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Taking advantage from phenotype variability in a local animal genetic resource: identification of genomic regions associated with the hairless phenotype in Casertana pigs

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SHORT COMMUNICATION

Taking advantage from phenotype variability in a local animal genetic resource: identification of genomic regions associated with the hairless phenotype in Casertana pigs

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Running title: Hairless in Casertana pigs

34 **Summary**

35 Casertana is an endangered autochthonous pig breed (raised in the Central-South of Italy) that
36 is considered the descendant of the influential Neapolitan pig population that was used to improve
37 British breeds in the 19th century. Casertana pigs are characterized by a typical, almost complete,
38 hairless phenotype. Despite this phenotype is the characteristic trait of this breed, few Casertana pigs
39 are normal-haired. In this work, using Illumina PorcineSNP60 BeadChip data, we carried out a
40 genome wide association study (GWAS) and an F_{ST} analysis in this breed by comparing animals
41 showing the classical hairless phenotype (n. 81) versus pigs classified as haired (n. 15). Combining
42 results obtained with the two approaches, we identified two significant regions, one on porcine
43 chromosome (SSC) 7 and one on SSC15. The SSC7 region contains the *forkhead box N3 (FOXN3)*
44 gene, the most plausible candidate gene of this region, considering that mutations in another gene of
45 the same family (*forkhead box N1; Foxn1* or *FOXN1*) are responsible for the *nude* locus in rodents
46 and alopecia in humans. Another potential candidate gene, *Rho guanine nucleotide exchange factor*
47 *10 (ARHGEF10)* is located on the SSC15 region. *FOXN3* and *ARHGEF10* have been detected as
48 differentially expressed in androgenetic and senescent alopecia, respectively. This study in an
49 autochthonous pig breed contributed to shed some lights on novel genes potentially involved in hair
50 development and growth, demonstrating that local animal breeds can be valuable genetic resources
51 to disclose genetic factors affecting unique traits, taking advantage from phenotype variability
52 segregating in small populations.

53

54 **Key words:** alopecia, animal genetic resource, animal model, baldness, hairless, F_{ST} , GWAS, SNP.

55 **Text**

56 Local animal genetic resources might be characterized by specific and inheritable phenotypes
57 with relevant importance for current or potential future use in breeding programs or for many other
58 purposes, including the definition of new biological models or to understand mechanisms of
59 biological adaptations to different environments (Leroy *et al.* 2016).

60 Casertana is an endangered autochthonous pig breed mainly raised in the Central-South of Italy,
61 accounting for about 100 boars and sows currently registered to its herd book (ANAS 2016).
62 Casertana pigs are usually raised in extensive or semi-extensive systems to produce niche pork
63 products. This local breed is considered the descendant of the influential Neapolitan breed of the late
64 18th and 19th centuries that was used to improve British pig populations from which several modern
65 commercial breeds were derived (Porter 1993). Casertana pigs are characterized by a black or grey
66 coat colour, wrinkled skin, forward ears, two goatlike wattles (not always present) and a typical,
67 almost complete, hairless phenotype not related to the age of the animals. This later characteristic is
68 also reported in one of its local names, i.e. *Pelatella* (that means plucked or bald). Despite the hairless
69 phenotype is the characteristic phenotype of this breed, Casertana population shows some variability
70 for this trait, including animals having from almost complete absence of hairs (hairless; the most
71 common pigs) to few animals having abundant hairs (normal-haired pigs; Figure 1a). The hairless
72 phenotype is also present in other pig breeds like the Creole hairless Mexican breed (also known as
73 Pelón Mexicano) and the black hairless Iberian strains, including the Guadyerbas strain maintained
74 as isolated population (Toro *et al.* 2000; Lemus-Flores *et al.* 2001). Casertana and all these other
75 hairless pigs seem historically connected through exchange of pig genetic material determined by
76 commercial activities in the 18th and 19th centuries (Porter 1993), suggesting a potential common
77 origin of the hairless phenotype.

78 Hairless or hairlessness in pigs can be better described as hypotrichosis or congenital deficiency
79 of hairs, as animals classified as “hairless” usually show a small number rather than a complete
80 absence of hairs. Roberts & Carroll (1931) were the first authors that reported a possible inheritance

81 model for this hypotrichotic condition in Mexican pigs, suggesting the presence of a monogenic
82 autosomal factor with a recessive mutated *h* allele that could give the hairless phenotype when
83 homozygous. Homozygous pigs for the wild type allele *H* might be normal-haired whereas
84 heterozygous *Hh* pigs might show an intermediate phenotype. This early study was not followed by
85 any other genetic investigations on the hairless condition in pigs. More recently, variability in the
86 porcine *hairless* gene (known as *HR*, *lysine demethylase and nuclear receptor corepressor*), located
87 on porcine chromosome (SSC) 14, was evaluated in a candidate gene approach to study the hairless
88 phenotype in Iberian pigs but no association with this trait was reported (Fernández *et al.* 2003, 2006).
89 Mutations in the *HR* gene have been shown to impair hair growth in different mammals (i.e. Stoye *et*
90 *al.* 1988; Ahmad *et al.* 1998; Finocchiaro *et al.* 2003). A high number of other genes in humans and
91 rodents have been implicated in abnormal hair development and hypotrichosis (Shimomura &
92 Christiano 2010; Ramot & Zlotogorski 2015), making impractical a candidate gene approach to
93 successfully identify polymorphisms associated with the hairless phenotype in pig populations.

94 In this work, with the aim to restrict the number of potential causative genes involved in the
95 hypotrichotic phenotype in pigs, we carried out a genome wide association study (GWAS) and a
96 genome wide F_{ST} analysis in the Casertana breed by comparing animals showing the classical hairless
97 phenotype (n. 81, 35 males and 46 females) versus pigs classified as haired (n. 15, 7 males and 8
98 females; a quite rare phenotype in this breed), without any distinction between possible different hair
99 levels that could not be precisely recorded in outdoor animals. Casertana breed offers a unique
100 possibility to investigate this phenotype that is segregating within the same population. This is one of
101 the first population based genome wide study in a local pig breed that is not only useful to characterize
102 a breed specific trait but also to obtain basic biology information that could be important to better
103 define an interesting animal model for alopecia or related phenotypes in humans (Shimomura 2012).

104 Blood or hair roots were collected from all these Casertana pigs raised in six different farms
105 located in the Campania and Molise regions (Central-South of Italy), having from 5 to 49 pigs each,
106 with unknown relationships. A two tailed chi-square analyses with Yates correction confirmed that

107 the occurrence of the observed phenotypes is not associated to the sex in the sampled animals
108 ($P>0.10$). Extracted DNA was used for genotyping with the Illumina PorcineSNP60 BeadChip v.2
109 (Illumina, Inc., San Diego, CA, USA) interrogating 61,565 single nucleotide polymorphisms (SNPs).
110 Genotyping data were processed with PLINK 1.9 software (Chang *et al.* 2015) using the following
111 criteria to filter SNPs: call rate >0.9 , minor allele frequency >0.01 and Hardy-Weinberg equilibrium
112 $P>0.001$. A total of 36,533 autosomal SNPs, assigned to a unique position in the Sscrofa11.1 genome
113 version, were used for multidimensional scaling (MDS) obtained with the PLINK 1.9 software
114 (Chang et al. 2015) to evidence distance relationships among the animals of the investigated cohort.
115 The obtained MDS plot showed some structures not well defined in the analysed pigs that however
116 did not clearly separate the two Casertana groups (i.e. hairless and haired; Figure S1).

117 Genome wide association study was then carried out using the filtered SNPs by applying the
118 univariate mixed model of GEMMA to be able to correct for population relatedness and possible
119 clusterisation (Zhou & Stephens 2012). The centered relatedness matrix calculated from SNP
120 genotypes was included in the model to correct for population stratification. Figure S2 reports the
121 genomic inflation factor (λ) and quantile–quantile (Q–Q) plot, obtained with GenABEL (Aulchenko
122 *et al.* 2007). Figure 1b reports the Manhattan plot produced in this GWAS. Relevant data reported in
123 this work have been submitted to the Zenodo digital repository. At the $P<0.05$ Bonferroni corrected
124 level (P nominal value $< 1.37\text{E-}06$), three SNPs were significant whereas at the $P<0.1$ Bonferroni
125 corrected threshold (P nominal value $= 2.74\text{E-}06$) other three SNPs were suggestively significant
126 (Table 1). Two of these SNPs were located on SSC7 (170.17 kb apart) and four on SSC15, in two
127 distinct regions of approximately 1.14 Mb and 338.61 kb.

128 F_{ST} analysis was performed on the same dataset using PLINK 1.9 software (Chang *et al.* 2015).
129 Missing SNPs were imputed using the Beagle 3.3.2 software (Browning and Browning, 2009). Figure
130 1c reported the Manhattan plot of the F_{ST} analysis. The top 0.9998 SNPs of the percentile distribution
131 ($F_{ST}=0.345$) were considered as the most divergent across the comparison and therefore retained for
132 subsequent evaluation (Table 1). A total of 8 SNPs was above the selected threshold: one on SSC4,

133 one on SSC2, two on SSC7 (170.17 kb apart), two on SSC15 (1.14 Mb apart) and two on SSC17
134 (32.00 kb apart).

135 The comparison among GEMMA and F_{ST} genome-wide analyses identified two overlapping
136 regions encompassing two SNPs on SSC7 and two SNPs on SSC15 that constituted the 1.14 Mb
137 region previously mentioned (Table 1). A total of eight and nine genes were annotated in the SSC7
138 and SSC15 regions, respectively (in a window ± 500 kb from the first and the last SNPs; Table 1).
139 The most plausible candidate gene in the SSC7 region was the *forkhead box N3 (FOXN3)* gene
140 (position: 111036492-111454106 bp), that is 66.56 kb far from INRA0028322 (one of the two most
141 significant SNPs in the GWAS; Table 1). This gene has a role in the regulation of hepatic glucose
142 utilization (Karanth *et al.* 2016), craniofacial development (Samaan *et al.* 2010) and growth and
143 migration of colon cancer cells (Dai *et al.* 2017). The *FOXN3* gene was also found differentially
144 expressed in a case-control study for androgenetic alopecia in humans (Mirmirani & Karnik 2010).
145 Forkhead box proteins constitute a family of transcription factors involved in embryo and fetal
146 development and function of adult organisms (Hannenhalli & Kaestner 2009). This group of proteins
147 list about 50 members in mammals, divided in 19 subfamilies indicated with the letters from A to S
148 (Jackson *et al.* 2010; Benayoun *et al.* 2011). Among the N subfamily, forkhead box N1 (FOXN1)
149 regulates keratin gene expression and the gene (*Foxn1*) is responsible for the *nude* locus in rodents
150 (Flanagan 1966; Meier *et al.* 1999). Mutations in this gene determine hairlessness, alopecia and other
151 pleiotropic effects in mice and rats (Nehls *et al.* 1994) and congenital alopecia, nail dystrophy, and
152 primary T-cell immunodeficiency in humans (Frank *et al.* 1999). Therefore, considering the
153 phylogenetic relationships and the partially conserved domains between the *FOXN1* and *FOXN3*
154 genes (Benayoun *et al.* 2011), it seems plausible that FOXN3 might have conserved similar regulatory
155 functions of FOXN1 that could explain the effect of this SSC7 chromosome region on the hairless
156 phenotype in Casertana pigs. This indication might contribute to understand the involvement of
157 forkhead box proteins in hair development and, if confirmed by functional studies, adds another
158 candidate gene to the list of those potentially involved in alopecia and baldness.

159 No strong candidate gene could be identified in the SSC15 region. A possible candidate could
160 be *Rho Guanine Nucleotide Exchange Factor 10 (ARHGEF10)* gene. ARHGEF10 is involved in
161 neural morphogenesis and connectivity and in the regulation of small RhoGTPases (Verhoeven *et al.*
162 2003). The *ARHGEF10* has been reported to be differentially expressed in a case-control study of
163 senescent alopecia in human (Mirmirani & Karnik 2010), supporting, to some extent, its possible role
164 in the hairless phenotype in the Casertana breed. According to the available functional information,
165 no other gene in the two identified regions might be involved in hair or follicle development or
166 phenotypes similar to the hairless condition we investigated.

167 The combination of the GWAS and F_{ST} results with the annotated gene functions was useful to
168 draft a possible biological explanation of the hairless phenotype in Casertana pigs and to identify
169 significant regions, excluding other regions that reached or were close to the defined thresholds in
170 one or the other genome wide investigation methods derived by several confounding factors that
171 could not be better managed in our study (i.e. genetic drift, population structure, ascertain bias of the
172 SNP chip tool). However, the results obtained in this breed, even if based on a small group of pigs
173 with normal-haired phenotype (that is a quite rare in this breed) in contrast with the hairless group,
174 seems to support the presence of more than one locus affecting this trait. A few of the associated
175 genomic regions contain candidate genes that, based on their function or inferred function may be
176 involved in the hypotricotic condition of the Casertana pigs, with the hypothesis that this trait might
177 be more complex than previously suggested.

178 This study adds another contribution to the genetic characterization of morphological traits in
179 pigs that have been reported to describe breed specific phenotypes (i.e. ear size and coat colours) in
180 other autochthonous populations (i.e. Ren *et al.* 2011; Fontanesi *et al.* 2016). This work demonstrated
181 that endangered animal genetic resources could be investigated to disclose genetic factors affecting
182 unique traits taking advantage from phenotype variability segregating within a small population.
183 Other investigations are needed to refine these results obtained in Casertana and to evaluate if the
184 hairless condition in other pig breeds is derived by the same genetic factors identified in this study.

185

186 **Competing interests**

187 The authors declare that they do not have competing interests. Data reported in this work can be

188 shared after signature of an agreement on their use with University of Bologna.

189

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195 responsible for any use that may be made of the information it contains.

196

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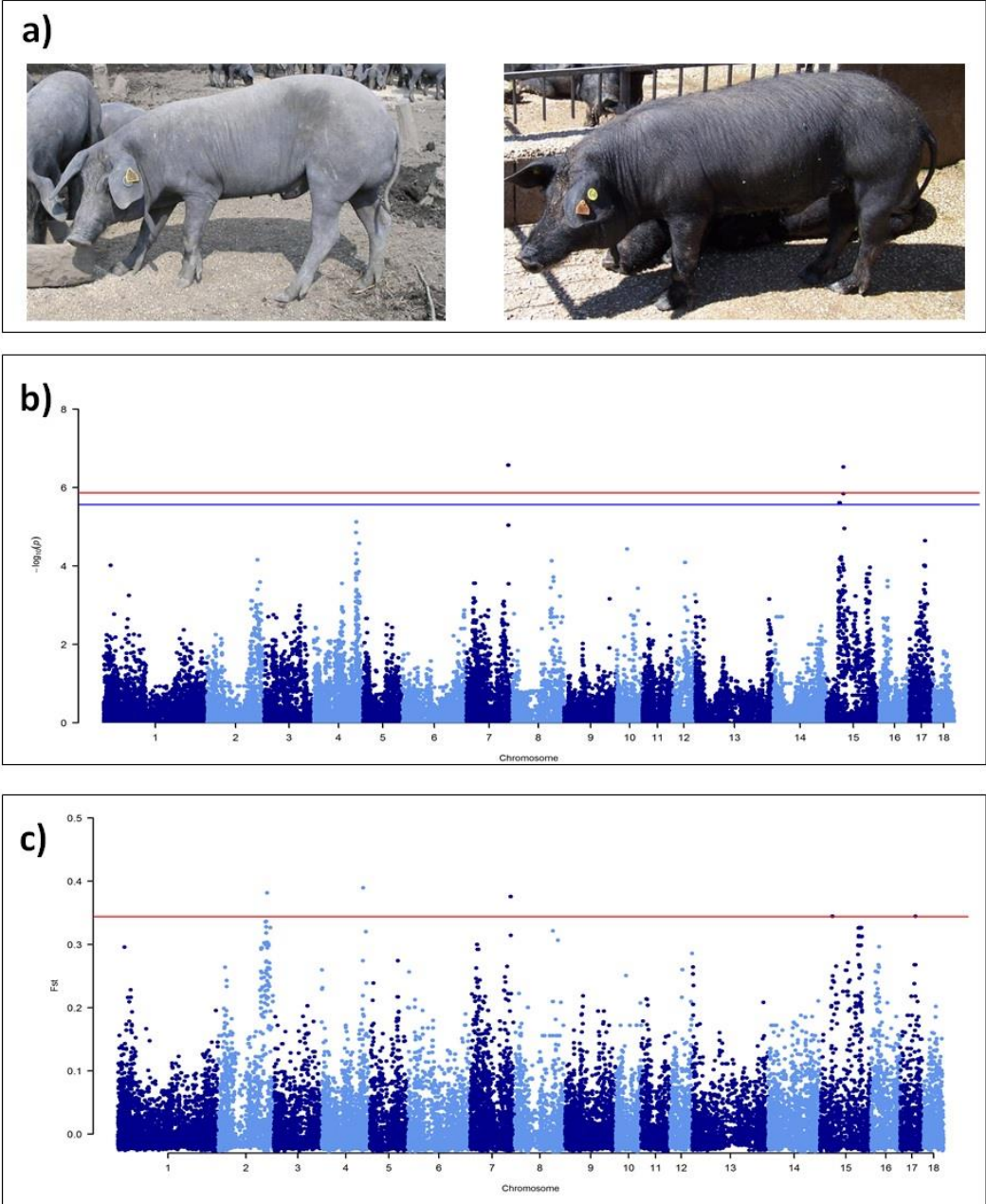
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268 **Figure 1.** Casertana pigs and results of the genome wide association study (GWAS). a) Casertana
269 pigs with the hairless (left) and haired (right) phenotypes. b) Manhattan plot of the GWAS results
270 showing Bonferroni significant (red line: $P<0.05$) and suggestively significant (blue line: $P<0.10$)
271 single nucleotide polymorphisms (SNPs; thresholds are Bonferroni corrected P values). c) F_{ST} plot.
272 Single nucleotide polymorphisms above the red line ($F_{ST}=0.345$) are the top 0.9998 SNPs.
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276 **Table 1.** List of significant ($P<0.05$) and suggestively significant ($0.05<P<0.10$; Bonferroni
 277 corrected) single nucleotide polymorphisms (SNPs) obtained in the genome wide association study
 278 (GWAS) in the Casertana pigs (GEMMA) and the top 0.998 detected in the F_{ST} analysis. For the
 279 overlapping regions among the two approaches, annotated genes nearby the SNPs (± 500 kb from the
 280 first to the last SNP of the region) were reported (Sscrofa11.1 genome version). The candidate genes
 281 that could be involved in the hair phenotype are indicated with the “*” symbol. P , F_{ST} and annotated
 282 genes are reported only for the SNPs and regions for which both P and F_{ST} values trespassed the
 283 indicated thresholds.

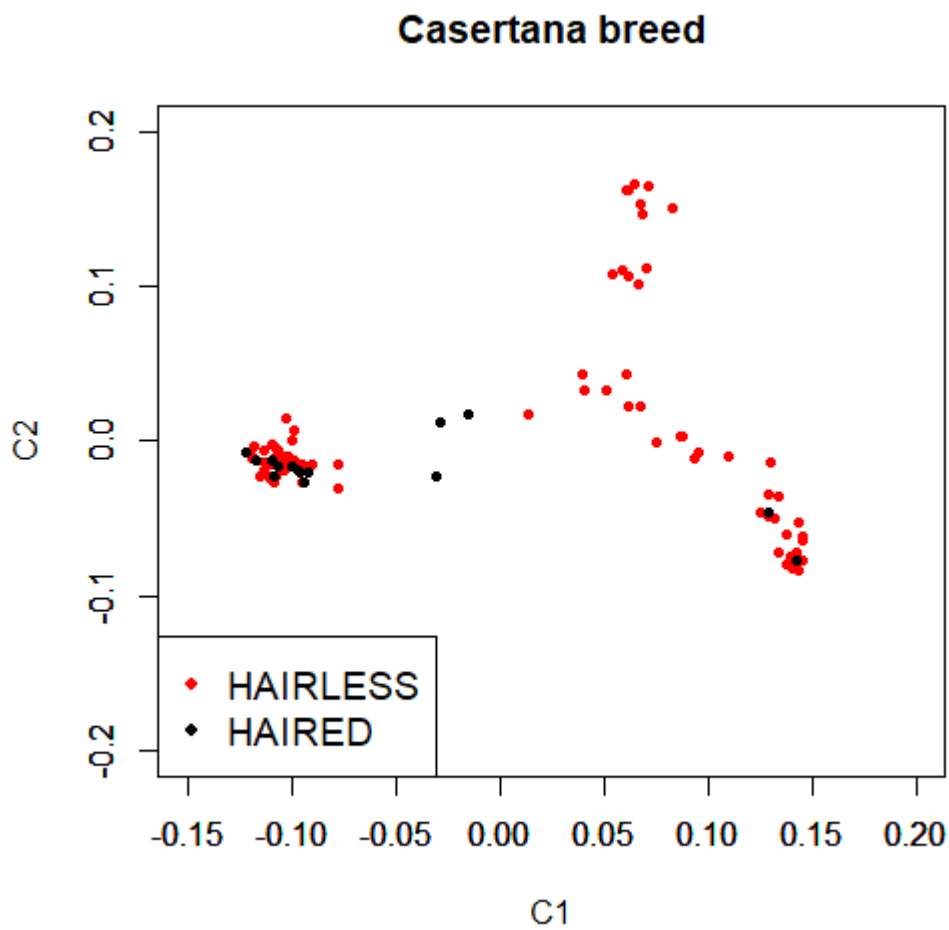
SSC	SNP	position	GWAS, P nominal value	F_{ST} value	Annotated genes
2	ALGA0016212	134598604	-	0.381	-
4	INRA0016870	113277535	-	0.390	-
7	INRA0028322	111520662	2.68E-07	0.376	<i>LOC106504536, PSMC1, EFCAB11, NRDE2, CALM1, TDPI, KCNK13, FOXN3*</i>
7	ALGA0044817	111690832	2.68E-07	0.376	
15	MARC0009352	33679138	2.45E-06	0.345	<i>C110257074, CLN8, KBTBD11, DLGAP2, LOC106509653, ARHGEF10*, LOC106506202, CSMD1, MYOM2</i>
15	ALGA0084906	34793592	2.45E-06	0.345	
15	H3GA0044265	44006149	3.00E-07	-	-
15	INRA0049225	44344760	1.43E-06	-	-
17	DRGA0016747	41675886	-	0.345	-
17	H3GA0049027	41643251	-	0.345	-

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286 **Figure S1.** Multidimensional scaling (MDS) plot of hairless (red spots) and haired (black spots)
287 pigs, on the first and second dimension.

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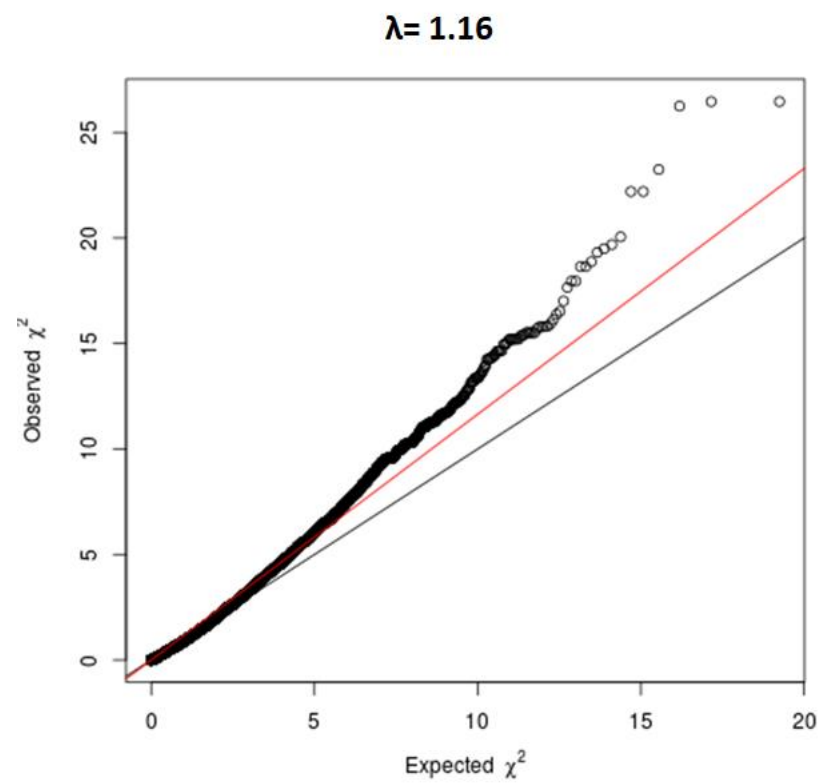


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293 **Figure S2.** Q-Q plot.



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