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Lethal white foal syndrome: a review

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Abstract

A congenital abnormality most commonly associated with frame overo American Paint horses is termed overo lethal white foal syndrome, lethal white foal syndrome (LWFS), or lethal white overo syndrome, where foals homozygous for a missense Ile118Lys mutation in *endothelin-B receptor* gene are born completely white with an abnormal intestinal tract. Parents with frame overo phenotype are at higher risk of producing overo lethal white foals; however, some breeds not known for spotted pattern phenotypes have also produced LWFS foals. The neural crest cells of affected foals do not differentiate into melanocytes and enteric neuronal ganglions leading to the phenotypic presentation. As the disease progresses, a lack of neuronal innervation at the intestinal obstruction leads to intestinal rupture, toxicity, and death. No cure for this disease is known. The disease can be prevented through genetic testing of parents whether from overo lineage or not. Other examples of disease models similar to LWFS include Hirschsprung disease and Waardenburg Shah Syndrome in human medicine and piebald lethal in mice and lethal spotting in rats.

Key words: equine, Hirschsprung disease, neural crest cells, enteric ganglion, melanocytes, overo

Introduction

Overo lethal white foal syndrome (OLWFS), lethal white foal syndrome (LWFS), lethal white overo syndrome, ileocolonic aganglionosis, congenital megacolon, or aganglionic megacolon are all terminologies that are synonyms for the same disease. LWFS was first observed in 1998 and was the first molecular level pigmentation-related pleiotropic effect seen in the horse (Bellone 2010). Inherited as a simple Mendelian recessive trait, LWFS results in the inability of neural crest cells (NCCs) during embryogenesis to differentiate, proliferate, and migrate into melanocyte and enteric ganglion cells leading to phenotypic presentation. Foals are born with hair follicles lacking pigmentation along with sensory organ abnormalities and deficiency in neuronal innervation of the intestinal tract (Lightbody 2002). Colic symptoms begin to appear due to intestinal obstruction and lead to the progression of intestinal rupture and toxicity resulting in death. There is no treatment or cure. Prevention as a result is key in decreasing occurrence of LWFS and can be done through genetic testing of potential parents. Although LWFS is more common in frame overo lineages, it can also be seen in other overo patterning lines and spontaneously in breeds unassociated with spotting patterns. As a result, phenotype cannot determine genotype of heterozygote individuals that are carriers for LWFS. Humans, mice, and rats have also shown endothelin-B receptor (EDNRB) mutations that result in phenotypic presentations similar to LWFS; however, the mutation itself varies among species. By understanding the molecular pathways and developmental outcomes of LWFS, novel diagnostics, treatment options, and breakthroughs may assist in understanding similar diseases in other species.

Etiology

LWFS is a congenital disease associated with a missense mutation in the *EDNRB* gene where endothelin-3 (EDN3) is the main ligand. The EDNRB is a G-protein coupled transmembrane protein comprised of 443-amino acids that functions in cell migration and proliferation of enteric ganglia and melanocytes (Metallinos et al. 1998). The transmembrane protein substitution in the first transmembrane domain where a 2-bp change changes TC to AG leads to a single amino acid change at codon position 118 where isoleucine is replaced with lysine, classified as Ile118Lys mutation (Lightbody 2002). This missense mutation replaces a hydrophobic side chain with a large, positively charged (at physiological pH) side chain that could result in disruption of receptor characteristics such as location, binding, and signaling abilities (Metallinos et al. 1998). The actual disruption mechanism of the *EDNRB* mutation is to be determined. Heterozygote carriers of this mutation have normal enteric ganglion migration, proliferation, and function. Heterozygotes are often associated with the frame overo phenotype (Fig. 1). The breeding of two heterozygote parents can lead to homozygote offspring with Lys118/Lys118, which results in a lethal white foal. Two heterozygote parents would be expected to produce 25% nonovero, normal foals, 50% overo, normal foals, and 25% LWFS foals. However, LWFS foals are produced less

Fig. 1. Pigmentation phenotype and associated genotype in the horse. (*a*) Overo, normal Ile118/Lys118 horse. (*b*) Overo, normal Ile118/Lys118 horse. (*c*) Nonovero, normal Ile118/Ile118 horse. (*d*) White, overo lethal white syndrome Lys118/Lys118 foal. It should be noted that (*a*) and (*b*) are both considered overo; however, phenotype pigmentation varies.



than 25% of the time, which could be due to spontaneous abortion of Lys118/Lys118 foals and incomplete LWFS reporting (Lightbody 2002). Some breeds of horse that produced LWFS offspring had no frame overo pattern suggesting that the heterozygous phenotype can have incomplete penetrance (Metallinos et al. 1998). Heterozygotes that result in homozygote Lys118/Lys118 offspring are commonly associated with overo American Paint horses, which is why this syndrome can also be called OLWFS. With American Paint horses, the white spotting Overo allele is associated with a defective transmembrane protein that prevents melanocyte migration, leaving large, pigmented areas along with white areas of no pigmentation (Nicholas 2013). When white coloration is observed, melanocytes are absent from this part of the body.

Molecular events

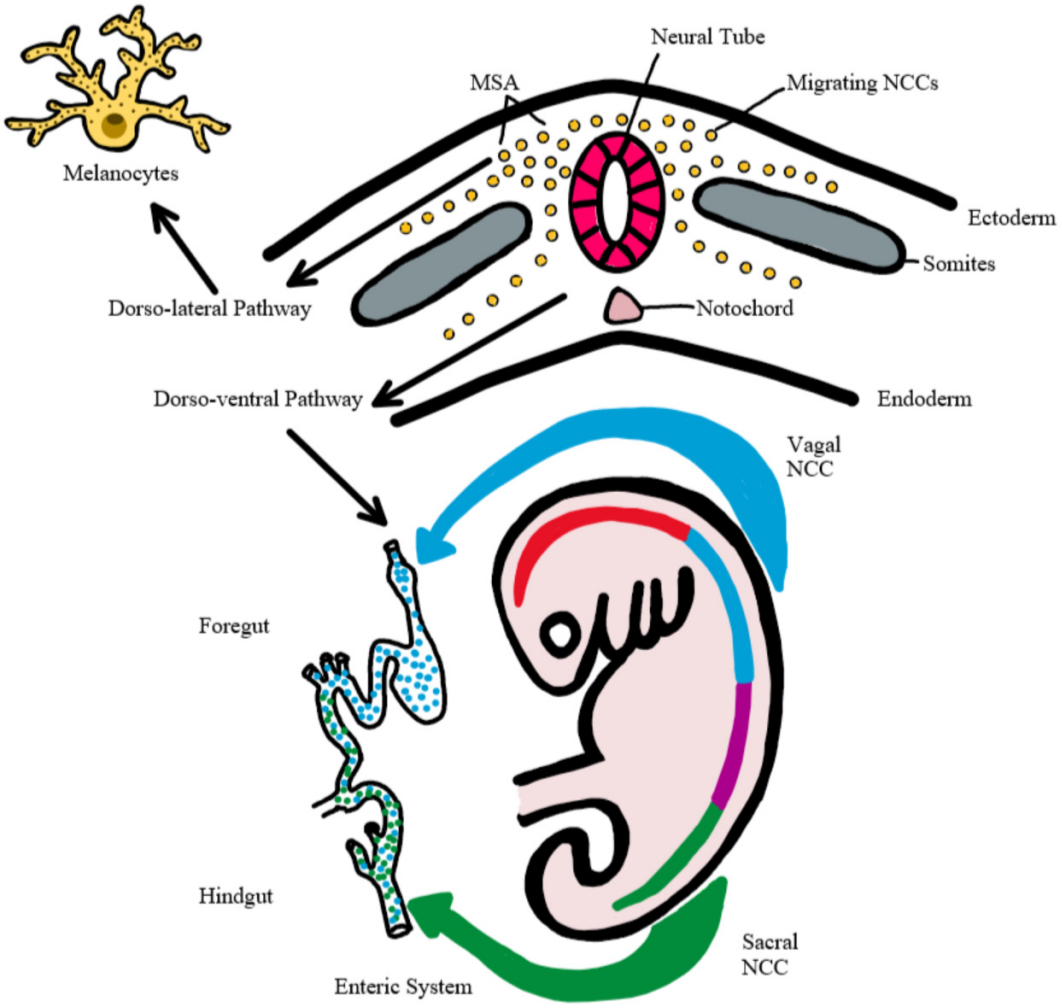
Normal role of ENDRB in development

During normal embryonic development, the blastocyst undergoes gastrulation where germ layers of ectoderm, mesoderm, and endoderm differentiate. The notochord is positioned between the ectoderm and endoderm germ layers initiating transformation of ectoderm into neuroectoderm. Neuroectoderm then can undergo the neurulation process differentiating into the neural crest that makes NCCs that in turn differentiate into melanocytes, neurons, and neurolemmocytes of the peripheral nervous system, adrenal medulla cells, and mesenchyme structures of the head (Fletcher and Weber 2013). Endothelin receptors are stimulatory G protein coupled receptors that are important in NCC migration and differentiation. Specifically, EDNRB is important in the development of melanocytes and enteric neurons along with differentiation of adrenal medulla cells and mesenchymal structures of the head (Bellone 2010). A similar disease in mice where mutations in *EDNRB* lead to lethal spotting (ls) and piebald-lethal (s^l) phenotypes has been observed. Enteric neurons from neural crest lineage in mice with aganglionic megacolon and a piebald-lethal mutations were observed due to mutations in *EDNRB* (Reid et al. 1996; Reissmann and Ludwig 2013). The Sry-related HMG-Box gene 10 (*SOX10*) and Paired Box 3 (*Pax3*) transcription factors also were associated with signaling NCC to differentiate into diverse cell lineages (Pla and Larue 2003). The *SOX10* protein is found within migratory NCCs that transform into melanocytes, glia, and neurons functioning in maintenance of NCCs and differentiation of melanophores and enteric glia (Nelms and Labosky 2010). *Pax3* is important in proliferation, preventing apoptosis, migration, and differentiation of melanocytes (Kubic et al. 2008). As a result, transcription factors *SOX10* and *Pax3* are also important in NCC differentiation.

Abnormal role of *EDNRB* in development

Foals suffering from LWFS have mutations in *EDNRB* receptor genes that lead to impairment of pigmentation and enteric ganglia development (Pla and Larue 2003). As a result, a white foal homozygous for Lys118/Lys118 in the EDNRB protein leads to an 80% loss of function of this protein in comparison to Ile118/Ile118 and Ile118/Lys118 foals (Lightbody 2002). This loss of function leads to impairment in innervation of the intestine and lack of coat pigmentation. Even though EDNRB affects differentiation of NCC into melanocytes, neurons, adrenal medulla cells, and mesenchymal structures of the head, only melanocytes and enteric neuronal ganglions are affected. Although the reason is unknown, cellular

Fig. 2. Diagram depicting neural crest cell (NCC) migration in dorso-lateral and dorso-ventral pathways. Melanocytes differentiate due to precursors proliferating in migration staging area (MSA). Enteric ganglions arise from the vagal and sacral NCC and develop cranial to caudal from foregut to hindgut. Please see fig. 1 in Delalande et al. (2008) and fig. 13.1 in Taneyhill et al. (2013) for further details.



descendants of NCC that migrate the furthest show more prominent effects due to lack of EDNRB function (Pla and Larue 2003). Melanocytes and enteric precursors colonize large surface areas of the body. The 80% loss of EDNRB function may have the largest effect on cells, like melanocytes and enteric ganglia, that need to migrate the furthest.

Developmental events

Normal

Pluripotent cells of the neural crest give rise to somites of NCC that can migrate either dorso-ventral or dorso-lateral directions based on EDNRB signaling. The dorso-ventral pathway differentiates into ganglions of the noncranial peripheral nervous system (Pla and Larue 2003). The enteric nervous system controls peristalsis and secretions within the gastrointestinal tract and is composed of ganglia made of integrated neurons and glial cells (Heanue and Pachnis 2006). Glial cells of the enteric system provide nutrients to neurons, regulate synaptic transmission, maintain the blood–brain barrier, and mediate nervous and immune system communication by controlling autonomic gastrointestinal homeostasis (Boesmans et al. 2015). Enteric ganglions, due to their caudal position, arise mainly from vagal and sacral NCC, where the enteric precursors enter the foregut and hindgut in a cranial to caudal direction of the embryo (Fig. 2). Signaling through cell shape and adhesion is required between enteric cells and gut environment to allow migration of vagal and sacral NCC to the foregut and hindgut, proliferation, and differentiation into neuronal subtypes (Heanue and Pachnis 2006). Sympathetic fibers arising from ganglia of the NCC innervate a horse's intestines along with tunica muscularis of the pelvic flexure (Giancola et al. 2016). The exact EDNRB signaling cascade that allows migration of NCC is yet to be determined. However, a gene expression study using microarrays observed potential enteric nervous system marker genes of the mammalian gut that are expressed during NCC

migration, proliferation, and differentiation (Heanue and Pachnis 2006). This is a step in the direction of understanding the intracellular signaling cascade that allows migration of NCC.

Melanocytes are located in many areas of the body including skin, hair, eye, inner ear, and leptomeninges (Bellone 2010). Melanocyte precursors begin in the dorso-ventral direction similar to the ganglions of enteric nervous system; however, these precursors are signaled later by EDNRB to proliferate in the migration staging area (Fig. 2). This migration pattern allows the NCC to merge into the dorsolateral pathway creating melanocytes (Pla and Larue 2003). Melanocytes and ganglia cells both migrate along a dorsoventral pathway; however, melanocytes convert to the dorsolateral pathway due to later EDNRB signaling. As a result, the timing and expression of endothelin signaling is important in the process of NCC differentiation for both ganglions and melanocytes.

Abnormal

Melanocytes and intestinal ganglion cells are affected by the congenital recessive genotype in LWFS. The genetic defect alters NCC migration and survival in the developing embryo by three possible avenues: (1) factors of migration, (2) NCC division or decreased survival, and (3) factors in target tissues (McCabe et al. 1990). When a foal is born homozygous for the recessive *EDNRB* allele, abnormalities within the NCC precursors of enteric ganglia and melanocytes lead to intestinal akinesia due to aganglionosis and white coat colour due to lack of pigmentation. Models of aganglionosis show presence of hypertrophied nerve bundles within the myenteric and submucous plexus, and LWFS foals have an increased extent of adrenergic fiber bundles distributed aberrantly between the tunica muscularis external longitudinal layer and the internal circular layer of the pelvic flexure (Giancola et al. 2016). The cascade of events leading to neuronal and melanocyte disfunction is yet to be resolved. Dispersed cells of enteric NCC and melanoblasts were more severely affected by *EDNRB* loss of function, which is linked to failure of migration of these cells (Pla and Larue 2003). Therefore, decreased functionality may be caused by the inability of the dispersed cells to reach their target of the caudal intestines and pigmentation of the skin.

Coat color and enteric nervous system physiology

A normal enteric nervous system is dependent on the functionality of the ganglia in the myenteric and submucosal plexus that mediate reflex behavior from central nervous system signaling along with innervation of the tunica muscularis layers of the pelvic flexure (Freeman 2006). In comparison, LWFS intestinal constriction was observed with absence of submucosal and myenteric neuronal ganglia from the distal small intestine to the rectum (Metallinos et al. 1998). The poorly developed intestinal tract leads to obstruction due to intestinal akinesia presenting the foal with a distended abdomen and colic symptoms. The distended abdomen occurs due to gas, fluid, and ingesta build up that adds pressure to the intestinal veins leading to increased capillary filtration and edema resulting in villi shortening, loss of mesothelial cells, and infiltration of neutrophils (Freeman 2006). Increased pressure leads to rupture of the intestines or ingesta buildup causing toxin release into the bloodstream; either way sudden death will occur. The cause of atresia coli is still unknown; however, damage to blood supply and possibly the lack of innervation of enteric ganglions causes the inability to pass meconium due to intestinal akinesia (Zachary 2022). As a result, atresia coli could be associated with LWFS due to the similarity of presentation.

Melanocytes not only produces pigment but also play a role in sensory organs of the eye and ear. Eye color and visual acuity are determined by the amount of melanin present. Development of the cochlea in the ear is affected by melanocyte function, but is not fully understood (Reissmann and Ludwig 2013). LWFS phenotypically presents as all white with pink skin, where some foals can have slight coat colouration on the tip of their ears, muzzle, or tail but mainly lack pigmentation presenting as white coat color. As a result, many loci result in pigmentation changes, resulting in outcomes that do not affect cell types, including NCCs, equally. Sensory organs can also be affected due to melanocytes' function in these organs, resulting in abnormalities in vision, hearing, and neurological functions (Bellone 2010). Foals with LWFS often present with blue eyes due to lack of pigmentation in the irides. Deafness can also occur due to either conduction deafness or sensorineural deafness, where LWFS foals most commonly are affected by the congenital form of sensorineural deafness that is associated with coat color and is described specifically with substantial white patterning and blue irides (Webb and Cullen 2010). This deafness is caused by the NCC of melanocyte precursors and their functionality in cochlea development.

Melanocytes also have important roles in protecting against ultraviolet radiation, inflammation, and preventing reactive oxygen agents from binding (Reissmann and Ludwig 2013). Coat colour pigmentation is affected by many different genes associated with migration, proliferation, and survival of melanocyte precursor cells. For example, *receptor tyrosine kinase type III* (*KIT*) variants can result in sabino-1, tobiano, and dominant white color, *EDNRB* variants cause frame overo coloration, *syntaxin 17* (*STX17*) variants caused grey color, and all of these variants result in affected melanocyte stem cell populations (Metallinos et al. 1998; Santschi et al. 1998; Yang et al. 1998; Brooks and Bailey 2005; Pielberg et al. 2005; Brooks et al. 2007; Haase et al. 2007). Horse breeds with white coat colour pigmentation do not all experience known pleiotropic effects with aganglionosis. The *EDNRB* gene leads to white coat color with pleiotropic effects in comparison to horses with the *KIT* variant that leads to white coat color with nonpleiotropic effects. Among similar mammalian species, the same or different genes can act on pathways leading to influences on pigmentation in several ways (Reissmann and Ludwig 2013). For example, the *KIT* gene can epistatically lead to variable pigmentation such as Sabino-1, Tobiano, and Dominant white colourations in horses (Bellone 2010). Gene mutations in coat patterning can also lead to coat

colouring dilutions. For example, cream colorations are caused by variants in *solute carrier family 45member 2* (*SLC45A2*), silver color is caused by variants in *silver* (*SILV*), variants in *solute carrier family 36 member 1* (*SLC36A1*) cause champagne coat color, pearl coat color is caused by variants in *SLC45A2*, and lavender foals are caused by variants in *myosin 5* A (*MYO5A*) (Mariat et al. 2003; Brunberg et al. 2006; Cook et al. 2008; Sponenberg et al. 2009; Brooks et al. 2010). As shown with *EDNRB*, sometimes these variants have pleiotropic effects on other traits (Reissmann and Ludwig 2013). As a result, aganglionosis of the submucosal and myenteric neuronal ganglia, lack of pigmentation, blue irides, and possibly deafness may all be caused by the congenital defect of the *EDNRB* gene.

Progression of disease

Foals suffering from LWFS are born clinically normal at birth, nurse willingly, and present phenotypically as a nearly completely white coated foal. The ability of meconium to be passed within the first 4 h of life is of importance when determining bowel motility. In the beginning, the foal will present with signs of colic, heart rate may be slightly elevated, lung sounds may increase, and lack of flatulence on abdomen auscultation may be observed (Lightbody 2002). At this point, the foal may begin to have disinterest in nursing due to intestinal tract obstruction. As the syndrome progresses, the signs of colic that began within 5–20 h of birth then progresses to the foal succumbing to death within a couple of days of life due to intestinal obstruction and toxin buildup (McCabe et al. 1990). The prognosis as a result is grave due to the "lethal" component of the syndrome via intestinal obstruction, rupture, and toxicity.

Equine breeds affected

American Paint horses with frame overo pattern are the breeds most associated with LWFS cases. However, not all carriers of LWFS are frame overos and vice versa. The diverse patterns of registered overo could be the reason why the relationship between overo patterning and LWFS is not always straightforward (Metallinos et al. 1998). For example, a horse with ventral jagged white markings and variable patterning may be called a frame overo. Similarly, a horse with four white legs along with a white face may also be classified as frame overo (Fig. 1). Frame overo is therefore used as a general term for a poorly defined coat color pattern. Although frame overo horses are more commonly associated with carrying one copy of the Lys118 allele, this allele can also be found in horses that present as solid instead of overo patterning, revealing that the *EDNRB* has variable penetrance (Metallinos et al. 1998). In Fig. 1, horse (a) with phenotype frame overo was bred to horse (b) with phenotype solid; however, this mating still produced a LWFS foal (d). Both horses were later confirmed to be heterozygous Ile118/Lys118. The *EDNRB* mutation has been observed in horse breeds with and without overo patterning such as American Paint horses that are solid, American Paint horses with Tobiano patterning, American Quarter horses, Miniature horses, and Thoroughbreds (Metallinos et al. 1998; Edwards and Finno 2020). The potential of a horse breed unassociated with spotting patterns being bred to a frame overo resulting in a foal with LWFS could be explained by variable expressivity of alleles and decreased to absent spotting on the heterozygous Ile118/Lys118 horse (McCabe et al. 1990). The term "crop-out" is used to describe overo horses with two parents who were solid colored, such as Quarter Horses. "Crop-out" foals could possibly occur due to variable expressivity of alleles and mutations that occur spontaneously (McCabe et al. 1990). The actual occurrence of spontaneous mutation in horse breeds lacking spotting pattern association is yet to be estimated. However, spontaneous mutations have been observed in other higher eukaryote species to range from 0.1 to 100 per genome (Drake et al. 1998). Genetic testing is therefore critical for determining true LWFS carriers where nonspotting pattern associated horses and spotting pattern associated horses could be heterozygous for Ile118/Lys118 and could possibly produce offspring with LWFS.

Diagnosis and treatment

Foals born with solid white colouration to an American Paint Horse are highly likely to be suffering from LWFS. However, as previously discussed, a foal presenting with a fully white coat does not prove that they are LWFS foals but rather a multitude of clinical signs and genetic testing should be used to confirm this condition. Blood can be drawn from mares and stallions to confirm heterozygosity of parents. Horse hairs with roots can also be sampled and sent to UC Davis Veterinary Genetics Laboratory to determine if there are copies of LWFS. Due to rapid progression of LWFS, genetic testing of foals is of no benefit as foal's clinical signs worsen with time. Prior to the development of the genetic test, the use of phenotype identification of the amount of white pigmentation in a coat was used to determine possible carriers (Lightbody 2002). This process may produce incorrect genotype prediction, as previously discussed. Thus, genetic testing allows more accurate identification of carriers and makes elimination of the disease possible.

This disease at present is noncurable, making preventative strategies important. Prior to breeding, it is essential for owners to test for carrier status of mares and stallions to understand the possibility of throwing a LWFS foal. Treatment for LWFS foals can include supportive care, enema administration of 120 mL mineral oil for the attempt of meconium plug passage, and 150 mg of flunixin meglumine to alleviate pain in the abdomen (Lightbody 2002). Humans suffer from a similar condition called Hirschsprung's disease (HSCR), where at birth children present with aganglionosis and inability to pass stool. Therapy for humans can include surgical resection of the colon affected with aganglionosis and possibly stimulation of intestine motility via administration of enterotoxins (Menezes et al. 2006; Zachary 2022). Surgical resection of foals with LWFS has been attempted with no success (Metallinos et al. 1998). Lack of success could possibly relate to horses being hindgut fermenters because the disease affects the large intestine and therefore the hindgut. The use of enterotoxins could possibly be used to help

stimulate and pass the meconium plug; however, success of this therapy has not been reported. As a result, LWFS progresses to the point where humane euthanasia is advised to alleviate pain.

Models of LWFS

Diseases that present similarly to LWFS can include HSCR and Waardenburg Shah Syndrome (WS4) that affect humans, piebald lethal that affect mice, and lethal spotting in rats. Humans can suffer from WS4 disease where aganglionosis, hypopigmentation, and deafness occur in comparison to HSCR, where humans only suffer from aganglionosis (Waardenburg 1951). Humans with aganglionosis from WS4 or HSCR are diagnosed after birth having abdominal distention, failure to pass meconium, and painful abdomen due to the lack of proper innervation (Parisi 2006). Both human diseases are observed to have an association with *EDNRB* receptor and *EDN3* ligand gene mutations, where patients that are heterozygous show signs of aganglionosis just as homozygous patients, possibly due to incomplete penetrance and variable expression of *EDNRB* or unlinked genetic variations (Shin et al. 1997; Brooks et al. 2005). Human WS4 and HSCR are different as both heterozygotes and homozygotes show signs of aganglionosis, in comparison to equine, where homozygotes are the only ones that are observed to suffer from abnormal enteric innervation. Comparing EDNRB protein sequence of humans and horses 88.5% similarity was observed leaving room for variability between the diseases (Metallinos et al. 1998). For humans, other genes are also associated with aganglionosis such as *Receptor tyrosine kinase* (*RET*) and *Glial cell line-derived neurotrophic factor* (*GDNF*) (Brookset al. 2005). The *GDNF* is a protein that activates *RET* to signal the cascade of intracellular events leading to enteric nervous system development (Brooks et al. 2005). Mutations in *SOX10* along with *EDNRB* also cause pigmentation and aganglionosis defects, indicating the importance of *SOX10* for the developing enteric nervous system and melanocyte formation (Nelms and Labosky 2010). As a result, mutations in *EDNRB*, *RET*, *GDNF*, or *SOX10* can result in failure of NCCs to proliferate, migrate, and differentiate appropriately. Therefore, LWFS, HSCR, and WS4 have similarities that could be explored further to understand the connections of these diseases.

The rodent models (mice and rats) also are characterized by melanocyte abnormalities resulting in coat colour patterning and aganglionosis that suggests *EDNRB* missense mutations similar to LWFS. However, the *EDNRB* mutation is different between mice and rats. *EDNRB* gene is completely deleted in mice, whereas in rats a 301 bp chromosomal deletion occurs (Gariepy et al. 1996; Shin et al. 1997). These mutations result in similar outcomes as LWFS, where NCC has failure to differentiate and migrate into melanocyte and enteric ganglion precursors leading to phenotypic changes and aganglionosis (Gariepy et al. 1996). Heterozygous rats are similar to horses by lacking abnormal pigmentation and aganglionosis; however, there is some suggestion that minor changes of premature ganglionic precursors can occur (von Boyen et al. 2002). Within mice, functionality of *EDNRB* varies depending on the level of gene expression within the melanocytes leading to varying spotting degrees within melanocyte coat colorations (Shin et al. 1997). This variable level of gene expression can also explain the incomplete penetrance with variable expressivity observed in HSCR homozygote and heterozygote patients (Shin et al. 1997). Overall, the EDNRB receptor plays a critical role in migration of NCC across different species even if the exact mechanism of action varies.

Future

Understanding the mechanism of action of EDNRB signaling for NCC migration can identify where and how abnormalities could occur in melanocyte and enteric ganglion precursors that lead to LWFS. A promising area of research is why only abnormalities in melanocyte and enteric ganglia and not in adrenal medulla cells and mesenchymal structures of the head are observed. Mutations in the EDNRB signaling pathway have varying phenotypes for humans and horses. A further understanding of differences between human and horse intracellular signaling cascades involving EDNRB could elucidate the reasons for differing phenotypes (Bellone 2010). Understanding the prevalence of this mutation in horse breeds lacking association with spotting pattern can provide clarity on the risk that a horse carries the mutation that causes LWFS. These questions can lead to a better understanding of LWFS and provide scientists with additional information that could help in interpreting similar diseases in other species.

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Data availability

Data generated or analyzed during this study are provided in full within the published article.

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Competing interests

The authors declare there are no competing interests.

References

Bellone, R.R. 2010. Pleiotropic effects of pigmentation genes in horses. Anim. Genet. **41**(Suppl 2): 100–110. doi:10.1111/j.1365-2052.2010.02116.x. PMID: 21070283.

Boesmans, W., Lasrado, R., Berghe, P.V., and Pachnis, V. 2015. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. Glia, **63**(2): 229–241. doi:10.1002/glia.22746. PMID: 25161129.

Brooks, A.S., Oostra, B.A., and Hofstra, R.M. 2005. Studying the genetics of Hirschsprung's disease: unraveling an oligogenic disorder. Clin. Genet. **67**(1): 6–14. doi:10.1111/j.1399-0004.2004.00319.x. PMID: 15617541.

Brooks, S.A., and Bailey, E. 2005. Exon skipping in the KIT gene causes a sabino spotting pattern in horses. Mamm. Genome, **16**: 893–899. doi:10.1007/s00335-005-2472-y. PMID: 16284805.

Brooks, S.A., Gabreski, N., Miller, D., Brisbin, A., Brown, H.E., Streeter, C., et al. 2010. Whole genome SNP association in the horse: identification of deletion in myosin Va responsible for lavender foal syndrome. PLOS Genet. **6**: e1000909. doi:10.1371/journal.pgen.1000909. PMID: 20419149.

Brooks, S.A., Lear, T.L., Adelson, D., and Bailey, E. 2007. A chromosome inversion near the KIT gene and the tobiano spotting pattern in horses. CGR, **119**: 225–230.

Brunberg, E., Andersson, L., Cothran, G., Sandberg, K., Mikko, S., and Lindgren, G. 2006. A missense mutation in PMEL17 is associated with the silver coat color in the horse. BMC Genet. **7**: 46. doi:10.1186/1471-2156-7-4. PMID: 17029645.

Cook, D., Brooks, S., Bellone, R., and Bailey, E. 2008. Missense mutation in exon 2 of SLC36A1 responsible for champagne dilution in horses. PLOS Genet. **4**: e1000195. doi:10.1371/journal.pgen.1000195. PMID: 18802473.

Delalande, J.-M., Barlow, A.J., Thomas, A.J., Wallace, A.S., Thapar, N., Erickson, C.A., and Burns, A.J. 2008. The receptor tyrosine kinase RET regulates hindgut colonization by sacral neural crest cells. Dev. Biol. **313**(1): 279–292. doi:10.1016/j.ydbio.2007.10.028. PMID: 18031721.

Drake, J.W., Charlesworth, B., Charlesworth, D., and Crow, J.F. 1998 Rates of spontaneous mutation. Genetics, **148**(4): 1667–1686. doi:10.1093/genetics/148.4.1667. PMID: 9560386.

Edwards, L., and Finno, C.J. 2020. Genetics of equine neurologic disease. Vet. Clin. North Am. **36**(2): 255–272. doi:10.1016/j.cveq.2020.03.006.

Fletcher, T.F., and Weber, A.F. 2013. Veterinary developmental anatomy: veterinary embryology. University of Minnesota. pp. 6–10. Available from http://vanat.cvm.umn.edu/vanatpdf/EmbryoLectNotes.pdf [accessed 20 March 2024].

Freeman. 2006. Small intestine. *In* Equine surgery. W. B. Saunders Company. pp. 401–436. doi:10.1016/B1-41-600123-9/50037-1.

Gariepy, C.E., Cass, D.T., and Yanagisawa, M. 1996. Null mutation of endothelin receptor type B gene in spotting lethal rats causes aganglionic megacolon and white coat color. Proc. Natl. Acad. Sci. **93**(2): 867–872. doi:10.1073/pnas.93.2.867.

Giancola, F., Gentilini, F., Romagnoli, N., Spadari, A., Turba, M.E., Giunta, M., et al. 2016. Extrinsic innervation of ileum and pelvic flexure of foals with ileocolonic aganglionosis. Cell Tissue Res. **366**(1): 13–22. doi:10.1007/s00441-016- 2422-x. PMID: 27230228.

Haase, B., Brooks, S.A., Schlumbaum, A., Azor, P.J., Bailey, E., Alaeddine, F., et al. 2007. Allelic heterogeneity at the equine KIT locus in dominant white (W) horses. PLOS Genet. **3**: e195. doi:10.1371/journal.pgen.0030195. PMID: 17997609.

Heanue, T.A., and Pachnis, V. 2006. Expression profiling the developing mammalian enteric nervous system identifies marker and candidate Hirschsprung disease genes. Proc. Natl. Acad. Sci. **103**(18): 6919–6924. doi:10.1073/pnas.0602152103.

Kubic, J.D., Young, K.P., Plummer, R.S., Ludvik, A.E., and Lang, D. 2008. Pigmentation PAX-ways: the role of Pax3 in melanogenesis, melanocyte stem cell maintenance, and disease. Pigm. Cell Melanoma Res. **21**(6): 627–645. doi:10.1111/j.1755-148X.2008.00514.x. PMID: 18983540.

Lightbody, T. 2002. Foal with overo lethal white syndrome born to a registered quarter horse mare. Can. Vet. J. **43**(9): 715–717. PMID: 12240532.

Mariat, D., Taourit, S., and Guerin, G. 2003. A mutation in the MATP gene causes the cream coat colour in the horse. GSE, **35**: 119–133. PMID: 12605854.

McCabe, L., Griffin, L.D., Kinzer, A., Chandler, M., Beckwith, J.B., and McCabe, E.R. 1990. Overo lethal white foal syndrome: equine model of aganglionic megacolon (Hirschsprung disease). Am. J. Med. Genet. **36**(3): 336–340. doi:10.1002/ajmg.1320360319. PMID: 2363434.

Menezes, M., Corbally, M., and Puri, P. 2006. Long-term results of bowel function after treatment for Hirschsprung's disease: a 29-year review. Pediatr. Surg. Int. **22**(12): 987–990. doi:10.1007/s00383-006-1783-8. PMID: 17006709.

Metallinos, D.L., Bowling, A.T., and Rine, J. 1998. A missense mutation in the endothelin-B receptor gene is associated with lethal white foal syndrome: an equine version of Hirschsprung disease. Mamm. Genome, **9**(6): 426–431. doi:10.1007/s003359900790. PMID: 9585428.

Nelms, B.L., and Labosky, P.A. 2010. Transcriptional control of neural crest development: SOX genes. Morgan Claypool Life Sci. 120–129. Available from https://www.ncbi.nlm.nih.gov/books/NBK53136/ [accessed 20 March 2024].

Nicholas, F.W. 2013. Introduction to veterinary genetics. 3rd ed. Wiley-Blackwell Ltd. pp. 196–197.

Parisi, M.A. 2006. Hirschsprung disease overview. GeneReviews.

Pielberg, G., Mikko, S., Sandberg, K., and Andersson, L. 2005. Comparative linkage mapping of the grey coat colour gene in horses. Anim. Genet. **36**: 390–395. doi:10.1111/j.1365-2052.2005.01334.x.

Pla, P., and Larue, L. 2003. Involvement of endothelin receptors in normal and pathological development of neural crest cells. Int. J. Dev. Biol. **47**(5): 315–325.

Reid, K., Turnley, A.M., Maxwell, G.D., Kurihara, Y., Kurihara, H., Bartlett, P.F., and Murphy, M. 1996. Multiple roles for endothelin in melanocyte development: regulation of progenitor number and stimulation of differentiation. Development, **122**(12): 3911–3919. doi:10.1242/dev.122.12.3911.

Reissmann, M., and Ludwig, A. 2013. Pleiotropic effects of coat colour-associated mutations in humans, mice and other mammals. Semin. Cell Dev. Biol. **24**(6–7): 576–586. doi:10.1016/j.semcdb.2013.03.014.

Santschi, E.M., Purdy, A.K., Valberg, S.J., Vrotsos, P.D., Kaese, H., and Mickelson, J.R. 1998. Endothelin receptor B polymorphism associated with lethal white foal syndrome in horses. Mamm. Genome, **9**: 306–309. doi:10.1007/s003359900754.

Shin, M.K., Russell, L.B., and Tilghman, S.M. 1997. Molecular characterization of four induced alleles at the Ednrb locus. Proc. Natl. Acad. Sci. **94**(24): 13105–13110. doi:10.1073/pnas.94.24.13105.

Sponenberg, D.P., Archer, S., and Bellone, R. 2009. Patterns of white with symmetric white patches: the leopard complex. 3rd ed. Sponenberg DP Equine Color Genetics. pp. 110–120.

Taneyhill, L.A., Schiffmacher, A.T., and Roy, F.(Editors). 2013. Cadherin dynamics during neural crest cell ontogeny. PMBTS, **116**: 291–315. doi:10.1016/B978-0-12-394311- 8.00013-3.

von Boyen, G.B., Krammer, H.J., Süss, A., Dembowski, C., Ehrenreich, H., and Wedel, T. 2002. Abnormalities of the enteric nervous system in heterozygous endothelin B receptor deficient (spotting lethal) rats resembling intestinal neuronal dysplasia. Gut, **51**(3): 414–419. doi:10.1136/gut.51.3.414.

Waardenburg, P.J. 1951. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. Am. J. Hum. Genet. **3**(3): 195–253.

Webb, A.A., and Cullen, C.L. 2010. Coat color and coat color pattern-related neurologic and neuro- ophthalmic diseases. Can. Vet. J. **51**(6): 653–657.

Yang, G.C., Croaker, D., Zhang, A.L., Manglick, P., Cartmill, T., and Cass, D. 1998. A dinucleotide mutation in the endothelin-B receptor gene is associated with lethal white foal syndrome (LWFS); a horse variant of Hirschsprung disease. Hum. Mol. Genet. **7**(6): 1047–1052. doi:10.1093/hmg/7.6.1047.

Zachary, J.F. 2022. Pathologic basis of veterinary disease. 7th ed.Vol. 406. Elsevier Inc. p. 439.