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Department of
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Master Thesis

European Master - Animal Breeding and Genetics

Looking for recessive disorders through missing homozygous patterns in Tyrol Grey Cattle

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Abstract

Recessive genetic disorders are caused by homozygous recessive genes. Because of the recessive nature of gene action, the frequency of the damaging alleles may be quite high in a population because heterozygous carriers are non-affected. Several studies have been carried out within various breeds of livestock in different locations associating the haplotypes, i.e., segments of the genome holding the damaging mutation, towards defects in reproduction and other functional traits. In this study, we identifed haplotypes using different versions of high throughput (SNP chip) genotype data of 220 Austrian Tyrol Grey cattle and 80 Italian Tyrol Grey cattle, looking for genes that cause classic recessive disorders or embryonal death of affected individuals. In such cases, one homozygous haplotype is missing in the population, and statistical tests are employed as to whether this is very unlikely under Hardy-Weinberg equilibrium. PLINK software was used to merge datasets and quality control step with settings only allowing individuals and SNPs with missing call rates less than 0.1 and no limitation on minor allele frequency and Hardy-Weinberg equilibrium. SHAPEIT2 software was used for phasing the haplotypes. GHap package in R calculated the number of observed and expected homozygous based on the number of sampling animals and frequency of the haplotypes. The scanning window was set to 500 kbp and sliding step of 100 kbp a time. We found 93 haplotype blocks with deficiency of observed homozygous (lower tail) with P-value<0.01 and 185 haplotype blocks with an excess of observed homozygous (higher tail) passing line genome-wide significance level of P<0.000000005. In the lower tail analysis, we found regions with functioning genes related to response to mycobacterial infections, secretion of PGF2α, self-clearance of the respiratory tract, nutrient transport, fat synthesis, the transmembrane protein, cardiac function, and glucose and lipid metabolism. In the higher tail analysis, we found regions with functioning genes related to reproduction system, milk synthesis, vision function, immune response, blood system, and also regions which carrying genetic defects of strabismus, chondrodysplastic dwarfism, and osteopetrosis. The small number of genotyped animals may be the reason why we could not detect any of known recessive diseases in Tyrol Grey in this study. Nonetheless, this result can be a reference for the further study to uncover the reasons of why we found more observed homozygous in higher tail analysis and if a new case of recessive defects is appearing.

Zusammenfassung

Rezessive genetische Störungen werden durch homozygote rezessive Gene verursacht. Wegen der rezessiven Natur der Gen-Aktion kann die Häufigkeit der schädigenden Allele in einer Population ziemlich hoch sein, da heterozygote Träger nicht betroffen sind. Mehrere Studien wurden in verschiedenen Rassen an verschiedenen Orten durchgeführt, welche die Haplotypen assoziieren, d.h. Segmente des Genoms, die die schädigende Mutation halten, mit Auswirkungen auf Fehler in der Reproduktion und andere funktionale Merkmale. In dieser Studie identifizierten wir Haplotypen mit verschiedenen Versionen von High-Throughput (SNP-Chip) Genotyp Daten von 220 Österreichischen Tiroler Grauvieh und 80 Italienischen Tiroler Grauvieh Rindern, auf der Suche nach Genen, die klassische rezessive Störungen oder embryonalen Tod der betroffenen Individuen verursachen. In solchen Fällen fehlt ein homozygoser Haplotyp in der Population, und es werden statistische Tests angewendet, ob dies unter dem Hardy-Weinberg-Gleichgewicht sehr unwahrscheinlich ist. PLINK-Software wurde verwendet, um Datensätze und Qualitätskontrollschritt mit Einstellungen zu kombinieren. SHAPEIT2 Software wurde für die Phasierung der Haplotypen verwendet. Das GHap-Paket in R berechnete die Anzahl der beobachteten und erwarteten homozygoten Individuen, basierend auf der Anzahl der genotypisierten Tiere und der Häufigkeit der Haplotypen. Das Scan-Fenster wurde auf 500 kbp mit einem gleitenden Schritt von 100 kbp gesetzt. Wir fanden 93 Haplotypenblöcke mit einem Mangel an beobachtetem Homozygoten (lower tail analysis) mit P-Wert <0,01 und 185 Haplotypenblöcke mit einem Überschuss an beobachtetem Homozygoten (higher tail analysis), der die genomweite Bedeutung von P<0,000000005 aufweist. In der lower tail analysis fanden wir Regionen mit Genen im Zusammenhang mit der Reaktion auf mykobakterielle Infektionen, die Sekretion von PGF2α, die Funktion der Atemwege, den Nährstofftransport, die Fettsynthese, das Transmembranprotein, die Herzfunktion und den Glukose- und Lipidstoffwechsel. In der higher tail analysis fanden wir Regionen mit Genen, die sich auf Reproduktionssystem, Milchsynthese, Sehfunktion, Immunantwort, Blutsystem und auch Regionen mit genetischen Defekten von Strabismus, chondrodysplastischem Zwergwuchs und Osteopetrose beziehen. Die geringe Anzahl von genotypisierten Tieren kann der Grund sein, warum wir in dieser Studie die bekannten rezessiven Erkrankungen beim Tiroler Grauvieh nicht erkennen konnten. Dennoch kann dieses Ergebnis eine Referenz für weitere Studien sein, um die Gründe aufzudecken, warum wir mehr beobachtete homozygoten in der higher tail analysis gefunden haben und wenn ein neuer Fall von rezessiven Defekten auftritt.

Acknowledgements

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I would like to thank you Univ. Prof. Dipl.-Ing Dr. Johann Sölkner and Ass. Prof. Dr. Gabor Meszaros for letting me work on this topic and uncountable support since the beginning of my study.

Thank you for my wife, family, and all my friends here in Vienna and in-home who support me to finish my study.

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1. Introduction

Diploid organisms carry two sets of chromosomes, such when considering two alleles on a gene can be in the form of the first homozygous (AA), heterozygous (AB), and second homozygous(BB). In the normal situation where an infinite population with random mating and no selection applied, the genotype ratio is in 1:2:1, though the phenotypic ratio could be different based on dominance type or epistasis effect of the gene towards the phenotypic expression. Deviation of the genotypic ratio from the normal one could indicate phenomena affecting the segregation of genotype.

Selection for production, genetic drift, and natural selection will lead to increase of one type of allele frequency in the population compared what we expect in a situation where random mating is applied. Thus, the homozygosity for favorable alleles with high production performance will increase in the population. In natural selection, the survival of fittest concept leads to increase of homozygosity frequency of animals carrying genes that required for adaptation. In contrast, decreasing the homozygosity of allele indicate the adverse selection due to lesser production level or health status associated with recessive disorders.

Expression of recessive disorders happens in an individual with homozygous recessive alleles. The recessive disorders can be both lethal and non-lethal. The recessive haplotypes appear in the population genotype but little to never occur in a homozygous form in the healthy individual. Continuance of this haplotypes to exist in the population is due to carrier heterozygous animals which are not directly affected (Sahana et al., 2013).

In the past, breeders depended highly on phenotypic records and pedigrees of the potential carriers. Using the currently available genotyping technologies the available genotype data from healthy individuals could be utilized to find the causal variants for recessive disorders by identifying haplotypes that do not occur in either of the homozygous forms (VanRaden et al., 2011; Sahana et al., 2013).

Regions with homozygous haplotypes which are likely harboring deleterious mutations have been identified and postulated in several cattle breeds causing early embryonic losses (Pausch et al., 2015). Using the genotypic data and confirmed by phenotype database, five different haplotypes were identified in North America Holstein cattle which have large effects on conception rate, complex vertebral malformation (CVM), and brachyspina (VanRaden et al., 2011). A similar approach was used in Nordic Holstein cattle observing eight genomic regions with 17 haplotypes that less appear in homozygous state, six out of these were confirmed affecting non-return rates and calving interval (Sahana et al., 2013). In Brauenvieh

cattle, deficiency in homozygous haplotypes in short segment of chromosome 19, called BH2, is associated with juvenile mortality as the impact of impaired function of airway cilia (Schwarzenbacher et al., 2016).

By using genomic data, finding the potential recessive disorders is possible without observing the affected individuals but based on the identification of homozygous haplotypes. The appearance of the missing homozygous is simply not by chance when considering large size of genotyped animals (VanRaden et al., 2011; Pausch et al., 2015).

Following the success of previous studies finding the recessive disorders through missing/minor homozygous haplotypes, the same approach will be used for Tyrol Grey cattle, a small breed of Tyrol Area. We would like to study the deviation patterns of expected and observed haplotypes thus search through the physical sites in the genome to find functional genes and to study on its association towards the potential recessive disorders in Tyrol Grey Cattle.

2. Aim of the thesis

The objective of the thesis is to investigate the deviation pattern of homozygous haplotypes, and their association towards recessive disorders in Tyrol Grey cattle.

3. Literature Review

- Quality control and methodology from previous similar studies

Genomic data is very substantial in detecting lethal recessive disorders which cannot be done solely by large sets of phenotypic and pedigree data. Recent a method was developed to identify several defects by looking through haplotypes that are common in a population but never occur in the homozygous state. This method can be used without phenotypic data, by providing large sets of genotyped animals. Thus, the absence of homozygous haplotypes will happen not by chance. Born abnormal calves or embryonic mortality used in the past to confirm the lethal recessive conform by pedigree and haplotype of suspected carriers (VanRaden et al., 2011). Lethal recessive could be discovered through haplotypes pattern that frequent in population but missing in homozygous state live animals. Therefore the genotype data has to come from mostly phenotypically normal (live) animals (Sahana et al., 2013).

To locate the potential of lethal recessive alleles through haplotype pattern, VanRaden (2011) used 58,453 and 24,341 Holsteins, 5,288 and 4,549 Jerseys, 1,991 and 121 Brown Swiss, with different BeadChip of Bovine SNP50 and GoldenGate Bovine3K respectively. Haplotypes were defined using Fortran version 2 program findhap.f90. It created examined haplotypes decreasing from 600 markers in length until final output haplotype of fewer than 75 markers for further analysis corresponding to 4 to 7 Mbp in physical distance.

Genotyped data of 7,937 Nordic Holstein Cattle were used to find novel harmful recessive haplotypes related to fertility traits. Quality control set to allow only SNPs with minor allele frequency of 0.05 and the GenCall score of 0.65 resulting 36,387 SNPs on 29 BTA for further analysis. Default scale and shift parameters without applying relationships between individuals were set in Beagle software version 3.3 to impute missing markers and determining phase. Constructing haplotypes were done by using two sizes of windows, i.e., 25 and 75 consecutive markers(Sahana et al., 2013).

Genotypic data of 25,544 Fleckvieh cattle from semen samples of artificial insemination (AI) bulls passing quality control were used to find deleterious mutations towards reproductive and rearing success by the pattern of deficiency in homozygous haplotypes. Using Illumina Bovine SNP50 BeadChip, quality control carried out with only considering animals and SNPs with call rate higher than 95%, minor allele frequency below 2%, and significant deviation ($P<10^{-6}$) from the Hardy-Weinberg equilibrium. Animals with significant discrepancy from the comparison of relationship based on pedigree and realized genomic were excluded. SNPs with more than 500 Mendelian errors based on genotype sire-offspring pairs were excluded. Beagle software was used to fixed haplotypes and impute missing

genotypes. Windows with variable size ranging from 0.75 to 10 Mb was shifted in half size of each window size to identify the deficiency of homozygous haplotype. Haplotypes with the frequency higher than 2% were kept for identifying homozygous haplotype deficiency(Pausch et al., 2015).

Genotypic data of 47,878 Holstein, 16,833 Montbeliarde, and 11,466 Normande breeds were used to detect recessive lethal regions and characterize them to identify the strong candidate causative mutation. Quality control was set to discard markers with minor allele frequency lower than 3% and or deviating from Hardy-Weinberg equilibrium ($P<10^{-6}$). Like other similar research, only autosomal markers with confirmed position within UMD3.1 genome assembly were used. DualPhase was used for phasing the haplotypes combining pedigree information of at least two generations of all animals and linkage disequilibrium at the population level. The window for analyzing the haplotype was set to 20 markers correspond to one to 1.5 Mb in physical distances and sliding by a single marker at a time. After that, only haplotypes with a frequency higher than 1% were counted for calculation of observed and expected homozygous. The final interval defined by merging all windows from the first marker on the left to the last marker in the right window proving the same minimum number of homozygous products(Fritz et al., 2013).

Not only in cattle, similar research looking for recessive disorders also carried out in pigs using 871 Finnish Yorkshire. Prior defining the haplotypes, SNP data are undergoing quality control procedures considering only autosomal chromosomes for this type of analysis. Quality control was set to only allow animals with genotype call rate of 90% and SNPs with a call rate of 0.9 with no setting for minor allele frequency or Hardy-Weinberg equilibrium. Beagle software version 3.3 used to impute missing genotypes and determining haplotype phases with relationship information between individuals were discarded (Häggman & Uimari, 2017).

- Defining number of expected homozygous

VanRaden et al. (2011) determine the expected number of homozygous in two ways. First, by assuming random mating across the population, they used the number of genotyped animals divided by four times the square of the carrier frequency. Second is by using the actual mating plans for each in the population where the number of carrier service sire x carrier maternal grandsire matings divided by 4 in an assumption of allele frequencies maternal grandsire equals to maternal grand dams.

Sahana et al. (2013) calculated the expected number of homozygous individuals for any haplotype following VanRaden et al. (2011) by using the number of genotyped animals

divided by 4 and multiplied by the square of the carrier frequency assuming random mating. However, this simple method might be overestimated if we underrate the inbreeding and changes of allele frequency over a period of time. The inbreeding coefficient was compared with his research and the reference, i.e., 3.7±1.9% in Nordic Holstein population and 5.5±1.9% in American Holstein population, respectively.

$$E(k) = \sum_{i=1}^{ns} p_{ik} \sum_{j=1}^{nmgs} 0.5 \left[q_{jk} + f_k \right] \quad n_{ij}$$

Fritz et al. (2013) estimated the expected haplotype following the equation above, *E(k)* deriving from the genotypes of sire, maternal grandsire, and frequency of the haplotype in the population. *E(k)* based on the above equation was a function of *ns* (number of conception sires), *nmgs* (number of maternal grandsires), f_k (frequency of haplotype), p_{ik} (probability of transmission haplotype from sire to progeny), q_{jk} (probability of transmission haplotype from maternal grandsire), and n_{ij} (the number of progeny with sire i and maternal grandsire j).

Pausch et al. (2015) calculated the expected number of homozygous animals for that haplotypes using sire, maternal grandsire, and haplotype frequency information. Application of exact binomial test compared observed number of homozygous with the expectation. Further inspection for harmful phenotypic effects considered haplotypes with a significant deficit of homozygous animals ($P < 1 \times 10^{-6}$). Homozygous animals as result of the carrier mating test were inspected in an animal clinic to confirm the effect. This test is important due to the possible unintentional mating of carriers that could happen in Fleckvieh farms (Pausch et al., 2015).

- Known cases of bovine deleterious haplotypes

The pattern of missing homozygous haplotypes found by genotyped data was analyzed further with the phenotypic record and pedigree of the population. Thus, it can be confirmed that those recessive haplotypes have effects on traits of interest.

VanRaden et al. (2011) found 11 haplotypes from three breeds having missing homozygous in the population. Further investigation using phenotypic data, confirmed five haplotypes that are strongly affected the fertility traits, i.e., conception rate and stillbirth calves as seen in table 1. Such when HH1 in homozygous form, which is haplotype number 10 on the segment of 133 (based on the potential lethal data column) in chromosome 5 gave effect minus 3.1 percent towards conception rate and increasing the percentage of stillbirth animals by 0.7 percent. This is proven by phenotypic data from 24,555 recorded matings and 11,905 born calves.

Hap.	Breed	Chr.	Potential lethal data	Map location Mbp	Conception rate, %			Stillbirth calves effect, %		
					Matings	Effect	SE	Calves	Effect	SE
JH1	Jersey	15	355.10	13-18	52,449	-3.7	0.2	1,612	-0.4	0,8
HH1	Holstein	5	133.74	58-66	24,555	-3.1	0.3	11,905	0.7	0,3
HH2	Holstein	1	21.337	92-97	3,252	-3.0	0.8	896	1.8	1,0
HH3	Holstein	8	218.61	90-95	14,114	-3.2	0.4	7,510	1.0	0,3
BH1	Brown Swiss	7	183.13	41-47	936	-3.4	1.5	NA	NA	NA

Table 1. Known recessive haplotypes (VanRaden et al. 2011).

Those haplotypes were confirmed and widely used nowadays as reference to avoid matings between the carrier and the expression of recessive alleles. By July 2011, there were 195 carriers for one of these haplotypes impacting the fertility out of 1,349 bulls which semen is available for purchase. However, due to a large population of Holstein, the probability of mating two carrier carrying the same haplotype is 2.5 times out of 1000(Holstein Association USA, 2011).

Hap.	Breed	Chr.	Map Location Mbp	Heifer Matings	Loss in heifer calving rate, %	Cow Matings	Loss in cow calving rate, %
MH1	MON	19	27.6-29.4	145978	-5.96	403695	-4.84
MH2	MON	29	27.9-29.1	112585	-5.26	207697	-4.85
BY	HOL	21	20.2-22.3	21386	-6.67	70918	-4.25
HH1	HOL	5	61.4-66.2	9388	-9.89	38072	-4.90
HH3	HOL	8	94.0-96.5	5281	-5.40	7315	-5.54
HH4	HOL	1	1.9-3.3	31663	-5.80	71788	-1.74

Table 2. Recessive haplotypes in French population (Fritz et al., 2013)

Further research found additional 13 haplotypes HH4-HH17, 11 haplotypes MH1-MH11, and six haplotypes NH1-NH6, for Holstein, Montbeliarde, and Normande breeds in the French population, respectively, which are less in observed homozygous forms than expected. Assuming complete lethality which is in range of minus 4.75% and minus 6.25% following the average conception rate. The effect of six haplotypes towards fertility traits was close to the expectations, namely MH1, MH2, BY, HH1, HH3, and HH4 as listed in table 2 (Fritz et al., 2013).

Cole et al. (2016) investigated 18 recessive haplotypes from Ayrshire, Brown Swiss, Holstein, and Jersey breeds on daughter pregnancy rate, heifer conception rate, and cow

conception rate. They found Jersey Haplotype 2 (JH2) which is located on BTA 26 of 8.812-9.414 Mbp was significantly associated with reducing cow conception rate by 7.17 %.

A similar study carried out in 25,444 Fleckvieh cattle found four haplotypes namely FH1, FH2, FH3, and FH4 were missing or significantly less observed in homozygous form. Those haplotypes were confirmed affecting the reproductive and rearing success as seen in table3.

Hap	Chr	Location Mbp	Homozygous animals			Matings	Insemination success, %	Stillbirth rate, %
			Exp.	Obs.	P-value			
FH1	1	1.668-6.187	20	0	$4.8x10^{-9}$	178,337	-6.64	-0.4
FH2	1	96.169-97.123	37	2	$1.2x10^{-13}$	117,814	-1.57	0.7
FH3	10	26.929-35.479	41	3	$2.1x10^{-14}$	147,222	-4.06	1.4
FH4	12	10.859-12.805	33	0	$1.3x10^{-14}$	91,257	-5.99	0.4

Table 3. Recessive haplotypes in Fleckvieh population (Pausch et al., 2015)

- Known recessive disorders in cattle

Many studies research have been carried out to find out causative mutations in the genomic regions associated with known recessive disorders. Most of the recessive disorders are caused by copy number variation, either by insertion or deletion some base pairs that lead to mutation. Therefore, it is important to review existing recessive diseases in cattle. In table 4 listed recessive disease found in cattle together with the position on the chromosome and the associated genes.

Chr.	Disorders	Genes	Causative Mutation
2	Muscular hypertrophy	*MSTN*	c.821del11 c.c.938G>A c.871G>T c.3811T>G c.282C>A
3	Proportionate dwarfism with inflammatory lesions	*RFN11*	c.124_2A>G
4	Osteopetrosis	*SLC4A2*	-2.8 kb deletion
6	Chondrodysplasia	*EVC2*	c.2993_2994ACdel
6	Dwarfism in Angus	*PRKG2*	c.2032C>T
15	Syndactylism	*LPR4(MEGF7)*	c.241G>A c.3595G>A c.5385+1G>A
19	Crooked tail syndrome	*MRC2*	c.2904_2905delAG

			c.1906T>C
19	Glycogen storage disease type II	*GAA*	c.2454_2455delCA c.1057_1058delTA c.1783C>T c.1351C>T c.2223G>A
21	Aggrecan type dwarfism	*ACAN*	c.2266_2267insGGCA c.-198C>T
23	Arachnomelia	*MOCS1*	c.1224_1225delCA
24	Protoporphyria	*FECH*	c.1250G>T c.1252C>A c.1258C>T
25	Osteopetrosis with gingival hamartomas	*CLCN7*	c.2244G>C c.2248T>C c.2250C>A
29	Glycogen storage disease type V	*PYGM*	c.1468C>T

Table 4. Known recessive disease in cattle (Ciepłoch et al., 2017)

- Characteristics of Tyrol Grey Cattle

Tyrol Grey Cattle has occupied the Alpen areas in the last 3000 years. Before the end of 19th century, the breeders have differentiated it as Oberinntaler, Lechtaler, and Wipptaler cattle. The merging started as the founding of the association for more organized breeding activities. It is widespread in the Tyrol area of Alps partitioned into Austrian Tyrol and Italian Tyrol by country borders. It has phenotypic characteristics of a dual-purpose breed with medium body size, silver to iron grey with black muzzle and claw. The appearance of the mature cow is as shown in figure 1. There are separate herd books for the breed in Austria and Italy. This breed has robustness for production in high alpine regions with reasonable high milk yield based on proximate available raw feed. The average production of the first lactation is 4400 kg milk with 4.0% fat and 3.4% protein content and in the fourth lactation with 5300 kg milk production with 4.0% fat and 3.3% protein content. ÖNGENE, the Austrian national association for animal genetic resources, considered this breed as an endangered breed. Currently, there are 850 control herds with 3700 breeding animals for milk production in Austria and around 1681 breeding farm in Italy (Tiroler Grauviehzuchtverband, 2017; ÖNGENE, 2017; L'Associazione Nazionale Allevatori Bovini di Razza Grigio Alpina, 2017).

Figure 1. Tyrol Grey cattle (Tiroler Grauviehzuchtverband, 2017)

A clear distinction of Tyrolean Grey Cattle from other breeds in the region is shown by principal component analysis in figure 2. Run of homozygosity of available AI bulls in the population of Austrian Tyrol grey, based on covering regions of 4, 8, and 16Mb, showed that the inbreeding coefficient (F_{ROH}) were 4.0%, 2.9%, and 1.6%; and those animals have the common ancestors at around 3, 6, and 12 generations ago, respectively. In average, the generation interval in the population is 5.66 years. There is effort to strictly avoid close inbreeding as shown by estimated effective population size based on ROH 4, 8, and 16 Mb, Ne_{ROH} were 370, 186, and 125, respectively (Mészáros et al., 2015)

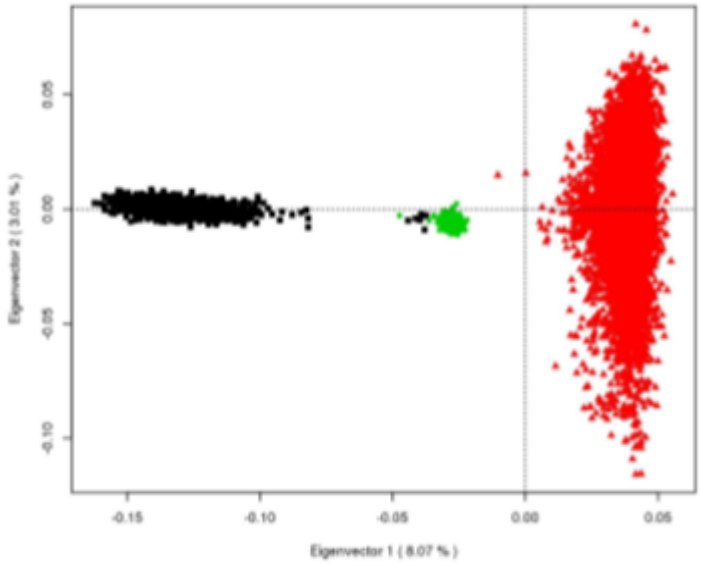

Figure 2. Principal component analysis; Brown Swiss = Black, Fleckvieh = Red, and Tyrolean Grey = Green (Mészáros et al., 2015)

- Reported recessive disorders in Tyrol Grey Cattle

Tyrol Grey is relatively small breeds compared to other commercial breeds such as Frisian Holstein, Simmental, Brown Swiss. On those breeds, lethal and non-lethal genetic disorders have been reported and found in the production population from various countries. For Tyrol Grey, Sölkner et al. (2009) reported 31 cases of calves losing control over the hind part of the body due to a nervous system akin to the weaver in Brown Swiss from 2003 to 2008. What makes it distinctive from Weaver Brown Swiss is the manifest of this disorder at the early age of 3-5 months while in weaver cases occur later in life. Gusti, a cow born in 1972 was the suspected carrier with current 81 sons and grandsons being used as breeding bulls. Genotyping was done for affected animals, potential carriers, and some unrelated animals. As shown in figure 3 by runs of homozygosity, all affected animals share a homozygous region, and identical in chromosome 16 of 38.33 – 39.61 Mb correspond to SNP markers number 738-764. Conceivably due to the usage of Gusti's progenies as breeding bulls, leads to a high frequency of the allele in the population, more than 10%.

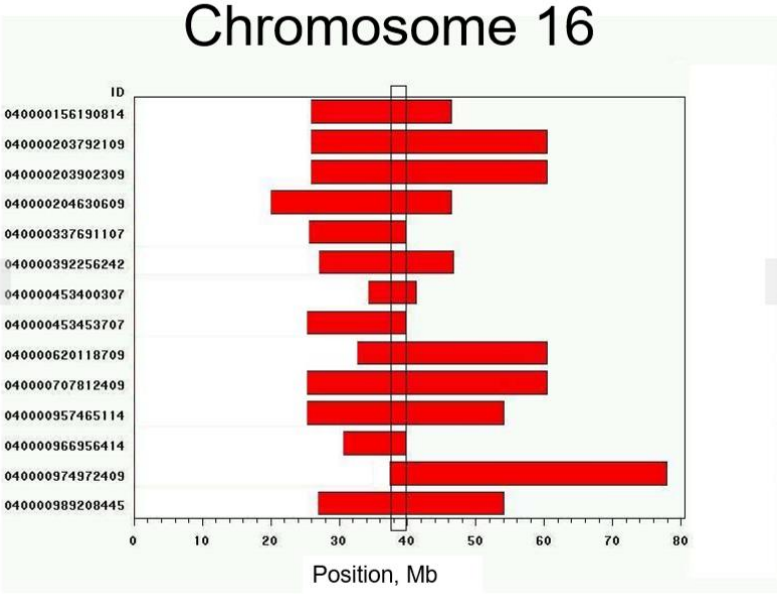

Figure 3. Run of homozygosity for affected cattle (Sölkner et al., 2009)

The case was further investigated with a neuropathological method on affected animals showed axonopathy degeneration in the central nervous system and femoral nerve, figure 4. Based on the pedigree of affected calves, a monogenic autosomal recessive inheritance is suggested as the mode of genetic defects transmission. Genome-wide association and haplotype mapping were carried out identifying the 1.9 Mb region in the chromosome 16 of 37.85-39.75 Mb, as in figure 5. Mutation analysis was performed on affected Tyrol Grey cattle with *MFN2* as the candidate gene. Silent SNP within a putative exonic splice enhancer

(ESE) region of exon 20 of *MFN2* leads to premature stop codon from *MFN2* transcript (Drogemuller et al., 2011).

Figure 4. Degenerative axonopathy case in Tyrolean Grey cattle (Drogemuller et al., 2011)

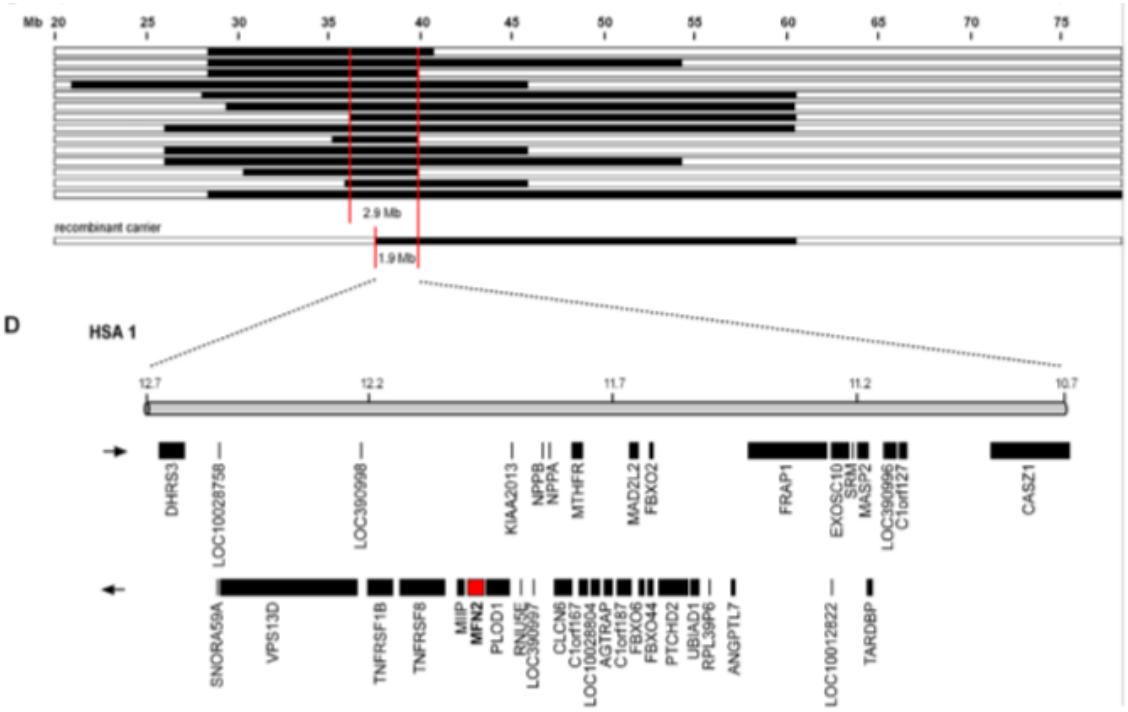

Figure 5. *MFN2* gene causing degenerative axonopathy (Drogemuller et al., 2011)

As seen in figure 6, a similar case to chondrodysplastic dwarfism found in seven inbred Italian Tyrol Grey calves aged one week to 2.5 months, the parents of which were normal. Affected animals had difficulty to stand up and to maintain quadrupedal stance with head, axial skeleton, and genital tracts apparently to be normal. Radiograph results showed there were no fractures or osteopenic of bones. Instead, bones, particularly on femur and humerus,

were shortened and twisted. Autosomal monogenic recessive transmission of the detective allele assumed through pedigree analysis linked to common female ancestor Anka born in 1982, see figure 7. Genome-wide association and homozygosity mapping were carried out to find an interval in the chromosome 6 of 104.9-106.5 Mb as candidate region associated with the disease. A single mutation in *EVC2* gene (p.Asp998GlufsTer13) was identified causing a frameshift and premature stop codon so that any mutant will shorten protein by 13 amino acids than the normal ones (Murgiano et al., 2014).

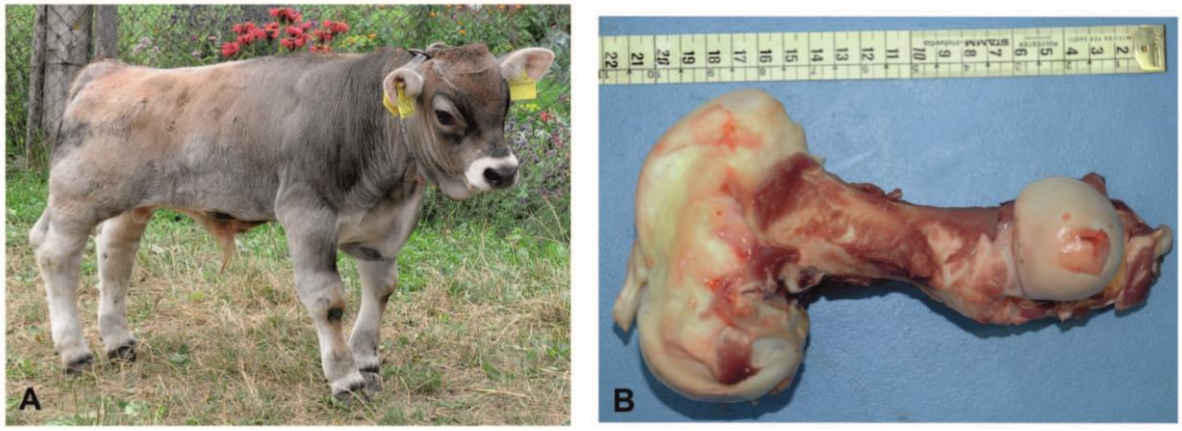

Figure 6. The phenotype of affected animals in chondrodysplasia dwarfism; A.Live Animal, B.Femur bone (Murgiano et al., 2014)

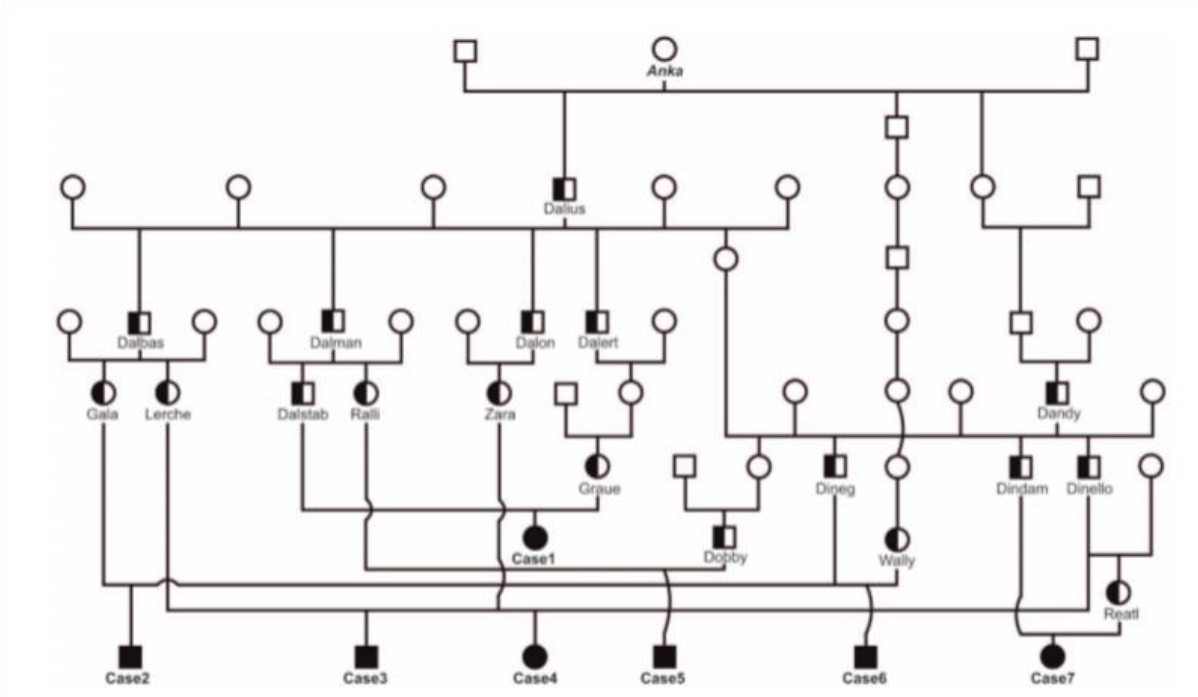

Figure 7. Pedigree of affected animals in chondrodysplasia dwarfism; fully black is affected, and half-black is carrier (Murgiano et al., 2014)

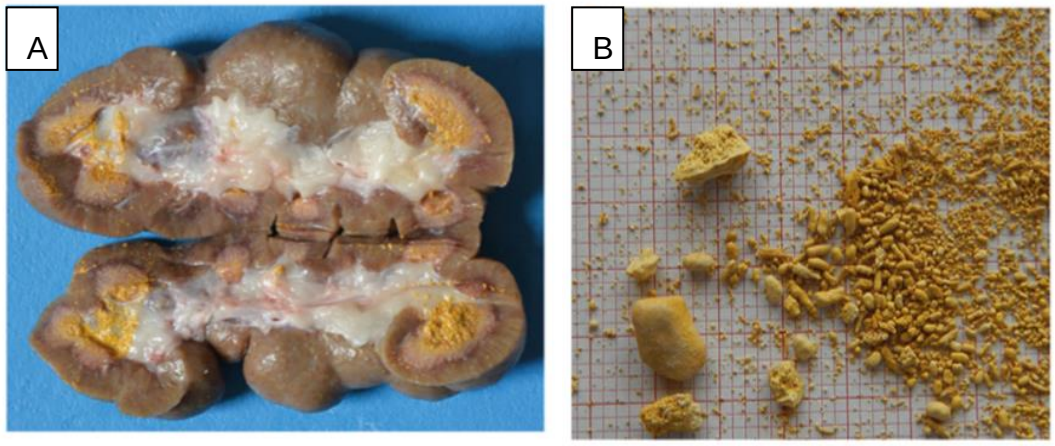

Figure 8. Xanthinuria case in Tyrolean Grey; A. Affected kidney, B. Uroliths (Murgiano et al., 2016)

It is reported that two female twin cattle of Tyrol Grey aged eight months had kidney abnormalities followed by apparent signs of growth hindrance, continuous loss of weight, overgrowth of hooves and flawed skeletal development without declining of appetite and vitamin integration. Blood phosphate concentration by clinical biochemistry data indicated a renal failure(Xanthinuria). Please refer to figure 8 for the effect of xanthinuria on kidney. Whole genome sequencing study revealed that the observed reinal syndrome is caused by mutation of 1 bp deletion in the bovine *MOCOS* gene leads to frameshift causing premature stop codon on both transcripts (p.Ser628Valfs9* and p.Ser595Valfs9*). Combined with the pedigree of Tyrol Grey cattle, it is confirmed that affected animals were homozygous and carried two copies of the mutation, while non-affected animals had no copies and parents as the carrier had one copy of the mutation (Murgiano et al., 2016).

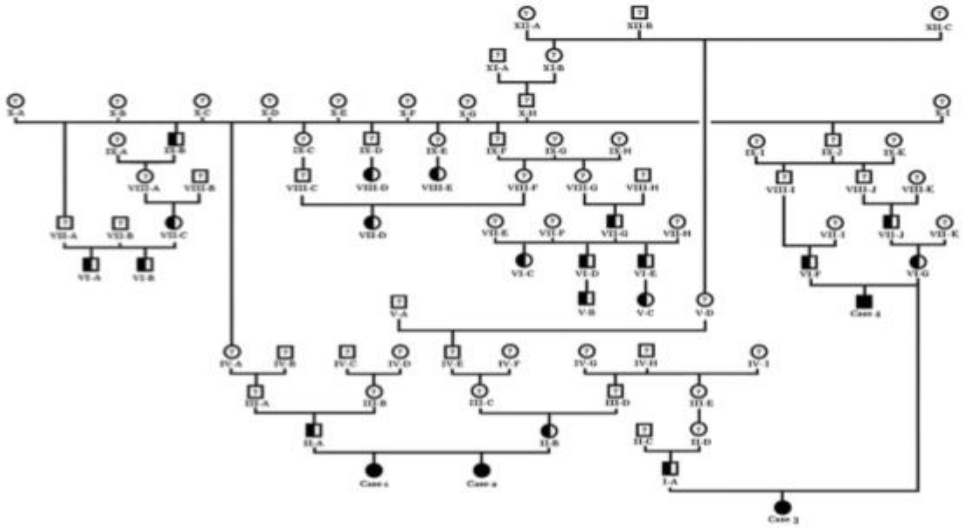

Figure 9. Pedigree of affected animals in Xanthinuria; fully black is affected, and half-black is carrier (Murgiano et al., 2014)

4. Materials and Methods

- General concept

Genotype data were followed several steps to identify missing or deficient homozygous haplotypes likely harboring deleterious mutations that could affect the survival of animals bearing homozygous state. The procedures started from merging the data set, quality control, phasing the haplotypes, and then identifying the deficiency of homozygous haplotype. Providing significant deviation of observed homozygous from expected, a search for the haplotype region on cattle genome database was performed to find candidate genes in those regions.

- Genotyped data

Genotyped data of cattle used in this study were provided by University of Natural Resources and Life Sciences Vienna, and the University of Bern for Austrian and Italian Tyrol Grey, respectively.

Genotyped Animals	Chip Name	Sources
100	Illumina Bovine SNP 50K v.1	Austrian Tyrol Grey Cattle
120	Illumina Bovine SNP HD	Austrian Tyrol Grey Cattle
48	Illumina Bovine SNP 50K v.2	Italian Tyrol Grey Cattle
32	Illumina Bovine SNP HD	Italian Tyrol Grey Cattle

Table 5. Genotyped materials

Table 5 lists the number of genotyped animals, sources, and chip name being used in this research. All Austrian Tyrol cattle were AI bulls, and the data set was also used in a previous study about managing small and endangered population (Mészáros et al., 2015). While we do not have the support of phenotypic data, we assume all genotyped animals were in the state of normal health.

- Quality Control and Phasing

PLINK software was used to merge datasets of 50 K and HD chips, and also for data quality control (Purcell & Chang, 2017). The script for running the program is attached in Appendix1. Markers in 50K SNP chips were used as a reference to update the chromosome and position of HD chip. Afterward, all the genotype data were merged, and parameters were set to allow only individuals and SNPs with missing call rates less than 0.1, with no limitation on minor allele frequency and Hardy-Weinberg equilibrium. 276 cattle and 44035 markers

passed QC and retained in the data set with the total genotyping rate in remaining samples is 0.966. Extracting each chromosome from the data set was needed to run the next step.

Phasing to statistical estimation of haplotypes was done with SHAPEIT2 software with default parameters coming with it. This software uses Gibbs sampling scheme like in other accurate methods of estimation where haplotypes of each are sampled tentatively upon sequence reads of that particular individual and the current estimates of all other individuals (Delaneau et al., 2017). At monomorphic sites, missing genotypes were automatically imputed. During phasing, several markers with overlapping physical position were corrected by adding a single base for troubleshooting, see Appendix2. The output files of SHAPEIT2 are files with the extension of .haps and .sample.

For the next procedure, output files of SHAPEIT2 were converted into three files using unix code. The three files are space-delimited files. It contained phased genotype matrix with a dimension of m x 2n where m is the number of markers and n is the number of individuals (.phase extension). File with two columns of population and ID (.samples extension). And file containing five columns of the chromosome, marker, position, reference allele and alternative allele (.markers extension).

- Identification of homozygous haplotype

In this study, we did not calculate the expected haplotype of animals manually like carried out by the similar previous studies. Instead, we used GHap package (Utsunomiya & Milanesi, 2017) in R which can call haplotypes from phased SNP data then identifying and scoring the different haplotype alleles based on the copy number of 0, 1 or 2 copies. Expected homozygous is calculated following np^2, where n is sample size, and p is the sampling frequency of the haplotype.

The adjusted files from phasing were loaded into the GHap environment using the loadphase function which then converted the input files into a native GHap.phase object. Then, Haplotyping function generated a matrix of HapGenotypes based on the arbitrary window size of 500 kbp and step size sliding every 100 kbp.

The hapstats function created a table consisting of several columns which are the statistical summary of scanning haplotype blocks. The first column (Block) stated a serial number of haplotype blocks. Second to fourth columns stated the position of the haplotype blocks by the chromosome number (Chr), starting (Bp1) and end (Bp2) points. Fifth to seventh columns are allele combination for particular haplotypes (Allele), the number of observation (N) and its frequency (Freq) in the population. Columns eight to ten are the number of observed homozygous (O.Hom), observed heterozygous (O.Het) and expected

homozygous (E.Hom) of haplotypes found in the population. Column (Ratio) is shrinkage ratio for the expected to the observed number of homozygotes. (BIN.LogP) and (POI.LogP) are -log10(P) of deficiency number observed from expected homozygotes following a binomial and Poisson distribution, respectively for lower tail analysis. Column (Type) is the category of the haplotype compared to others in the same block. An additional column (Pless) indicating raw P-value was obtained using the manual script as in Appendix1. The default analysis of GHap is further on called lower tail analysis.

- Identification of excess homozygous haplotype

Interesting phenomena was found during the analysis where some of the haplotype blocks are more frequent in the homozygous state than expected. Thus, we checked how significant the excess deviation of observed to expected homozygous by using the same analysis output of Ghap and adding a new column (P-excess) using a manual script as seen in Appendix1, namely higher tail analysis.

- Plots and Genome-wide association

Manhattan plots were build based on P-value in the column (Pless) for the lower tail and (Pexcess) for higher tail analysis which then plotted in the figure as -log10(P-value) from the deviation of observed haplotype blocks to expected homozygous by the qqman package (Turner, 2014). Expected vs. observed homozygous plots both in lower and higher tail analysis were build using a function in R.

In the lower tail analysis, due to none of the haplotype blocks passing the suggestive default line of qqman -log10(1e-5), we used the threshold of raw P-value<0.01 for further annotation. In the higher tail analysis, haplotype blocks passing genome-wide significant of qqman -log10(5e-8) were annotated. Annotation of haplotype blocks towards gene functions were based on reference genome of *Bos taurus* UMD 3.1.1 on NCBI database website.

5. Results

- Lower tail analysis

There are 93 blocks of haplotypes across 24 bovine Taurus autosomes with Pvalue<0.01 based on the lower tail analysis, lower counts of observed homozygous than the expected homozygous (see Appendix2). Not all of haplotype blocks have genes with specific functions, most of it is in the NCBI database as part of whole genome assembly project of domestic cows, *Bos Taurus*, or part of the generation and initial analysis of cDNA sequences (Zimin et al., 2009; Strausberg et al., 2002). Lower counts of homozygous haplotype block do not appear in autosome 4, 7, 13, 16, and 20. In average, the observed number of homozygous is 5.14 times lower than expected and 54 blocks of haplotypes were found with no homozygous form.

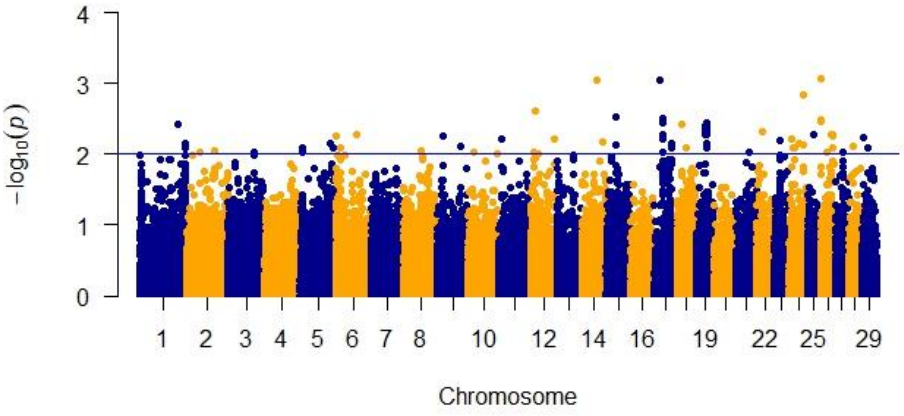

Figure 10. Manhattan plot of haplotype blocks with lower observed than expected homozygous

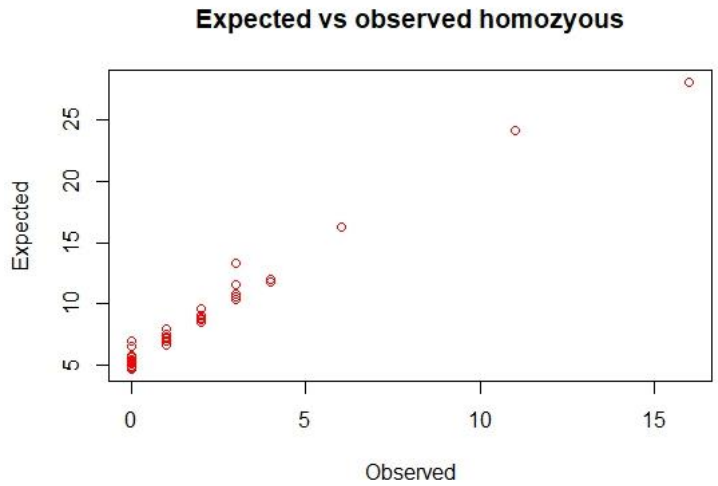

Figure 11. Plot of expected vs. observed homozygous blocks in lower tail analysis

Instead of SNPs like in Genome-wide association study, in this study, we are plotting blocks of haplotypes in the Manhattan graphs. All haplotype blocks generated by the GHap package for lower tail analysis are plotted in figure 10. Haplotype blocks with p-value <0.01 are in the range of $-\log_{10}(P)$ of 2 to 3. Apparently, there are no haplotype blocks passing the suggestive line of Manhattan plot which in default is on $-\log_{10}(P)$ of 5.

The observed to expected lower homozygous seems following a linear pattern, as seen in figure 11. Such those observed haplotypes with no homozygous are those with expectation appearing in homozygous in range of 4 to 7 times. The observed homozygous is increasing as the escalation of the expectation.

In table 6 is listed haplotype blocks of lower observed homozygous with associated genes. *PRKAA2* gene in chromosome 3 of 89.6-90.1 Mb is functioning in the glucose and lipid metabolism (Zhang et al., 2011) with the haplotype of BAABABBBBBBAB and frequency of 13% in our sample. We expect 4.69 homozygous while none was observed. *PRKAA2* encodes the α2 catalytic subunit of AMP-activated protein kinase(AMPK). AMPK acts as a cellular fuel gauge regulating metabolic pathways of protein synthesis and metabolism of glucose and fatty acid. In three Chinese breeds, there were six haplotypes identified based on four SNPs, with the most common haplotype (TGCT) has a frequency of 53.7%.

In chromosome 5 of 99.9-100.4 Mb with 2 observed homozygous haplotype of BBBBBBBABA, while we expect 8.69 homozygous. The frequency of this haplotype is 17.9%. In this region, there is *OLR1* playing a role in the degradation of oxidized low-density lipoprotein(LDL), well-known as bad cholesterol causing damage to the arterial endothelium. Polymorphism in a SNP in the 3' UTR is associated with milk production and health traits in dairy cattle. While in Qinchuan beef cattle, the polymorphism is associated with loin eye and marbling traits. Thus they proposed to use the polymorphism as a marker for the breeding program (Wang et al., 2013). In the same region, *there is CLEC7A* gene, which it's amino acid variants associated with the status of *Mycobacterium avium ss. Paratuberculosis* (MAP) infection. SNP c.589A>G in the exon of this gene encodes bovine Dectin-1, a carbohydrate domain which can recognize and generate a proinflammatory response against mycobacterial ligands working together with Toll-like receptor (TLR) (Pant et al., 2014).

In chromosome 12 of 18.3-18.8 Mb with the haplotype of ABBB, 11 homozygous is observed while we expect 24 homozygous. The frequency of this haplotype is 29.5% corresponding to 163 times observation among the sample. In this region, the *CYSTLR2* gene

is playing a role in stimulation and secretion of PGF2α at the end of cattle cycle (Korzekwa et al., 2016).

In chromosome 15 of 35.5-36 Mb, haplotype BAAABBBABBAAABB is one time observed in homozygous while we expected at least seven homozygous. The frequency of this haplotype is 15.9% with 86 times in the form of heterozygous with other haplotypes. The expression of *KCNJ11* gene is related to meat tenderness in Nelore cattle where the allele-specific of parents origin was assessed using rs379610823 SNP marker as the reference (de Souza et al., 2016). In the same region, there is nucleotide binding nucleobindin2 *(NUCB2)* gene. Research in rats showed NUCB2 protein is expressed in the appetite control mechanisms within hypothalamic nuclei. Polymorphisms in the exon one to eleven of *NUCB2* gene are associated with growth traits in Qingchuan and Nanyang cattle breeds. The linkage of two mutations g.27451G>A and g.27472T>C of this gene had significant effects on body length, body weight, heart girth, and average daily gain (Li et al., 2010).

In chromosome 19 of 33.8-34.3 Mb with haplotype ABABBBBBB, we observed no homozygous while expecting 5.2 in homozygous form. The frequency of this haplotype is 13.7% with 76 times observed in heterozygous form. In this region, there is Adenosine activation of A_{2b} receptor *(ADORA2B)* gene. Adenosine family genes are well-known for its interaction with its cell-surface receptors in respond towards pulmonary inflammation. *ADORA2 gene* stimulates cilia beat frequency (CBF) which is likely mediated by the activation of cAMP-dependent PKA. Regulation of CBF is critical to coordinate mucociliary transport, a host defense mechanism clearing the lung of aspirated microorganism and inhaled debris. Nevertheless, a stressful condition such as inflammation or exercise causes faster CBF, increasing clearance of more inhaled particles (Allen-Gipson et al., 2011).

BLOCK	CHR	BP1	BP2	ALLELE	N	FREQ	O.HOM	O.HET	E.HOM	RATIO	BIN.logP	POI.logP	TYPE	P-Value	Functional Genes
CHR3_B885	3	89600001	90100001	BAABABBBBBBAB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.009135	PRKAA2
CHR5_B986	5	99900001	100400001	ABBAB	99	0.1793	2	95	8.8777	3.2926	2.2022	2.1628	REGULAR	0.006873	OLR1, CLEC7A
CHR12_B169	12	18300001	18800001	ABBB	163	0.2953	11	141	24.0661	2.0888	2.7661	2.6143	MAJOR	0.002431	CYSLTR2
CHR15_B333	15	35500001	36000001	BAAABBBABBAAABB	88	0.1594	1	86	7.0145	4.0072	2.1721	2.1425	MAJOR	0.007203	KCNJ11, NUCB2
CHR19_B326	19	33800001	34300001	AABABBBBBB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.005343	ADORA2B
CHR19_B336	19	34800001	35300001	BBAAAAABBB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.004652	SLC5A10, SREBF1
CHR19_B351	19	36300001	36800001	BABABBABBBB	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	REGULAR	0.007012	CACNA1G
CHR26_B391	26	39700001	40200001	AABABBBAAA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.005343	GRK5

Table 6. Low observed homozygous haplotypes which have functional genes

In chromosome 19 of 34.8-35.3 Mb with the haplotype of BBAAAAABBB is none in homozygous form observed while we expect at least five homozygous. The frequency of this haplotype is 13.95% with all 77 of the observed haplotype in heterozygous form. In this region, *SLC5A10* gene is playing a role in sodium and glucose transport against an electrochemical gradient, this expression of this gene is predominantly found in kidney (Zhao et al., 2005). *SREBF1* gene is associated with fat synthesis of mammary epithelial cells of the dairy cow and its polymorphisms are also affecting beef fatty acid composition in Simmental bulls (Xu et al., 2013; Li et al., 2014).

In chromosome 19 of 36.3-36.8 Mb with haplotype BABABBABBBB, none is observed in homozygous form while we expect at least 4.9 homozygous. *CACNA1G* gene which is abbreviation from calcium voltage-gated channel subunit alpha1 G has widespread effects on cellular levels towards physiological process such as neuronal excitability, muscle excitation-contraction coupling, and secretion (Walsh et al., 2009).

In chromosome 26 of 39.7-40.2 Mb with haplotype AABABBBAAA, no homozygous observed while the expectation is at least 5. In this region, *GRK5* gene which is regulating signaling events in cardiac function and predominantly expressed in the heart and acting in a kinase-independent manner and is responsible for pathological hypertrophic transcription (Hullmann et al., 2014).

- Higher tail analysis

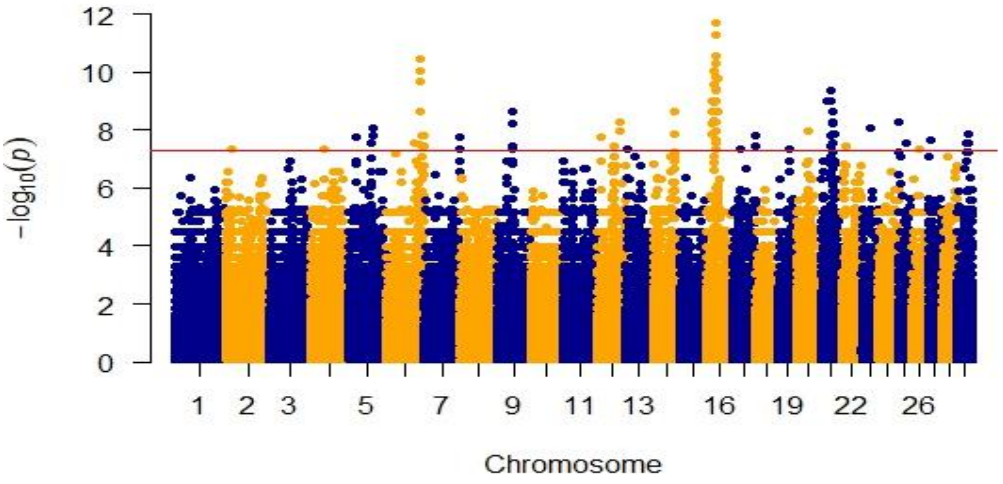

Figure 12. Manhattan plot of haplotype blocks with higher observed than expected homozygous

As seen in figure 12, some haplotype blocks in higher tail analysis pass the threshold of the genome-wide significant line of Manhattan plot which is on $-\log_{10}(5e\text{-}8)$. Thus, we looked into those haplotypes and sought for the genes within. Higher counts of homozygous haplotype block do not appear in autosome 1, 3, 8, 10, 11, 15, 18, 23, 24 and 28. As seen in figure 13, these haplotypes are less expected to exist in the form of homozygous with a mean value of 0.398 while the observed homozygous average is 6.583783784. Such those observed haplotypes are in average 16.5 times higher than expected.

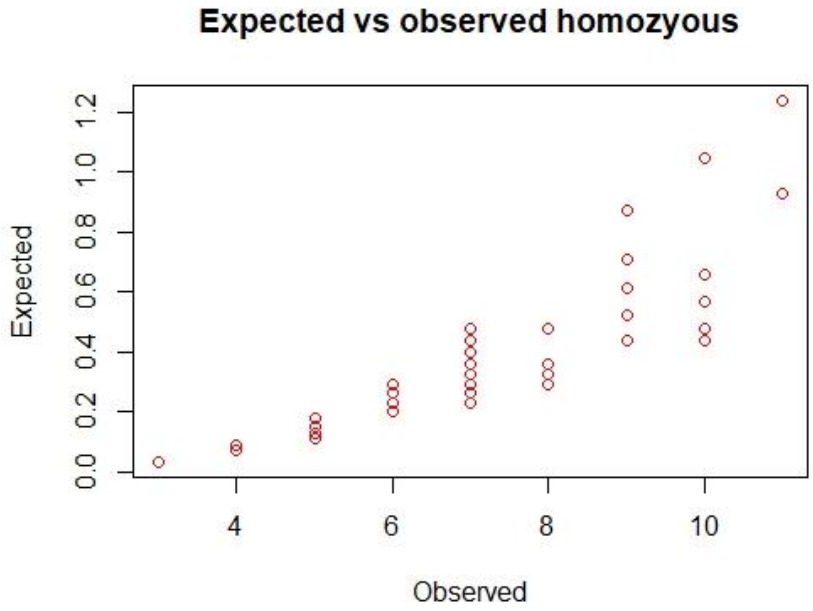

Figure 13. Plot of expected vs. observed homozygous blocks in high tail analysis

CHR	BP1	BP2	ALLELE	FREQ	O.HOM	O.HET	E.HOM	RATIO	Genes
2	19100001	19600001	ABBBABBBABBBB	0.01087	3	0	0.032609	0.258152	NFE2L2
5	23800001	24300001	BAABBBB	0.016304	4	1	0.07337	0.214674	PLXNC1
6	105000001	105500001	BBABBBBAB	0.041667	8	7	0.479167	0.164352	EVC2
6	105800001	106300001	AAABBBBB	0.056159	9	13	0.870471	0.187047	MSX1
12	53400001	53900001	ABBBBBBAAAA	0.025362	5	4	0.177536	0.196256	EDNRB
16	22100001	22600001	AAAABABB	0.03442	8	3	0.326993	0.147444	TGFB2
16	26800001	27300001	AAABBAABAB	0.039855	10	2	0.438406	0.130764	TLR5
17	73600001	74100001	BBBBBBABAB	0.023551	5	3	0.15308	0.19218	MAPK1
21	22200001	22700001	BBABBABBAB	0.032609	7	4	0.293478	0.161685	IQGAP1
21	34000001	34500001	BBAAABBABAAAB	0.032609	7	4	0.293478	0.161685	CYP1A1
21	34700001	35200001	ABBBAABAB	0.032609	7	4	0.293478	0.161685	STRA6
21	40200001	40700001	AAABAABAABB	0.032609	6	6	0.293478	0.184783	PRKD1
23	24300001	24800001	BBBABBB	0.271739	50	50	20.38043	0.419224	IL17A
25	1000001	1500001	BBBAABBAABBAA	0.036232	7	6	0.362319	0.17029	CLCN7,IGFALS
25	1100001	1600001	BAABBAABBAAA	0.036232	7	6	0.362319	0.17029	SLC9A3R2
25	1300001	1800001	AABBAAABAAB	0.036232	7	6	0.362319	0.17029	CASKIN1
26	22200001	22700001	BBBBAABABBBBAB	0.01087	3	0	0.032609	0.258152	FGF8
29	32300001	32800001	ABBBBBABBBB	0.032609	6	6	0.293478	0.184783	ETS1,KCNJ1

Table 7. Merged region of higher observed homozygous with functional genes

In total, there are 185 haplotype blocks across 19 chromosomes having higher counts of observed homozygous than expected, together with all genes within is listed in Appendix4. In table 7 is listed the block of haplotypes of higher observed homozygous with associated genes within. *NFE2L2* gene in chromosome 2 of 19.1-19.6 Mb is associated with survival and development responses of embryos which are cultured under oxidative stress (Amin et al., 2014) with the haplotype of ABBBABBBABBBB, and we observed three homozygous while we expect only 0.03 homozygous.

In chromosome 5 of 23.8-24.3 Mb with the haplotype of BAABBBB, we found four homozygous with 0.07 expectation. In this region, the *PLXCN1* gene is associated with bilateral convergent strabismus together with *RDH13* gene in German Brown cattle (Fink et al., 2012). In chromosome 5 of 75.6-76.1 Mb with the haplotype of BBBABAAAAA, we observed 11 homozygous while expecting only 1.24. In this region, NCF4 gene is a key factor in pathways and innate immune responses in which its splice variants are important risk factors for mastitis susceptibility in dairy cattle (Ju et al., 2015). In the same region, *CSF2RB* is playing an integrative role in the production of erythropoietin, hormone for red blood production, signaling-mediated of endothelial nitric oxide synthase (Su et al., 2011).

In chromosome 6 of 105-105.5 Mb with the haplotype of BBABBBBAB, we observed eight homozygous while expecting only 0.47. *EVC2* gene in this region associated with chondrodysplastic dwarfism in Tyrolean grey cattle caused by two bp deletion in exon 19 of this gene led to a premature stop codon of the sequence (Murgiano et al., 2014).

In chromosome 6 of 105.8-106.3 Mb with the haplotype of AAABBBBB, we observed nine homozygous while expecting only 0.87. *MSX1* gene in this region is functioning in embryo development linked to oocyte maturation and embryo cleavage rate (Tesfaye et al., 2010).

In chromosome 12 of 53.4-53.9 Mb with the haplotype of ABBBBBBAAAA, we observed five homozygous while expecting only 0,17. *EDNRB* expression together with other endothelin-1 system playing a role in the regulation of vascular and cellular functions in the bovine Utero-placental unit during pregnancy (Hayashi et al., 2012).

In chromosome 16 of 22.1-22.6 Mb with the haplotype of AAAABABB, we observed eight homozygous while expecting only 0.32. *TGFB2* gene within this region is operating in fetal ovarian development. Proteins expressed by *TGFB2* is bound with fibrillin3 which is highly expressed at an early critical stage in the fetal development of human and bovine with polycystic ovary syndrome, hormone levels, periods, and ovulation out of balance (Hatzirodos et al., 2011).

In chromosome 16 of 26.8-27.3 Mb with haplotype AAABBAABAB, we observed ten homozygous while expecting only 0.43. *TLR5* gene in this region has a functional association with immune IgA responses after following systemic immunization with H7 flagella in cattle (Tahoun et al., 2015).

In chromosome 17 of 73.6-74.1 Mb with haplotype, BBBBBBABAB is five times observed in homozygous while we expect only 0.15. In this region, *the MAPK1* gene upregulated milk protein synthesis through several pathways (Lu et al., 2012).

In chromosome 21 of 22.2-22.7 Mb, haplotype BBABBABBAB is seven observed in homozygous while expecting only 0.29. *IQGAP1* in this region is associated with sole hemorrhage during hoof trimming when the intronic mutation in SNP rs29017173 of this gene happens (Swalve et al., 2014).

In chromosome 21 of 34-34.5 Mb with BBAAABBABAAAB is seven times observed while we expect only 0.29. *CYP1A1* is inducing in cumulus-oocyte complexes that necessary for in vitro oocyte maturation proceeding in a correct way (Pocar et al., 2004).

In chromosome 21 of 34.7-35.2 Mb with ABBBAABAB is seven times observed while we expect 0.29. *STRA6* is identified as a membrane receptor for retinol binding protein (RBP). RBP is bound by *STRA6* with high affinity and robust vitamin A-uptake activity from the vitamin A-RBP complex (Kawaguchi et al., 2007).

In chromosome 21 of 40.2-40.7 Mb, haplotype AAABAABAABB is six observed in homozygous while expected with 0.29. *PRKD1* is activated by angiotensin II stimulation. Which then regulates the secretion of aldosterone, a steroid hormone found in the kidney, salivary glands, sweat glands, and colon, which is essential for regulation plasma sodium, extracellular potassium, and arterial blood pressure(Olala et al., 2014).

In chromosome 23 of 24.3-24.8 Mb, haplotype BBBABBB is 50 observed homozygous while expecting 20.38. The response of *IL17A* in this region is increasing when cattle infected by a respiratory syncytial virus, together with Mannheimia haemolytyca contributes to bovine respiratory disease complex. In vitro model of BRDC showed a significant increase of IL17A to produce gamma delta T cells (McGill et al., 2016).

In chromosome 25 of 1-1.5 Mb with haplotype BBBAABBAABBAA, we observed seven homozygous while expecting only 0.362. In this region, mutations of *CLCN7*, encoding the chloride-proton (CL^-/H^+) exchanger ClC-7, that caused by several diseases in humans and mice leads to acceleration of CIC-7/Ostm1 gate, important in lysosomal function and bone resorption, which is supposedly work in slow voltage-activation. The speeding up of this CIC-7/Ostm1 is deleterious and lead to osteopetrosis, also known as marble bone disease (Sartelet

et al., 2014). In the same region, polymorphism in *IGFALS*, a gene encoding for serum protein that binds IGFs, can be used as potential biomarker due to its association with growth trait (Liu et al., 2014).

In chromosome 25 of 1.1-1.6 Mb with the haplotype of BAABBAABBAAA, we observed seven homozygous with expecting only 0.362. In this region, *SLC9A3R2*, also known as *NHERF2* gene, is playing an essential role in phosphorylation process of ezrin/radixin/moesin (ERM) binding domains in pulmonary endothelial cells for adhesion/migration and angiogenesis (Boratko & Csortos, 2013).

In chromosome 25 of 1.3-1.8 Mb with the haplotype of AABBAAABAAB, we observed seven homozygous with expecting only 0.362. *CASKIN1* gene shows more functions in in the bovine retina, namely specialized functions in distinct sets of retinal synapses, conceivably for neuronal pathway formation and stabilization of different synaptic contacts (Anjum et al., 2014).

In chromosome 26 of 22.2-22.7 Mb with the haplotype of BBBBAABABBBBAB observed three homozygous while expecting only 0.03. The polymorphism of *FGF8* gene together with *GDF9, BMRP2*, and *LHCGR* are associated with the number of oocytes collected during ovum pickup. Thus, for the sake of the number of the antral follicles in the bovine ovary, the genetic variability is an essential component (Santos-Biase et al., 2012).

In chromosome 29 of 32.3-32.8 Mb with haplotype ABBBBBABBBB, we observed six homozygous when expecting only 0.29. In this region, a transcription factor of *ETS1* is up-regulating the development of retinal neovascularization, the formation of new blood vessels in abnormal tissue or position, by mediating ischemia- and vascular endothelial growth factor (Watanabe et al., 2004). In this region, there is *KCNJ1* gene. In the human case, a substantial reduction in blood pressure, considered as a recessive disease is associated with the mutation of this gene. Observed mutations are always in the form of heterozygous and rare, and can significantly reduce the blood pressure and lower the risk of hypertension development (Ji et al., 2008).

6. Discussion

- Lower tail analysis

Initially, we were expecting to detect the potential recessive disease through missing homozygous patterns as known in various breeds with exact position and gene which underlining the mutation. Also, we expected to find the same regions of recessive disease in accordance to several cases from previous studies in Tyrol Grey Cattle. After running the analysis through different steps, we found that those haplotypes are appearing in the population in heterozygous form but never in homozygous comprise of 93 haplotype blocks across 24 Bovine Taurus autosome with P-value < 0.01. All the haplotype blocks with the deficiency in homozygous form are in the frequency above 10 %, see Appendix3.

The physical regions pointed by these haplotypes bear many genes which the functions have not identified in bovine and listed in NCBI database due to the conserved synteny to human genomes (Zimin et al., 2009). Although those haplotype blocks are not having gene related to known recessive diseases, they have the function related to pathogenic disease, immunology system, and metabolism.

In general, genotyped animals in this study has potential defects due to missing homozygous is related to glucose and lipid metabolism as pointed out by *PRKAA2* gene in chromosome 3. Arterial endothelium damage due to degradation of oxidized low-density lipoprotein and proinflammatory response due to mycobacterial infections as indicated by *OLR1* and *CLEC7A* genes in chromosome 5. Stimulation and secretion of PGF2α pointed out by *CYSTLR2* gene in chromosome 12. Meat tenderness and growth by *KCNJ11* and *NUCB2* genes on chromosome 15. Self-Clearance of the respiratory tract by *ADORA2B* in chromosome 19. Nutrients transport and fat synthesis by *SLC5A10* and *SREBF1* in chromosome 19. The transmembrane protein is forming ion channels as pointed out by *CACNA1G*. And signaling events of cardiac function by *GRK5* in chromosome 26. However, in this study, we uncovered only potential defects due to genetic data and were not able to define which alleles combination in different haplotype are developing the shortcomings. Phenotypic record of the affected animals is necessary in such cases.

A possible reason why we could not detect any of the known recessive diseases in Tyrol Grey Cattle potential in this study is due to a small number of genotyped animals. In previous similar studies done in different breeds in various locations, thousands of animals were included. Thus, more various combinations of haplotypes by different animals were possible. Genotyping of thousands of samples for a small breed like Tyrol Grey Cattle is only possible if genomic data get part of the genetic management system of such breeds (Mészáros et al.,

2015). Nevertheless, the haplotype blocks found in this study can be a reference later, if any case of the new recessive disease appears due to a high frequency of more than 10% in the population.

- Higher tail analysis

An interesting feature of this study was the discovery of regions where the observed homozygous individuals are higher than expected. Possible reasons for this are genetic drift or a selective sweep. Nevertheless, those regions with haplotypes higher observed homozygous are related to some genetic defects such as convergent strabismus pointed out by *PLXCN1* gene in chromosome 5, chondrodysplastic dwarfism indicated by *EVC2* gene in chromosome 6, and osteopetrosis by *CLCN7* gene in chromosome 25. Had it been significant and found for lower tail analysis, then it is likely we would assume that some of those genotyped animals are a carrier for these three recessive diseases.

Looking the underlying reason causing the three recessive diseases, convergent strabismus in German brown cattle, as reported by Fink et al. (2012), is due to the mutations of four SNPs in the coding sequence of *PLXNC1* and one SNP in the *RDH13*, a neighbor gene of *PLXCN1*. Chondrodysplastic dwarfism, as reported by Murgiano et al. (2014) in Tyrol Grey Cattle, causing dwarfism mainly and abnormal nails and teeth development is due to deletion of two bp in exon (c.2993_2994ACdel) leading to a premature stop codon in the coding sequence of *EVC2*. Osteopetrosis, as reported by Sartelet et al. (2014), is characterized by increasing of bone density as an impact of failure to release excess minerals into the bloodstream by osteoclasts. Impairment of osteoclast function is due to mutations in *CLCN7* gene. Thus, these animals cannot be homozygous for that haplotype with mutation due to no defects on the genotyped animals. However, if the selection or genetic drift leads to more wild-type alleles of these three haplotypes in the population, then the recessive disease will never have the chance to appear.

Favorable traits that could be underlying the excess observed homozygous than expected also could be the reason as pointed out by several genes with similar functions found in these haplotypes. *NFEL2* on chromosome 2, *MSX1* on chromosome 6, *EDRNB* on chromosome 12, *TGFB2* on chromosome 16, *CYP1A1* on chromosome 21 and *FGF8* on chromosome 26 are essential in the reproduction system. Starting from the embryo development under stress condition and linked to oocyte numbers and maturation, fetal development, the vascular function of bovine utero-placental, regulation of hormone and ovulation periods, as well as milk protein synthesis by *MAPK1* gene in chromosome 17.

RBP in chromosome 21, *CASKIN1* in chromosome 25, *ETS1* in chromosome 29 are affecting the vision function of cattle. Such by regulating the uptake of vitamin A, setting distinct retinal synapses, and upregulating the retinal neovascularization. While for the immune responses, *TLR5* in chromosome 16 and *IL17A* on chromosome 23 have a function in immune IgA response and producing gamma delta T cells.

CSF2RB in chromosome 5, *PRKD1* in chromosome 21, and *KCNJ1* in chromosome 29 contribute to red blood production, regulation of plasma sodium, extracellular potassium, and arterial blood pressure that might be substantial functions for survival in the high altitude of Alpen.

Whether the excess observed homozygosity is due to artificial selection by human interests since the breeding organization formed a century ago or due to the natural condition of the alpine regions that allow only the fittest animals. Apparently, the excess observed homozygosity for the haplotypes are relevant to genes that have functions in the reproduction system, ocular and vision quality, and blood system to adapt and keep produce under that environment. What keeps hindering us from the assumption of selection sweep and genetic drift causing the excess observed homozygous, is that none of those haplotypes have a frequency above 10% and we have no phenotypic information of genotyped animals, see Appendix3.

7. Conclusions

In this study, conducted with 300 genotyped animals of Tyrol Grey Cattle, we found missing homozygous and excess homozygous of haplotypes. A possible reason that we could not find an association of currently known recessive diseases towards the missing homozygous patterns is the small number of genotyped animals. Due to a high frequency of the haplotypes found in the population, it can be a reference in the future if a new recessive genetic defect will be appearing.

Genes in regions with excess homozygous haplotypes show function patterns related to reproduction system, ocular and vision quality, and blood. However, further study is needed to uncover the reason why there are more observed homozygous on those haplotypes in the higher tail analysis.

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Appendix1. General Script for PLINK, SHAPEIT2, and GHap

###PLINK###

Updating chr n position at once

plink --bfile Bovine_GDG_UniBern.raw --cow --update-map Grauvieh_map.txt 4 2 --update-chr Grauvieh_map.txt 1 2 --make-bed --out UniBern54

Allowing only list of SNPs into the data

plink --bfile UniBern --cow --extract snplist.txt --make-bed --out UniBernReduced

Merging Data

plink --bfile GV50kReduced --cow --merge-list allfiles.txt --make-bed --out Grauvieh

Excluding list of SNPs that fall on 0 chromosome, after managing the list through excel

plink --bfile Grauvieh --cow --exclude ExclSNP.txt --make-bed --out GrauviehCut

Quality Control

Plink –-bfile GrauviehCut –-cow -–geno 0.1 -–mind 0.1 –-nonfounders –-make-bed -–out GrauviehQC

Extracting Chromosome

Plink –-bfile GrauviehQC -–cow -–chr 1 -–make-bed -–out Chr1

###SHAPEIT2###

./shapeit --input-bed Chr1.bed Chr1.bim Chr1.fam -–output-max Chr1.phased.haps Chr1.phased.sample

Unix code to convert output of SHAPEIT2 to fit GHap

tail -n +3 Chr1.phased.sample | cut -d' ' -f1,2 > Chr1.samples

cut -d' ' -f1-5 Chr1.phased.haps > Chr1.markers

cut -d' ' -f1-5 --complement Chr1.phased.haps > Chr1.phase

###GHap in R###

```
library(GHap)

#Loading haplotype object
phase1 <- ghap.loadphase(
            samples.file = "Chr1.samples",
            markers.file = "Chr1.markers",
            phase.file = "Chr1.phase" )

# Generate blocks of 100 kb without overlapping
Chr1.blocks.kb <- ghap.blockgen(phase1,
                    windowsize = 500, slide = 100, unit = "kbp")

# Generate matrix of haplotype genotypes
ghap.haplotyping(phase1, Chr1.blocks.kb, batchsize = 100, ncores = 1, outfile = "Chr1")

# Load haplotype genotypes
haplo1 <- ghap.loadhaplo ("Chr1.hapsamples",
             "Chr1.hapalleles",
            "Chr1.hapgenotypes")

#Haplotype statistics
hapstats1 <- ghap.hapstats(haplo1, ncores = 1)

#Probability of any random draw X being less than x (lower tail analysis-Pless)
inData$Pless<-ppois(q = inData$O.HOM, lambda = inData$E.HOM, lower.tail = TRUE)

#Probability of any random draw X being greater than x (higher tail analysis-Pexcess)
inData$Pexcess<-ppois(q = inData$O.HOM, lambda = inData$E.HOM, lower.tail = FALSE)

#Plotting in manhattan
library(qqman)
#to combine the data to other chr based on row to row using rbind
inData=rbind(hapstats1,….,hapstats29)
manhattan(inData,chr = "CHR",bp = "BP1",p = "Pless/Pexcess",snp = "BLOCK", logp = T,
            suggestiveline = F, col = c("blue4","orange1"))
```

Appendix2. Correction for markers with duplicate sites

1	ARS-USMARC-Parent-DQ404150-rs29012530	0	59409838	A	B	
1	UA-IFASA-2167	0	59409839	A	B	
1	ARS-USMARC-Parent-DQ404151-rs29019282	0	151349514	B	A	
1	Hapmap35832-SCAFFOLD197372_885	0	151349515	B	A	
2	ARS-USMARC-Parent-DQ786757-rs29019900	0	111155237	A	B	
2	Hapmap36382-SCAFFOLD210095_19074	0	111155238	A	B	
3	ARS-USMARC-Parent-DQ435443-rs29010802	0	58040470	B	A	
3	Hapmap52375-rs29010802	0	58040471	B	A	
3	ARS-USMARC-Parent-DQ839235-rs29012691	0	116448759	A	B	
3	Hapmap38870-BTA-01737	0	116448760	A	B	
4	ARS-USMARC-Parent-DQ647186-rs29014143	0	17200594	A	B	
4	Hapmap58054-rs29014143	0	17200595	A	B	
7	ARS-USMARC-Parent-DQ786758-rs29024430	0	18454636	A	B	
7	Hapmap36218-SCAFFOLD41765_2717	0	18454637	A	B	
8	ARS-USMARC-Parent-DQ837644-rs29010468	0	88974063	A	B	
8	UA-IFASA-2827	0	88974064	A	B	
8	ARS-USMARC-Parent-DQ674265-rs29011266	0	106174871	A	B	
8	Hapmap36391-SCAFFOLD165033_11046	0	106174872	A	B	
9	ARS-USMARC-Parent-DQ846689-rs29011985	0	45729853	A	B	
9	UA-IFASA-1922	0	45729854	A	B	
9	ARS-USMARC-Parent-DQ786765-rs29009858	0	98483346	B	A	
9	UA-IFASA-2515	0	98483347	B	A	
11	ARS-USMARC-Parent-DQ837646-rs29012894	0	1703612	A	B	
11	Hapmap57799-rs29012894	0	1703613	A	B	
12	ARS-USMARC-Parent-DQ832700-rs29012872	0	80629629	B	A	
12	Hapmap36566-SCAFFOLD135238_3808	0	80629630	B	A	
13	ARS-USMARC-Parent-EF034081-rs29009668	0	25606469	A	B	
13	Hapmap36096-SCAFFOLD140080_30362	0	25606470	A	B	
14	ARS-USMARC-Parent-DQ846691-rs29019814	0	48380429	A	B	
14	Hapmap35881-SCAFFOLD20653_10639	0	48380430	A	B	
15	ARS-USMARC-Parent-EF042090-no-rs	0	21207529	A	B	
15	Hapmap35077-BES9_Contig405_919	0	21207530	A	B	
15	ARS-USMARC-Parent-DQ866817-no-rs	0	38078775	A	B	
15	Hapmap34596-BES7_Contig444_1293	0	38078776	A	B	
15	ARS-USMARC-Parent-DQ866818-rs29011701	0	79187295	B	A	
15	UA-IFASA-5162	0	79187296	B	A	
18	ARS-USMARC-Parent-EF028073-rs29014953	0	1839733	A	B	
18	Hapmap57363-rs29014953	0	1839734	A	B	

20	ARS-USMARC-Parent-DQ888313-no-rs	0	17837675	A	B	
20	Hapmap34041-BES1_Contig298_838	0	17837676	A	B	
21	ARS-USMARC-Parent-EF026085-rs29021607	0	65198296	B	A	
21	Hapmap35417-SCAFFOLD255533_15525	0	65198297	B	A	
22	ARS-USMARC-Parent-EF034082-rs29013532	0	56526462	B	A	
22	Hapmap55319-rs29013532	0	56526463	B	A	
26	ARS-USMARC-Parent-DQ990834-rs29013727	0	8221270	A	B	
26	Hapmap53362-rs29013727	0	8221271	A	B	
28	ARS-USMARC-Parent-EF026086-rs29013660	0	35331560	A	B	
28	Hapmap36071-SCAFFOLD106623_11509	0	35331561	A	B	
28	ARS-USMARC-Parent-EF042091-rs29014974	0	44261945	B	A	
28	Hapmap36794-SCAFFOLD186736_5402	0	44261946	B	A	
29	ARS-USMARC-Parent-EF034080-rs29024749	0	28647816	B	A	
29	Hapmap36059-SCAFFOLD50303_4748	0	28647817	B	A	

Appendix3. Lower tail analysis results with block of haplotypes of P-value < 0.01

BLOCK	CHR	BP1	BP2	ALLELE	N	FREQ	O.HOM	O.HET	E.HOM	RATIO	BIN.logP	POI.logP	TYPE	P-value
CHR1_B1237	1	125300001	125800001	ABBBB	103	0.1866	2	99	9.6096	3.5365	2.4672	2.4192	MAJOR	0.0038
CHR1_B1500	1	151600001	152100001	ABAABBBAABABA	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR1_B1501	1	151700001	152200001	ABBBAABABABB	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	REGULAR	0.0070
CHR2_B455	2	46000001	46500001	BABBAA	86	0.1558	1	84	6.6993	3.8496	2.0496	2.0230	REGULAR	0.0095
CHR2_B913	2	92000001	92500001	BBBBBBABA	114	0.2065	4	106	11.7717	2.5543	2.1017	2.0502	MAJOR	0.0089
CHR3_B885	3	89600001	90100001	BAABABBBBBBAB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR3_B886	3	89700001	90200001	ABABBBBBBABB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR3_B887	3	89800001	90300001	BBBBBABBBB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR3_B888	3	89900001	90400001	BBBABBBBABBAB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR5_B66	5	6500001	7000001	BBAABBABAB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR5_B67	5	6600001	7100001	BAABBABABABB	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR5_B986	5	99900001	100400001	ABBAB	99	0.1793	2	95	8.8777	3.2926	2.2022	2.1628	REGULAR	0.0069
CHR5_B1124	5	114000001	114500001	BBBBBBBABA	98	0.1775	2	94	8.6993	3.2331	2.1384	2.1010	REGULAR	0.0079
CHR6_B29	6	2900001	3400001	BBBBAABA	90	0.1630	1	88	7.3370	4.1685	2.2982	2.2654	MAJOR	0.0054
CHR6_B147	6	15900001	16400001	BBABBA	98	0.1775	2	94	8.6993	3.2331	2.1384	2.1010	REGULAR	0.0079
CHR6_B669	6	69400001	69900001	ABABABBA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR8_B600	8	60000001	60500001	BABABBAAB	97	0.1757	2	93	8.5226	3.1742	2.0755	2.0401	REGULAR	0.0091
CHR9_B180	9	18600001	19100001	BBAAAA	90	0.1630	1	88	7.3370	4.1685	2.2982	2.2654	REGULAR	0.0054
CHR9_B762	9	77900001	78400001	AAABA	115	0.2083	4	107	11.9792	2.5958	2.1671	2.1128	MAJOR	0.0077
CHR10_B169	10	17400001	17900001	BABBBABAAB	86	0.1558	1	84	6.6993	3.8496	2.0496	2.0230	REGULAR	0.0095
CHR10_B170	10	17500001	18000001	ABBBABAABA	86	0.1558	1	84	6.6993	3.8496	2.0496	2.0230	REGULAR	0.0095
CHR11_B84	11	8300001	8800001	AABBABBABAA	75	0.1359	0	75	5.0951	6.0951	2.2335	2.2128	MAJOR	0.0061
CHR12_B117	12	13100001	13600001	AABABAABA	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR12_B169	12	18300001	18800001	ABBB	163	0.2953	11	141	24.0661	2.0888	2.7661	2.6143	MAJOR	0.0024
CHR12_B170	12	18400001	18900001	ABBBBA	163	0.2953	11	141	24.0661	2.0888	2.7661	2.6143	MAJOR	0.0024
CHR12_B265	12	28000001	28500001	BBAAAAAA	176	0.3188	16	144	28.0580	1.7093	2.1409	2.0056	MAJOR	0.0099
CHR12_B714	12	80500001	81000001	BAABBBBABA	75	0.1359	0	75	5.0951	6.0951	2.2335	2.2128	MAJOR	0.0061
CHR12_B715	12	80600001	81100001	AABBBBABABA	75	0.1359	0	75	5.0951	6.0951	2.2335	2.2128	MAJOR	0.0061
CHR14_B468	14	51600001	52100001	AAABBAA	88	0.1594	0	88	7.0145	8.0145	3.0857	3.0464	REGULAR	0.0009
CHR14_B664	14	71300001	71800001	BBABBBBA	108	0.1957	3	102	10.5652	2.8913	2.2151	2.1669	REGULAR	0.0068
CHR15_B324	15	34600001	35100001	AABBBAAAAB	94	0.1703	1	92	8.0036	4.5018	2.5615	2.5215	MAJOR	0.0030

CHR15_B333	15	35500001	36000001	BAAABBBABBAAABB	88	0.1594	1	86	7.0145	4.0072	2.1721	2.1425	MAJOR	0.0072
CHR17_B200	17	19900001	20400001	ABAB	88	0.1594	0	88	7.0145	8.0145	3.0857	3.0464	REGULAR	0.0009
CHR17_B259	17	26100001	26600001	AAABBAAB	100	0.1812	2	96	9.0580	3.3527	2.2669	2.2256	REGULAR	0.0059
CHR17_B261	17	26300001	26800001	ABBAABAB	86	0.1558	1	84	6.6993	3.8496	2.0496	2.0230	REGULAR	0.0095
CHR17_B263	17	26500001	27000001	ABABAAA	80	0.1449	0	80	5.7971	6.7971	2.5445	2.5176	REGULAR	0.0030
CHR17_B264	17	26600001	27100001	ABAAABB	79	0.1431	0	79	5.6531	6.6531	2.4806	2.4551	REGULAR	0.0035
CHR17_B265	17	26700001	27200001	ABAAABBAA	79	0.1431	0	79	5.6531	6.6531	2.4806	2.4551	REGULAR	0.0035
CHR17_B266	17	26800001	27300001	AAABBAA	79	0.1431	0	79	5.6531	6.6531	2.4806	2.4551	REGULAR	0.0035
CHR17_B267	17	26900001	27400001	AABBAAAA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR17_B268	17	27000001	27500001	BBAAAABB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR17_B553	17	56700001	57200001	BAAABABBBABB	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	MAJOR	0.0070
CHR17_B554	17	56800001	57300001	AABABBBABBAABA	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	MAJOR	0.0080
CHR17_B555	17	56900001	57400001	ABABBBABBAABABA	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	MAJOR	0.0080
CHR18_B150	18	15500001	16000001	BAABBBBA	103	0.1866	2	99	9.6096	3.5365	2.4672	2.4192	REGULAR	0.0038
CHR18_B151	18	15600001	16100001	AABBBBAAB	103	0.1866	2	99	9.6096	3.5365	2.4672	2.4192	REGULAR	0.0038
CHR18_B314	18	32600001	33100001	BBBABA	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR19_B318	19	33000001	33500001	AABBA	78	0.1413	0	78	5.5109	6.5109	2.4176	2.3933	REGULAR	0.0040
CHR19_B319	19	33100001	33600001	ABBABA	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B320	19	33200001	33700001	BABAB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B321	19	33300001	33800001	ABAB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B323	19	33500001	34000001	BABAABAB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	MAJOR	0.0053
CHR19_B326	19	33800001	34300001	AABABBBBBB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR19_B330	19	34200001	34700001	BBAAAAAB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR19_B331	19	34300001	34800001	AAAAABAA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR19_B334	19	34600001	35100001	ABAABBAAAA	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B335	19	34700001	35200001	AABBAAAAAB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B336	19	34800001	35300001	BBAAAAABBB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B337	19	34900001	35400001	AAAABBBBB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B338	19	35000001	35500001	AAABBBBB	77	0.1395	0	77	5.3705	6.3705	2.3554	2.3324	REGULAR	0.0047
CHR19_B339	19	35100001	35600001	ABBBBBAB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR19_B340	19	35200001	35700001	BBBBABBAA	79	0.1431	0	79	5.6531	6.6531	2.4806	2.4551	REGULAR	0.0035
CHR19_B341	19	35300001	35800001	BBABBAAB	79	0.1431	0	79	5.6531	6.6531	2.4806	2.4551	REGULAR	0.0035
CHR19_B342	19	35400001	35900001	ABBAABAB	78	0.1413	0	78	5.5109	6.5109	2.4176	2.3933	REGULAR	0.0040
CHR19_B343	19	35500001	36000001	ABBAABABB	78	0.1413	0	78	5.5109	6.5109	2.4176	2.3933	REGULAR	0.0040

CHR19_B350	19	36200001	36700001	ABABABBAB	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	REGULAR	0.0070
CHR19_B351	19	36300001	36800001	BABABBABBBB	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	REGULAR	0.0070
CHR19_B352	19	36400001	36900001	BABBABBBBBAB	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR21_B453	21	47000001	47500001	ABBAAA	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR22_B201	22	20000001	20500001	BABABBBBAAA	91	0.1649	1	89	7.5009	4.2505	2.3626	2.3281	MAJOR	0.0047
CHR23_B199	23	20200001	20700001	ABBABAB	89	0.1612	1	87	7.1748	4.0874	2.2347	2.2035	REGULAR	0.0063
CHR24_B88	24	8800001	9300001	BBBBB	75	0.1359	0	75	5.0951	6.0951	2.2335	2.2128	REGULAR	0.0061
CHR24_B120	24	12000001	12500001	BAAAABB	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	MAJOR	0.0080
CHR24_B182	24	18200001	18700001	AABBBBB	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR24_B313	24	31300001	31800001	BABABBBAAABAAA	74	0.1341	0	74	4.9601	5.9601	2.1738	2.1542	REGULAR	0.0070
CHR24_B480	24	48100001	48600001	AABBBBAAABAA	85	0.1540	0	85	6.5444	7.5444	2.8764	2.8422	MAJOR	0.0014
CHR24_B481	24	48200001	48700001	BBBBAAABAABAB	88	0.1594	1	86	7.0145	4.0072	2.1721	2.1425	MAJOR	0.0072
CHR25_B210	25	21000001	21500001	BBBBBAB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR26_B15	26	1700001	2200001	BAB	113	0.2047	3	107	11.5661	3.1415	2.5565	2.4950	REGULAR	0.0032
CHR26_B16	26	1800001	2300001	AB	121	0.2192	3	115	13.2618	3.5654	3.1564	3.0685	MINOR	0.0009
CHR26_B28	26	3400001	3900001	AAABAABA	134	0.2428	6	122	16.2645	2.4664	2.5635	2.4728	MAJOR	0.0034
CHR26_B196	26	20200001	20700001	BBBBAAAB	72	0.1304	0	72	4.6957	5.6957	2.0568	2.0393	REGULAR	0.0091
CHR26_B391	26	39700001	40200001	AABABBBAAA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR26_B392	26	39800001	40300001	ABABBBAAAA	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR26_B395	26	40100001	40600001	AAAABAA	73	0.1322	0	73	4.8270	5.8270	2.1149	2.0963	REGULAR	0.0080
CHR26_B396	26	40200001	40700001	AABAAB	90	0.1630	1	88	7.3370	4.1685	2.2982	2.2654	REGULAR	0.0054
CHR26_B397	26	40300001	40800001	ABAABB	76	0.1377	0	76	5.2319	6.2319	2.2940	2.2722	REGULAR	0.0053
CHR27_B243	27	25100001	25600001	BAAABAAAABB	86	0.1558	1	84	6.6993	3.8496	2.0496	2.0230	REGULAR	0.0095
CHR28_B143	28	15900001	16400001	AABABBBBBBABA	107	0.1938	3	101	10.3705	2.8426	2.1499	2.1041	MAJOR	0.0079
CHR29_B48	29	5000001	5500001	BBAB	109	0.1975	3	103	10.7618	2.9404	2.2813	2.2307	REGULAR	0.0059
CHR29_B49	29	5100001	5600001	BBAB	109	0.1975	3	103	10.7618	2.9404	2.2813	2.2307	REGULAR	0.0059
CHR29_B50	29	5200001	5700001	BAB	109	0.1975	3	103	10.7618	2.9404	2.2813	2.2307	REGULAR	0.0059
CHR29_B183	29	18600001	19100001	BABAABB	98	0.1775	2	94	8.6993	3.2331	2.1384	2.1010	REGULAR	0.0079

Appendix4. Higher tail analysis results with block of haplotypes of -$\log_{10}$(5e-8)

BLOCK	CHR	BP1	BP2	ALLELE	N	FREQ	O.HOM	O.HET	E.HOM	RATIO	BIN.logP	POI.logP	TYPE	-logPvalue
CHR2_B184	2	18900001	19400001	BAABBBABBBABB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR2_B185	2	19000001	19500001	ABBBABBBABBB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR2_B186	2	19100001	19600001	ABBBABBBABBBB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR2_B187	2	19200001	19700001	ABBBABBBBAAB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR2_B188	2	19300001	19800001	BABBBBAABA	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR4_B421	4	42100001	42600001	ABBAABBAA	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR5_B238	5	23800001	24300001	BAABBBB	9	0.016	4	1	0.073	0.215	6.99E-09	7.24E-09	REGULAR	7.778
CHR5_B682	5	69500001	70000001	ABAABABAABB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR5_B696	5	70900001	71400001	BBABAAB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR5_B743	5	75600001	76100001	BBBABAAAAA	37	0.067	11	15	1.240	0.187	3.15E-09	3.83E-09	REGULAR	8.054
CHR5_B749	5	76200001	76700001	ABABBBBABBA	34	0.062	10	14	1.047	0.186	5.88E-09	6.94E-09	REGULAR	7.797
CHR5_B750	5	76300001	76800001	ABBBBABBABBB	34	0.062	10	14	1.047	0.186	5.88E-09	6.94E-09	REGULAR	7.797
CHR6_B865	6	89100001	89600001	BBAAAAAAABB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR6_B1024	6	105000001	105500001	BBABBBBAB	23	0.042	8	7	0.479	0.164	9.21E-10	1.04E-09	REGULAR	8.622
CHR6_B1026	6	105200001	105700001	BBABAABBA	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR6_B1027	6	105300001	105800001	ABAABBAB	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR6_B1028	6	105400001	105900001	BAABBAB	20	0.036	8	4	0.362	0.151	8.24E-11	9.30E-11	REGULAR	9.669
CHR6_B1029	6	105500001	106000001	AABBABA	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR6_B1032	6	105800001	106300001	AAABBBBB	31	0.056	9	13	0.870	0.187	1.18E-08	1.36E-08	REGULAR	7.505
CHR6_B1033	6	105900001	106400001	AAABBBBBBBA	18	0.033	8	2	0.293	0.144	1.31E-11	1.48E-11	REGULAR	10.466
CHR6_B1034	6	106000001	106500001	AABBBBBBBA	18	0.033	8	2	0.293	0.144	1.31E-11	1.48E-11	REGULAR	10.466
CHR6_B1079	6	110500001	111000001	BABBBAABAAAAA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1080	6	110600001	111100001	BBAABAAAAAA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1081	6	110700001	111200001	BAABAAAAAABBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1082	6	110800001	111300001	ABAAAAAABBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR6_B1083	6	110900001	111400001	AAAAABBBBAA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1084	6	111000001	111500001	ABBBBAAAAAA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1085	6	111100001	111600001	BBBBAAAAAABB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1086	6	111200001	111700001	BAAAAAABBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1087	6	111300001	111800001	BAAAAAABBBBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1088	6	111400001	111900001	AAAABBBBBA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805

CHR6_B1101	6	112700001	113200001	AAABBBBABABAB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1104	6	113000001	113500001	BABABABBBABB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1107	6	113300001	113800001	ABBAAABBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR6_B1108	6	113400001	113900001	BBAAABBBBAA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR6_B1109	6	113500001	114000001	AAABBBBAABA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1110	6	113600001	114100001	ABBBBAABAAAB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1111	6	113700001	114200001	BBBAABAAABAABB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1112	6	113800001	114300001	BAABAAABAABBBA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1113	6	113900001	114400001	BAAABAABBBAABB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1114	6	114000001	114500001	AABAABBBAABBBBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1118	6	114400001	114900001	BBBABAAABBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR6_B1120	6	114600001	115100001	BAAABBBBBBAA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR6_B1121	6	114700001	115200001	AABBBBBBAABAAB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR7_B1037	7	108500001	109000001	BBBBABBBAAB	9	0.016	4	1	0.073	0.215	6.99E-09	7.24E-09	REGULAR	7.778
CHR7_B1044	7	109200001	109700001	ABABBAABBABABA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR9_B476	9	48400001	48900001	BBBB	11	0.020	5	1	0.110	0.185	9.03E-10	9.52E-10	REGULAR	8.659
CHR9_B477	9	48500001	49000001	BBBBAAAA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR9_B486	9	49400001	49900001	ABABAAABBBAB	11	0.020	5	1	0.110	0.185	9.03E-10	9.52E-10	REGULAR	8.659
CHR9_B487	9	49500001	50000001	BAAABBBABABB	12	0.022	5	2	0.130	0.188	2.52E-09	2.66E-09	REGULAR	8.213
CHR9_B488	9	49600001	50100001	AAABBBABABBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR9_B492	9	50000001	50500001	BBBBBBBA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR9_B493	9	50100001	50600001	BBBBBBABA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR12_B104	12	11800001	12300001	ABAAAABAAAA	9	0.016	4	1	0.073	0.215	6.99E-09	7.24E-09	REGULAR	7.778
CHR12_B508	12	53400001	53900001	ABBBBBBAAAA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B509	12	53500001	54000001	BBBBBAAAABAAB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B510	12	53600001	54100001	BBBBAAAABAABABA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B511	12	53700001	54200001	BAAAABAABABAAAA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B515	12	54100001	54600001	AAABAAAABABBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B516	12	54200001	54700001	BAAAABABBBBA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B518	12	54400001	54900001	ABBBBABAAA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B519	12	54500001	55000001	BBBABAAAB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B520	12	54600001	55100001	BABAAABBBBA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR12_B657	12	69100001	69600001	BABAABBBBBBAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR12_B658	12	69200001	69700001	AABBBBBBABB	21	0.038	7	7	0.399	0.175	4.47E-09	4.90E-09	REGULAR	7.948

CHR13_B44	13	4400001	4900001	AAABBBAB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR13_B45	13	4500001	5000001	AAABBBABAAB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR14_B617	14	66600001	67100001	ABABBABA	15	0.027	6	3	0.204	0.172	9.80E-10	1.05E-09	REGULAR	8.615
CHR14_B618	14	66700001	67200001	ABBABAA	15	0.027	6	3	0.204	0.172	9.80E-10	1.05E-09	REGULAR	8.615
CHR14_B619	14	66800001	67300001	BBABAAB	15	0.027	6	3	0.204	0.172	9.80E-10	1.05E-09	REGULAR	8.615
CHR14_B626	14	67500001	68000001	ABAABBBABBAA	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR16_B140	16	16100001	16600001	BAABBBBA	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR16_B141	16	16200001	16700001	AABBBBABB	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR16_B159	16	18000001	18500001	BBBABA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B175	16	19600001	20100001	AAABABB	19	0.034	7	5	0.327	0.166	9.59E-10	1.05E-09	REGULAR	8.615
CHR16_B176	16	19700001	20200001	AAABABBAB	19	0.034	7	5	0.327	0.166	9.59E-10	1.05E-09	REGULAR	8.615
CHR16_B180	16	20100001	20600001	ABAABAABA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B181	16	20200001	20700001	AABAABABA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B182	16	20300001	20800001	BAABABABA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B183	16	20400001	20900001	AABABABAB	19	0.034	7	5	0.327	0.166	9.59E-10	1.05E-09	REGULAR	8.615
CHR16_B189	16	21000001	21500001	BBAABBABABBAAB	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR16_B190	16	21100001	21600001	ABBABABBAABAB	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR16_B193	16	21400001	21900001	AABABABBBBB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR16_B194	16	21500001	22000001	ABABBBBB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR16_B195	16	21600001	22100001	ABBBBBBAA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B196	16	21700001	22200001	BBBBBBAAAAA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B197	16	21800001	22300001	BBBAAAAAA	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR16_B198	16	21900001	22400001	BAAAAAAB	23	0.042	8	7	0.479	0.164	9.21E-10	1.04E-09	REGULAR	8.622
CHR16_B199	16	22000001	22500001	BAAAAAABA	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR16_B200	16	22100001	22600001	AAAABABB	19	0.034	8	3	0.327	0.147	3.37E-11	3.81E-11	REGULAR	10.057
CHR16_B206	16	22700001	23200001	AAABAABBBBB	26	0.047	9	8	0.612	0.161	4.40E-10	5.09E-10	REGULAR	8.931
CHR16_B207	16	22800001	23300001	AABAABBBBB	26	0.047	9	8	0.612	0.161	4.40E-10	5.09E-10	REGULAR	8.931
CHR16_B208	16	22900001	23400001	AABBBBBA	24	0.043	9	6	0.522	0.152	9.61E-11	1.11E-10	REGULAR	9.591
CHR16_B209	16	23000001	23500001	BBBBBA	28	0.051	9	10	0.710	0.171	1.78E-09	2.05E-09	REGULAR	8.326
CHR16_B210	16	23100001	23600001	BBBA	28	0.051	9	10	0.710	0.171	1.78E-09	2.05E-09	REGULAR	8.326
CHR16_B220	16	26700001	27200001	BAAAABBAAB	27	0.049	10	7	0.660	0.151	5.18E-11	6.19E-11	REGULAR	9.846
CHR16_B221	16	26800001	27300001	AAABBAABAB	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B222	16	26900001	27400001	ABBAABABA	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B223	16	27000001	27500001	BAABABABAAA	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715

CHR16_B224	16	27100001	27600001	ABABABAAAAA	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B225	16	27200001	27700001	ABABAAAAABAAB	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B226	16	27300001	27800001	ABAAAAABAABBB	25	0.045	10	5	0.566	0.142	1.03E-11	1.24E-11	REGULAR	10.544
CHR16_B227	16	27400001	27900001	BAAAAABAABBBAAB	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B228	16	27500001	28000001	AABAABBBAABBA	22	0.040	10	2	0.438	0.131	6.95E-13	8.38E-13	REGULAR	11.715
CHR16_B229	16	27600001	28100001	BAABBBAABBABA	23	0.042	10	3	0.479	0.134	1.78E-12	2.15E-12	REGULAR	11.306
CHR16_B230	16	27700001	28200001	BBAABBABAB	32	0.058	11	10	0.928	0.161	1.27E-10	1.57E-10	REGULAR	9.443
CHR16_B231	16	27800001	28300001	AABBABABB	32	0.058	11	10	0.928	0.161	1.27E-10	1.57E-10	REGULAR	9.443
CHR16_B233	16	28000001	28500001	BABBAABA	23	0.042	8	7	0.479	0.164	9.21E-10	1.04E-09	REGULAR	8.622
CHR16_B247	16	29400001	29900001	BBAAABAB	23	0.042	7	9	0.479	0.185	1.79E-08	1.96E-08	REGULAR	7.346
CHR16_B248	16	29500001	30000001	BBAAABABA	22	0.040	7	8	0.438	0.180	9.09E-09	9.96E-09	REGULAR	7.639
CHR16_B249	16	29600001	30100001	BAAABABAB	21	0.038	7	7	0.399	0.175	4.47E-09	4.90E-09	REGULAR	7.948
CHR16_B251	16	29800001	30300001	BABAABBBB	22	0.040	9	4	0.438	0.144	1.81E-11	2.11E-11	REGULAR	10.314
CHR16_B252	16	29900001	30400001	ABAABBBBABB	19	0.034	7	5	0.327	0.166	9.59E-10	1.05E-09	REGULAR	8.615
CHR16_B253	16	30000001	30500001	BAABBBBABBB	22	0.040	7	8	0.438	0.180	9.09E-09	9.96E-09	REGULAR	7.639
CHR16_B254	16	30100001	30600001	AABBBBABBBAA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B255	16	30200001	30700001	BBABBBAABABA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B256	16	30300001	30800001	ABBBAABABABB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR16_B257	16	30400001	30900001	BAABABABBAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR16_B258	16	30500001	31000001	AABABABBABBB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR16_B259	16	30600001	31100001	BABABBABBBAA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR16_B262	16	30900001	31400001	BBAABBBBABB	17	0.031	7	3	0.262	0.158	1.71E-10	1.88E-10	REGULAR	9.363
CHR16_B298	16	34500001	35000001	ABABBABBAB	15	0.027	6	3	0.204	0.172	9.80E-10	1.05E-09	REGULAR	8.615
CHR16_B299	16	34600001	35100001	BABBABBABAA	16	0.029	7	2	0.232	0.154	6.65E-11	7.33E-11	REGULAR	9.773
CHR17_B271	17	27300001	27800001	BBABBBBBA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR17_B272	17	27400001	27900001	ABBBBBAAA	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR17_B719	17	73300001	73800001	ABABBBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR17_B720	17	73400001	73900001	BABBBBBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR17_B721	17	73500001	74000001	ABBBBBBABA	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR17_B722	17	73600001	74100001	BBBBBBABAB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR19_B376	19	38800001	39300001	AAAABBBBAABB	10	0.018	4	2	0.091	0.218	1.98E-08	2.05E-08	REGULAR	7.327
CHR20_B344	20	34400001	34900001	ABBBABBBAB	21	0.038	7	7	0.399	0.175	4.47E-09	4.90E-09	REGULAR	7.948
CHR21_B205	21	22200001	22700001	BBABBABBAB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B323	21	34000001	34500001	BBAAABBABAAAB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978

CHR21_B326	21	34300001	34800001	BAAABBBAB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B327	21	34400001	34900001	AABBBABBB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B328	21	34500001	35000001	BBABBBAA	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B329	21	34600001	35100001	BABBBAAB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B330	21	34700001	35200001	ABBBAABAB	18	0.033	7	4	0.293	0.162	4.15E-10	4.57E-10	REGULAR	8.978
CHR21_B338	21	35500001	36000001	ABBBBABAB	17	0.031	7	3	0.262	0.158	1.71E-10	1.88E-10	REGULAR	9.363
CHR21_B339	21	35600001	36100001	BBBABABBB	13	0.024	5	3	0.153	0.192	6.46E-09	6.81E-09	REGULAR	7.805
CHR21_B340	21	35700001	36200001	BABABBBBA	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR21_B376	21	39300001	39800001	AABAAABA	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR21_B385	21	40200001	40700001	AAABAABAABB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR21_B386	21	40300001	40800001	BAABAABBB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR21_B387	21	40400001	40900001	BAABAABBBBAA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR21_B398	21	41500001	42000001	AABBBAABA	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B399	21	41600001	42100001	BBBAABABA	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B400	21	41700001	42200001	BAABABA	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B401	21	41800001	42300001	BAABABABA	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B402	21	41900001	42400001	ABABABAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR21_B405	21	42200001	42700001	BABABABAB	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B406	21	42300001	42800001	BABABABAAA	15	0.027	6	3	0.204	0.172	9.80E-10	1.05E-09	REGULAR	8.615
CHR21_B407	21	42400001	42900001	ABABABAAAB	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B408	21	42500001	43000001	ABABAAAB	16	0.029	6	4	0.232	0.176	2.36E-09	2.54E-09	REGULAR	8.234
CHR21_B414	21	43100001	43600001	AAABBAABABABB	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR22_B84	22	8300001	8800001	ABABBBBB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR22_B85	22	8400001	8900001	ABBBBBAB	14	0.025	5	4	0.178	0.196	1.54E-08	1.62E-08	REGULAR	7.428
CHR25_B11	25	1000001	1500001	BBBAABBAABBAA	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B12	25	1100001	1600001	BAABBAABBAAA	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B13	25	1200001	1700001	BBAABBAAAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B14	25	1300001	1800001	AABBAAABAAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B15	25	1400001	1900001	BBAAABAABBBBBB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B16	25	1500001	2000001	ABAABBBBBBB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B17	25	1600001	2100001	BAABBBBBBBBAB	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B18	25	1700001	2200001	AABBBBBBBBABABA	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B19	25	1800001	2300001	BBBBBBBABABABAAAA	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272
CHR25_B20	25	1900001	2400001	BBABABABAAAA	20	0.036	7	6	0.362	0.170	2.11E-09	2.32E-09	REGULAR	8.272

CHR25_B237	25	23700001	24200001	BBBAAABA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR26_B216	26	22200001	22700001	BBBBAABABBBBAB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR26_B217	26	22300001	22800001	BBAABABBBBAB	6	0.011	3	0	0.033	0.258	1.95E-08	1.99E-08	REGULAR	7.338
CHR27_B77	27	8500001	9000001	AABABAAAAB	22	0.040	7	8	0.438	0.180	9.09E-09	9.96E-09	REGULAR	7.639
CHR29_B309	29	31200001	31700001	BABAABBB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B310	29	31300001	31800001	BABAABBBA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B311	29	31400001	31900001	ABAABBBABBA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B315	29	31800001	32300001	BBAABABBABA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B317	29	32000001	32500001	BABBABAABBBB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B318	29	32100001	32600001	BABAABBBBBAB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B319	29	32200001	32700001	BAABBBBBABB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B320	29	32300001	32800001	ABBBBBABBBB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B332	29	33500001	34000001	ABBBAAABAA	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B333	29	33600001	34100001	BBAAABAABABB	18	0.033	6	6	0.293	0.185	1.17E-08	1.25E-08	REGULAR	7.541
CHR29_B334	29	33700001	34200001	AAABAABABBB	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR29_B335	29	33800001	34300001	BAABABBBAAB	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876
CHR29_B336	29	33900001	34400001	BAABABBBAAB	17	0.031	6	5	0.262	0.180	5.38E-09	5.78E-09	REGULAR	7.876