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ABSTRACT

Transmission Ratio Distortion (**TRD**) is a genetic phenomenon widely demonstrated in several livestock species, but barely in equine species. The TRD occurs when certain genotypes are over- or under-represented in the offspring of a particular mating and can be caused by a variety of factors during gamete formation or during embryonic development. For this study, 126 394 trios consisting of a stallion, mare, and offspring were genotyped using a panel of 17 neutral microsatellite markers recommended by the International Society for Animal Genetics for paternity tests and individual identification. The number of alleles available for each marker ranges from 13 to 18, been 268 the total number of alleles investigated. The TRDscan v.2.0 software was used with the biallelic procedure to identify regions with distorted segregation ratios. After completing the analysis, a total of 12 alleles (out of 11 microsatellites) were identified with decisive evidence for genotypic TRD; 3 and 9 with additive and heterosis patterns, respectively. In addition, 19 alleles (out of 10 microsatellites) were identified displaying allelic TRD. Among them, 14 and 5 were parent-unspecific and stallion-mare-specific TRD. Out of the TRD regions, 24 genes were identified and annotated, predominantly associated with cholesterol metabolism and homeostasis. These genes are often linked to non-specific symptoms like impaired fertility, stunted growth, and compromised overall health. The results suggest a significant impact on the inheritance of certain genetic traits in horses. Further analysis and validation are needed to better understand the TRD impact before the potential implementation in the horse breeding programme strategies.

Implications

Transmission Ratio Distortion occurs when certain genotypes are over- or under-represented in the next generation. The Pura Raza Española horse is known for the harmony of its forms, highly desired by breeders. This study's objective was to elucidate if genetic and/or allelic Transmission Ratio Distortion patterns are present in genomic regions in this population. Results indicated that those regions exist, and which are related to 24 annotated genes, all of them associated with potential health issues. Therefore, rigorous Transmission Ratio Distortion analysis and validation are crucial to manage breeding programmes and ensure the well-being of the Pura Raza Española horse population.

Introduction

Mendel's first law, also known as the law of segregation, is a fundamental principle in biology. It states that each parent has two alleles for a given trait, and these alleles separate during gamete formation, with each gamete receiving only one allele. As a result, each offspring has an equal chance of inheriting either allele from its parent. Nevertheless, exceptions to this Mendelian principle have been described (Ostberg et al., 2013). This event remains still not completely clear in practically all livestock species, especially in the case of the horse, where it has been barely studied up to now. Biologically speaking, Transmission Ratio Distortion (**TRD**) can arise from various mechanisms that impact germ cells, such as meiotic drive, germline selection, gametic competition (Huang et al., 2013), embryonic lethality (Zöllner et al., 2004), or postnatal survival (Moore, 2006). Various genetic phenomena such as linkage disequilibrium (which can contribute to

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the lack of Mendelian inheritance rules by affecting the expected frequencies of particular genotype combinations in a population), genomic imprinting or inbreeding depression, contribute also to this lack of mendelian inheritance rules, among others. Therefore, the TRD can be regarded as the end result of multiple genetic factors that occur during various phases of the reproductive process and early neonatal development (Fishman and McIntosh, 2019).

The Pura Raza Española (**PRE**) horse is an indigenous Spanish horse breed and one of the oldest in Europe, which has influenced the creation of numerous horse breeds worldwide, including the Lipizzan, Lusitano, and several American strains. (Valera et al., 2005). Since its inception in 1912, the PRE studbook has been entirely closed, permitting only the registration of horses with registered parents. Currently, PRE has more than 260 000 active animals distributed in 65 countries across the five continents, but the management of the breed is overseen by a sole association, the Real Asociación Nacional de Criadores de Caballos de Pura Raza Española (**ANCCE**). In the early 1980s, paternity tests were conducted on PRE horses using various molecular techniques, including blood grouping, serum biochemical polymorphism, and DNA microsatellites. Consequently, this breed boasts a comprehensive pedigree with more than 40 years of established parental information (Perdomo-González et al., 2021). Although the number of molecular studies on Iberian horses has increased in recent decades, populational genomic studies in horses remain scarce compared to other livestock species.

Microsatellite (**STR**) markers are widely used in horses for various applications such as molecular forensics, parentage testing, assessing the genetic structure of populations, analysing phylogenetic relationships, and conducting linkage and association analysis. These markers are composed of tandemly repeated sequence motifs that are distributed throughout eukaryotic genomes. (Goldstein and Schlötterer, 1999). Despite the fact that STRs were traditionally considered neutral markers, there is evidence that they may be playing a much more important role. Thereby, analysis of genomes sequenced to date has revealed that, in many species, tandemly repeated sequence motifs (**STRs**) are often found within coding regions, and that genes with specific biological functions are frequently enriched for variable STRs (Gemayel et al., 2010).

The approach of TRD aims to enhance the reproductive success of livestock through strategic interventions (Casellas et al., 2017). Within this context, studying TRD can lead to finding lethal alleles and the associated genes related to mechanisms and processes affecting reproduction. In this study, the two parameterisation TRD models described by Id-Lahoucine et al. (Id-Lahoucine et al., 2019; 2023) have been implemented in PRE horse genomic data. The allelic model includes sire and dam-TRD and the sire and dam-TRD merged both into one overall TRD (Casellas et al., 2014; 2017). The genotypic model, which includes interaction between alleles, that is, additive and dominance components of TRD (Casellas et al., 2012; 2020).

The primary aim of this study is to identify significant genomic regions of individual STRs that undergo TRD and their corresponding inheritance pattern, as well as to evaluate the inheritance pattern of regions in horses that have known direct or indirect effect on reproduction health.

Material and methods

The Real ANCCE has been carrying out paternity controls since 2005, with a panel of 17 STR markers (Table 1), which has been recommended for paternity tests and individual identification by the International Society for Animal Genetics. Among them, only those with both parents being genotyped were selected. A total of 126 394 genotyped trios (offspring-stallion-mare), from 16 980 males and 56 268 mares, were analysed. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid as an anticoagulant. Genomic DNA extraction was carried out using the salting-out method described by Miller et al. (1988) from the whole blood samples.

Table 1
Chromosome location of the microsatellites analysed in the Pura Raza Española horse population.

STR	Position (Chr:Start-End)	Reference
VHL20	30:19633080-19633103	Van Haeringen et al., 1994
HTG4	9:1575179-1575202	Ellegren et al., 1992
AHT4	24:23322762-23322781	Binns et al., 1995
HMS7	1:164176474-164176819	Guérin et al., 1994
HTG6	15:75225113-75225136	Ellegren et al., 1992
AHT5	8:639503-639522	Binns et al., 1995
HMS6	4:7227180-7227669	Guérin et al., 1994
ASB23	3:81088813-81089169	Lear et al., 1999
ASB2	15:55601476-55601925	Breen et al., 1997
HTG10	21:17758344-1775847	Marklund et al., 1994
HTG7	4:64408146-64408169	Marklund et al., 1994
HMS3	9:17480089-17480528	Marklund et al., 1994
HMS2	10:53843752-53844168	Guérin et al., 1994
ASB17	2:30679403-30679913	Breen et al., 1997
HMS1	15:86105445-86105984	Guérin et al., 1994
CA425	28:41798688-41799069	Eggleston-Stott et al., 1997
LEX33	4:59684351-59684563	Shiue et al., 1999

STR = Microsatellite marker; Chr = Chromosome.

The microsatellite markers were amplified using fluorescent-labelled primers (StockMarks for horses, PE Applied Biosystems, Foster City, CA) with PCR conditions specified by Dimsoski (2003), and the PCR was performed using a Mastercycler ep gradient S thermal cycler (Eppendorf, Germany) with the following conditions: activation of AmpliTaq Gold DNA polymerase at 95 °C for 10 min, followed by 30 cycles of denaturation at 95 °C for 30 s, annealing at 60 °C for 30 s, and extension at 72 °C for 60 s, with a final extension at 72 °C for 60 min. The PCR products were stored frozen until they were analysed by capillary electrophoresis using an Applied Biosystems 3 100 DNA sequencer. Allele sizes were determined by processing the raw data with GeneScan 3.7 and Genotyper 3.7 using a 500 bp LIZ internal size standard (Applied Biosystems).

Statistical analysis

The TRD analyses were performed with the biallelic procedure within a Bayesian framework using TRDscan v.2.0 software (Id-Lahoucine et al., 2019) with a unique Monte Carlo Markov chain of 110 000 iterations where the first 10 000 iterations were discarded as burn-in. The degree of statistical significance of TRD was assessed using a Bayes Factor (**BF**). Both the allele and genotypic parameterisations were analysed to determine the inheritance pattern of each region.

Allelic parameterisation of transmission ratio distortion

As described in previous studies by Casellas et al. (2014 and 2017), the probability of allele transmission (P) from heterozygote parents (A/B) to offspring was parameterised, to include an overall TRD effect (α) in a parent-unspecific model or differentiate between sire-specific (α_s) and dam-specific (α_d) TRD effects in a parent-specific model:

$$P(A) = 1 - P(B) = 0.5 + \alpha \quad \text{and} \quad P(B) = 1 - P(A) = 0.5 - \alpha,$$

$$Pi(A) = 1 - Pi(B) = 0.5 + \alpha_i \quad \text{and} \quad P_i(B) = 1 - P_i(A) = 0.5 - \alpha_i \quad \text{with } i = [s\,U\,d]$$

The TRD parameters α, α_s, and α_d assumed flat priors within a parametric space ranging from −0.5 to 0.5.

Genotypic parameterisation of transmission ratio distortion

Modelling the genotypic parameterisation as described by Casellas et al. (2012), the additive (α_g) and dominance (δ_g) parameters can be assumed, without considering the origin of each allele. According to Casellas et al. (2020), the probability of offspring (P_{off}) from heterozygous-by-heterozygous mating can be given as:

$$P_{off}(AA) = (1 + \alpha_g - \delta_g)/4,$$

$$P_{off}(AB) = (1 + \delta_g)/2 \text{ and}$$

$$P_{off}(BB) = (1 - \alpha_g - \delta_g)/4$$

whereas α_g and δ_g refer to additive and dominance-TRD parameters, respectively. In the case of heterozygous-by-homozygous mating, it is necessary to correct for overall losses of individuals regarding genotypic frequency to ensure that $P_{off}(AA) + P_{off}(AB) + P_{off}(BB)$ equals 1. Therefore, the genotypic frequencies of offspring resulting from AA × AB mating are adjusted as follows:

$$P_{off}(AA) = (1 + \alpha_g - \delta_g)/(2 \times (1 + \alpha_g/2)),$$

$$P_{off}(AB) = (1 + \delta_g)/(2 \times (1 + \alpha_g/2)) \text{ and}$$

$$P_{off}(BB) = 0$$

Flat priors were assumed for both α_g and δ_g.

Female- and male offspring-specific transmission ratio distortion

The transmission of alleles from heterozygous parents can be modelled separately for female (**Fo**) and male (**Mo**) offspring, taking into account the sex of the offspring, to assess TRD. Following Id-Lahoucine et al. (2022), considering female offspring, the probability of transmission of the A allele from heterozygous parents (A/B) can be stated as $P(A) = 1 - P(B) = 0.5 + \alpha_{Fo}$ and $P(B) = 1 - P(A) = 0.5 - \alpha_{Fo}$, where α_{Fo} is the TRD parameter for female offspring ranging between −0.5 and 0.5. As described by Casellas et al. (2017), this model is easily expanded to account for sire – ($\alpha_{s\text{-}Fo}$) and dam-specific TRD ($\alpha_{d\text{-}Fo}$). The same logic applies to male offspring to obtain α_{Mo}, $\alpha_{s\text{-}Mo}$, and $\alpha_{d\text{-}Mo}$ and also to the parameters of genotypic model (i.e., $\alpha_{g\text{-}Fo}$, $\delta_{g\text{-}Fo}$, $\alpha_{g\text{-}Mo}$, and $\delta_{g\text{-}Mo}$).

Gene annotation

Genes located in the regions with significant TRD were annotated. An interval of 500 Kilobase pairs (**Kb**) upstream and downstream of the marker coordinate was used to identify genes in the vicinity of markers showing significant TRD. This interval of 1 Mb has been described as the average block of recombination across the cattle genome (Arias et al., 2009; Weng et al., 2014; Fonseca et al., 2018). The equine Ensembl ID and the corresponding gene name for each positional candidate gene were obtained using the R package biomaRt (Durinck et al., 2009).

Functional analysis

Gene Ontology (**GO**) analysis was performed including the three main GO categories: biological processes (**BPs**), molecular function (**MF**) and cellular component (**CC**) as described by Cánovas et al. (2012) using Equus Caballus database. The GO analysis was performed using AmiGO 2 (Carbon et al., 2009). In addition, canonical metabolic pathways, diseases, and functions enriched using the list of positional candidate genes annotated within the TRD regions were identified. The Database for Annotation, Visualisation and Integrated Discovery (**DAVID**) (Sherman et al., 2022) was also used to perform functional analysis (both GO and metabolic pathways). To identify potential interactions between positional candidate genes, an interaction network analysis was conducted using the protein–protein interaction database STRING (Asselstine et al., 2019; Szklarczyk et al., 2021). Significance was considered with *P*-value < 0.05.

Results

Significant evidence (BF ≥ 10) based on Jeffreys' (1984) scale was found for TRD in STRs in the PRE genome. The TRD regions initially identified with at least one of the models were then filtered following Id-Lahoucine et al., (2019). First, a minimal number of informative parents (≥2 heterozygous sires and/or ≥5 heterozygous dams) were considered to minimise the possible false TRD from genotyping errors. Then, the approximate empirical null distribution of TRD (Id-Lahoucine et al., 2019) at <0.01% margin error was used to eliminate the TRD generated by chance (i.e. gametes sampling).

A total of 19 alleles with distorted segregation ratios were identified after applying the previously given filtering criteria. Of all STRs analysed, 10 of them (HTG4, HTG6, AHT5, HMS6, ASB23, ASB2, HTG7, HMS1, CA425 and LEX33) have shown an allele with the allelic TRD pattern. Table 2 shows the distribution of offspring for each type of mating, the pattern of TRD and the corresponding TRD estimates for the allelic model. Within the allelic pattern, 14 regions have shown overall TRD (α), two regions with sire-TRD (α_s), and three regions with dame-TRD (α_d).

As can be seen in Table 3, any region with dominance-TRD has been identified from STRs in the PRE population, but three additive TRD regions have been identified in 3 STRs (HTG10, ASB17 and CA425). In addition, nine regions showed a heterosis pattern, four of them are offspring-specific TRD (three female offspring and one male offspring). From heterosis pattern regions, despite the dominant effect is more significant than the additive effect, in terms of BF, the additive effect is still important and should not be ignored. Exactly from these 9, four have significant additive effect.

Functional analysis

Gene Ontology analysis

Positional annotation of genes with TRD regions was performed. A total of 13 genes were annotated in an interval of 500 Kb up- and downstream from the STRs position. The genes were characterised into three main GO categories, i.e., BP, CC, and MF and into the respective metabolic pathways using different software and databases. In total, these genes were classified in 8 BP, 2 MF and 3 CC with a *P*-value < 0.05 (Tables 4–6). In turn, GO terms were clustered using PANTHER GO-Slim as shown in Fig. 1. A gene name list is provided in the Supplementary Table S1.

Among them, the main significant biological processes (Table 4) included cholesterol metabolism processes such as cholesterol efflux (GO:0033344), negative regulation of intestinal cholesterol absorption (GO:0045796), lipid homeostasis (GO:0055088), cholesterol homeostasis (GO:0042632) and cellular transport as excretion (GO:0007588) and regulation of mitochondrial translation (GO:0070129). These biological processes involve genes such *ABCG8*, *ABCG5*, *APOB*, *SLIRP*, *LRPPRC*, *ADCK1*, *PNPLA3*, *THADA*, and *ALKBH1*.

Table 2
Distorted regions with allelic Transmission Ratio Distortion pattern detected in the Pura Raza Española horse population.

STR	n_s	n_d	ABxAA[1]		ABxBB		AAxAB		BBxAB		ABxAB			Pat	TRD effect (log_{10}(BF))
			AA[2]	AB	AB	BB	AA	AB	AB	BB	AA	AB	BB		
HTG4	5	12	0	0	0	27	0	0	0	27	0	0	0	O	α = −0.48 (14.51)
HTG6	0	7	0	0	0	0	0	0	0	15	0	0	0	O	α = −0.43 (3.31)
HTG6	1	6	0	0	0	14	0	0	0	9	0	0	0	O	α = −0.45 (5.54)
HTG6	5	29	0	0	0	22	0	0	0	72	0	0	0	O	α = −0.49 (26.30)
AHT5	4	28	0	0	3	33	0	0	21	51	0	0	0	O	α = −0.27 (6.66)
HMS6	2	4	0	0	0	4	0	0	0	11	0	0	0	O	α = −0.43 (3.31)
ASB23	10	13	0	0	84	96	0	0	7	34	0	0	0	D	α_s = −0.03 (−0.86); α_d = −0.31 (3.37)
ASB2	2	3	0	0	3	20	0	0	2	2	0	0	0	S	α_s = −0.34 (2.30); α_d = −0.01 (−0.27)
ASB2	25	82	0	0	82	145	0	0	63	157	5	1	3	O	α = −0.16 (9.88)
HTG7	0	8	0	0	0	0	0	0	0	15	0	0	0	O	α = −0.43 (3.31)
HTG7	197	911	2	0	829	886	2	1	1 133	1 337	19	39	24	D	α_s = −0.02 (−1.13); α_d = −0.04 (2.09)
HTG7	2 137	9 016	8 119	7 840	525	533	7 961	7 606	524	499	1 871	3 616	1 756	O	α = 0.01 (1.47)
HTG7	3	23	0	0	0	7	0	0	0	54	0	0	0	O	α = −0.48 (16.56)
HTG7	8	30	0	0	23	93	0	0	23	63	0	3	0	O	α = −0.26 (12.17)
HMS1	11	48	0	0	37	39	0	0	47	84	0	1	1	D	α_s = −0.02 (−0.83); α_d = −0.14 (1.42)
HMS1	4	11	0	0	0	7	0	0	1	26	0	0	2	O	α = −0.45 (8.27)
CA425	1	8	0	0	0	1	0	0	2	17	0	0	0	O	α = −0.36 (2.42)
CA425	14	54	0	0	30	56	0	0	38	42	0	0	2	S	α_s = −0.16 (1.07); α_d = −0.04 (−0.77)
LEX33	2	2	0	0	0	9	0	0	0	2	0	0	0	O	α = −0.42 (2.23)

Distribution of offspring from all matings and corresponding Transmission Ratio Distortion (TRD) estimates. STR = Microsatellite marker; n_s = Heterozygote sires; n_d =-Heterozygote dams; Pat = Pattern; O = Overall pattern; D = Dam pattern; S = Sire pattern; BF = Bayes Factor; α = Overall TRD; α_s = Sire-TRD; α_d = Dam-TRD.
[1] Sire × dam mating genotypes.
[2] Offspring genotype from the corresponding mating.

Table 3
Distorted regions with genotypic Transmission Ratio Distortion pattern detected in the Pura Raza Española horse population.

STR	n_s	n_d	ABxAA[1]		ABxBB		ABxAB			Pat	TRD effect (log10 BF)
			AA[2]	AB	AB	BB	AA	AB	BB		
HTG10	1 210	5 372	116	109	11 502	11 738	430	992	481	A	α_g = 0.06 (2.80); δ_g = 0.02 (−0.19)
ASB17	376	1 246	21	14	3 830	4 032	36	96	48	A	α_g = 0.09 (1.65); δ_g = 0.02 (−1.41)
CA425	348	1 196	12	13	3 440	3 335	89	144	64	A	α_g = −0.12 (4.36); δ_g = −0.04 (1.56)
HTG4	1 468	5 924	176	171	14 097	14 231	735	1 336	693	H−	α_g = −0.04 (0.58); δ_g = −0.02 (1.79)
HTG6	66	294	0	0	668	693	12	11	9	H−	α_g = −0.33 (7.05); δ_g = −0.18 (13.38)
HMS6	1 310	5 178	97	102	12 570	12 288	495	1 091	540	H+	α_g = 0.03 (−0.01); δ_g = 0.03 (2.24)
ASB23	983	3 614	36	51	9 977	9 560	297	657	291	H+	α_g = 0.03 (−0.90); δ_g = 0.04 (3.93)
ASB17	112	462	0	0	1 335	1 243	5	24	10	H+	α_g = 0.25 (8.73); δ_g = 0.17 (11.09)
VHL20	723	2 698	21	19	4 472	4 753	149	252	142	H− Fo[3]	$\alpha_{g\text{-}Fo}$ = −0.05 (−0.32); $\delta_{g\text{-}Fo}$ = −0.06 (4.94)
HMS3	407	1 229	19	18	2 413	2 509	66	101	69	H− Fo	$\alpha_{g\text{-}Fo}$ = −0.07 (−0.18); $\delta_{g\text{-}Fo}$ = −0.06 (2.17)
HMS2	112	443	1	1	716	760	14	20	7	H− Fo	$\alpha_{g\text{-}Fo}$ = −0.23 (2.92); $\delta_{g\text{-}Fo}$ = −0.14 (6.32)
AHT4	118	408	0	0	702	775	10	10	9	H− Mo	$\alpha_{g\text{-}Mo}$ = −0.28 (4.62); $\delta_{g\text{-}Mo}$ = −0.18 (13.40)

Distribution of offspring from all matings and corresponding Transmission Ratio Distortion (TRD) estimates. STR = Microsatellite marker; n_s = Heterozygous sires; n_d =-Heterozygous dams; Pat = Pattern; A = Additive pattern; H− = Heterosis deficiency; H+ = Heterosis excesses; BF = Bayes Factor; α_g = Additive TRD; δ_g = Dominance-TRD; TRD genotypic parameters for female offspring ($\alpha_{g\text{-}Fo}$ and $\delta_{g\text{-}Fo}$); TRD genotypic parameters for male offspring ($\alpha_{g\text{-}Mo}$ and $\delta_{g\text{-}Mo}$).
[1]Sire × dam mating genotypes.
[2]Offspring genotype from the corresponding mating.
[3]The distribution of offspring only correspond to female (Fo) or male (Mo) offspring.

Table 4
Significant biological process related to microsatellite markers displaying Transmission Ratio Distortion in the Pura Raza Española horse.

GO TERM	Count	List total	%	Genes[1]	*P*-value	Fold Enrichment
GO:0033344 ~ cholesterol efflux	3	78	3.2	*ABCG8, ABCG5, APOB*	0.004	29.8
GO:0000961 ~ negative regulation of mitochondrial RNA catabolic process	2	78	2.1	*SLIRP, LRPPRC*	0.010	198.7
GO:0045796 ~ negative regulation of intestinal cholesterol absorption	2	78	2.1	*ABCG8, ABCG5*	0.010	198.7
GO:0010949 ~ negative regulation of intestinal phytosterol absorption	2	78	2.1	*ABCG8, ABCG5*	0.010	198.7
GO:0055088 ~ lipid homeostasis	3	78	3.2	*ADCK1, PNPLA3, THADA*	0.011	18.6
GO:0007588 ~ excretion	2	78	2.1	*ABCG8, ABCG5*	0.020	99.3
GO:0070129 ~ regulation of mitochondrial translation	2	78	2.1	*ALKBH1, LRPPRC*	0.034	56.7
GO:0042632 ~ cholesterol homeostasis	3	78	3.2	*ABCG8, ABCG5, APOB*	0.041	9.1

Analysis was made using the DAVID database. GO = Gene Ontology.
[1] Gene name list in Supplementary Table S1.

Significant molecular functions (Table 5) were related in most cases with transmembrane transport as oxalate transmembrane transporter activity (GO:0019531) and secondary active sulphate transmembrane transporter activity (GO:0008271). These molecular functions included only two genes, *SLC26A4* and *SLC26A3*.

The significant terms for the cellular components were mainly related to the membrane components and transport as the ATP-binding cassette (**ABC**) transporter complex (GO:0043190), nuclear speck (GO:0016607), apical plasma (GO:0016324) and integral components of the plasma membrane (GO:0005887). The genes

Table 5
Significant molecular functions related to microsatellite markers displaying Transmission Ratio Distortion in the Pura Raza Española horse.

GO TERM	Count	List total	%	Genes[1]	*P*-value	Fold Enrichment
GO:0019531 ~ oxalate transmembrane transporter activity	2	69	2.1	*SLC26A4, SLC26A3*	0.042	45.8
GO:0008271 ~ secondary active sulphate transmembrane transporter activity	2	69	2.1	*SLC26A4, SLC26A3*	0.046	41.6

Analysis was made using the DAVID database. GO = Gene Ontology.
[1] Gene name list in Supplementary Table S1.

Table 6
Significant cellular components related to microsatellite markers displaying Transmission Ratio Distortion in the Pura Raza Española horse.

GO TERM	Count	List total	%	Genes[1]	*P*-value	Fold Enrichment
GO:0043190 ~ ATP-binding cassette (ABC) transporter complex	2	82	2.1	*ABCG8, ABCG5*	0.009	216.3
GO:0016020 ~ membrane	9	82	9.7	*CCDC188, PPM1B, RASL11B, COG5, NIPAL3, PNPLA3, MBOAT2, COMT, PIK3CG*	0.019	2.6
GO:0016607 ~ nuclear speck	5	82	5.4	*SNW1, HBP1, SRSF10, CBLL1, SRRM1*	0.050	3.5

Analysis was made using the DAVID database. GO = Gene Ontology.
[1] Gene name list in Supplementary Table S1.

involved in these processes are *ABCG8*, *ABCG5*, *CCDC188*, *PPM1B*, *RASL11B*, *COG5*, *NIPAL3*, *PNPLA3*, *MBOAT2*, *COMT*, *PIK3CG*, *SNW1*, *HBP1*, *SRSF10*, *CBLL1*, and *SRRM1*.

As shown in Fig. 1, genes related to TRD regions in the Pura Raza Española horse are linked to a large list of biological processes, molecular function, and cellular components processes. According to the percent of gene hit against total number of genes, the most representative processes for biological process category are cellular process (GO:0009987, 46.6%), metabolic process (GO:0008152, 27.2%) and biological regulation (GO:00665007, 26.0%), while for molecular function category, the most representative processes are binding (GO:0005488, 28.2%) and catalytic activity (GO:0003824, 18.3%).

Metabolic pathway analysis

Two metabolic pathways significantly related to TRD regions in the PRE horse were identified using DAVID software (Table 7). These pathways are fat digestion and absorption (ecb04975) and cholesterol metabolism (ebc04979), both of them represented for the same three genes: *ABCG8*, *ABCG5*, and *APOB*. Interestingly, the gene network analysis also revealed how these three genes, *ABCG8*, *ABCG5*, and *APOB*, show interactions between them (Fig. 2). Using the AmiGO and PANTHER GO-Slim databases, the significative genes related to TRD in the PRE horse are linked to a total of 160 different pathways, where the most important, according to the percent of genes affected against the total number of genes, are inflammation mediated by the chemokine and cytokine signalling pathways (P0031, 1.3%), Wnt signalling pathway (P00057, 1.3%) and gonadotropin-releasing hormone receptor pathways (P06664, 1.1%).

Discussion

The TRD occurs in the genome when certain alleles/genotypes are over- or under-represented in the offspring generation. This can occur due to a variety of factors, including the presence of germline selection, gametic competition, meiotic drive, embryo lethality (Seidel et al., 2011), functional complementarity (Gaouar, 2002 and 2009), inbreeding depression, imprint resetting error, diseases, and even differential postnatal viability. Depending on the penetrance of TRD in a population, it can have a significant impact on the efficiency of animal breeding programmes, as it can result in a decreased genetic gain on reproductive traits, a reduction in selection response or a reduced genetic diversity within a population. Therefore, the overall impact of TRD on animal breeding programmes is generally negative, and it is important for animal breeders to be aware of the potential for TRD and to take steps to mitigate its effects, such as using molecular markers to detect and track the spread of TRD-causing alleles. This can allow breeders to make informed decisions about mattings and avoid producing offspring with unwanted alleles/genotypes. In addition, it allows them to select and propagate desirable genotypes that can lead to better animal performance and increase the overall efficiency of breeding programmes.

Timid evidence of TRD has been present in livestock since 1985, as revealed by a segregation study of eleven swine leukocyte antigen haplotypes in two breeds of pigs (Philipsen and Kristensen, 1985). While there are some studies related to mendelian inheritance alteration in horses, the extent and prevalence of TRD in this specie have not been analysed so far. In an extended family of American Standardbreed horses, Bailey (1986) observed a clear excess male transmission for haplotype of the equine lymphocyte antigen system, which is a segregation distortion analogous to the T/t complex in mice. Years later, the first sire-specific gene TRD, affecting all typed alleles at 12 protein marker loci in a cohort of over 5 000 phenotyped horses, was reported by Weitkamp et al. (1988) in American Standardbred stallions. When this type of study is carried out, the first precaution to take into account is to rule out that the Mendelian inconsistency is not due to genotyping errors.

Microsatellite markers are a useful and powerful genetic tool due to their extensive length polymorphism, which results in allelic variation in the number of tandemly arranged perfect repeats. Compared to the SNPs markers, STRs have the advantage of the high number of markers present in current commercial arrays and the disadvantage of presenting only two variants, compared to 6–18 for STR markers (Tautz, 1989). Although the use of microsatellites has clearly declined in recent years (due to their relatively higher cost and poorer standardisation than other types of markers), they are gaining renewed interest in certain aspects (Berber et al., 2014; Benahamadi et al., 2020). Thus, studies of the human genome have revealed several examples of functional STRs, whose length variations can alter susceptibility to disease (Contente et al., 2002). There is additional evidence supporting the functional role of STRs in human disease, as seen in numerous disorders resulting from the expansion of large repeat sequences in coding or non-coding regions (Gemayel et al., 2010). While the pathogenic effect of STRs has been primarily studied in humans,

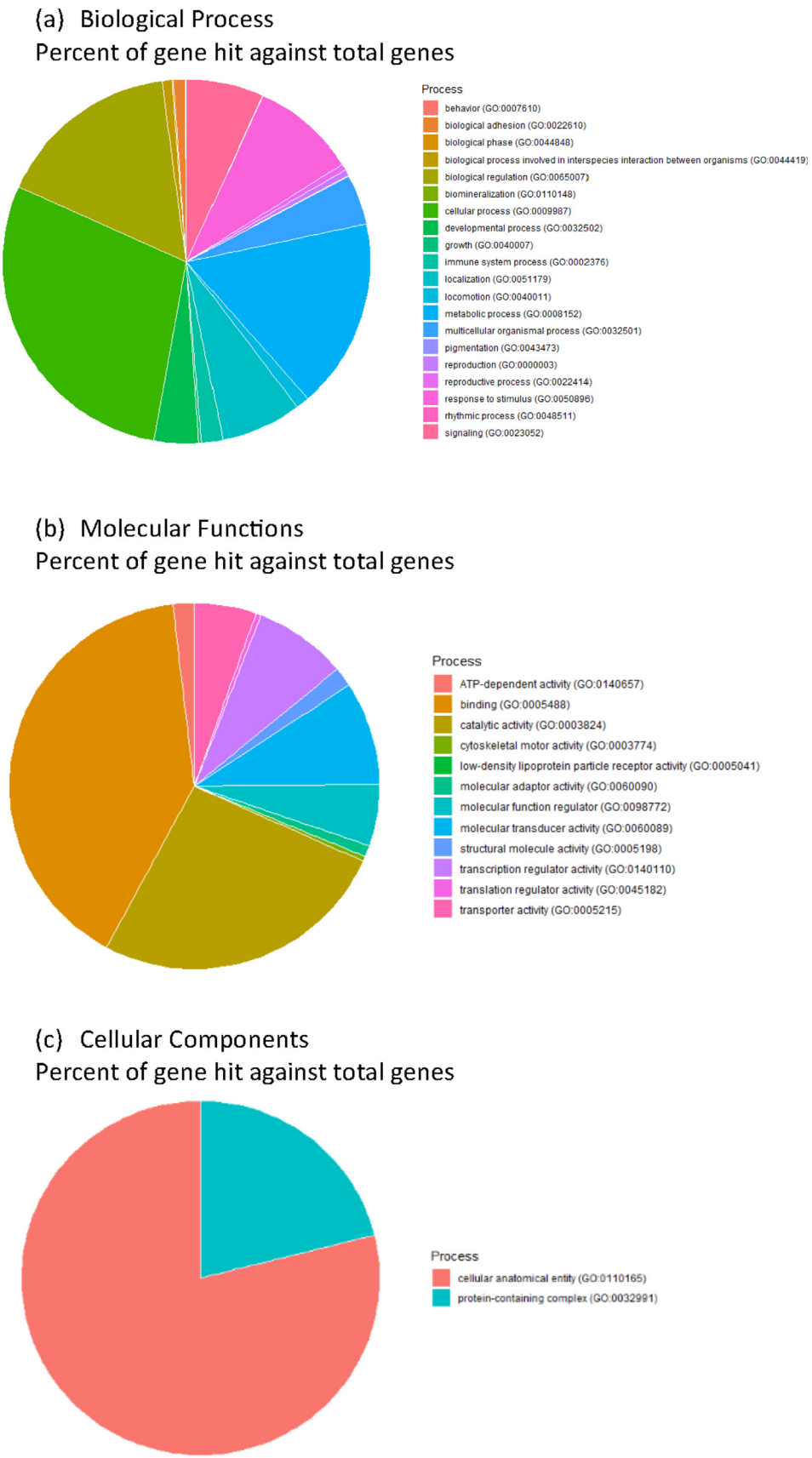

Fig. 1. Functional analysis of gene ontology terms using the list of positional genes with Transmission Ratio Distortion in the Pura Raza Española horse. Positional genes with Transmission Ratio Distortion in the Pura Raza Española horse using AmiGO and PANTHER GO-Slim. a = Biological process; b = Molecular functions, c = Cellular components from the Gene Ontology categories.

Table 7
Significant metabolic pathways related to microsatellite markers displaying Transmission Ratio Distortion in the Pura Raza Española horse.

KEGG PATHWAY	Count	List total	%	Genes[1]	*P*-value	Fold Enrichment
ecb04975: Fat digestion and absorption	3	39	3.261	*ABCG8, ABCG5, APOB*	0.016	14.915
ecb04979: Cholesterol metabolism	3	39	3.261	*ABCG8, ABCG5, APOB*	0.018	14.020

Analysis was made using the DAVID database. KEGG = Kyoto Encyclopedia of Genes and Genomes.
[1] Gene name list in Supplementary Table S1.

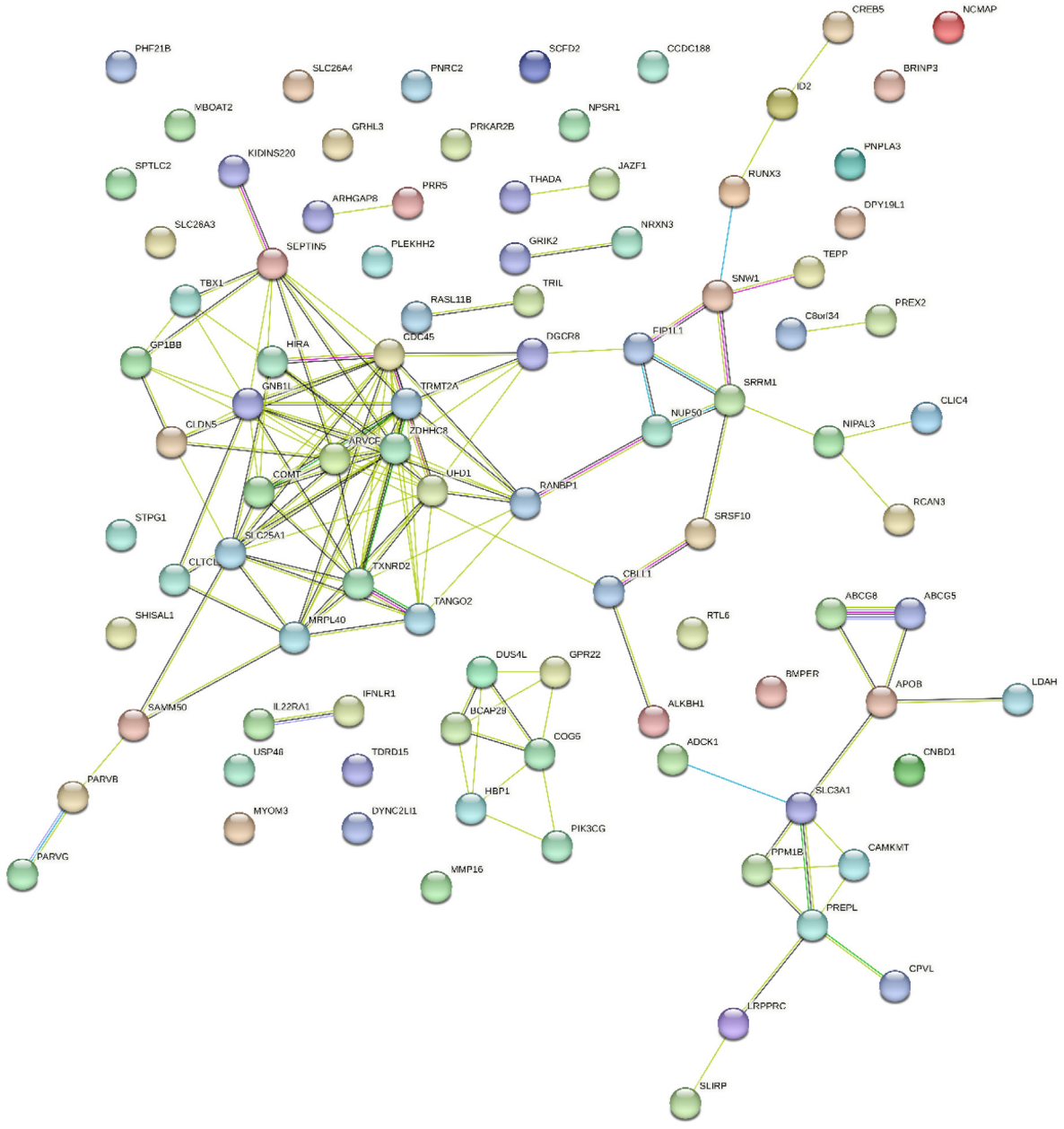

Fig. 2. Gene network of genes annotated within the Transmission Ratio Distortion regions identified in the Pura Raza Española horse.

there are also instances of their impact in other vertebrates. Furthermore, variable STRs in both coding and non-coding regions have been shown to modulate quantitative phenotypes in dogs (Körberg et al., 2014). Finally, there are authors (Cánovas et al., 2012) who consider that STRs can operate as loci of quantitative expression traits and methylation in pigs and humans, respectively, demonstrating the association with variation in local gene expression of neighbouring gene promoters, thus playing a role in genome functionality.

In this study, different TRD models were identified among STRs suggesting strong evidence of the corresponding inheritance pattern of the observed TRD when the $\log_{10}$ BF value was higher than 1 (BF > 10), and statistically decisive evidence of the model when $\log_{10}$BF > 2 (BF > 100). Both, allelic and genotypic patterns have been observed in the Pura Raza Española horse genome. In this context, among the 31 identified alleles, 19 fit better to the allelic model (Table 2) and 12 fit better with the genotypic model (Table 3).

From the distorted regions with allelic TRD pattern (Table 2), 14 alleles have shown evidence of overall TRD, ($\log_{10}$ BF > 2) which can be seen as a merge between specific sire- and dam-TRD (Casellas et al., 2014 and 2017). For regions with parent-specific TRD, three regions showed dam- and two regions exhibited sire-TRD. For these alleles, we also observed an overall TRD but with lower TRD magnitudes, it means that the parent's origin of TRD can be confirmed, even if it is identified as overall TRD, by having sufficient informative offspring from the parent who did not exhibit TRD. This is in concordance with Id-Lahoucine et al. (2023), highlighting the importance of modelling the probability of inheritance considering the paternal- and maternal-origin in search of parent-specific TRD. One should keep in mind that certain biological mechanisms that lead to TRD may be restricted to only one of the parental genders. In fact, sex-dependent TRD has been previously reported in other studies on beef cattle (Casellas et al., 2017).

The TRD magnitude is a measure of the degree to which one allele/genotype is over- or under-transmitted to the next generation. A value of $\alpha = 0.5$ or (-0.5) indicates complete skewing of transmission for a single allele, while null TRD ($\alpha = 0$) means an equal probability of transmission from parents to offspring. Within allelic TRD pattern, it can be observed that most regions with significant overall TRD, TRD value ranged from -0.16 to -0.49, which means moderate to high under-transmission. When parent-specific TRD regions are analysed, both sire and dam-TRD values were close to the null distribution. Only dam-specific TRD in the ASB23 STR marker and sire-specific TRD in the ASB2 STR marker showed significant log10 BF and TRD value closest to the complete skewing under-transmission.

The genotypic model highlighted three regions with additive pattern and nine with either excess or deficiency of heterozygous offspring (Table 3). The results indicate varying levels of statistical significance for TRD estimates, indicating different levels of model fit. Within this context, the three distorted regions with genotypic ratio distortion pattern and additive pattern showed TRD values with moderate transmission. The heterosis effect may be responsible for the other patterns observed in the genotypic model. An excess or deficiency of heterozygous offspring was observed in these regions. It is worth mentioning that there were three female- and one male-specific offspring regions with clear evidence of TRD, which were similar pattern that described across the cattle genome (Id-Lahoucine et al., 2022).

For all this, it is worth to mention that both models presented supportive analytical methods which permit recording different types of TRD and spotlight the importance of accomplishing both models. After the TRD detection, TRD analyses and characterisation can aid in the discovery of new candidate lethal alleles and genes related to TRD, which directly affect reproduction. For this, potential regions subjected to TRD were analysed and genes related to BP, CC, MF, and metabolic pathways were studied.

A total of 24 annotated genes [see Supplementary Table S1] have been located within the TRD regions using STRs in the PRE population, and most of them have a function related with fertility and/or play an important role of reproductive problems. The ATP-binding cassette subfamily G member 5 (*ABCG5*) and member 8 (*ABCG8*) are located at the sitosterolemia locus, where each gene encodes a membrane-bound ABC half-transporter and forms a functional unit. The activity of this unit is responsible for biliary and intestinal excretion. However, knockout mice for these genes exhibit infertility and a loss of abdominal fat (Solca et al., 2013). Furthermore, complementation factors for *APOB* mRNA editing have been shown to be essential for embryogenesis and fertility in Caenorhabditis elegans (Kinnaird et al., 2004) and *APOB* deficiency produces malabsorption of dietary lipids but also deleterious effects on liver lipid metabolism, steroid biosynthesis, and cell membrane function that can result in unspecific symptoms of reduced fertility, growth, and health in caws (Gross et al., 2016). Mice that express a human *APOB* gene are unable to deliver their offspring if the transgene is present in a homozygous state, but not when present in a heterozygous form (Word et al., 2005). The *SLIRP* gene encodes a steroid receptor RNA activator (SRA) RNA-binding protein that acts as a potent repressor of nuclear receptor activity. Its coregulators have essential functions in initiating and directing gene expression that affects mammalian reproduction, development, and metabolism (Colley et al., 2013). Studies with *SLIRP* knockout mouse showed subfertile response, specifically when homozygous knockout males were crossed with wild-type females and the resultant average litter size is reduced by approximately one third compared with those produced by wild males and females (Colley et al., 2013). On the other hand, a human study revealed a reduced level of *SLIRP* mRNA and protein expression in men with asthenospermia compared to normospermia (Shan et al., 2020). They concluded that in men with asthenospermia, *SLIRP* expression is reduced, oxidative damage is increased, and energy metabolism is decreased in spermatozoa. The *LRPPRC* gene is related to gene expression, mitochondrial DNA replication, and protein synthesis and degradation, but until date, they are not totally related to primary ovarian insufficiency (**POI**). However, the implication of mitochondrial dysfunction in POI suggests that manipulating mitochondrial function is a crucial therapeutic target for preventing or treating POI in humans (Tiosano et al., 2019). Furthermore, alterations in the *THADA* gene seem to be related with obesity, hirsutism, and amenorrea, which are directly implicated in enlarged polycystic ovaries in humans (Cariati et al., 2019). Engrossing, the gene network analysis also revealed how these two genes, *SLIRP*, and *LRPPRC* show interactions between them (Fig. 2), and both are associated to *PPM1B*.

The *PPM1B* gene, a metal-dependent serine/theonine protein phosphatase, is related to foliculogenesis and ovulation; its depletion induces premature senescence in human fibroblasts (Park et al., 2014). In addition, Ishii et al. (2019) suggests that the development of the follicles is excessive in $PPM1B^{+}/^{-}$ mice, and that this leads to a partial depletion of mature follicles and a corresponding decrease in the number of ovulated oocytes. The *NIPAL3* gene has been identified as a germline cancer predisposition gene in humans (Park et al., 2018). Uncommon germline variants in these genes contribute significantly to cancer risk, accounting for approximately 14% of ovarian carcinomas, 7% of breast tumours, and 4% of endometrial carcinomas of the uterine corpus. The *PIK3CG* gene is specifically expressed in mononuclear cells and was significantly associated with age-at-menopause in humans and daughter stillbirth in cattle (Liu et al., 2020).

The *ALKBH1* gene belongs to the family of mammalian dioxygenases. Nordstrand et al. (2010) demonstrated that the allele *ALKBH1* shows non-mendelian inheritance in mice. Offspring with $ALKBH1^{-/-}$ or heterozygous $ALKBH1^{+/-}$ genotypes are born at significantly reduced frequencies. Moreover, the sex ratio is heavily skewed against female offspring, with only one female born for every three to four males. Genetic and phenotypic assessments indicate that ALKBH1 plays a role in regulating gene expression during spermatogenesis and is critical for normal embryonic development and sex ratio distribution in mice.

The *SLC26A3* gene encodes a chloride/bicarbonate exchanger that is predominantly expressed in gastrointestinal, pancreatic, and renal tissues. In humans, mutations in the *SLC26A3* gene have been shown to cause congenital chloride-losing diarrhoea (**CLD**), an infrequent autosomal recessive disorder characterised by chronic secretory diarrhoea. El Khouri et al. (2018) showed that the absence of *SLC26A3* is linked to significant abnormalities in the epididymis' cytoarchitecture, causing severe lesions, and in the quantity, quality, and morphology of sperm. These findings compromised male fertility, which is supported by reports indicat-

ing subfertility in some male CLD patients, as well as the expression of *SLC26A6* and *SLC26A3* in sperm cells and the male genital tract. At the same time, a study in mice (Hihnala et al., 2006) showed that the pathophysiological mechanisms that can disturb reproductive functions and cause male subfertility in CLD patients are similar to those induced by cystic fibrosis transmembrane conductance regulator deficiency in the male reproductive system. That also suggests a primary role for *SLC26A3* in male reproduction. Ultimately, the splicing factor *SRSF10* plays a crucial role in spermatogenesis and male fertility. Without *SRSF10*, the formation of spermatogonial stem cells may occur, but the expansion of Promyelocytic Zinc Finger-positive undifferentiated progenitors could be hindered, leading to a failure in spermatogonia differentiation and the initiation of meiosis. (Liu et al., 2022). The *SRSF10* gene also appears to be a downregulated gene at high temperature on the ovine sperm transcriptome (Ureña et al., 2022).

Although more research is needed to understand how common the TRD phenomenon is and how it affects the inheritance of different traits in horses, 19 alleles of TRD with allelic pattern and 12 alleles with genotypic pattern of TRD have been identified in this work from 268 alleles investigated across 17 STRs markers in the Pura Raza Española horse. From those regions, 24 genes were annotated, most of which play an important role in functions and biological processes resulting in symptoms of reduced fertility. Overall, TRD is a complex event that is not fully understood in horses, but that clearly is an important aspect for animal breeding programmes, which has a significant impact on the inheritance of reproductive and fertility traits. For these reasons, after further analysis and validation, TRD could be considered to optimise the genetic conformation and performance of a population.

Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.animal.2023.101012.

Ethics approval

Not applicable.

Data and model availability statement

The dataset supporting the results of this study was supplied by the National Association of Pura Raza Española Horse Breeders (ANCCE). The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use any artificial intelligence-assisted technologies in the writing process.

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Declaration of interest

None.

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