smaller SVs, OM has a very high sensitivity and specificity, allowing for the generation of high-quality catalogues of SVs in individuals[17]. A study in humans successfully used OM reads to identify SVs in a total of 26 genomes revealing population-specific patterns of structural variation[18].
In this study, we generated the first catalogue of cattle OM data for 18 animals from 9 different global breeds, and three continents, to better characterise common SVs across the cattle pan-genome. This data is a particularly valuable resource of SVs for the cattle species to intersect with other datasets, for example, for the validation of SV calls from other approaches.

Methods

Sample preparation

We selected a set of 18 cattle across 9 divergent European, African and Indian breeds representative of Indicine, Sanga and Taurine ancestries (Table 1). Blood was collected by jugular venipuncture into EDTA vacutainers. Somatic recombination in B cells and T cells means the Ig and TCR loci in these cell types will be highly heterogenous, confounding accurate reconstruction of germline SVs at these loci from whole blood samples. Consequently, after the erthyrocyte lysis, monocytes were purified from the leukocytes using a MACS positive selection protocol with an anti-bovine SIRPα mono-clonal antibody (ILA-24[19]). Agarose plugs containing 5 $x10^5$ – $1x10^6$ of isolated monocytes were prepared using the Bionano Blood and cell culture DNA isolation kit (Bionano Genomics, San Diego, US) according to the manufacturer's instructions and the extracted DNA used for analysis on the Bionano Saphyr platform to generate ~100X optical mapping coverage of each genome.

Bionano Solve optical mapping processing

OM reads were filtered using the filter_SNR_dynamic.pl script with default parameters included with the Solve workflow, and then processed through the Bionano Solve[20] pipeline (v3.3_10252018) using two different releases of RefAligner to overcome bugs preventing the successful assembly of the reads (version 7915.7989rel and 10330.10436rel). We generated the reference CMAP for the ARS-UCD1.2 genome with the Y chromosome from the 1000 bulls genome project (https://sites.ualberta.ca/~stothard/1000_bull_genomes/) using fa2cmap_multi_color.pl (default options and specifying the DLE1 as enzyme). The resulting data were imported into the Bionano Access (v1.6) software, and single-sample SVs were filtered using the recommended thresholds for SVs generated using Bionano Solve prior to v1.6.0 with the sizes recommended to achieve 90% sensitivity (see https://bionanogenomics.com/wp-content/uploads/2018/04/30110-Bionano-Solve-Theory-of-Operation-Structural-Variant-Calling.pdf): minimum insertion size of 5Kb, minimum deletion size of 5Kb, minimum inversion size of 100Kb, and minimum duplication size of 150kb.

Filtered smap format files were converted to vcf format using smap_to_vcf_v2.py and sorted with bcftools (v1.10.2[21]). The resulting SVs were screened using bcftools and retained if 1) they had successfully been genotyped, 2) their size was >1Kb and 3) their quality was >= 20. The latter filtering largely removed all translocations, duplications, and complex events due to these having either very low (<1) or nil quality values.

We then defined the total amount of non-redundant reference sequence involved in a high-quality deletion. For each deletion, we calculated the central point in the genomic region affected by the SV:

$$Center = \frac{POS + abs(CIPOS) + END - abs(CIEND)}{2}$$

Where POS is the initial position, END is the end position, CIPOS is the confidence interval of POS and CIEND is the confidence intervals of END. Having defined the central point of the region, we defined the initial and final positions of the SV as:

$$BPI = Center - \frac{abs(SVLEN)}{2}; BPE = Center + \frac{abs(SVLEN)}{2}$$

Where BPI and BPE are the limits of the SV and SVLEN is the size of the SV.

139 We then concatenated the regions for all the individuals, sorted them and merged them using
140 bedtools sort and bedtools merge[22] to remove any redundancies among the regions.
141 Following filtering, we merged the resulting variants within samples using SURVIVOR (v1.0.7[2])
142 accounting for the SV type and collapsing those whose break points were within 1kb. We
143 represented the intersection of SVs across individuals by extracting the support vectors
144 generated by SURVIVOR[2] at merging time, and plotted them using the UpSet function from
145 the R[23] package ComplexHeatmap[24] (v2.8.0). We extracted the support value (i.e. how many
146 animals present a specific SV) and SV size for each variant in the combined VCF and tested
147 whether the SVs found in one individual only (support = 1) were significantly larger than those
148 shared among individuals (support > 1) by performing a Wilcoxon signed-rank test in a custom
149 R script.
150 Finally, we defined which of the final set of SVs were found to potentially affect a gene. We
151 ran VEP v105[25] to predict which SVs were likely to disrupt a gene's function, with the options
152 --sift b (both preditions score and term), --nearest symbol (report the gene symbol), and --
153 distance 200 (200 bp up and downstream consequence prediction). Those variants presenting
154 coordinates referring to the negative strand (end position smaller than initial position) were
155 manually fixed through an in-house script. We then investigated which SVs putatively overlap
156 a coding region annotated in the cow genome by intersecting merged SVs with coding
157 sequence intervals. Intersecting genes were investigated with FUMA[26] to identify enriched
158 gene ontologies and gene sets using all 35,142 gene elements with a unique Entrez gene ID
159 as the background list.
160

Data Records

The datasets presented here are stored at ENA under analysis IDs PRJEB47998 and PRJEB52551. The data are uploaded in Bionano BNX format compatible with downstream analyses. The output of the Solve workflows can be downloaded from Zenodo (DOIs: 10.5281/zenodo.6516993 and 10.5281/zenodo.6517172). The raw VCF files, converted using smap_2_vcf_v2.py, can be found on Zenodo with DOI: 10.5281/zenodo.6516933.

Technical Validation

Assembly statistics and SV calling

We aligned the Saphyr optical mapping reads to the ARS-UCD1.2 genome[27], expanded with the BTau5 Y chromosome generated by the 1000 bulls genome project, using Bionano Solve (v3.3 and 3.5) to assemble the genome maps and call SVs. The two NDama samples had previously been used to validate SV using graph genome approaches[28].

Workflow metrics are provided in Supplementary Data 1, summarising key metrics for the analysis of these samples in comparison to the recommended values from Bionano (see https://bionanogenomics.com/wp-content/uploads/2017/03/30255-Bionano-Access-Assembly-Report-Guidelines.pdf).

Unfiltered molecules had average read lengths of 131.9-219.8kb (recommended >150kb for both metrics) and molecule N50s ranged from 185.2-361.9kb across the samples (recommended >150Kbp). Following molecule filtering, all samples were within the recommended average length (245.5-383.1, recommended >230Kbp) and molecule N50 (245.0-426.5, recommended >230Kbp), and only 1 sample (Angoni 1) was slightly below the recommended label density (13.1-16.4, recommended 14-17). Importantly all samples passed the recommended values for the effective coverage of the reference (72.5-128.2, recommended >70) and of average confidence (30.1-43.2, recommended >20).

All samples also generated assemblies with high genome map N50s for both the diploid (71.7-85.0, recommended >50) and haploid (71.3-84.5, recommended >50) assemblies. Despite the low proportion of assembled contigs aligning to the reference genome (0.14-0.25, recommended >0.70), the high uniquely aligned length by reference length (0.835-0.906,

recommended >0.85) shows the presence of long assembled contigs. The contigs present a high fraction of molecules aligned (0.77-0.94, recommended >0.80), effective coverage assembly (37.7-66.7, recommended >40) and average confidence (38.5-51.3, recommended >20).

Overall, 1 sample had 11 metrics within the recommended values, 6 had 12 metrics within the recommended values, 9 had 13 metrics within the recommended values and 2 had 14 metrics within the recommended values.

The Bionano Solve workflow identified a number of SV in each sample, ranging from 4,944 to 11,184 for a Hereford and Nelore, respectively (Table 2). This mirrors the evolutionary distance of each sample from the reference genome, with the European taurine possessing fewer SVs (4,944-5,652) than the other samples, and an African taurine N'Dama possessing the least among the non-European individuals (N = 6,254). Relative SV numbers consequently broadly mirror prior expectations.

Variant statistics

SVs were filtered using Bionano Access, excluding SVs with unknown dosages, and retaining those larger than 1Kb and with a quality >20. SVs for each individual were then combined using SURVIVOR[2] if the breakpoints were within 1Kb, i.e. below the effective resolution of the approach[2]. This process allowed us to select a catalogue of 13,457 SVs across the genome, containing 8,262 insertions, 5,191 deletions and 4 inversions (see Supplementary Data 2 and 3 for the details on the type of SV identified). No duplications, inverted duplications and translocations passed the quality filtering. Consistent with results from previous studies[28], most of the post-filtering insertions and deletions identified fell into the smaller classes, though 1,796 SVs (403 deletions, 1,389 insertions and 4 inversions) of over 50kb in length were identified (Figure 1).

These SVs longer than 1Kb and of high quality involve a total of 2,656 unique regions, for an estimated total of over 90Mb of non-redundant bases (Supplementary Data 4). This number is comparable to what has been seen for novel sequences (i.e. insertions) using graph genome approaches, where an extra 70Mb and 116Mb of novel sequence were reported on 5 and 4 cattle reference genomes, respectively[28,29]. After merging the filtered variants from all the

220 samples, most of the SVs were found to be private to an individual (Figure 2), consistent with
221 what has been observed in previous studies[1]. Individuals of indicine ancestry (Nelore and
222 Boran) carry almost twice as many SVs relative to the Hereford reference as taurine
223 individuals, further highlighting that the current reference poorly represents these breeds
224 (Figure 2).
225 Interestingly, we find that SVs only found in one animal (support = 1; n = 7,445, mean SV
226 length = 85,954.23bp) are generally larger (Wilcoxon rank-sum test P-value = $8.99 * 10^{-37}$)
227 than the SVs found in more than one animal (support > 1; n = 6,012, mean SV length =
228 27,747.17bp, Figure 1, Supplementary Figure 1). The list of all SVs, with their position, support
229 and size, are reported in Supplementary Data 5.
230 Finally, we investigated whether any of the high-quality SVs potentially impact annotated
231 genes. VEP successfully processed 12,999 out of 13,457 SVs (see HTML report on GitHub).
232 Some variants were too large to be successfully processed by VEP, and other were called as
233 incomplete by VEP. Of these, 6,946 were intergenic, and the remaining 5,934
234 overlapped5,780 genes and 17,386 transcripts, suggesting the potential for functional
235 variants among the SVs detected. A total of 1,200 SVs putatively overlap a coding sequence.
236 These coding sequences are included in a total of 884 unique gene elements in the cow
237 annotation (Ensembl v105), and of these 483 have an associated gene name (Supplementary
238 Data 6). A total of 292 out of 483 genes had an ID recognized by FUMA[26]. These 292 genes
239 belong to a number of gene sets such as the Hallmark bile acid metabolism and interferon γ
240 and α response sets (Supplementary Figure 2), as well as the olfactory receptor curated gene
241 set (Supplementary Figure 3). All gene set results from FUMA are reported in Supplementary
242 Data 7.

243 Usage Notes

244 Even with the ever-decreasing cost of long read sequencing making it increasingly tractable
245 to call SVs across sets of samples using HTS, validation of the SV calls remain challenging. This
246 compendium of SVs across global cattle breeds provides a validation set called using an
247 independent technology that can be used to assess the quality of cattle SV calls. In fact, optical
248 mapping data has previously been used to validate sequencing based SV calls[28], and we
249 believe this dataset provides the largest set of optical maps to date for a livestock species.

With many SVs shared across the two animals of each breed, the raw molecules in this dataset can also be used to help scaffold and validate novel assemblies of cattle of breeds closely related to the individuals represented here, potentially reducing the cost of future genome assembly projects.

Unlike most cattle studies, this database is not focused just on European cattle breeds, meaning this will be a valuable resource to researchers across the globe. Importantly, it will allow for SVs to inform the interpretation of results from GWAS and population genetics studies by providing candidate functional variants in relevant regions.

Ultimately, we expect the database to enable further insights into SVs, an understudied class of genetic variation in cattle, giving access to a catalogue of thousands of variants present across multiple breeds worldwide.

Code availability

The code used in this article were deposited at https://github.com/evotools/CattleOManalyses.

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Author contribution

J.G.D.P. and T.C. conceived the study, A.T. and J.G.D.P. designed the analyses and A.T. performed them. J.G.D.P. and A.T. prepared the initial manuscript with all authors contributing to subsequent drafts. J.Po., M.C. and T.C. prepared the DNA and Bionano samples. D.W. and P.T. provided samples and expertise for the study. M.E.Z.M., I.M.S., A.F., B.R.F., C.E., E.T.O., D.M., W.A., I.S., J.B.M., G.M. and R.F.K provided samples for the study.

Figure captions

Figure 1: Histogram of the structural variant (SV) sizes. Histogram of the size of the identified SVs in bins of 5Kb.

Figure 2: Upset plot of the structural variants. Upset plot of the structural variants by individual for the 40 sets containing the most SVs.

Tables

Sampling Continent	Sampling Country	Group	Breed	ENA project ID	ENA sample ID
S. America	Brazil	Indicine	Nelore	PRJEB52551	ERS11891755
				PRJEB52551	ERS11891754
Africa	Kenya	Indicine	Boran	PRJEB52551	ERS11891767
				PRJEB52551	ERS11891766
Africa	Nigeria	Indicine	White Fulani	PRJEB52551	ERS11891768
				PRJEB52551	ERS11891769
Africa	Zambia	Indicine	Angoni	PRJEB52551	ERS11891764
				PRJEB52551	ERS11891765
Africa	Uganda	Sanga	Ankole	PRJEB52551	ERS11891756

				PRJEB52551	ERS11891757
Africa	Zambia	Taurine	Barotse	PRJEB52551	ERS11891762
				PRJEB52551	ERS11891763
Africa	Nigeria	Taurine	N'Dama	PRJEB47998	ERS8452869
				PRJEB47998	ERS8452868
Europe	United Kingdom	Taurine	Hereford	PRJEB52551	ERS11891760
				PRJEB52551	ERS11891761
Europe	United Kingdom	Taurine	Holstein-Friesian	PRJEB52551	ERS11891759
				PRJEB52551	ERS11891758

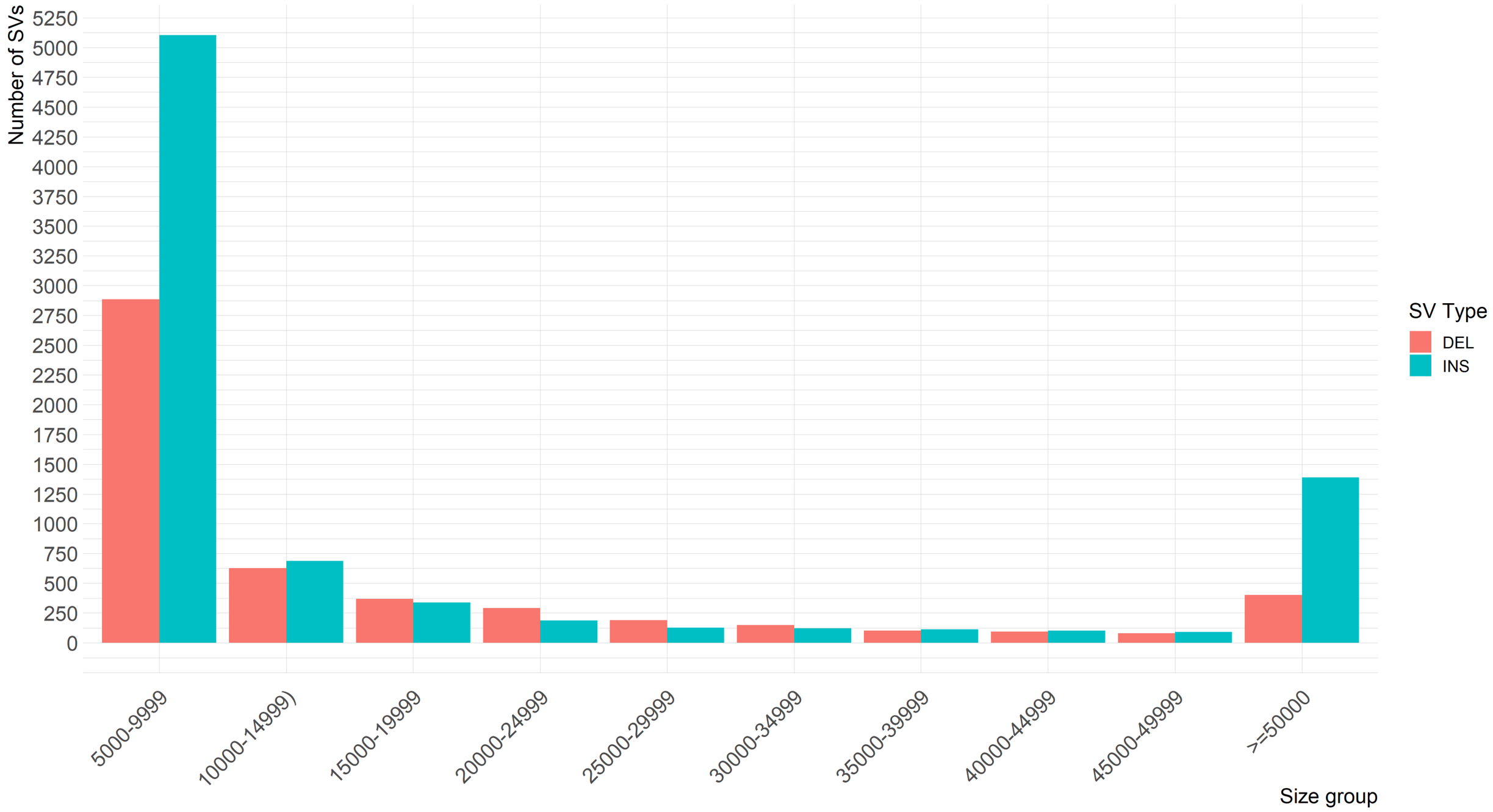
Table 1: Description of the samples. Table describing the breeds and ancestry of samples, with the continent and country of origin. The identifiers, as well as the ENA accession codes, for each of the two animals sampled per breed are also reported.

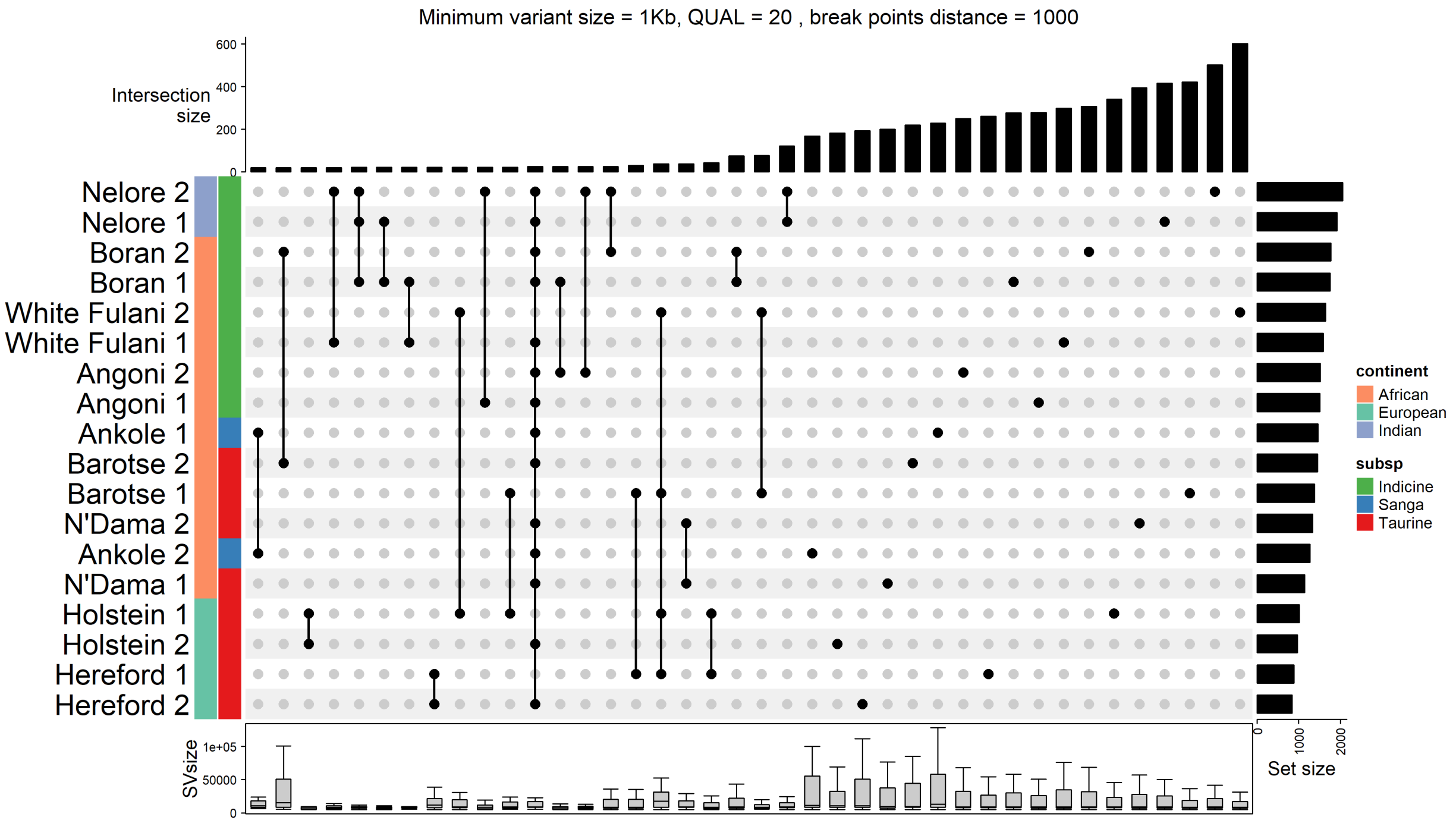
Sample	**Dels**	**Insert.**	**Dups.**	**Inversion breakpoints**	**Interchr. translocation breakpoints**	**Intrachr. translocation breakpoints**	**Total**
Angoni 1	4349	4505	45	91	13	4	9007
Angoni 2	4387	4673	64	100	11	7	9242
Ankole 1	4314	4324	67	111	10	8	8834
Ankole 2	3911	3984	66	101	8	5	8075
Barotse 1	3971	4044	42	52	11	6	8126
Barotse 2	4199	4159	67	106	7	9	8547
Boran 1	4935	5087	56	113	15	6	10212
Boran 2	4990	5007	68	138	6	14	10223
Hereford 1	2465	2380	43	41	11	4	4944
Hereford 2	2435	2437	77	88	9	7	5053
Holstein 1	2756	2759	48	52	15	18	5648
Holstein 2	2702	2801	59	76	9	5	5652
N'Dama 1	3411	3481	92	125	10	13	7132
N'Dama 2	3005	3082	67	86	6	8	6254
Nelore 2	5294	5508	58	113	11	5	10989
Nelore 1	5420	5499	96	136	15	18	11184
White Fulani 1	4467	4642	54	114	11	3	9291

White Fulani 2	4782	4805	41	45	17	14	9704

354

355 Table 2: Raw number of structural variants (SVs) and type detected in the different samples.
356 This table summarises the number of raw SVs detected in each sample, and their
357 classification (e.g. insertion, deletion, duplication, inversion and inter- and intra-
358 chromosomal translocation).


Number of SVs
5250
5000
4750
4500
4250
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
5000-9999
10000-14999)
15000-19999
20000-24999
25000-29999
30000-34999
35000-39999
40000-44999
45000-49999
>=50000
Size group
SV Type
DEL
INS


Minimum variant size = 1Kb, QUAL = 20 , break points distance = 1000
Intersection size
600
400
200
0
Nelore 2
Nelore 1
Boran 2
Boran 1
White Fulani 2
White Fulani 1
Angoni 2
Angoni 1
Ankole 1
Barotse 2
Barotse 1
N'Dama 2
Ankole 2
N'Dama 1
Holstein 1
Holstein 2
Hereford 1
Hereford 2
SVsize
1e+05
50000
0
0
1000
2000
Set size
continent
African
European
Indian
subsp
Indicine
Sanga
Taurine