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RESEARCH ARTICLE

Detection of genomic signatures for pig hairlessness using high-density SNP data

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Abstract Hair provides thermal regulation for mammals and protects the skin from wounds, bites and ultraviolet (UV) radiation, and is important in adaptation to volatile environments. Pigs in nature are divided into hairy and hairless, which provide a good model for deciphering the molecular mechanisms of hairlessness. We conducted a genomic scan for genetically differentiated regions between hairy and hairless pigs using 60K SNP data, with the aim to better understand the genetic basis for the hairless phenotype in pigs. A total of 38405 SNPs in 498 animals from 36 diverse breeds were used to detect genomic signatures for pig hairlessness by estimating between-population (F_{ST}) values. Seven diversifying signatures between Yucatan hairless pig and hairy pigs were identified on pig chromosomes (SSC) 1, 3, 7, 8, 10, 11 and 16, and the biological functions of two notable genes, *RGS17* and *RB1,* were revealed. When Mexican hairless pigs were contrasted with hairypigs, strong signatures were detected on SSC1 and SSC10, which harbor two functionally plausible genes, *REV3L* and *BAMBI*. KEGG pathway analysis showed a subset of overrepresented genes involved in the T cell receptor signaling pathway, MAPK signaling pathway and the tight junction pathways. All of these pathways may be important in local adaptability of hairless pigs. The potential mechanisms underlying the hairless phenotype in pigs are reported for the first time. *RB1* and *BAMBI* are interesting candidate genes for the hairless phenotype in Yucatan hairless and Mexico hairless pigs, respectively. *RGS17*, *REV3L*, *ICOS* and *RASGRP1* as well as other genes involved in the MAPK and T cell receptor signaling pathways may be important in environmental adaption by improved tolerance to UV damage in hairless pigs. These findings improve our understanding of the genetic basis for inherited hairlessness in pigs.

Keywords hairlessness, pig, selective sweeping

1 Introduction

Hair is a filamentous biomaterial grown from follicles in the dermis, and serves as one of the defining characteristics of mammals. It is not merely anesthetic characteristic, but also protects the skin from wounds, bites, heat, cold and ultraviolet (UV) radiation [1]. However, animals such as elephants, rhinoceroses, hippopotamuses, and naked mole rats have developed significant hairlessness during evolution.

For new hairs, existing follicles undergo cycles of growth (anagen), regression (catagen) and rest (telogen). Some molecular regulators of the hair cycle have been identified, but how they work together is not yet understood. Molecules that promote the transition to catagen include the growth factors FGF5 and EGF, neurotrophins such as BDNF and possibly the p75-neurotrophin receptor, p53 and TGFβ-family pathway members [2–6]. Factors including MshHomeobox 2(Msx2) and Serum/Glucocorticoid Regulated Kinase Family, Member 3(SGK3) are known to maintain anagen [7,8]. Signaling by Wnts signaling pathways [9,10] and Sonic Hedgehog(Shh) [11] is indispensable for new anagen, whereas Bone morphogenic proteins (Bmps) [12] has been implicated in follicle differentiation.

Mexico hairless and US Yucatan micro pigs are two kind of hairless pig breeds. However, the molecular mechanism of hairlessness remains elusive. The purpose of this study was to identify, in a genome scan, genomic signatures for hairlessness in the two breeds.

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2 Materials and methods

2.1 Animals

The data of two hairless pig breeds (Yucatan and Mexico hairless pigs) and 37 normal breeds used for this study were publicly available and download from the Dryad data package [13–15]. The detailed information for the tested breeds was shown in Table 1.

2.2 Population stratification

Complete linkage clustering based on pairwise identity-by-state distance of individuals were performed using autosomal genome-wide SNP data and the PLINK software [16]. Neighbor-joining relationship trees between individuals were constructed using Neighbor in the PHYLIP version 3.69 package [17], and visualized by Figtree v1.4.0 (BEAST Software, http://beast.bio.ed.ac.uk/FigTree).

2.3 Determination of genetic differentiation estimates

F_{ST} is an effective approach for detecting selective sweeps [18]. F_{ST} values were calculated for comparative purposes using GENEPOP version 4.0 [19]. The F_{ST} was estimated as follows. The distributions of the F_{ST} density for selection signatures in Mexico hairless pig and Yucatan pigs were shown in Fig. 1. The dotted line is the outlier that is analogous to the top 0.5% of the empirical distribution [20,21]. The data to the right of the dotted line ran to an extreme.

$$F_{ST} = \frac{MSP - MSG}{MSP + (n_c - 1)MSG}$$

where MSG and MSP denote the observed mean square errors for loci within and between populations, respectively, and n_c is the average sample size across samples that also incorporates and corrects for the variance in sample size over the population.

$$MSG = \frac{1}{\sum_{i=1}^{s} n_i - 1} \sum_{i}^{s} n_i p_{Ai}(1 - p_{Ai})$$

$$MSP = \frac{1}{s-1} \sum_{i}^{s} n_i (p_{Ai} - \overline{p}_A)^2$$

$$n_c = \frac{1}{s-1} \sum_{i-1}^{s} n_i - \frac{\sum_i n_i^2}{\sum_i n_i}$$

In the above formulae, s is the population group number, as hairless and normal hair group were used in this study, s is equal to 2, n_i denotes the sample size in the ith population, p_{Ai} is the frequency of SNP allele A in the ith population, and $\overline{P}_A$ is a weighted average of PA across

Table 1 Pig breeds, their origin and sample size in this study

N	Breed	Code	Country	No.
1	Iberian	IB	Spain	16
2	Bisaro	PTBI	Portugal	14
3	Landrance	L	-	40
4	Large White	Y	-	40
5	Duroc	D	-	40
6	MeiShan	MS	China	17
7	XiangPig	XI	China	13
8	JinHua	JH	China	17
9	JiangQuHai	JQ	China	11
10	Hampshire	HA	USA	14
11	Peru Creole pig	PECR	Peru	16
12	Bolivia Creole pig	BOCR	Bolivia	3
13	Ecuador Creole pig	ECCR	Ecuador	4
14	Colombia Creole pig	COCR	Colombia	11
15	Guatemala Creole pig	GUCR	guatemala	14
16	Argentina Creole pig	ARMS	Argentina	9
17	Costa rica Creole pig	CRCR	Costa	12
18	Cuba Creole pig	CUEA	Cuba	5
19	Cuba Creole pig	CUCE	Cuba	1
20	Cuba Creole pig	CUWE	Cuba	12
21	Guadeloupe Creole pig	GPCR	Guadeloupe	4
22	Argentina Creole pig	ARFP	Argentina	6
23	Argentina semi feral	ARFO	Argentina	10
24	Guinea hog	USGH	USA	15
25	Mexico hairless	MXHL	Mexico	9
26	Brazil Monteiro	BRNT	Brazil	10
27	Brazil moura	BRMO	Brazil	9
28	Brazil nilo	BRNI	Brazil	2
29	Ossabaw pig	USOB	USA	7
30	Brazil piau	BRPU	Brazil	9
31	Black sicily	ITSI	Italy	4
32	Wild Boar	WB	Poland	13
33	USA Yucatan	USYU	USA	10
34	Colombia zungo	COZU	Colombia	10
35	Canarian	ESCN	Spain	4
36	British Saddleback	BS	British	20
37	Pietrain	PI	-	20
38	Tamworth	TA	British	20
39	Mexico cuino	MXCU	Mexico	7
				498

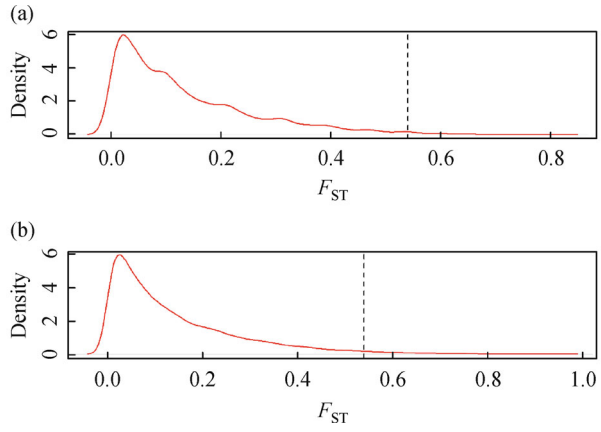

Fig. 1 The distribution of the F_{ST} density for selection signatures in Mexico hairless pig (a) and Yucatan pigs (b). The dotted line is the outlier analogous to the top 0.5% of the empirical distribution. The data on the right of the vertical dotted line ran to an extreme.

populations. Given that the range of F_{ST} is originally defined between 0 and 1, negative F_{ST} values that do not have a biological interpretation were set to 0.

2.4 Gene contents and functional annotation

The gene list (the nearest upstream and downstream genes and the annotated genes of the top 0.5% SNPs) in Table S1 and Table S2 (Appendix A) were submitted to the DAVID bioinformatics resources v6.7 (http://david.abcc.ncifcrf.gov/summary.jsp) for Gene Ontology (GO) terms, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses, to understand the biological meaning of these genes.

3 Results

3.1 Quality control of phenotypes and genotypes

Quality control procedures for the 60K SNP genotype data were carried out using Plink (Version 1.07) (http://pngu.mgh.harvard.edu/purcell/plink/). We first excluded the SNPs that had greater than 10% missing genotypes, or were monomorphic across all the breeds (MAF < 0.01). Then, we tested Hardy–Weinberg equilibrium within each breed using an exact test. At a critical rejection of 8.33×10^{-7} (0.05 per number of SNPs), SNPs that did not confirm to the Hardy–Weinberg equilibrium were further removed. Finally, we discarded SNPs on the sex chromosomes and those ambiguously mapped to the current pig genome assembly [Susscrofa (SSC) Build 10.2]. After quality control, a subset of 38405 SNPs was used for the further analysis.

3.2 Population structure of the tested breeds

Normal hair pig breeds were compared to the two hairless pig breeds to detect genomic loci that are fixed and unique to the hairless breeds. To visualize the relationship of the pig breeds used in the analysis, the initial data set of 498 samples was assessed for a neighbor-joining tree by pairwise identity-by-state distance. The results are plotted in Fig. 2. Duroc, moura, Mexico cuino and Mexico hairless pigs define a separate grouping, while Iberian, European Wild boar, Black sicily,Argentina Creole, Argentina semi, Peru Creole, Bolivia Creole, Ecuador Creole, Guatemala Creole, Cuba Creoleand Yucatan pigs appear as a closely related population cluster.

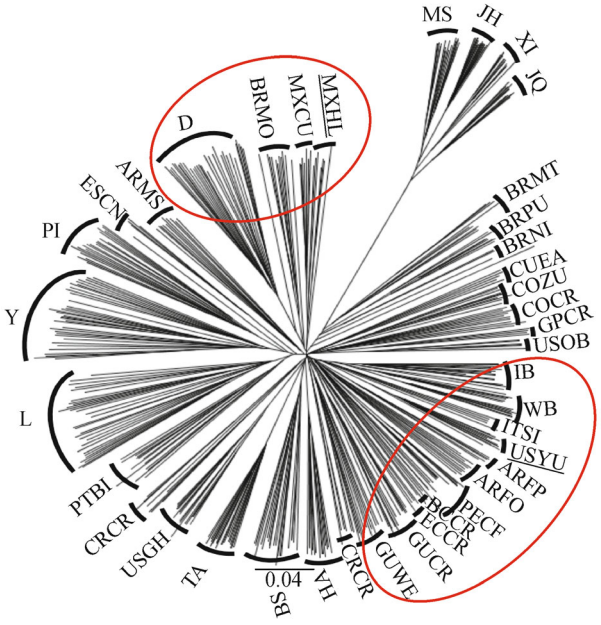

Fig. 2 Neighbor-joining phylogenetic tree of the tested breeds. MXHL and USYU are underlined. Duroc (D), Brazil moura (BRMO), Mexico cuino (MXCU) and Mexico hairless (MXHL) pig define a separate grouping, while Iberian (IB), Wild boar (WB), Black sicily (ITSI), Argentina Creole pig (ARFP), Argentina semi pig (ARFO), Peru Creole pig (PECR), Bolivia Creole pig (BOCR), Ecuador Creole pig (ECCR), Guatemala Creole pig (GUCR), Cuba Creole pig (CUWE) and USA Yucatan (USYU) appear as a closely related population cluster.

3.3 Genomic signatures for hairlessness in Yucatan pigs

We looked across the genome to identity genomic loci for hairlessness in Yucatan pigs. To identify these loci, we calculated an F_{ST} value between this hairless breed and other normal breeds for each of the informative SNPs in the whole data set (SNPs). The F_{ST} analysis was performed on two groups, i.e., the Mexico hairless pig as one group, and the Duroc, moura, Mexico cuino pig breeds as the

other group. The two-group test identified SNP outliers that have highly differentiated allele frequencies in the hairless group relative to the normal pig breeds. These outlier SNPs are strong candidate loci (or to be in linkage disequilibrium with causative variants) for hairlessness.

A total of 185 SNP outliers (Appendix A, Table S1) were identified for hairlessness in Yucatan pigs. Seven diversifying signatures between Yucatan hairless pig and hairy pigs were identified on pig chromosomes (SSC) 1, 3, 7, 8, 10, 11 and 16, The outliers are analogous to the top 0.5% of the empirical distribution and correspond to 179 genes (the nearest upstream and downstream of the SNP). A majority (71.7%) of candidate SNPs fall in the intergenic regions. The F_{ST} value plots are depicted in Fig. 3a. At the top of the list was an SNP located in the gene *ENSSSCG00000017266* (DRGA0011613, F_{ST} = 0.90). The biological role of *ENSSSCG00000017266* in relation to hairlessness has not been established and warrants further investigations. The second strongest F_{ST} SNP (INRA0000803) was located in the *RGS17* gene, a biologically plausible gene (see Discussion). *RB1* is located at 1.4 kb upstream of SNP ASGA0050108, one of the top outlier SNPs (F_{ST} = 0.83). This gene is also functionally related to hairlessness (discussed below).

3.4 Genomic signatures of selection in Mexico hairless pigs

When Mexico hairless pigs were contrasted with normal pig breeds (Duroc, Moura, and Mexico cuino pig), the strongest signals were observed on SSC1 and SSC10 (Fig. 3b). The top results from our analysis include several candidate genes that have biological functions related to hairlessness and/or response to UV. These genes include *REV3L* and *BAMBI*. Table S2 (Appendix A) includes the SNPs in the top 0.5% of the empirical distribution ($F_{ST} > 0.54$).

3.5 GO and KEGG enrichment analysis

Two gene lists including 164 and 179 candidate genes for Mexico hairlessness and US Yucatan were identified from our analysis, respectively (Appendix A, Table S1 and Table S2). These genes were submitted to the DAVID bioinformatics resources v6.7. We sequentially performed a GO and KEGG pathway enrichment analysis on these candidate genes. The GO results and three KEGG pathways were identified (Appendix A, Tables S3 and S4), including T cell receptor signaling pathway, MAPK signaling pathway and the tight junction pathways.

4 Discussion

Naked skin is alleged to have several benefits in high temperature environments. It might allow animals to tolerate higher environmental temperatures and levels of metabolic heat production. However, naked skin also brings challenges, for example strong UV radiation and increased thermal loads are experienced by hairless skin. To our knowledge, this study identified for the first time the potential genetic mechanisms of hairlessness in pigs.

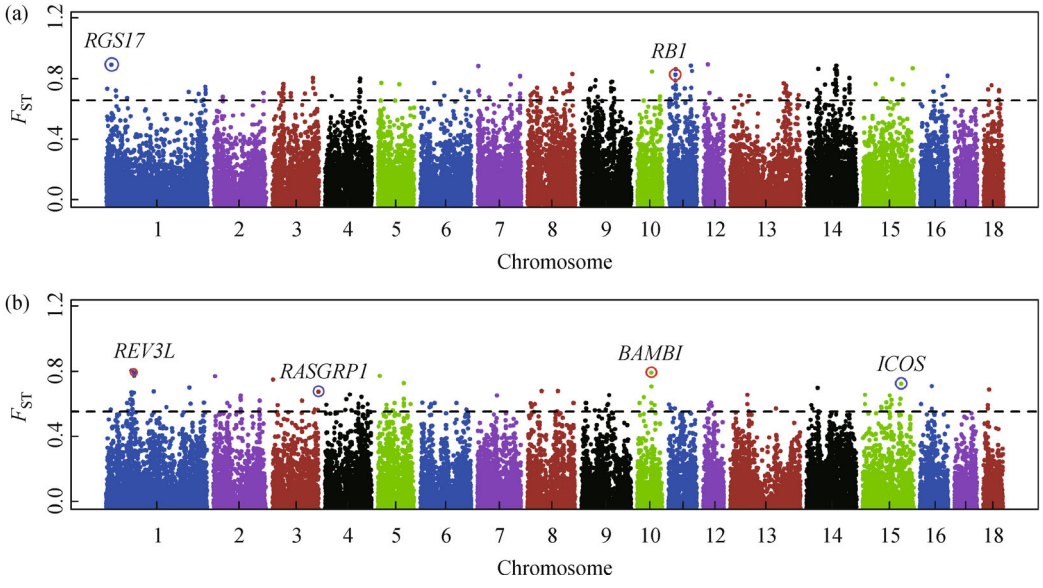

Fig. 3 Genome-wide distribution of F_{ST} values between hairless pigs and norml pigs. (a) Genomic signatures for hairlessness in Yucatan pigs; (b) genomic signatures of selection in Mexico hairless pigs. The chromosomes are plotted along the *x*-axis, and the F_{ST} values are plotted along the *y*-axis, and the 99.5% percentile is denoted with a dashed line. The top candidate gene SNPs for hairlessness are circled in red, while candidate gene SNPs for UV radiation are circled in blue, with the gene names labeled above.

4.1 The potential genetic mechanism of hairlessness in US Yucatan pigs and Mexico hairless pigs

In this study, *RB1* and *BAMBI* were identified to be associated with hairlessness in US Yucatan and Mexico hairless pig, respectively. *RB1* has been shown to be involved in the melanoma pathway, and late-stage melanomas often exhibit epidermal growth factor receptor (EGFR) overexpression [22]. Elevated TGF-α/EGFR activities can lead to a hairless phenotype in mouse [23]. Moreover, melanoma progression is associated with a loss of Wnt/β-catenin signaling [24], and β-catenin knock out mice show hairless skin [10]. Therefore, the *RB1* gene may be related to hairlessness through melanoma and Wnt/β-catenin signaling pathways. *BAMBI* is involved in the TGF-β and β-catenin pathways. Overexpression of *BAMBI* inhibits the response to TGF-β signaling [25]. Stem cell activation in hair follicles is delayed when TGF-β signaling is lost [26]. Additionally, Bmps are implicated in follicle differentiation (discussed above). So *BAMBI* is an interesting candidate gene for hairlessness. It should be noted that we did not observe identical signatures associated with the two hairless pig breeds. This indicates that the molecular mechanisms of hairlessness in the two breeds may not the same.

4.2 Candidate genes for damage tolerance response to UV in hairless pigs

Globally, an estimated 2.5 million non-melanoma skin cancers and 132000 malignant melanomas are diagnosed each year [27], Ultraviolet (UV) radiation is recognized as the main etiological agent causing skin cancer [28], and acts as both a tumor initiator and promoter. As naked skin is vulnerable to the strong UV radiation, cells may have evolved a damage tolerance response to UV induced damage in hairless pigs.

RGS17 (regulator of G-protein signaling 17), a highlighted candidate gene in this study, is a member of the RZ subfamily of the RGS family of proteins, which inhibits G-protein-coupled receptor signaling by binding and activating GTPase activity of G(i/o), G(z) and G(q), but not G(s) [29]. RGS can enhance or inhibit cAMP formation by modulation of either G(i)-coupled or G(s)-coupled signaling [30]. The cAMP pathway is key to the regulation of melanogenesis [31]. Melanogenesis can protect skin from UV radiation damage. Thus, the *RGS17* gene may be involved in protecting the naked skin from UV radiation in hairless pigs.

Another candidate gene, *RB1,* was identified in Yucatan pigs. It is known that E2F transcription factors regulate the expression of genes involved in cell cycle progression, DNA repair, cell proliferation, and apoptosis [32]. There are physical interaction between RB1 protein and E2F transcription factors [33], so the *RB1* gene may not only have a function related to hairlessness but may also function in DNA repair.

Polζ, whose catalytic subunit is encoded by *REV3L*, is important in the bypass of many types of DNA damage, including pyrimidine (6-4) pyrimidone photoproducts induced by UV radiation [34]. Moreover, *REV3L*-deleted mice are extremely sensitive to UV radiation. Thus, the *REV3L* gene may contain beneficial variants for UV induced DNA repair and adaptation to the environment.

At the pathway level, genes in the MAPK signaling pathway likely protect skin from UV radiation damage. ERK1/2, JNKs, and p38 MAPK are the most extensively studied groups of mammalian MAPKs. UV radiation is a major environmental factor that causes DNA damage, inflammation, erythema, sunburn, immunosuppression, photoaging, gene mutations and skin cancer. MAPK are strongly activated by UV radiation and are important in regulation of cellular responses to UV radiation [35]. Thus, overrepresented genes (*RASGRP1, ICOS*) involved in the MAPK pathway function in response to UV radiation, in order for the organism to better adapt to the environment. Another pathway, the T cell receptor signaling pathway, may be related to the immunosuppression caused by UV radiation. In summary, our results illustrate that *RGS17*, *RB1*, *REV3L*, *RASGRP1* and *ICOS* involved in MAPK pathway may contribute to the fact that hairless pigs have a level of adaption to UV radiation.

5 Conclusions

The potential mechanisms underlying the hairless phenotype in pigs are reported for the first time. *RB1* and *BAMBI* are interesting candidate genes for the hairless phenotype in Yucatan hairless and Mexico hairless pigs, respectively. *RGS17*, *REV3L*, *ICOS* and *RASGRP1,* as well as other genes involved in the MAPK and T cell receptor signaling pathways, may be important in environmental adaption through improved tolerance to UV damage in hairless pigs. These findings improve our understanding of the genetic basis for inherited hairlessness in pigs.

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Supplementary materials The online version of this article at http://dx.doi.org/10.15302/J-FASE-2014039 contains supplementary material (Appendix A).

Compliance with ethics guidelines Ying Su, Yi Long, Xinjun Liao, Huashui Ai, Zhiyan Zhang, Bin Yang, Shijun Xiao, Jianhong Tang, Wenshui Xin, Lusheng Huang, Jun Ren and Nengshui Ding declare that they have no conflict of interest or financial conflicts to disclose.

All applicable institutional and national guidelines for the care and use of animals were followed.

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