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Short communication

Genome-based analysis for the identification of candidate genes associated with skin-photosensitization tolerance in sheep

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ABSTRACT

In ruminant livestock, skin photosensitization, caused by the ingestion of toxic plants, is relatively common and affects animal production. In this study, genotyping data from the Illumina OvineSNP50 BeadChip from two Italian local sheep breeds (Leccese and Altamurana) were used to identify putative genomic regions associated with response to skin photosensitization. We identified four genomic regions harbouring several candidate genes related to dermatitis, immune response, and coat color, that could be potentially involved in modulating photosensitization in sheep. These findings enhance our understanding of the genetic mechanisms underlying skin photosensitization in sheep and provide valuable insights into livestock adaptation to local environmental pressure.

Photosensitization in animals refers to an intense dermatitis triggered by an increased sensitivity and reactivity of skin cells and surrounding tissues to sunlight. There are different types of photosensitization, including Type I (primary photosensitization) which occurs following the ingestion or direct contact with UV-reactive secondary compounds found in certain plants (Patel et al., 2022). This condition can lead to significant production and reproductive losses, ultimately causing substantial economic damage for farmers. The sensitivity of grazing herbivorous animals to dermal toxins or photosensitizing compounds is governed by several factors, including species, breed, skin pigmentation, fur or hide thickness, and environmental conditions (Gupta, 2012). In susceptible animals, this reaction is most severe in non-pigmented skin, as it has the least protection against UV or visible light exposure (Quinn et al., 2014).

The Leccese sheep is a local Italian breed raised in Salento (Apulia, South Italy), a traditional breeding site characterised by the presence in the pastures of *Hypericum crispum*, a plant containing hypericin, a compound known to induce photosensitivity in grazing animals upon ingestion. Starting from local populations, the Leccese sheep has been selected and reared to tolerate skin photosensitivity (Registro Regionale Filiere agro-alimentari, https://filiereagroalimentari.regione.puglia.it/agrobiodiversit%C3%A0-registro-regionale accessed on 31 January 2025). The breed is generally white fleeced with black areas in the head, ears, legs, and the ventral region, with tongue and palate being generally totally black (Supplementary Fig. S1). Notably, beyond its high-quality dairy and lamb meat production, the Leccese sheep is also recognized for its exceptional adaptability to marginal pasturelands (D`Alessandro et al., 2013).

A previous study showed that Leccese sheep share ancestral genetic components with the white-coated, sensitive Altamurana breed (Ciani et al., 2014). Because of differences in photosensitization despite a shared genetic background, the two breeds represent an interesting model for studying the genomic regions under selection that might explain such differences (Mastrangelo et al., 2019). This is even more important given that specific candidate genes directly associated with photosensitization in sheep are not yet extensively documented. Some reports indicate that genes with function related to coat color (Baazaoui et al., 2019) or skin cancer (Yahyaoui et al., 2024) could be involved in the mechanism of photosensitization in sheep.

Availability of high-throughput genomic techniques and progress in statistical analyses have allowed the identification of genomic regions shaped by selection that could be associated with phenotypic differences among breeds (Kim et al., 2016; Serranito et al., 2021). In this study, genotyping data and two complementary selection signatures

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approaches (the standardized log-ratio of the integrated site-specific extended haplotype homozygosity (EHH) test between pairs of populations (Rsb) and the integrated haplotype score (iHS)) were used in comparative analyses to identify putative genomic regions related to dermatitis by skin photosensitization in sheep.

Genotype data from the Illumina OvineSNP50 BeadChip for 25 Leccese and 23 Altamurana animals were available from the Ovine HapMap project (http://www.sheephapmap.org) (Kijas et al. 2012). Only single nucleotide polymorphism (SNPs) located on autosomes were considered. The markers were mapped to the ARS-UI_Ramb_v2.0 (*Ovis aries*) genome sequence assembly. We used PLINK ver. 1.9 software (Chang et al., 2015) to perform quality control. We removed markers with a call rate lower than 95 % and minor allele frequency (MAF) lower than 5 %; individuals with more than 10 % of missing genotypes were also discarded.

Two EHH-based metrics were used to detect genomic regions with high level of haplotype homozygosity over an unexpected long distance, either within Leccese (iHS) or between Leccese and Altamurana (Rsb) breeds. The two statistics were computed using the R package rehh (Gautier and Vitalis, 2012). Haplotypes were reconstructed from the SNPs data using fastPHASE v. 1.4 (Scheet and Stephens, 2006). In iHS computation, the information on the ancestral and derived allele state is needed for each SNP because this statistic is based on the ratio of the EHH associated to each allele. In our analysis, the ancestral allele was inferred as the most common allele in the dataset. Selection signature detection was performed in 1-Mb sliding windows with 50-kb overlapping step. A window is classified as putatively under selection when it contains at least 3 markers exceeding the significance threshold of $-\log10$ (p-value) $= 3$ (corresponding to a significance of $P < 0.001$). Annotated genes within the significant genomic regions were obtained from Genome Data Viewer provided by NCBI according to the ARS-UI_Ramb_v2.0 (*Ovis aries*) genome sequence assembly.

After quality control, a total of 46,827 SNPs and all animals were retained and used for further analysis. The iHS approach revealed a total of 29 genomic regions, distributed across 13 *Ovis aries* chromosomes (OAR), putatively under positive selection in the Leccese breed (Fig. 1a; Supplementary Table S1). The results from the Rsb test revealed 25 significant genomic regions distributed across nine chromosomes (Fig. 1b; Supplementary Table S2). Chromosome 1 showed the highest number of regions for both approaches A total of four regions on chromosomes 1 and 10, encompassing 23 protein coding genes, were jointly identified by the two statistics (Table 1). At the genome-wide level, the strongest signal was found on chromosome 10, with 9 highly significant variants (-log(p-value) between 5.15 and 9.21) concentrated within a 706-kb region (OAR10: 39.93–40.63 Mb). In this region, the only protein coding gene is *PCDH9* which included four highly significant SNPs. The *PCDH9* gene has been implicated in processes related to melanocyte biology and melanoma progression in humans, although its precise role in skin remains to be fully elucidated (Cai et al., 2022). Many studies have reported the role of melanocytes that specialize in producing melanin pigments in protecting organisms from ultraviolet radiation (Solano, 2014). In human, the *PCDH9* gene was also associated with moderate-to severe atopic dermatitis with allergic sensitization (Kim et al., 2015). Moreover, *PCDH9* has been identified as gene under selection in sheep (Kim et al., 2016), with an important role in local adaptation. Altogether, these findings make *PCDH9* a strong candidate

Table 1
Genomic regions overlapping between iHs and Rsb approaches in the Leccese sheep breed.

OAR[a]	START	END	Genes
1	113,100,000	115,100,000	*FCRLA, FCRLB, DUSP12, ATF6, OLFML2B, SPATA46, SH2D1B, UHMK1, UAP1, DDR2, HSD17B7, CCDC190, RGS4, RGS5, NUF2*
1	124,750,000	126,900,000	*TIAM1, KRTAP6-1, CLDN8, CLDN17, GRIK1*
10	39,600,000	41,450,000	*PCDH9*
10	44,450,000	47,400,000	*KLHL1, DACH1*

[a] *Ovis aries* chromosome.

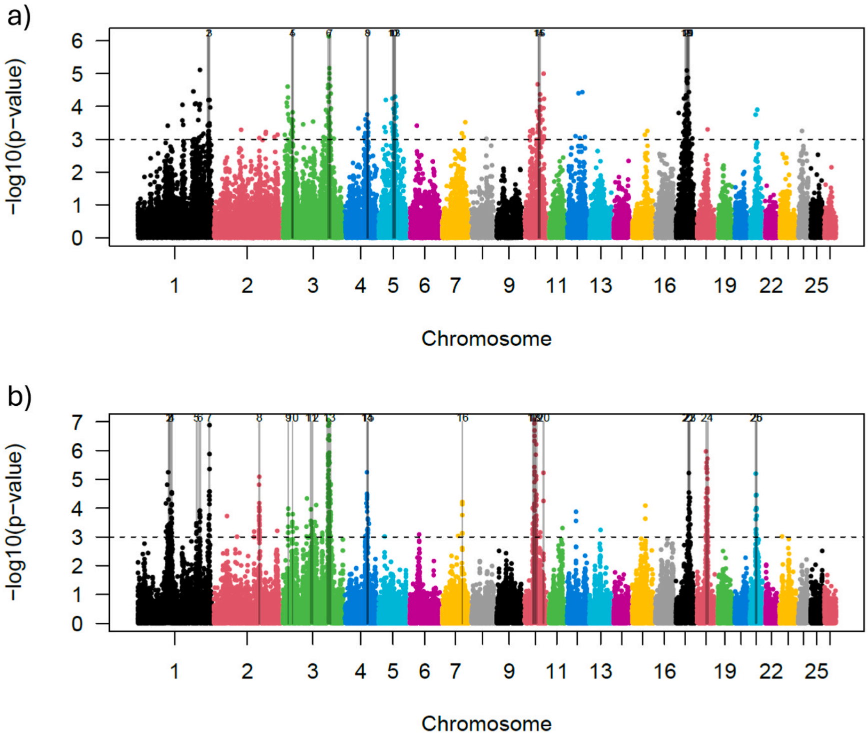

Fig. 1. Manhattan plot of the: a) iHS analysis for Leccese sheep breed; b) Rsb test for Leccese vs Altamurana breeds. Horizontal dashed lines mark the significance threshold applied to detect the outlier SNPs–log10 (p-value) = 3.

gene for skin photosensitivity in sheep.

A further result is that we found three genes (*HSD17B7*, *TIAM1*, and *KRTAP6–1*) within the two candidate regions on chromosome 1, clearly related to keratinocyte function (Adelson et al., 2004; Pfisterer et al., 2023). Keratinocytes constitute the major cell type of the epidermis and play significant roles in both photosensitization and dermatitis. *HSD17B7* is reported as the top-ranked differentially expressed gene in human keratinocytes from individuals of Black African versus Caucasian ancestries (Xu et al., 2021). Two other genes on chromosome 1, related to keratinocytes are *CLDN8* and *CLDN17*. These two genes are members of the claudin family, which are crucial structural and functional components of tight junctions. Tight junctions contribute to the permeability barrier in epidermal keratinocytes (Yuki et al., 2007). The *CLDN17* gene has been also identified in a KEGG enrichment of differentially expressed genes in black and white coat color skin of Mongolian horses (Li et al., 2018), whereas the *CLDN8* has been identified as a barrier gene in atopic dermatitis (Esaki et al., 2015).

We also found that several variants under selective pressure are located within genes involved in common pathogenetic pathways associated with allergic reactions. Among them, the most striking is *DACH1* (OAR10), an inhibitor of Transforming Growth Factor-β pathway signaling, which plays a key role in regulating inflammatory responses, including contact hypersensitivity in mice. Interestingly, *DACH1* has also been identified as a candidate gene for spotted coat color in pigs (Wang et al., 2018) and is associated with fibroblast proliferation (Sun et al., 2024). Likewise, a previous study on local sheep breeds (Baazaoui et al., 2019) revealed selection signatures within the *KIT,* a candidate gene for coat color and with a potential role in skin photosensitization in sheep.

The candidate region on chromosome 1 (113–115 Mb) includes two Fc receptors for immunoglobulins (*FCRLA* and F*CRLB*), which are crucial components of immune regulation (Bovo et al., 2024). Notably, increased Fc receptor expression has been reported in atopic dermatitis (Kiekens et al., 2000), further supporting their involvement in allergic responses (Bournazos et al., 2020).

Taken together, these finding suggest that selection may have favored genetic variants within genes modulating immune response pathways, potentially linking historical selective pressures to adaptations related to hypersensitivity and inflammation in Leccese sheep.

It is important to acknowledge the limitations of this study, including the use of a medium-density SNP array, a limited number of breeds and the lack of anamnestic data. These constraints underscore the need for future research to incorporate higher-density genotyping to refine the identified candidate genomic regions. Additionally, expanding the study to include more detailed phenotypic information and additional breeds would help evaluate the generalizability and potential breed-specificity of the identified selection signals.

In summary, we identified potential selection signals associated with dermatitis caused by skin photosensitization in sheep. The candidate genes uncovered in our analysis may play a key role in the physiological response to photosensitive symptoms triggered by toxic plant exposure. However, further validation through genome-wide association studies (GWAS) incorporating phenotypic data is necessary to confirm the involvement of these genes in photosensitization tolerance and to elucidate their specific roles in shaping adaptive traits in livestock.

CRediT authorship contribution statement

Alberto Cesarani: Writing – review & editing, Formal analysis, Data curation. **Slim Ben Jemaa:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Salvatore Mastrangelo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Elena Ciani:** Writing – review & editing, Visualization, Data curation, Conceptualization.

Ethical statement

No experimental studies were conducted on these animals. Genotyping data included in this study were retrieved from a previous (Kijas et al. 2012). Therefore, no ethical approval was required.

Declaration of Competing Interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2025.106380.

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