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Recent Advances in the Genomic Resources for Sheep

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1 **Recent Advances in the Genomic Resources for Sheep**

2

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11 **Keywords:** Sheep, genome, transcriptome, pangenome, gene editing

12

13 **Abstract**

14 Sheep (*Ovis aries*) provide a vital source of protein and fibre to human populations. In
15 coming decades, as the pressures associated with rapidly changing climates increase,
16 breeding sheep sustainably as well as producing enough protein to feed a growing human
17 population will pose a considerable challenge for sheep production across the globe. High
18 quality reference genomes and other genomic resources can help to meet these challenges
19 by: 1) informing breeding programmes by adding *a priori* information about the genome, 2)
20 providing tools such as pangenomes for characterising and conserving global genetic
21 diversity, and 3) improving our understanding of fundamental biology using the power of
22 genomic information to link cell, tissue and whole animal scale knowledge. In this review we
23 describe recent advances in the genomic resources available for sheep, discuss how these
24 might help to meet future challenges for sheep production, and provide some insight into
25 what the future might hold.

26

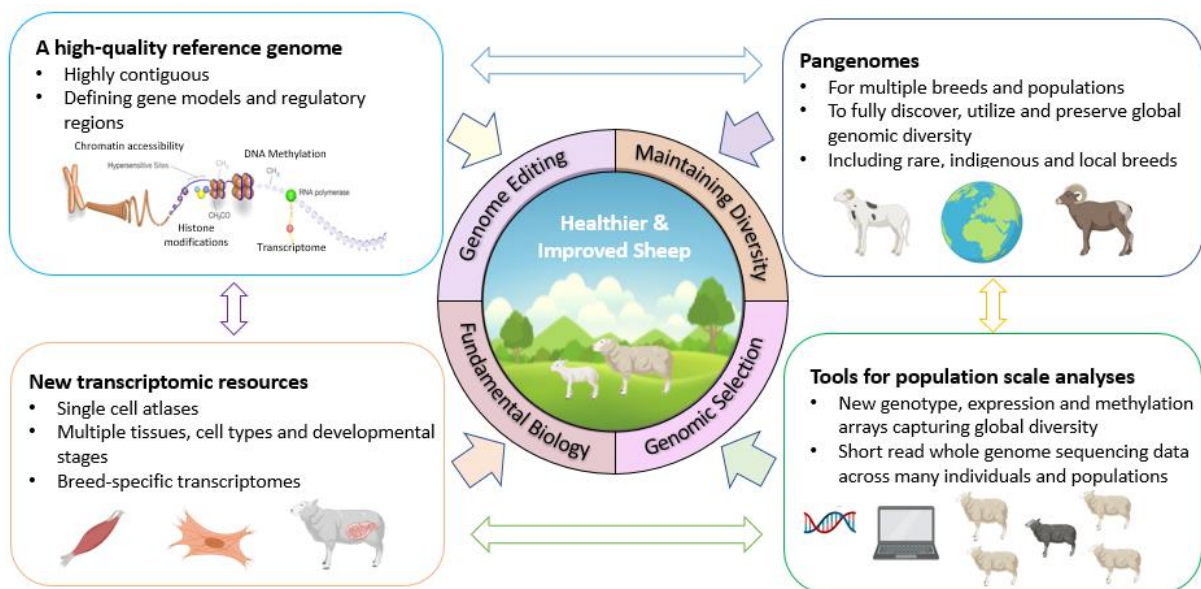
27 Introduction

28 The domestic sheep (*Ovis aries*) is an important farmed animal species providing a
29 source of protein and fibre to human populations across the globe. Sheep have excelled over
30 the centuries in a range of production systems and environments (Mignon-Grasteau et al.,
31 2005; Marshall et al., 2014; Alberto et al., 2018). Production systems differ across the globe,
32 often with arable land, breed, environment, and key local and international markets playing
33 a role in the type of production system used. The UK sheep industry, for example, is primarily
34 based on sheep meat production, where the stratified system consists of three sectors: hill,
35 upland and lowland, each utilising different breeds and production systems (Conington et al.,
36 2001). The UK sheep sector currently largely uses traditional breeding practices, with a few
37 exceptions, while in other countries such as Australia, New Zealand advanced genomics
38 enabled breeding schemes have been widely implemented (Daetwyler et al., 2010; Brito et
39 al., 2017a). Sheep production systems in place in countries that produce a large amount of
40 sheep meat, including the UK, Australia and New Zealand rely on a relatively small number of
41 popular breeds, to support large export markets. In contrast sheep production within low and
42 middle income countries (LMICs) is orientated towards small holder systems that make use
43 of a diverse range of breeds that are adapted to harsh climatic and nutritional conditions
44 (Marshall et al., 2019). In LMICs sheep production is vital to the livelihoods and nutritional
45 needs of both individuals and communities, and often plays a multifaceted role within society
46 (Marshall et al., 2019).

47 The future of sheep production, and its contributing role in global food production,
48 will become more apparent in coming decades, due to predicted extremes of climate, and a
49 growing human population that is expected to reach almost 9 billion by 2050 (McKenzie and
50 Williams, 2015). Any increase in global food production from sheep needs to be achieved with
51 societal expectations around animal health and welfare in mind and should be guided through
52 initiatives for responsible animal breeding such as Code EFABAR (EFFAB 2020). Sheep are also
53 a source of greenhouse gases (Marino et al., 2016), and ambitious targets are being set to cut
54 greenhouse gas emissions across the globe by 2030. Meeting these targets will require
55 breeding strategies that reduce environmental impact (Mollenhorst and de Haas 2019). In
56 addition, future breeding programmes will need to maintain genetic diversity for
57 performance and resilience in the face of climatic extremes and other pressures (Dumont et
58 al., 2020). In coming years breeding sheep sustainably using fewer resources, whilst flexibly

59 meeting societal expectations, as well as producing enough protein to feed a growing human
 60 population, will pose a considerable challenge for sheep breeders and producers across the
 61 globe (Hayes et al., 2013). High quality reference genomes and other genomic tools and
 62 resources can help to meet these challenges (Clark et al., 2020). For example, they can: 1)
 63 inform breeding programmes including those enabled by genomic selection and genome
 64 editing (Georges et al., 2019), 2) provide tools for characterising and conserving genetic
 65 diversity (Talenti et al., 2022), and 3) improve our understanding of fundamental biology to
 66 link cell, tissue and whole animal scale knowledge (Giuffra and Tuggle, 2019) (Figure 1). Here
 67 we describe recent advances in the genomic resources available for sheep, discuss how these
 68 might help to meet future challenges for sheep production, and provide some insight into
 69 potential future opportunities.

70



71

72 **Figure 1:** Schematic describing how new genomic resources for sheep will help to inform
 73 sheep breeding with the goal of providing healthier and improved animals, to meet growing
 74 pressures on food production, while maintaining genomic diversity (adapted from Clark et al.
 75 2020).

76

77 **Towards a high quality highly contiguous reference genome for sheep**

78 The genomic resources for sheep have gradually been improving in quality and
 79 resolution over the last twenty years in parallel with advances in sequencing technology. This
 80 is particularly evident when describing improvements in the quality and contiguity of the

81 reference genome for sheep. The reference genome is the version of the sheep genome
82 accepted by the sheep genomics community as a standard for comparison to sequence
83 information generated in their own studies. A contiguous, high quality, well annotated and
84 assembled reference genome for sheep is a hugely valuable research tool, providing a
85 searchable map of the genome including the locations of expressed and regulatory regions.
86 There have been several versions of the reference genome for sheep and each new version
87 has kept pace with advancements in sequencing technology, starting with the ovine radiation
88 hybrid panel (Cockett 2006). The first true version of a reference genome sequence for sheep
89 (*Ovis_aries_1.0*; GCA_000005525.1) was a guided assembly using the bovine genome. It was
90 generated from six female sheep of different breeds sequenced at 0.5× coverage by 454 FLX
91 (Dalrymple et al., 2007). Seven years later in 2014 the Texel reference genome *Oar_v3.1*
92 (GCA_000298735.1), assembled from two unrelated Texel sheep using Illumina short read
93 sequencing at 150× coverage, was released (Jiang et al., 2014). This assembly offered an
94 improved contiguity (N50 contig length of approximately 40 Kb) and a genome length of 2.6
95 Gb (Jiang et al., 2014) (Table 1). The *Oar_v3.1* genome assembly revealed segmental
96 duplications within Texel sheep, along with a large run of homozygosity that contained the
97 *MSTN* gene (Jiang et al., 2014). Previously a variant in the 3' UTR region in the *MSTN* gene,
98 that disrupted miRNA binding, had been shown to control the muscle hypertrophy (double
99 muscling) phenotype in Texel sheep (Clouet et al., 2006). The *Oar_v3.1* reference genome
100 provided a resource to interrogate the genomic regions associated with muscling in Texel
101 sheep in more detail including the *MSTN* gene and the Texel muscling QTL (TM-QTL) on
102 chromosome 18 (Macfarlane et al., 2014).

103 More recently, long read sequencing technologies capable of generating contiguous
104 reads of greater than 10 Kb in length have provided a means to significantly improve the
105 contiguity of a reference genome sequence (Pollard et al., 2018). A combination of Illumina®
106 GAI sequencing, Roche 454 sequencing and PacBio® RSII technologies were used to gap fill
107 *Oar_v3.1* generating the more contiguous Texel *Oar_v4.0* (GCA_000298735.2) genome (Table
108 1). *Oar_v3.1* and *Oar_v4.0* remained the gold standard reference genome sequences for
109 sheep until 2020 when a new reference genome sequence was released that was generated
110 using both Illumina® HiSeq X short reads and PacBio® RS II long read technology. This new
111 reference genome *Oar_rambouillet_v1.0* (GCA_002742125.1) was built from the DNA of a
112 single Rambouillet ewe Benz2616 (Liu et al., 2016). *Oar_rambouillet_v1.0* had fewer contigs

113 and a considerably greater contig N50 length than Oar_v3.1 and Oar_v4.0, replacing the Texel
 114 as the new reference genome sequence for sheep (Table 1).

115 In 2022 a *de novo* assembly of the same Rambouillet ewe used to generate the
 116 Oar_rambouillet_v1.0 assembly was published, ARS-UI_Ramb_v2.0 (GCA_016772045.1)
 117 (Davenport et al., 2022). This new assembly was built using ~50× coverage Oxford Nanopore®
 118 PromethION reads (N50 47 kb) and 75× coverage Pacific Biosciences (PacBio) reads (N50 13
 119 kb), with Hi-C data for scaffolding and Illumina short read data for final polishing (Davenport
 120 et al., 2022). The result was a 15-fold improvement in contiguity and increased accuracy over
 121 Oar_rambouillet_v1.0 (Table 1). The ARS-UI_Ramb_v2.0 genome is now the community
 122 adopted reference genome sequence. It has provided the sheep genomics community with a
 123 very high quality reference genome assembled into fewer contigs than even the ARS1 goat
 124 genome (Table 1), which at the time of its release was considered the gold standard of farmed
 125 animal genomes (Bickhart et al., 2017; Worley, 2017).

126

127 **Table 1:** Genome summary statistics for popular sheep reference genome sequence releases
 128 based on information from the National Centre for Biotechnology Information (NCBI) genome
 129 database.

Genome assembly	Breed	Genome size (Mb)	Number of contigs	Contig N50 length	Contig L50 length
Ovis_aries_1.0 (GCA_000005525.1)	Mixed	2,861	2,352,347	685	545,914
Oar_v3.1 (GCA_000298735.1)	Texel	2,619	130,764	40,376	18,404
Oar_v4.0 (GCA_000298735.2)	Texel	2,616	48,481	150,472	5,008
Oar_rambouillet_v1.0 (GCA_002742125.1)	Rambouillet	2,870	7,486	2,572,683	313
ARS-UI_Ramb_v2.0 (GCA_016772045.1)	Rambouillet	2,628	226	43,178,051	24
ARS1 (GCA_001704415.1)	Goat	2,923	30,399	26,244,591	32

130

131 **Annotation of regulatory regions in the reference genome sequence by the Ovine FAANG**
 132 **project**

133 High resolution annotation information, that accurately defines gene models and
 134 regulatory regions, adds basic functional genomic knowledge to the reference genome
 135 sequences for farmed animals increasing their power and utility as research tools (Georges et
 136 al., 2019; Giuffra and Tuggle, 2019; Clark et al., 2020). The USDA NIFA funded Ovine FAANG

137 project, led by the University of Idaho, provided the opportunity to annotate regulatory
138 genomic regions in the new Rambouillet genome (Murdoch, 2019). The Functional
139 Annotation of Animal Genomes (FAANG) consortium is a concerted international effort to use
140 molecular assays, developed during the Human ENCODE project (Birney et al., 2007), to
141 annotate the majority of functional elements in the genomes of domesticated animals
142 (Andersson et al., 2015; Giuffra and Tuggle, 2019). By applying a set of core assays defined by
143 the FAANG consortium, including five ChIP-Seq marks, ATAC-Seq, CAGE-Seq, RNA-Seq and
144 methylation information, across a set of 56 tissues from Benz2616, the Ovine FAANG project
145 developed a set of deep and robust expressed elements and regulatory features in the
146 Rambouillet genome (Murdoch, 2019). Some of these datasets are already available, via the
147 FAANG Data Portal (<https://data.faang.org/dataset?species=Ovis%20aries>) (Harrison et al.,
148 2021), including the CAGE dataset which provides a high resolution annotation of
149 transcription start sites in the Oar_rambouillet_v1.0 genome (Salavati et al., 2020). RefSeq,
150 and Ensembl, have also provided annotations of the coding regions for ARS-UI_Ramb_v2.0
151 (GCF_016772045.1) using the mRNA-Seq, CAGE and Iso-Seq data. Once the ATAC-Seq and
152 ChIP-Seq data become available it will be possible for Ensembl to incorporate them into a
153 regulatory build (Zerbino et al., 2015) as a resource for the farmed animal genomics
154 community. The Ovine FAANG project provides a valuable resource to facilitate a deeper
155 understanding of how the regulatory regions of the genome control complex traits in sheep.
156 It also provides a foundation for comparative analysis with other farmed animal species in
157 which similar annotation datasets are available e.g. for cattle, chicken, goat and pig (Foissac
158 et al., 2019; Goszczynski et al., 2021; Kern et al., 2021).

159 From the human literature we know that as many as 90% of variants underlying
160 complex traits identified in Genome Wide Association Studies (GWAS) are located in non-
161 coding regions of the genome (Tam et al., 2019). In addition to the efforts of the Ovine FAANG
162 project in annotating the new Rambouillet reference genome sequence, there have been a
163 small number of other studies to date that have characterised regulatory regions in the sheep
164 genome. For example, Davenport et al. 2021 used histone modifications that distinguish
165 active or repressed chromatin states, CTCF binding, and DNA methylation to characterize
166 regulatory elements in liver, spleen, and cerebellum tissues from four yearling sheep to
167 identify the regulatory regions of genes that play key roles in defining health and economically
168 important traits. To evaluate the impact of selection and domestication on regulatory

169 sequences Naval-Sanchez et al., 2018 used histone modification and gene expression data.
170 Their analyses showed that selective sweeps were significantly enriched for protein coding
171 genes, proximal regulatory elements of genes and genome features associated with active
172 transcription. In addition they were able to show that remodelling of gene expression is likely
173 to have been one of the evolutionary forces driving phenotypic diversification in domestic
174 sheep (Naval-Sanchez et al., 2018). Both studies demonstrate the value of regulatory
175 annotation information in understanding the genomic processes driving complex traits and
176 shaping the characteristics and genetic diversity of global sheep populations.

177

178 **Annotating expressed regions in the sheep genome, the sheep gene expression atlas and** 179 **beyond**

180 Advances in transcriptome sequencing technology and reductions in cost have also led
181 to improvements in annotation of the reference genome for sheep over the last decade.
182 Coding regions in the Oar_v3.1 reference genome (Jiang et al., 2014) were annotated by
183 Ensembl with their 'Genebuild' pipeline (Aken et al., 2016) using RNA-sequencing data from
184 more than 80 tissues collected from a Texel ewe, lamb and ram trio
185 (http://useast.ensembl.org/Ovis_aries/Info/Annotation). When released the Oar_v3.1
186 annotation was one of the most comprehensive annotations of any of the farmed animal
187 species and was widely used by the community until Oar_rambouillet_v1.0 was annotated by
188 Ensembl in 2020 (http://www.ensembl.org/Ovis_aries_rambouillet/Info/Annotation). Over
189 the last decade a vast amount of RNA-sequencing data for sheep has been generated,
190 capturing global transcriptomic complexity across multiple tissues, cell types and
191 developmental stages (Jiang et al., 2014; Clark et al., 2017). In 2017 a large scale gene
192 expression atlas (<http://biogps.org/sheepatlas>) was generated from tissues and cells
193 collected from all of the major organ systems from adult Texel x Scottish Blackface sheep and
194 from juvenile, neonatal and prenatal developmental stages (Clark et al., 2017). Of the 20,921
195 protein coding genes, that were annotated in the Oar v3.1 reference genome, 19,921 (92%)
196 had detectable expression in at least one tissue in the sheep gene expression atlas dataset
197 (Clark et al., 2017). Network-based cluster analysis, using the software package Graphia
198 (Freeman et al., 2022), was used to describe the overall transcriptional signatures present in
199 the sheep gene expression atlas and assign those signatures, where possible, to specific
200 tissues or cell types.

201 The next frontier for the sheep transcriptome will be to fully resolve the tissue- and
202 cell- type specific transcriptional signatures generated for the sheep atlas from bulk tissue
203 samples, at a single cell resolution. Single-cell sequencing technologies enable the
204 deconvolution of transcriptional and regulatory complexity in tissues comprised of many
205 different cell types e.g. (Schaum et al. 2018). Atlases of gene expression generated using
206 single cell sequencing technologies have already been created for pig
207 (<https://dreamapp.biomed.au.dk/pigatlas/>) (Wang et al., 2022). Building similar single cell
208 transcriptomic resources for sheep from multiple tissue types and developmental stages and
209 adding regulatory information with single cell ATAC-seq, for example, would provide insights
210 into cell composition, cell-to-cell interactions and the cellular heterogeneity of tissues. As
211 datasets of this type are generated for more species of farmed animals sets of cell specific
212 marker genes that are conserved across species will be revealed. Such markers could be
213 applied as a proxy for a particular cell type e.g. (Herrera-Uribe et al. 2021) and may be useful
214 as a costly but high value intermediate phenotype for complex trait prediction, providing a
215 powerful tool for linking genotype to phenotype in sheep and other farmed animal species.

216

217 **The Power of PanGenomes – moving beyond a single reference genome sequence**

218 Recent advances in long read sequencing technologies, and reductions in cost, have
219 meant that in addition to a single very high quality reference genome per farmed animal
220 species it is now possible to generate chromosome level (relatively complete) genomes for
221 many different breeds and populations. Many new chromosome level genomes including, for
222 example, Hu sheep (Li et al., 2021), Dorper (Qiao et al., 2022), and Tibetan sheep (Li et al.,
223 2022) have recently been deposited in NCBI (Table 2). In addition, recently a pangenome for
224 sheep was generated that included new long-read assemblies for 13 different breeds (Li et
225 al., 2023). Currently, NCBI reports that there are 55 genome assemblies for sheep
226 (<https://www.ncbi.nlm.nih.gov/data-hub/genome/?taxon=9940>). Some of these are
227 alternate-pseudohaplotypes, where two pseudohaplotype assemblies of the diploid genome
228 have been generated, and each release of the reference genome sequences for the
229 Rambouillet and Texel are also included in the database. In total, at the time of writing this
230 review, there were 19 unique breeds of sheep that have chromosome level assemblies (Table
231 2), available in NCBI's repository of genomes. These breeds represent 11 different countries
232 (Table 2), and include the Suffolk, a British breed, that is a very popular terminal sire across

233 the globe (<https://www.suffolksheep.org/history/>), and the Dorper a versatile composite that
 234 is used extensively for production in tropical regions (<http://agtr.ilri.cgiar.org/dorper>).
 235 Assembly statistics for the Rambouillet reference genome sequence (ARS-UI_Ramb_v2.0) are
 236 included to demonstrate that the majority of these new genome assemblies, generated using
 237 different long read sequencing technologies, are close to reference quality in terms of
 238 contiguity.

239

240 **Table 2:** Chromosome level assemblies for breeds of sheep listed in NCBI, including basic
 241 assembly statistics and GenBank accessions, and with the reference genome ARS-
 242 UI_Ramb_v2.0 for comparison.

Breed	Country	GenBank Accession	Contig N50 (Mb)	No. of Contigs	Publication
Yunnan	China	GCA_022416785.1	71.9	1,354	Li et al. 2023
Chinese Merino	China	GCA_022432825.1	60	1,773	Li et al. 2023
Qaioke	China	GCA_022416685.1	75	1,654	Li et al. 2023
Hu	China	GCA_011170295.1	8.7	4,131	Li et al. 2021
Tibetan	Tibet	GCA_017524585.1	74.6	168	Li et al. 2022
Kermani	Iran	GCA_022432835.1	80.3	1,678	Li et al. 2023
Kazak	Kazakhstan	GCA_022432845.1	73.4	1,851	Li et al. 2023
Ujimqin	Mongolia	GCA_022416755.1	75.7	1,539	Li et al. 2023
Waggir	Afghanistan	GCA_024222265.1	73.6	843	-
Texel	Netherlands	GCA_022416775.1	47.6	1,838	Li et al. 2023
Romney	UK	GCA_022538005.1	68.3	1,553	Li et al. 2023
Suffolk	UK	GCA_022416725.1	64.5	1,520	Li et al. 2023
Charollais	UK	GCA_022416745.1	65.1	1,430	Li et al. 2023
Polled Dorset	UK	GCA_022416915.1	92.4	1,297	Li et al. 2023
East Friesian	Germany	GCA_018804185.1	85.3	972	Qiao et al. 2022
Romanov	Russia	GCA_024222175.1	31.8	1,179	Li et al. 2023
Romanov	Russia	GCA_022244705.1	62.3	499	-
Dorper	South Africa	GCA_019145175.1	73.3	142	Qiao et al. 2022
White Dorper	South Africa	GCA_022416695.1	17.9	2,133	Li et al. 2023
White Dorper	South Africa	GCA_022244695.1	61.8	1,178	-
Rambouillet (ARS-UI_Ramb_v2.0)	France	GCA_016772045.1	43.2	225	Davenport et al. 2022

243

244 The number of breeds and populations with chromosome level genome assemblies
 245 will rise significantly as global pangenome efforts that aim to capture the global diversity of
 246 sheep breeds gather pace. The concept of a ‘pangenome’ is probably most simply defined as
 247 ‘any collection of genomic sequences to be analysed jointly or to be used as a reference’ (The

248 Computational Pan-Genomics Consortium 2018). The USDA NIFA Ovine Pangenome Project,
249 for example, plans to generate eight new haplotype resolved assemblies from crosses of
250 breeds selected for their divergent characteristics, using the trio-binning approach developed
251 by Koren et al., 2018. For trio-binning usually an F1 cross of two disparate breeds of sheep,
252 chosen to maximise heterozygosity, is generated. The genome assembly then relies on using
253 short read Illumina data from the two parental genomes to first partition the long reads from
254 the offspring into haplotype-specific sets. Each parental haplotype is then assembled
255 independently, resulting in a complete diploid reconstruction, and effectively two new
256 reference assemblies, one for each of the two parental breeds (Koren et al., 2018). This
257 strategy has proved very successful in cattle (Koren et al., 2018; Rice et al. 2020) and has been
258 used so far to produce the White Dorper x Romanov haplotype assemblies for sheep Oar_ARS-
259 UKY_Romanov_v1.0 (GCA_022244705.1) and Oar_ARS-UKY_WhiteDorper_v1.0
260 (GCA_022244695.1) (Table 2).

261 These new chromosome level assemblies for sheep will improve our understanding of
262 genome diversity and the drivers of breed-specific characteristics. As such global pangenome
263 efforts should aim to capture the genomic diversity of global sheep populations.
264 Understanding global genomic diversity provides a foundational resource for breed
265 improvement and for the adaptation of sheep populations to changing environments and
266 changing demands (FAO 2015). The United Kingdom's native sheep breeds, for example, have
267 become the mainstay of sheep production across the globe and as such capturing the genomic
268 diversity represented by these breeds should be a priority (Bowles 2015; Romanov et al.,
269 2021). This is particularly important in the context of breed conservation as many of the UK
270 breeds, including for example the Norfolk Horn the ancestor of the Suffolk, are rare and
271 declining in numbers (<https://www.rbst.org.uk/norfolk-horn>). Many European rare and
272 indigenous breeds exhibit widespread heterozygote deficit due to declining diversity and are
273 being lost due to introgression into large commercial populations (Lawson Handley et al.
274 2007). In LMICs where small-holder farmers rely on a wide diversity of breeds adapted to local
275 conditions (Marshall et al. 2019), capturing the genomic diversity of indigenous African breeds
276 is also important. For example, West and Central African indigenous breeds, such as the
277 Cameroon sheep, represent a unique reservoir of genetic diversity and have followed the
278 tracks of human migration across the globe contributing to the formation of Caribbean hair
279 sheep breeds (Spangler et al., 2017; Wiener et al., 2022). The Cameroon sheep is also

280 anecdotally thought to be trypanotolerant (Geerts et al. 2009). Genomic drivers of adaptation
281 in local indigenous breeds to specific environmental challenges, including resistance or
282 tolerance to specific diseases, need to be better understood (FAO 2015). Genomic
283 information provided by global pangenome efforts for sheep should help to remedy this
284 through comparative approaches, such as those described in Dutta et al. 2020 for water
285 buffalo and cattle populations, to identify loci present in one breed, species or population
286 that are missing another.

287 Reference quality genome sequences representing the global diversity of sheep
288 breeds also provide genomic resources that are relevant in a country or continent specific
289 context. This is important because it can minimise reference mapping bias when working with
290 short read whole genome sequencing data (Chen et al., 2021). For example, for a study
291 investigating population genomics in sheep from the African continent using short read data,
292 the Dorper (Qiao et al., 2022) a South African breed, would be a more appropriate reference
293 assembly than the European Texel or Rambouillet. However, even when reference genome
294 sequences for multiple different breeds are available the use of reference genome sequences
295 that represent only a single individual, for understanding population diversity at genomic level
296 are still limited. There are two main reasons for this (described in Talenti et al., 2022); i)
297 because a single reference genome represents one consensus haplotype of a single individual,
298 and as such it would be expected that large sections of the diversity represented in the global
299 pangenome for sheep will be missing from the reference sequence, and ii) reference mapping
300 bias causes downstream analyses to be biased towards the alleles and haplotypes present in
301 the reference sequence. Graph-based genomes, that integrate long read genome sequences
302 for a subset of representative breeds and short read sequence data from hundreds of breeds
303 and individuals to build a pangenome graph, provide an alternative, to capture global
304 diversity. Graph based pangenomes have recently been produced for other ruminants
305 including, cattle (Crysnanto and Pausch, 2020; Crysnanto et al., 2021; Talenti et al., 2022) and
306 goats (Li et al., 2019), and a sheep pangenome graph which includes 13 breeds is also now
307 available (Li et al., 2023). The graph based pangenomes generated for cattle have been shown
308 to increase read mapping rates, reduce allelic biases and identify structural variants with a
309 high level of accuracy (Talenti et al., 2022). As such a graph-based genome for sheep
310 incorporating many different breeds and populations spanning the depth and breadth of

311 genetic diversity from across the globe, would provide a hugely informative research tool to
312 inform future breeding and conservation strategies.

313

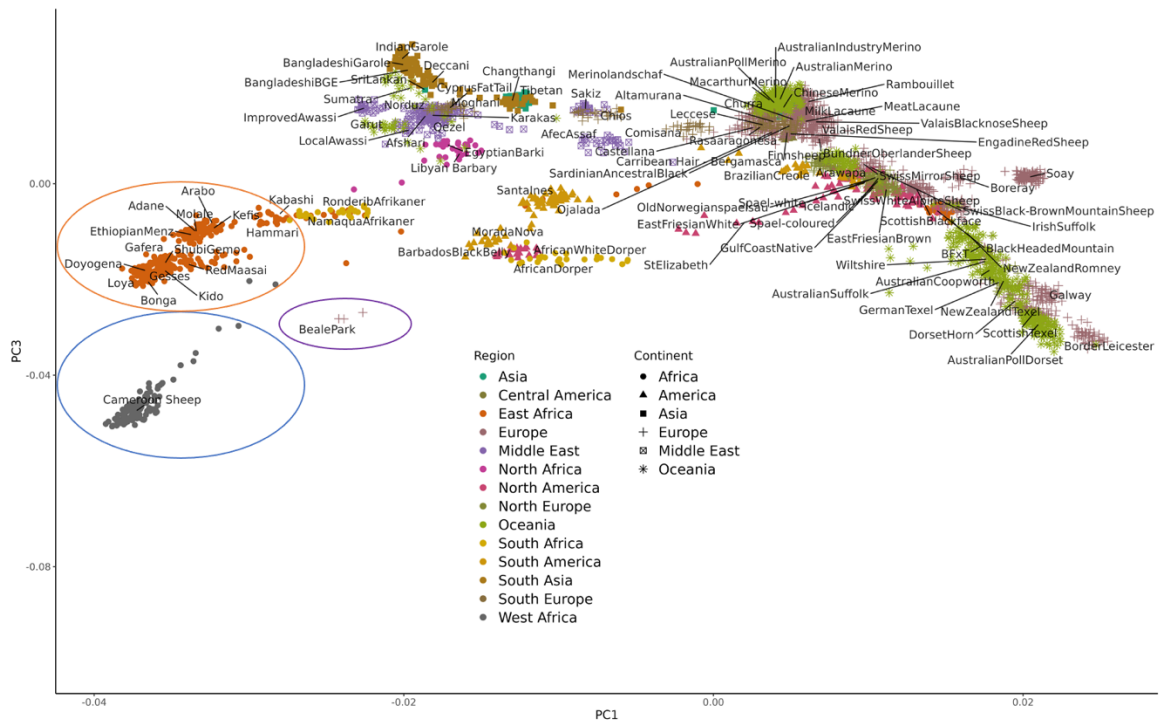
314 **Characterising global diversity in sheep populations using other genomic resources**

315 Before the development of long read sequencing and pangenomes, sheep benefitted
316 from the availability of several genotyping tools, including the Illumina® 50K Ovine Beadchip,
317 both for the purposes of genomic selection, and for capturing genetic diversity using a set of
318 genetic markers. The Illumina® OvineSNP50 BeadChip was developed by the International
319 Sheep Genomics Consortium (ISGC; www.sheephapmap.org; Kijas et al., 2009). Kijas et al.,
320 2012 used the Illumina® 50K chip to genotype 49,034 SNPs in 2,819 animals from a diverse
321 collection of 74 sheep breeds, generating the sheep HapMap dataset
322 (<https://www.sheephapmap.org/hapmap.php>), which provided a global picture of the
323 genetic history of sheep and variation across breeds. More recent studies have added 50K
324 genotyping data from additional geographical locations and local and indigenous breeds not
325 represented in the original HapMap dataset (Kijas et al., 2012), including from, Asia (Wei et
326 al., 2015), Russia (Deniskova et al., 2018), India (Kumar et al., 2021) and Eastern Europe
327 (Machová et al. 2023). Adding 50K genotypes from the African continent e.g. from North and
328 East Africa (Ahbara et al., 2019) and West/Central Africa (Wiener et al. 2022), to the HapMap
329 dataset, illustrates the unique diversity represented by these breeds and highlights the
330 importance of including the diversity they represent in new genomic resources for sheep
331 (Figure 2). In addition, characterising the genetics of production breeds is also important to
332 understand genetic relationships between breeds. The 50K chip has been used, for example,
333 to characterise the genetic diversity of terminal sires in the US (Davenport et al., 2020) and
334 the genetic diversity in New Zealand's composite flocks has also been characterised using a
335 higher density 600K chip (Brito et al., 2017b). When combined the genotyping datasets from
336 SNP arrays for sheep now probably capture a considerable amount of the genetic diversity
337 represented by sheep breeds from across the globe.

338 Genotyping data is also useful for conservation purposes. Many indigenous local
339 breeds are now very rare, including for example, the Cameroon sheep from West/Central
340 Africa. As such zoo populations often provide important reservoirs of genetic diversity that
341 can be used for breed conservation (Woodruff 2001). The three 'Beale Park' individuals shown
342 in Figure 2 below are a trio of Cameroon sheep from a wildlife park collection in the UK.

343 Although they are purportedly a “West/Central African” breed, these individuals originated
 344 from zoo populations that have been bred in Europe over several generations. Analysis of
 345 their 50K genotypes (shown in purple) reflect this, as they cluster some distance from the
 346 Cameroon sheep populations from West/Central Africa (shown in grey). As such their genetics
 347 may not be sufficiently representative of Cameroon sheep populations from West/Central
 348 Africa to be helpful for conservation purposes.

349



350

351 **Figure 2:** Principal component analysis illustrating the genetic diversity of sheep breeds from
 352 across the globe using 50K genotyping data (PC1 contributed 16% and PC3 7% to the
 353 variance). Included in the analysis are 50K genotypes from the HapMap dataset from Kijas et
 354 al. 2012, populations of East African sheep from Ahbara et al. 2019 (orange circle) and West
 355 and Central African sheep (blue circle) from Wiener et al. 2022. Cameroon sheep from the
 356 zoo collection at Beale Park (unpublished) are circled in purple.

357

358 A wealth of short read whole genome sequencing data also now exists for sheep
 359 breeds and populations from across the globe. Li et al., 2020, for example, performed deep
 360 resequencing of 248 sheep, including wild *Ovis orientalis* landraces and improved breeds, and
 361 were able to detect genomic regions containing genetic variation of relevance to
 362 domestication, breeding, and selection. With additional whole genome sequencing data they

363 were then able to define chromosomal evolution between wild, hybrid and domestic sheep
364 (Li et al., 2022). Recently, Deng et al. 2020 also provided a comprehensive genomic analysis
365 of haplotype diversity in the Y chromosome, mitochondrial DNA, and variants called from
366 whole genome sequence data from 595 sheep representing 118 domestic populations.

367 Climate change and the pressures it will place on food production will shape future
368 sheep populations and production systems, making characterising and conserving existing
369 genomic diversity increasingly important (Georges et al., 2019). Short read whole genome
370 sequencing data can provide a tool to investigate adaptation in populations of sheep living in
371 diverse and extreme environments at the genomic level e.g. (Yang et al., 2016; Wiener et al.,
372 2021). Wiener et al. 2021 identified over three million single nucleotide variants across twelve
373 Ethiopian sheep populations and applied landscape genomics approaches to investigate the
374 association between these variants and environmental variables. Yang et al. 2016 performed
375 whole genome sequencing of 77 sheep living at varying altitudes and detected a novel set of
376 candidate genes associated with hypoxia response at high altitudes and water reabsorption
377 in arid environments. These studies illustrate how informative large-scale short read whole
378 genome sequencing from diverse populations of sheep can be in identifying the genomic
379 variation driving complex traits such as environmental adaptation and resilience in extreme
380 environments. Harnessing the power of this functional variation will be important in future
381 breeding strategies that aim to select for resilience traits that will help to mitigate the effects
382 of extremes of climate on sheep production systems.

383 The wealth of short read whole genome sequencing data for sheep provides a rich and
384 diverse set of sequence information from which to call variants. There are several resources
385 available to view and mine this data including iSheep: an integrated resource for sheep
386 variant, phenotype and genome information (Wang et al., 2021). The Sheep Genomes
387 Database (SheepGenomesDB) (<https://sheepgenomesdb.org>) houses the sequence variants
388 called, using a standardised pipeline, from sheep short read whole genome sequencing data
389 that has been deposited in the public archives. It is a hugely valuable community resource,
390 not least because calling variants against the reference genome sequence takes a
391 considerable amount of time and computational resource. Through the application of a single
392 harmonised pipeline for read quality control, mapping, variant detection, and annotation,
393 SheepGenomesDB makes available variant collections derived in a standardised manner
394 against the reference genome. The recent change from the Texel Oarv3.1 to the Rambouillet

395 ARS-UI_Ramb_v2.0, as the community adopted reference genome sequence, has
396 necessitated generating a new consensus set of variant calls for sheep. The third run of
397 SheepGenomesDB will pull all the publicly available whole genome sequence data for sheep
398 in the Short Read Archive (SRA) of sufficient depth and quality (from >3000 animals) and call
399 variants against ARS-UI_Ramb_v2.0. The new variant call set will be deposited in the
400 European Variant Archive (EVA) with the other available variant call sets for sheep
401 (https://ftp.ebi.ac.uk/pub/databases/eva/rs_releases/release_4/by_species/ovis_aries/).

402 Once they are deposited in EVA variant tracks can be visualised against the available reference
403 genomes, e.g. Rambouillet ARS-UI_Ramb_v2.0, using the Ensembl genome browser (Hunt et
404 al., 2018). Generating this new set of consensus variant calls for sheep will provide a hugely
405 useful set of genetic markers representing global genetic diversity.

406 Given the amount and diversity of whole genome sequencing data that is publicly
407 available, it would now also be possible to generate a diverse haplotype reference panel for
408 sheep, similar to those available for pig (Nosková et al., 2021) and cattle (Snelling et al., 2020),
409 for imputation purposes. This resource would open-up a host of possibilities for low pass
410 sequencing of many individuals capturing both between and within population diversity and
411 providing the potential to improve genomic prediction by optimising the markers used in
412 genomic evaluation.

413

414 **Genomic selection in sheep – integrating available genomic resources as a priori** 415 **information in breeding programmes**

416 A key component of improving profit and production output in sheep, particularly in
417 Australia and New Zealand, has been the use of genomic selection (Daetwyler et al. 2010).
418 Genomic selection is a form of marker-assisted selection in which genetic markers covering
419 the whole genome are used to estimate an animal's breeding value (Goddard and Hayes,
420 2007). In sheep causative variants for production relevant traits with large phenotypic effects,
421 have been successfully detected, using quantitative, population and molecular genetics
422 approaches e.g. for carcass traits (Clop et al., 2006; Tellam et al., 2012; Matika et al., 2016).
423 However, the majority of health, welfare and resilience traits, are polygenic and any causative
424 variants are likely to have small effects, which makes detecting them more difficult (Georges
425 et al., 2019). Functional genomic data can help enrich for variance in quantitative traits
426 (reviewed in Johnsson 2023). Since most causal variants for complex traits are likely to be

427 located in regulatory regions of the genome and will impact complex traits by changing gene
428 expression (Tam et al., 2019) improvements in prediction accuracy could be achieved by
429 filtering the genetic marker information, used for genomic selection, based upon whether the
430 genetic variants reside in regulatory regions of the genome and then developing robust
431 prediction models that can accommodate information about genome function (Georges et
432 al., 2019).

433 Recently, new methods for integrating genomic information, such as gene expression
434 or methylation data, into genomic prediction models have been proposed e.g. (Xiang et al.,
435 2019, 2021). These multi-layered models, which are based on the combination and ranking of
436 many types of functional genomic data from multiple individuals, have been shown for cattle
437 to facilitate further improvements in predicting genetic merit and consequently on genomic
438 selection (Xiang et al., 2019, 2021). Liu et al., 2022 also recently demonstrated the feasibility
439 of linking variants associated with complex traits from GWAS with gene expression and
440 regulation information across tissues and cell types in cattle, for the cattle GTEx project. The
441 FarmGTEx project (<https://www.farmgtex.org/>) has now extended these efforts to pig (The
442 FarmGTEx-PigGTEx Consortium 2023) and chicken (Pan et al. 2023) and plan a similar initiative
443 for sheep. A priority for the sheep genomics community going forwards will be generating
444 suitable datasets for this purpose. There are currently only a handful of datasets for sheep
445 with matched genotypes and RNA-Seq data, that can be used to train the models for
446 FarmGTEx, such as a recently published expression QTL study from muscle and liver for
447 carcass traits (Yuan et al., 2021b). The opportunity does now exist, however, to generate gene
448 expression information at a population scale due to a reduction in cost of RNA-sequencing
449 and the development of new assays that are deployable at scale such as Illumina 3'-
450 sequencing. The challenge for sheep may also be accessing phenotype data for trait prediction
451 as recording in sheep is much less advanced across traits than for cattle, pigs, and chicken.
452 However, accurate recording to inform selection strategies will become increasingly
453 important as future extremes of climate put pressure on producers to select animals that are
454 more resilient.

455

456 **New genomic resources can inform genome editing and the use of sheep as biomedical**
457 **models**

458 While genomic selection is likely to provide the foundation of many future commercial
459 breeding programmes for sheep, it is limited by the genetic pool of the population under
460 selection. If a target trait is not encoded in the genome of a breeding population, then it is
461 not possible to select for it. Genome editing has the potential to offer an effective solution to
462 this problem (McFarlane et al., 2019). Sheep are particularly amenable to genome editing and
463 it has been applied successfully for a small number of production relevant target genes,
464 reviewed in Proudfoot et al. 2015. Advances in the genomic resources for sheep will provide
465 information to identify new editing targets particularly those that control breed-specific
466 characteristics that may be present in one breeding population but not in another. One
467 example is the 'polled' or hornlessness trait that is a distinct characteristic of some breeds
468 such as the Poll Dorset. Horns can cause injury both to the sheep themselves and to their
469 handlers and consequently, particularly in production animals, polledness is desirable.
470 However, some production breeds with desirable resilience and sustainability traits, like the
471 Wiltshire Horn, a wool-shedding breed with a good carcass and high feed efficiency, have
472 undesirable large horns that make them difficult to handle and manage. Gene editing for
473 polledness has been achieved successfully in cattle, reviewed in (Van Eenennaam, 2019), but
474 in sheep is likely to be more complex, reviewed in Simon et al. 2022. A 1.78Kb insertion in the
475 3'UTR region of the RXFP2 gene on chromosome 10 has been identified which is strongly
476 associated with polledness in GWAS (Wiedemar and Drögemüller, 2015) however it does not
477 segregate in the same way across all breeds (Lühken et al., 2016). Comparative approaches
478 to analyse breed specific genomic resources for sheep, across individuals and populations,
479 will help to reveal the functional basis of traits present in one breed or population that are
480 desirable in another providing novel targets for selective breeding and/or genome editing
481 (Clark 2022).

482 In addition to their role as food production animals sheep are also important
483 biomedical models (Banstola and Reynolds, 2022). The new highly contiguous ARS-
484 UI_Ramb_v2.0 reference genome and associated annotation, provides a research tool that
485 can inform studies designed to identify alleles encoding human physiological processes and
486 diseases. One recent example, is the novel sheep model of *CLN1* disease, in which gene
487 editing was used to insert a disease-causing *PPT1 (R151X)* human mutation into the
488 orthologous sheep locus (Eaton et al., 2019; Nelvagal et al., 2022). High-throughput
489 CRISPR/Cas9 knock-out libraries, such as those available for pigs e.g. (Yu et al., 2022), will help

490 considerably with identifying novel alleles for genome editing in both human and farmed
491 animal studies. At present, however, a lack of suitable primary cell lines for sheep is a barrier
492 to progress. As the applications of genome editing technologies in the biomedical field expand
493 a high-quality annotated reference genome for sheep on which to base target selection will
494 become even more useful.

495

496 **The future**

497 In addition to the new genomic resources for sheep described above there are further
498 exciting developments on the horizon (Figure 2). For example, recent improvements in tools
499 and resources for long read sequencing have made assembling fully contiguous assembled
500 telomere to telomere genomes possible. The human telomere-to-telomere genome assembly
501 is a revolutionary new tool for human research unlocking the complex regions of the genome
502 to study genome function and genetic variation (Nurk et al., 2022). A telomere-to-telomere
503 reference genome assembly for sheep is currently being generated for the Ruminant
504 Telomere-to-Telomere project which is led by the USDA and University of Idaho.

505 From a transcriptome perspective, since publication of the sheep gene expression
506 atlas, expanded transcriptomes, that include histological tissue maps and characterisation of
507 all RNA populations, have been published, e.g. for pig (Jin et al., 2021), and similar new
508 resources of this type for sheep will soon follow. Furthermore, long read RNA isoform
509 sequencing technologies, can now capture full-length isoform information, even at single cell
510 level resolution. These technologies make transcript annotation considerably easier and allow
511 for the characterisation of splicing events and prediction of full-length open reading frames.
512 Isoform sequencing (Iso-Seq) data for a small subset of tissues is available for sheep, for the
513 purposes of annotating the Rambouillet genome, and from a small number of published
514 studies that have focused on specific tissues relevant to phenotypes of interest (Yuan et al.,
515 2021a, 2022). New long read isoform sequencing datasets for multiple tissues, cell types and
516 developmental stages, will provide a valuable novel resource for genome annotation and
517 build on the transcriptomic resources already provided by short read RNA-Seq data. Long read
518 sequencing technologies will also facilitate, the generation of breed- specific transcriptomes.
519 These breed-specific transcriptomes based on full-length isoform information, will allow the
520 classification of sets of pan-genes and pan-transcriptomes for sheep providing new insights
521 into how isoform usage can influence key traits across different breeds.

522 The primary challenge facing the sheep and wider farmed animal genomics
523 community now is harnessing the power of a highly accurate reference genome with
524 functional genomics data at a population scale and from there how to leverage this
525 information to enhance genomic prediction (reviewed in Johnsson 2023). The potential to go
526 ‘beyond the genome’ by using epigenetic modifications to predict genetic merit also shows
527 significant potential, reviewed in Clarke et al. 2021. DNA methylation arrays, for example,
528 have proved to be useful tools for informing breeding programmes for sheep, and provide an
529 opportunity to accelerate the physiological response of breeding populations to
530 environmental pressures (Clarke et al., 2021). Tools to visualise the combination of genetic
531 variation with predicted function will be critical in advancing the sheep genomics field.
532 Functional genomic comparisons of different sheep breeds will become increasingly powerful
533 as haplotype-resolved reference genomes and pangenomes with matched functional
534 annotation data become the new standard for sheep and other economically important
535 farmed animal species.

536

537 **Conclusions**

538 The field of sheep genomics has undoubtedly moved into a new era. New functional
539 annotation datasets for sheep for many different tissues and cell types provide new resources
540 to link cell, tissue and whole animal scale knowledge. Novel opportunities also now exist for
541 interrogating gene regulation information at single cell resolution providing a much more
542 complete picture of transcriptional complexity in sheep. Affordable long read sequencing
543 technologies have caused an explosion in the number of new genome assemblies that are
544 being generated for many different breeds and populations. Genetic improvement in the
545 future will also almost certainly include the use of pangenomes to understand and visualise
546 the diversity of farmed animal genomes (Hayes and Daetwyler, 2019). For this reason,
547 pangenome efforts should ensure they capture the global genetic diversity of sheep breeds,
548 including those from the global south. Logistical considerations will inevitably arise with the
549 rapid expansion of genomes and genomic resources for sheep. Genome browsers, such as
550 Ensembl, will need to keep pace with how rapidly these new genomic and transcriptomic
551 resources are being generated. This will need to happen quickly in order that the community
552 can maximise the benefit of this new information, and will require resources, effort and
553 funding (Cunningham et al., 2022). The sheep genomics research community will also need to

554 work with stakeholders to decide what the priorities are for the coming decade. These
555 priorities should be centred around providing resources that can inform global sheep
556 breeding systems in a way that will help to accelerate their response to future extremes of
557 climate, produce healthier improved animals and provide enough food for a growing human
558 population.

559

560 **Competing Interests**

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563

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576

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