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Unusual occurrence of domestication syndrome amongst African mole-rats: Is the naked mole-rat a domestic animal?

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The Naked mole-rat (NMR) is becoming a prominent model organism due to its peculiar traits, such as eusociality, extreme longevity, cancer resistance, and reduced pain sensitivity. It belongs to the African mole-rats (AMR), a family of subterranean rodents that includes solitary, cooperative breeding and eusocial species. We identified and quantified the domestication syndrome (DS) across AMR, a set of morphological and behavioural traits significantly more common and pronounced amongst domesticated animals than in their wild counterparts. Surprisingly, the NMR shows apparent DS traits when compared to the solitary AMR. Animals can self-domesticate when a reduction of the fear response is naturally selected, such as in islands with no predators, or to improve the group's harmony in cooperative breeding species. The DS may be caused by alterations in the physiology of the neural crest cells (NCC), a transient population of cells that generate a full range of tissues during development. The NCC contribute to organs responsible for transmitting the fear response and various other tissues, including craniofacial bones. Therefore, mutations affecting the NCC can manifest as behavioural and morphological alterations in many structures across the body, as seen in neurocristopathies. We observed that all social AMRs are chisel-tooth diggers, an adaption to hard soils that requires the flattening of the skull. We hypothesise that chisel-tooth digging could impose a selective pressure on the NCC that triggered the DS's appearance, possibly facilitating the evolution of sociality. Finally, we discuss how DS traits are neutral or beneficial for the subterranean niche, strategies to test this hypothesis and report well-studied mutations in the NMR that are associated with the NCC physiology or with the control of the fear response. In conclusion, we argue that many of the NMR's unconventional traits are compatible with the DS and provide a hypothesis about its origins. Our model proposes a novel avenue to enhance the understanding of the extraordinary biology of the NMR.

KEYWORDS

naked mole-rat, African mole-rat, eusociality, domestication, neural crest, digging behaviour, chisel-tooth digging

Introduction

The reduction of the fight-or-flight response is a hallmark of domestication (Belyaev, 1969). From the Neolithic period, many animals adapted to the anthropogenic environment by reducing reactivity to humans and perhaps increasing their social tolerance (Tchernov and Horwitz, 1991). Surprisingly, there is a set of physical traits that often appear in domestic mammals but not in their wild equivalents, known as the domesticthat syndrome (DS). The DS includes depigmentation, a shorter snout, decreased brain size, floppy ears, reduced or missing teeth and hairlessness, amongst other traits (Darwin, 1868; Sánchez-Villagra et al., 2016). These traits rarely occur in the wild, and usually, only a subset of them is present in each individual or variety of a domestic species. DS most probably was not directly selected by humans (Darwin, 1868); but instead, it appeared as a side effect of selecting for tameness (Belyaev, 1969). Experiments with wild foxes, rats and minks show that DS traits can appear as a side effect of artificially selecting for tameness (Trut, 1999; Trut et al., 2009; Singh et al., 2017; Wang et al., 2018). However, they can also appear in wild animals when selective pressures favour a reduced fight-or-flight response (self-domestication), as it occurs in islands with no predators (Ramis and Bover, 2001; Cooper et al., 2014; Sánchez-Villagra et al., 2016). Finally, these traits can be observed in primates, including humans (Theofanopoulou et al., 2017; Sánchez-Villagra and van Schaik, 2019; Zanella et al., 2019), bonobos (Hare et al., 2012), and marmoset monkeys (Ghazanfar et al., 2020), where it has been suggested that the reduced aggression associated with the DS could have been selected to enhance cooperative breeding.

There have been many attempts to explain why selecting for tameness result in the distinct morphological traits encompassed by the DS, including changes in thyroid function (Crockford, 2004; Karlsson et al., 2016; Fitak et al., 2020), in the metabolism of the adrenaline (Keeler et al., 1970; Nätt et al., 2007; Cagan and Blass, 2016), or the retention of juvenile traits in the adult animal (Shea, 1989; Geiger et al., 2017). Recently, a new, more comprehensive theory proposed that the DS syndrome is derived from mutations affecting the development of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (Wilkins et al., 2014). The HPA axis converts the perception of dangerous stimuli into a hormonal response by transmitting information to the adrenal medulla, which results in the release of glucocorticoids and adrenaline, leading to a long-term elevated reactivity (Sapolsky, 2005). Similarly, the sympathetic nervous system mediates the short-term fight-or-flight response and directly stimulates the adrenal glands. Mutations producing a hypofunctional HPA axis could result in the reduced fear response characteristic of domestic animals. Remarkably, the sympathetic nervous system, the adrenal glands, skin melanocytes, bone and cartilage in the skull and teeth, amongst other tissues, are derived from the neural crest cells (NCC). This way, mild neurocristopathies (disorders derived from defects in the NCC) could explain tameness and the DS simultaneously (Wilkins et al., 2014).

The family of African mole-rats (AMR, family *Bathyergidae*) is a well-recognised model to study the evolution of cooperative breeding (Faulkes and Bennett, 2016). This family of subterranean rodents contains solitary, social cooperative breeders and two eusocial species: The naked mole-rat (NMR) and the Damaraland mole-rat. Eusociality is an extreme form of cooperative breeding where species show sexual suppression, reproductive division of labour, overlapping generations and cooperative care of the young (Burda et al., 2000). In the case of eusocial AMRs, most members renounce to reproduce and specialise in digging, defence, or pup-caring, whilst a single queen continuously produces offspring (Faulkes and Bennett, 2001). The NMR presents the most extreme and unusual traits of its family: it is eusocial, forms extensive colonies (Jarvis, 1981), and exhibits resistance to hypoxia, delayed senescence, cancer resistance, poor control of body temperature and reduced sensitivity to pain (reviewed in Braude et al., 2021). Its scientific name *Heterocephalus glaber* ("atypical bald head"), also refers to its rare morphological traits: it is hairless (except for sensory hairs), has wrinkled skin, and a flat skull with a reduced number of molars when compared with the other AMR (Jarvis and Sherman, 2002). Strikingly, many of these morphological traits can be accounted as part of the DS. Is the NMR a domestic animal?

Here we propose that the social behaviour of AMR is the product of self-domestication. We document that DS traits are more prominent in social AMR species, especially in the NMR. We focus on the NMR because it presents the most extreme morphological and behavioural phenotype, and it is the best-studied member of the family. We propose that many of the unusual NMR traits could be the result of a mild-neurocristopathy that recapitulated the DS. We discuss the possible interactions between the DS, the subterranean niche, and the digging mode. Finally, we suggest that the appearance of the DS facilitated the evolution of eusociality in AMRs and argue that this integrative theory will aid NMR research on many fronts.

Domestication syndrome in the naked mole-rat

The AMR family comprises six genera and more than 15 species. All family members are subterranean rodents and present a complete set of morphological, physiological, and behavioural adaptations to the underground environment. However, genera differ in some essential traits regarding their head, digging behaviours, and sociality. Surprisingly, many differences between the social AMR, especially the NMR, and the solitary species can be accounted for as part of the DS. We compiled a list of the DS traits across the AMR family.

Skull

The skulls of domestic animals present many characteristic traits. Many domestic animals (e.g., dog, fox, pig, sheep, goat, cat,

mouse, cow, and human) present a reduced snout in comparison to their wild counterparts (reviewed in Sánchez-Villagra et al., 2016; Sánchez-Villagra and van Schaik, 2019). Amongst subterranean rodents, the relative length of the snout is largely determined by their digging behaviours: forelimb diggers use their claws to scratch soft, sandy soil and possess more prominent faces, whilst chisel-tooth diggers use their incisors to exploit harder soil and have a relatively wider cranium (Lacey and Patton, 2000). Chisel-tooth diggers show enlarged zygomatic arcs (cheek bones) and shorter rostra, associated with larger masseter and temporalis muscles, presumably to enhance the bite force (Lacey and Patton, 2000; Mcintosh and Cox, 2016).

We gathered the width and length of the skull of the AMR, other African Hystricognath (the closest relatives to the AMR: Old World porcupines, the dassie rat and the cane rat) and examples of genetically unrelated convergent mole-rats (from genus *Spalax*, *Spalacopus*, and *Tachyoryctes*). We calculated the ratio between the length and the width of the skull for the chisel-tooth diggers in our data set (Figure 1, see Materials and methods in the Supplementary Material). In comparison, exclusive forelimb diggers (other African Hystricognath and *Bathyergus* mole-rats) tend to have a more prominent snout (Supplementary Figure 1). At the same time, *Tachyoryctes* members, which dig with both their limbs and teeth, present closer cranial proportions to exclusive chisel-tooth diggers (most AMR, *Spalax* and *Spalacopus*). We show that the NMR has a disproportionally shorter snout even for a chisel-tooth digger, probably due to a statistically significant reduction of the rostral length (Mcintosh and Cox, 2016). The relative shortening of the NMR's snout compared to other chisel-tooth diggers is a typical DS trait.

All AMR species share a similar diet of geophytes, tubers and rhyzomes (Kingdon, 2014). Unfortunately, there is no data available about the relative hardness of the plants (Dominy et al., 2008) consumed by AMR in comparison with the hardness of the soil. However, it seems unlikely that any tuber or rhyzome offer more resistance than the soil. In addition, whilst all AMR species eat similar plants (Kingdon, 2014), they inhabit areas with different soil properties (Faulkes and Bennett, 2013). Solitary forelimb diggers (*Bathyergus*) are restricted to more humid environments where digging is easier, whilst chisel-tooth diggers-especially the social species-tend to inhabit regions with harder soils (Faulkes and Bennett, 2013). Therefore, it seems that the type of soil correlates better with the head morphology, digging behaviour and sociality (see *The subterranean niche and self-domestication* below), than the type of diet, which suggests that the properties of the soil are the main determinant of the skull proportions amongst AMR.

Dentition

The skull of domestic animals often manifests dental abnormalities such as crowding of the cheek teeth or a reduction of teeth size or number (dogs, pigs, mouse, human; reviewed in Kleisner and Stella, 2009; Sánchez-Villagra et al., 2016;

Sánchez-Villagra and van Schaik, 2019; Lord et al., 2020). Most AMR species share the same dental formula (I 1/1, C 0/0, P 1/1, M 3/3; 20 teeth; Table 1), except for *Heliphobius* (Gomes Rodrigues and Šumbera, 2015), that shed their premolar teeth and substitutes them with new molars giving a higher, variable number from 20 to 28 teeth; and the NMR (Gomes Rodrigues and Šumbera, 2015) which only presents 3 molars (occasionally only 2) in each ramus for a total of 14–16 teeth (Kingdon, 2014). Therefore, the NMR also presents a reduced, variable number of teeth, when compared with other AMRs.

Ear

Another common trait of the DS is reduced or malformed ears (e.g., dogs, horses, pigs, rabbits, cattle, guinea pig; reviewed in Sánchez-Villagra et al., 2016; Lord et al., 2020). NCC contribute to the formation of all the components of the ear, and hearing defects are common in Human neurocristopathies (Ritter and Martin, 2019). Ears of AMR lack pinna whilst their closest relatives, the other African Hystricognath, all have well developed external auricles (Schlitter et al., 2014). The quantitative comparison of the NMR ear components with other AMRs (*B. suillus, C. hottentotus, F. micklemi, G. capensis*, and *H. argenteocinereus*) suggest that the NMR has a degenerated ear (Mason et al., 2016). They have a very narrow, semi occluded external canal, a smaller than expected and fused malleoincus, a poorly ossified part of the malleus, weakly developed long process of the incus, lack of structural stiffness of the stapes, reduced number of cochlear turns, and a relatively small auditory bulla (Mason et al., 2016). Furthermore, the ear morphology in the NMR shows a considerable intraspecific variation which could suggest that the ear is subjected to a relaxed selective pressure (Mason et al., 2016). Finally, some studies indicate that the NMR has relatively poor hearing, whilst other studies suggest that the auditory system is just adapted to the subterranean niche (reviewed in Braude et al., 2021).

Brain

Domestic animals (e.g., dog, cat, pig, alpaca, rabbit, mouse, horse) usually have smaller brains than their wild counterparts (reviewed in Sánchez-Villagra et al., 2016). Specifically, they tend to show an exacerbated reduction of the forebrain (mink, horse, pig, fox; Trut et al., 1991; Kruska, 2005; Wilkins et al., 2014). The brain size of the AMR has been quantitatively analysed under the hypothesis that social animals evolve larger brains in Kverková et al. (2018). However, on the contrary, they found that social AMR species have relatively smaller brains than solitary ones, with a statistically significant reduction in forebrain neurons. In particular, the NMR has a significantly smaller brain mass and fewer neurons in comparison with the other AMR (Supplementary Figure 1 in Kverková et al., 2018). This apparent
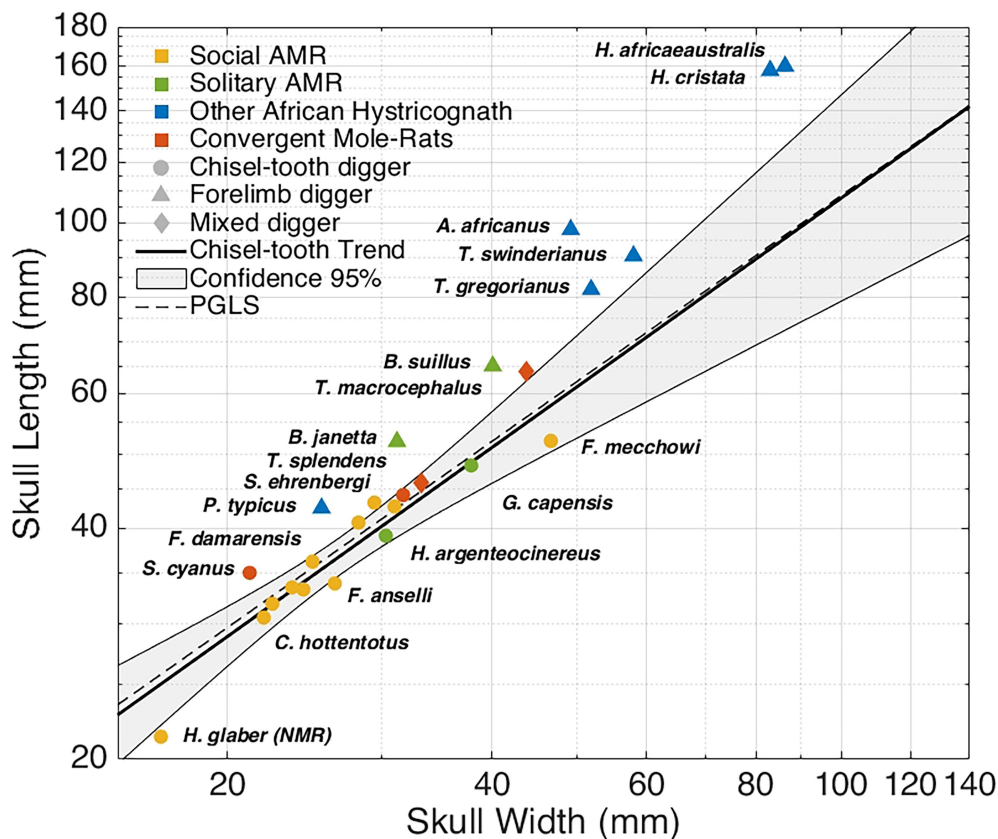
FIGURE 1

Relation between the length and width of the skull in African mole rats, their closes relatives, and convergent subterranean rodents. Chisel-tooth digging subterranean rodents present a smaller skull length/width ratio than forelimb diggers. The naked mole-rat (*Heterocephalus glaber*, NMR) has a significantly shorter snout even when compared to other chisel-tooth digging African mole-rats. Each data point is coloured according to its social or phylogenetic attributes as indicated in the figure. The shape represents digging mode. The linear regression line for chisel-tooth diggers with 95% confidence intervals is shown, together with the regression line based on phylogenetic generalized least squares (PGLS). All data was retrieved from Kingdon (2014) See Materials and methods in the SM for more details. PGLS was calculated using the evolutionary tree in Supplementary Figure 2.

contradiction could be explained by the self-domestication hypothesis, which instead predicts the smaller brain size of NMR.

Body and heart

A body size reduction occurred in early domestic breeds (pig, dog, cow, goat, and sheep) as a natural adaptation to the human environment (Tchernov and Horwitz, 1991). It could also be associated with self-domestication in islands (reviewed in Sánchez-Villagra et al., 2016), probably because of small or absent predation and low interspecies competition. The body size of AMR varies exponentially amongst species. Social AMR species tend to be smaller than the solitary ones (Table 1), with the NMR being the smallest ($\sim$30 g) and *B. suillus* the heaviest ($\sim$1 kg). In addition to its arguable dwarfism, the body of the NMR differs because it possesses a long tail (50% head-body length), whilst the other AMR present very short tails [8%−24% head-body length, depending on the genus (Table 1; Schlitter et al., 2014)]. Similarly, changes in the number of

caudal vertebrae occurred in a few domesticated species (dog, cat, sheep; Sánchez-Villagra et al., 2016). Moreover, many domestic animals show a shortening of the limbs (Sánchez-Villagra et al., 2016) and, likewise, the legs of the AMRs are generally described as "short and slender" (Schlitter et al., 2014). Recent analysis show that the forelimbs of NMR are less specialised and paedomorphic than the rest of AMR (Montoya-Sanhueza et al., 2022). Finally, a reduced heart size is one of the most common traits amongst domesticated species (e.g., mouse, rat, guinea pig, pig, dog; Sánchez-Villagra et al., 2016). Currently there are not quantitative comparisons of AMR heart sizes; however, allometric analysis suggests that the NMR has a disproportionally small heart in comparison with another rodent, the mouse (Grimes et al., 2013).

Skin and fur

Probably, complete or partial depigmentation is, along with increased tameness, the most frequent trait in the DS, appearing

TABLE 1 Selected domestication syndrome traits in the African mole rats.

Species	Sociality	Digging mode	Chisel-tooth digger rostrum length/ width ratio	Total teeth	Brain/ Body weight ratio	Weight (g)	Tail-Body length ratio	White forehead patch (size)	White forehead patch (frequency)	Breeding	Max litters/ year	Colony size
Heterocephalus glaber	Social	Chisel-tooth	Reduced	16*	Reduced	33.9	50%	NA	NA	Aseasonal	4	75 (2–300)
Cryptomys hottentotus	Social	Chisel-tooth	Normal	20	Expected	65.8	15%	Small	In some individuals	Seasonal	2	5 (2–14)
Fukomys bocagei	Social	Chisel-tooth	Normal	20	Expected	?	7%	?	Usually present	?	?	?
Fukomys darlingi	Social	Chisel-tooth	Normal	20	Expected	76.4	7%	Conspicuous	In some individuals	Aseasonal	4	5–9 individuals
Fukomys kafuensis	Social	Chisel-tooth	Normal	20	Expected	95	15%	Conspicuous	Most individuals	?	?	?
Fukomys anselli	Social	Chisel-tooth	Normal	20	Expected	96.1	8%	Conspicuous	Most individuals	Aseasonal	2	12 (2–25)
Fukomys damarensis	Social	Chisel-tooth	Normal	20	Expected	161	18%	Large	Always	Aseasonal	3	11 (2–41)
Fukomys foxi	Social	Chisel-tooth	Normal	20	Expected	?	8%	?	Usually present	?	?	?
Fukomys zechi	Social	Chisel-tooth	Normal	20	Expected	217	8%	?	Usually present	?	?	4 (1–7)
Fukomys ochraceocinereus	Social	Chisel-tooth	Normal	20	Expected	?	10%	Conspicuous	Usually present	?	?	?
Fukomys mecchowi	Social	Chisel-tooth	Reduced	20	Expected	370	8%	Very small	In some individuals	Aseasonal	3	2–20+
Heliophobius argenteocinereus	Solitary	Chisel-tooth	Normal	28*	Expected	190.1	9%	Small	In some individuals	Seasonal	?	NA
Georychus capensis	Solitary	Chisel-tooth	Normal	28	Expected	181	13%	Small	Often	Seasonal	2	NA
Bathyergus janetta	Solitary	Forelimb	Increased	28	Expected	439	24%	?	Often	Seasonal	1	NA
Bathyergus suillus	Solitary	Forelimb	Increased	28	Expected	896	18%	Small	In some individuals	Seasonal	2	NA

WHP: White forehead patch, not applicable (NA) for NMR because of its complete depigmentation. Colony size is NA for the solitary species. Interrogation mark (?) denotes missing data, * denotes a variable number of teeth (see Dentition). All data were retrieved from Kingdon (2014), except from "Brain/Body weight ratio" obtained from Kverková et al. (2018), and "Chisel-tooth digger rostrum" which compares the rostrum length of with the chisel-tooth digger trend as calculated in Figure 1.

in at least some varieties of each known domestic species (Sánchez-Villagra et al., 2016). In particular, a white forelock is a common characteristic of domestic animals and a noticeable feature of the Waardenburg syndrome, a human neurocristopathy (Wilkins et al., 2014). Furthermore, the white forelock has been recently associated with the self-domestication phenotype in marmoset monkeys (Ghazanfar et al., 2020). Interestingly, most AMR species occasionally present a white forehead patch of variable size (Figure 2). A recent report found no correlation between the size of the white forehead patch and the behaviour amongst *F. anselli* individuals (Begall et al., 2022). However, to our knowledge, the frequency and size of the white

forehead patch have not been quantified amongst different species. The currently available interspecies data, albeit incomplete and not completely quantitative (Kingdon, 2014), suggest that the white forehead patch tends to be more prominent and frequent amongst social species and reduced and only occasionally present in the solitary mole-rats (Table 1). The NMR appearance departs from the other AMRs because of its complete depigmentation, hairlessness, and skin folds. However, all these attributes are also characteristic of some domestic variates (dog, cow, pig, goat, rabbit; Sánchez-Villagra et al., 2016) and can be understood as a more extreme domestication phenotype.

FIGURE 2
White forehead patch in domestic species and African mole rats. Domestic species and some neurocristopathies are associated with large white patches on the forehead. Most African mole-rats present a white forehead patch which size and frequency could be associated with their social behaviour (Table 1). All images are available under Creative Common License. Authorship credit of the images in Supplementary Table 1.

Reproductive biology

A combination of body size reduction, earlier sexual maturation, increased litter size, non-seasonal oestrus cycles, and a decrease in sexual dimorphism generally allow domestic animals to have higher reproductive rates than their wild counterparts (Tchernov and Horwitz, 1991; Sánchez-Villagra et al., 2016). Non-seasonal reproduction, higher annual reproductive output, and absent or reduced sexual dimorphism seem to be more frequent amongst social AMR (*Cryptomys*, *Fukomys*, *Heterocephalus*), whilst the solitary, forelimb diggers (*Bathyergus*) present marked sexual dimorphism (Kingdon, 2014).

The lack of behavioural and morphological sexual dimorphism is exceptionally noticeable in the non-reproductive members of a NMR colony (MacManes and Lacey, 2012): The males lack scrotum, the females have an imperforated vagina; and, unlike any other mammal, the phallus (clitoris or penis), the anogenital distance, and the perineal muscles are sexually monomorphic (Jarvis, 1981; Peroulakis et al., 2002; Seney et al., 2009). They also lack sexual dimorphism in femoral bone structure and quality (Pinto et al., 2010) and forebrain regions (Holmes et al., 2008), which has been associated with the retention of a pre-pubertal phenotype in the worker castes (Holmes et al., 2007; Swift-Gallant et al., 2015; Peragine et al., 2017).

Whilst domestic animals seem to present an earlier sexual maturity, most of the individuals in a NMR colony never reproduce, and they remain all their life sexually suppressed in a pre-pubertal state until the breeding members need to be replaced (Faulkes et al., 1990, 1991). This phenomenon can be seen as an extreme version of neoteny. Indeed, neoteny has been classically used to explain many of the characteristic reproductive and behavioural changes that occur during domestication (Sánchez-Villagra et al., 2016). Many of the characteristic traits of the NMR can be considered neotenic (Skulachev et al., 2017; Buffenstein et al., 2020) such as the lack of hair, absence of scrotum or the decline of bone mineralisation with age (Buffenstein, 2008), which could be simultaneously related to the extraordinary social organisation and longevity of this species.

Hormones and social behaviour

Glucocorticoids mediate the long-term response to environmental and social stressful situations. A reduction of the concentration of corticosteroid hormones characterises both domestic animals (Belyaev, 1969; Trut, 1999; Wilkins et al., 2014; Kikusui et al., 2019) and subordinate individuals in cooperative breeding species (Creel, 2001; Sapolsky, 2005). In domesticated animals, the reduction of glucocorticoids could lower aggressive

behaviours and increase social tolerance, which could also be beneficial to maintain harmony within the group in cooperative breeding species. In this line, both eusocial species *F. damarensis* (Ganem and Bennett, 2004) and the NMR show little aggression amongst individuals of the same colony (O'riain and Jarvis, 1997). However, whilst *F. damarensis* manifest lower aggression against unfamiliar conspecifics, the NMR shows xenophobic behaviour (O'riain and Jarvis, 1997; Barker et al., 2021; Toor et al., 2022).

In NMR colonies, the queen displays most aggressive behaviours (Clarke and Faulkes, 2001); however, cortisol levels, the main glucocorticoid in the non-murine rodents (Buffenstein and Pinto, 2009), do not correlate with social or reproductive status either in the NMR (Clarke and Faulkes, 2001; Edwards et al., 2020) or *F. damarensis* (Medger et al., 2018) which suggest that social AMR do not suffer "stress of dominance" or "stress of subordination" (Edwards et al., 2020).

Nonetheless, cortisol levels rise after the death of the queen producing a violent period when individuals fight for the succession (Clarke and Faulkes, 1997; Medger et al., 2019), or in an individual isolated from the rest of the colony (Faykoo-Martinez et al., 2018; Edwards et al., 2020), indicating that they suffer from social stress as observed in marmoset monkeys (Smith and French, 1997) and tamarins (Ziegler et al., 1995), two cooperative breeding primates. Finally, in AMR species, there are no significant differences in the basal blood concentration of cortisol amongst non-pregnant females in one solitary species (*G. capensis*) and three social species (*F. darlingi, F. hottentotus pretoriae, F. damarensis*). However, only the solitary species showed an elevation of cortisol levels after repeated encounters with unfamiliar conspecific of the same sex (Ganem and Bennett, 2004). Altogether, these observations suggests that cooperative breeding species suppressed social stress to acquire social tolerance towards members of the same species.

Oxytocin is also a mediator of the HPA axis that has been associated with increased social cohesion and maternal behaviour in domesticated animals (Kikusui et al., 2019). In the same line, the NMR expresses more oxytocin receptor levels in the nucleus accumbens, a forebrain centre controlling monogamic, maternal and allomaternal behaviour in comparison with the solitary *G. capensis* (Kalamatianos et al., 2010). Moreover, non-breeding individuals of a NMR colony present more oxytocin-producing neurons than breeding individuals, suggesting that oxytocin contributes to maintaining the prosocial behaviour of the worker caste (Mooney and Holmes, 2013).

Other traits linked to an altered NCC functionality

The NMR shows a series of peculiar biological traits that are not generally included in the DS, but that could be explained through defects in the physiology of the NCC.

Peripheral nervous system

Most of the structures of the peripheral nervous system (cranial and spinal nerves and ganglia; and enteric nervous system) are derived from the NCC (Prendergast and Raible, 2014). The NMR also manifest alterations in the cutaneous innervation. It presents a significantly reduced ratio of unmyelinated nociceptive C-fibres and A-fibres in the saphenous and sural nerves (1.5:1), whilst in other AMRs (*H. argenteocinereus, F. mechowii, F. damarensis, F. darlingi, C. hottentotus*) and most mammals C-fibres generally are 3–4 times more abundant (Smith et al., 2012). Innervation defects are typical of certain neurocristopathies (Indo, 2009) and could be manifestation of mutations affecting the biology of NCC (see Trka below).

Thymus

NCC participate in the development of the stroma of the thymus, an organ necessary for the maturation of the T-cells (Zachariah and Cyster, 2010); and consequently, the T-cell population is affected in several neurocristopathies (Chinen et al., 2003; Vega-Lopez et al., 2018). The NMR has a reduced thymus/body weight ratio and presents a poor delineation between cortex and medulla in comparison to mice (Lin and Buffenstein, 2021). Moreover, the immune system of the NMR differs from mice and humans in having predominantly myeloid cells and a notable deficit in cytotoxic T-cells (Shebzukhov et al., 2019), which could be related to a defective thymus development due to alterations in the NCC.

Thyroid

The NCC also contribute to creating the stroma of the thyroids (Maeda et al., 2016) and altered thyroid function is a common trait amongst neurocristopathies (Vega-Lopez et al., 2018), and it has been previously associated with domestication (Crockford, 2004). Interestingly, the NMR exhibits unique low levels of thyroid hormone (Buffenstein et al., 2001; Buffenstein and Pinto, 2009).

Gall bladder

Gall bladder derives from the NCC (Mawe et al., 1997). Although most vertebrates possess this gland, it is absent in the NMR (Hill et al., 1957).

Gene candidates

Here we discuss some well-studied mutations in the NMR that are associated with the NCC physiology or with the control of the fear response.

Trka

Trka (tropomyosin receptor kinase A) binds to NGF (nerve growth factor), promoting survival and differentiation of the

sensory neurons during embryonic development, and modulating the sensitivity to pain later in life (Lewin et al., 2014). Trka is implicated in cell migration in normal and pathological conditions (Wislet et al., 2018); and it is necessary for the formation of the dorsal root and sympathetic ganglia by the trunk NCC in mouse (Smeyne et al., 1994).

In humans, mutations in the Trka gene produce congenital insensitivity to pain (CIP) with anhidrosis (CIPA), a neurocristopathy that results in a total loss of the C-fibres, lack of nociception, inability to sweat (hypotrophic sweat glands), lack of hair (bald patches in the scalp), poor thermoregulation, and oral and craniofacial manifestation including missing teeth and nasal malformations (Indo, 2009; Gao et al., 2013). Furthermore, CIPA patients seem to be unable to learn new fears and probably fail to exhibit a fight-or-flight response (Indo, 2009).

Knock out mice for Trka present a similar phenotype: Abnormal peripheral small nerves fibres, deficient nociception, small body size, early death, and severe cell loss in trigeminal, dorsal root, and sympathetic ganglia. However, they do not manifest anhidrosis, and over time they develop a mottled fur with scabs (Smeyne et al., 1994; Indo, 2009). Trka null mice also show an acute decrease of the basal forebrain cholinergic neurons (BFCNs). Notably, BFCNs have been implicated in the control of conditioned fear behaviours (Jiang et al., 2016), and mice lacking Trka signalling in the forebrain show defective fear conditioning (Sanchez-Ortiz et al., 2012). Furthermore, Trka null mice show a defective thymus formation with no clear delimitations between the cortex and the stroma and a reduced number of thymocites (Garcıa-Suárez et al., 2000).

The NCC hypothesis states that domesticated animals suffer a mild neurocristopathy produced by mutations that only partially reduce the activity of genes implicated in the NCC biology (Wilkins et al., 2014). The NMR possess between one and three amino acid substitutions in the kinase domain of Trka that turn the receptor hypofunctional which are absent or rare in other animals or amongst other AMR (Omerbašić et al., 2016). Moreover, the expression level of Trka in the NMR is significantly lower than that of mouse (Lewin, 2020). It is tempting to see many of the traits of the NMR as partly produced by a mild version of CIPA, caused by the reduced expression of a hypofunctional version of Trka. In this line, PRDM12 (PRDI-BF1 and RIZ homology domain containing protein 12), a transcription factor downstream of Trka also associated with CIP in humans (Desiderio et al., 2019), shows lower expression and unique amino acid variants in the NMR (Lewin, 2020). Altogether, mutations in the Trka pathway could explain the reduction in the C-fibres and the reduction in pain sensitivity in the NMR (Omerbašić et al., 2016); but also, the lack of fur and sweat glands, the poor thermoregulation, the reduced and defective thymus, missing teeth, shorter muzzle and the smaller forebrain. Indeed, Trka could provide a genetic connection between the neural crest and the reduction of the forebrain suggested by the neural crest domestication hypothesis (Wilkins et al., 2014). Finally, Trka mutations also seem to cause a reduction in the fear response in

mice and humans and could potentially explain the high social tolerance of the NMR.
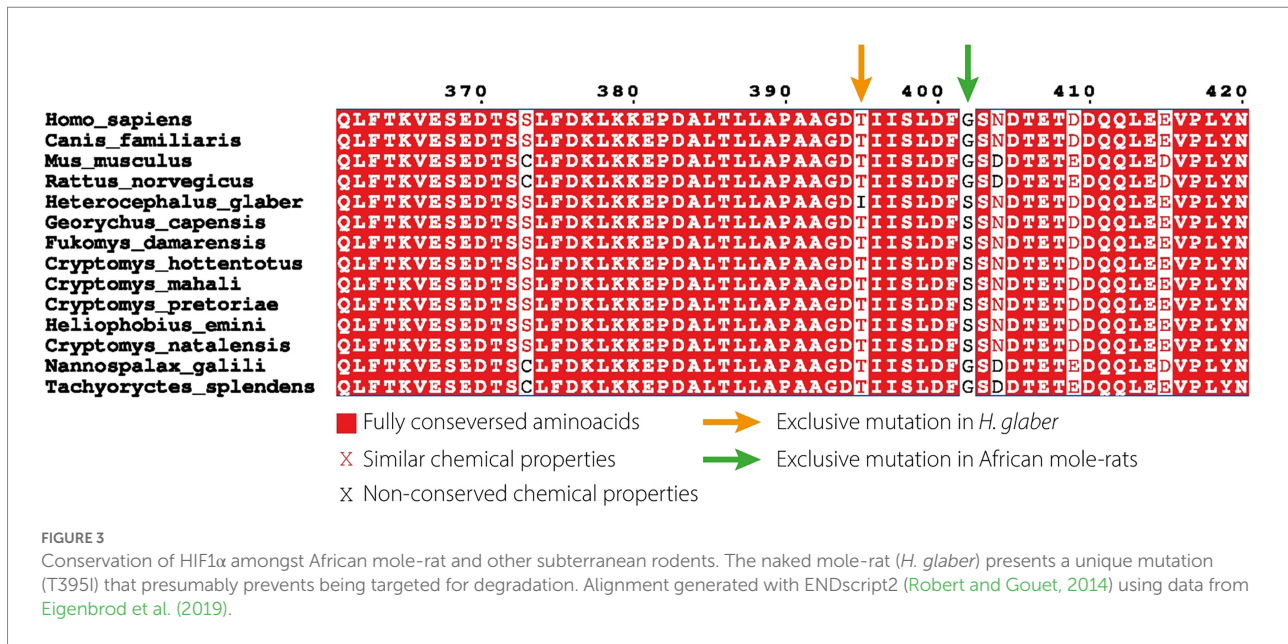
HIF1α

The NMR presents critical molecular adaptations to survive in hypoxic/hypercapnic environments produced by large numbers of individuals living in borrows (Park et al., 2021). For example, the NMR carries a hyperactive version of HIF1α (Hypoxia Inducible factor 1 α), a transcription factor that regulates the expression of dozens of genes in response to low-oxygen conditions. In normal-oxygen conditions, HIF1α is targeted for degradation by VHL (Von Hippel–Lindau tumour suppressor); however, low-oxygen levels prevent the HIF1α-VHL interaction. The NMR possesses a unique mutation in HIF1α (T395I, Figure 3) that prevents its interaction with VHL, as well as a mutation in VHL (V166I) which probably further reduces the ubiquitination of HIF1α (Kim et al., 2011). Moreover, the NMR expresses higher levels of HIF1α than mice in several tissues (Xiao et al., 2017). Lastly, HIF1α probably promotes a glycolytic metabolism (Varum et al., 2011; Prigione et al., 2014), a less efficient pathway to obtain ATP than oxidative phosphorylation that works in the absence of oxygen. Glycolysis produces lactic acid as a by-product, which blocks glycolysis by inhibiting PFK1 (phosphofructokinase 1). The NMR presents a unique adaptation to bypass the glycolysis block during hypoxia by using fructose (instead of glucose) as a substrate, enabling the glycolysis even in high lactic-acid conditions (Park et al., 2017).

Recently, it has been suggested that metabolic regulation is essential for the migration and differentiation of the NCC (Bhattacharya et al., 2021). Indeed, genetic disorders caused by mutations affecting the glucose metabolism produce severe congenital disabilities with severe craniofacial deformations similar to neurocristopathies (Chappell et al., 2009; Smith et al., 2014). The NCC switch to glycolytic metabolism during delamination and migration and return to oxidative phosphorylation during differentiation (Bhattacharya et al., 2021). In fact, HIF1α upregulates many NCC-specific genes and increased, and reduced HIF1α activity results in defects in the NCC migration (Barriga et al., 2013). Furthermore, alterations in VHL are associated with the von Hippel–Lindau syndrome, a neurocristopathy that can cause a variety of neoplasms, including the abnormal tissue growth of the adrenal gland (Vega-Lopez et al., 2018). Intriguingly, more than the 20% of the NMRs in a zoo study presented adrenal hyperplasia (Delaney et al., 2013).

ASIC4

The NMR also presents adaptations to protect the brain against acidification. Acidotoxicity occurs when the accumulation of lactic acid during hypoxia acidifies the medium to pathological

FIGURE 3
Conservation of HIF1α amongst African mole-rat and other subterranean rodents. The naked mole-rat (*H. glaber*) presents a unique mutation (T395I) that presumably prevents being targeted for degradation. Alignment generated with ENDscript2 (Robert and Gouet, 2014) using data from Eigenbrod et al. (2019).

levels, triggering the Ca^{2+} ASICs (acid-sensing ion channels; Xiong et al., 2004). The NMR shows a significantly reduced expression of ASIC4 in the brain compared to mouse, which protects its brain during acidosis (Husson and Smith, 2018). Furthermore, a recent report has identified ASIC4 as a marker of the early differentiation of the NCC (Faure et al., 2020), and ASICs expression has been implicated in the processing of the fear response (Wemmie et al., 2004; Vralsted et al., 2011; Taugher et al., 2017). In particular, ASIC4 in mice seems to modulate the freezing behaviour in the presence of predator odour, but not the shock-evoked fear learning (Lin et al., 2015). This way, mutations affecting the expression of ASICs could reduce the fight-or-flight response in the NMR giving rise to a more docile phenotype.

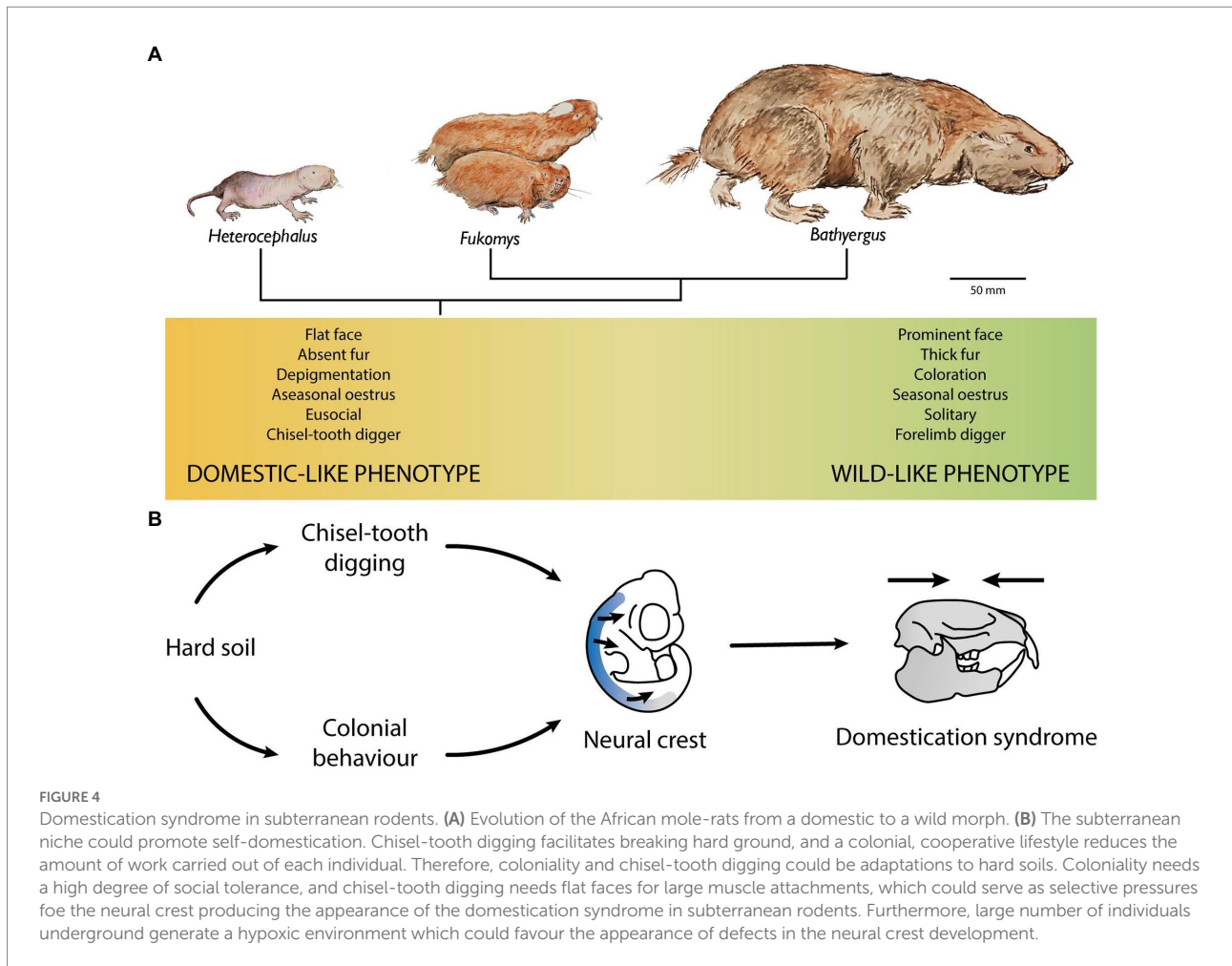## The subterranean niche and self-domestication

Although AMR and NMR present many of the expected attributes in underground rodents [fusiform body, short limbs, reduced external protuberances (Lacey and Patton, 2000)], many other NMR's traits cannot be simply explained by adaptation to subterranean niche (reduction of the forebrain, hairlessness, lack of sexual dimorphism, reduction of pain sensitivity, immature thymus). Instead, these traits could be associated with a mild-neurocristopathy.

Traditionally, the DS has been explained as a pleiotropic side effect of selecting for tameness (Belyaev, 1969; Wilkins et al., 2014). However, it is conceivable that the DS is a side effect of selecting for other traits associated with the NCC biology different from the reduction of the adrenal glands and the peripheral nervous system as proposed by Wilkins et al. (2014). We propose that the selection of chisel-tooth digging could result

in the appearance of the DS. Chisel-tooth digging is an adaptation to hard soils that requires the widening of the skull to enhance the attachment of larger muscles (Lacey and Patton, 2000; Mcintosh and Cox, 2016). Therefore, hard soils could impose an evolutionary pressure on the cranial NCC to favour the widening of the rostrum that, in turn, caused the appearance of the morphological and behavioural side effects associated with the DS. Furthermore, hard compacted soils can be better exploited in cooperation with other individuals to reduce the cost of burrowing extensive tunnels and improving the chances of finding dispersed food (Faulkes and Bennett, 2013). Consequently, the increased social tolerance associated with the DS could be directly beneficial for subterranean rodents. Curiously, amongst AMR, the only forelimb digger genus (*Bathyergus*) is solitary and territorially aggressive, whilst all social species (*Fukomys, Cryptomys, Heterocephalus*) are chisel-tooth diggers (Kingdon, 2014) which suggest that evolution of sociality is easier in chisel-tooth digging species.

Another factor that might have an important impact in the physiology of the NCC is the hypoxic subterranean environment. Adaptations to low oxygen conditions that affect the HIF1α gene-regulatory network and that promote a glycolytic metabolism could have an impact in the NCC migration (see HIF1α). Nevertheless, it is probable that hypoxic environments only get relevant to changing the NCC physiology as subterranean species become more social with larger colony sizes, as seen in the NMR, where hundreds of individuals can inhabit the same colony.

Finally, some of the characteristic traits of the DS could be either beneficial or neutral for a subterranean animal: the dwarfism, reduction of the ear, shortening of the limbs and flattening of the rostrum could be beneficial for moving through tunnels and digging, whilst alterations in colouration are probably

FIGURE 4
Domestication syndrome in subterranean rodents. **(A)** Evolution of the African mole-rats from a domestic to a wild morph. **(B)** The subterranean niche could promote self-domestication. Chisel-tooth digging facilitates breaking hard ground, and a colonial, cooperative lifestyle reduces the amount of work carried out of each individual. Therefore, coloniality and chisel-tooth digging could be adaptations to hard soils. Coloniality needs a high degree of social tolerance, and chisel-tooth digging needs flat faces for large muscle attachments, which could serve as selective pressures foe the neural crest producing the appearance of the domestication syndrome in subterranean rodents. Furthermore, large number of individuals underground generate a hypoxic environment which could favour the appearance of defects in the neural crest development.

less critical to animals living underground. Therefore, once a DS trait is selected (e.g., the flattening of the rostrum for chisel-tooth digging) the other associated traits will be maintained during evolution because they are beneficial or neutral for the subterranean environment.

In summary, we argue that the genes associated with the physiology of the NCC in the NMR have been under evolutionary pressure (Figure 4). We propose that hard soils associated with chisel-tooth digging, in conjunction with the tolerance of subterranean niche for DS traits, fostered the evolution of the DS in AMR. AMR ancestors evolved more solitary and aggressive behaviours -a wild-like phenotype- as they radiated towards more humid areas and encountered more resources and softer soils (Faulkes and Bennett, 2013). Indeed, whilst the solitary AMR (*Bathyergus*, *Georychus*, and *Heliophobius*) are restricted to more humid environments where digging is easier, all social AMR are chisel-tooth diggers (*Fukomys* and *Cryptomys*) that mostly inhabit coarse sandy soils and the eusocial AMR (NMR and Damaraland mole-rat) tend to live in areas with hard, compacted soils (Faulkes and Bennett, 2013).

Still, the preferred digging mode in the great majority of rodents is scratching the soil with their forelimbs (Vassallo et al., 2021). Indeed, forelimb digging is the primary digging mode in *Geomys* and *Ctenomys*, whilst many *Spalax* species are head-lift diggers (Lacey and Patton, 2000). Altogether, this suggest that that most subterranean rodents will not present domestication syndrome traits. Yet other, genetically unrelated, subterranean chisel-tooth digging species could also present signs of self-domestication. For example, *Spalax ehrenbergi* is a superspecies of chisel-tooth digging subterranean rodents that inhabit the eastern Mediterranean from Israel to Egypt. Similarly, to AMRs, they present morphological adaptations to living underground such as short limbs, wide crania (Figure 1), with varying coat colouration with occasional white forehead patches (Wolff and Sherman, 2008). Strikingly, although they are described as solitary, chromosomally distinct species present different ratios of aggressive and "pacifist" individuals. The Egyptian *Spalax* variant, which includes only "pacifist" animals, inhabits the aridest environment (Beiles et al., 1992) and can be distinguished by its shorter mandible (Corti et al., 1996). Furthermore, they present convergent genetic adaptations to the hypoxic environment (Fang et al., 2014; Zheng et al., 2022). Therefore, the Egyptian *Spalax* could also present DS traits.

Testing the NMR self-domestication hypothesis

The self-domestication hypothesis for NMR presented in this paper can be tested in various ways. First, new behavioural studies are necessary to evaluate the fear response in different AMR species, for example through the evaluation of the freezing behaviour in classic fear-conditioning experiments where a mild electric footshock is applied after an acoustic stimulus. However, the voltage threshold must be carefully calibrated for each species because they potentially present very different pain sensitivities (Lewin, 2020). Alternatively, the freezing behaviour could be measured in the presence of the odour of a predator relevant for AMR species, for example, using snake or small carnivore faeces (Kingdon, 2014). We expect AMRs with a more domesticated phenotype to present an altered fear-conditioned behaviour compared to solitary, forelimb diggers. Furthermore, it is difficult to compare the aggressiveness and fear response of eusocial and solitary species, because cooperative breeders can be affected by their ranking a reproductive status (Toor et al., 2022), variables that should be controlled. Gathering data on the size and activity of the adrenal glands and stress hormones during the fear response across different species could also be informative to test this hypothesis.

To test the implication of NCC in the evolution of AMRs we propose inter-species GFP-labelled NCC grafting experiments (Wilkins et al., 2014). We expect NCC from the NMR to show a deficient migration and/or differentiation in comparison with *Bathyergus* mole-rats. In addition, we expect that phylogenetic analysis of genes undergoing positive and relaxed selection (Mitterboeck et al., 2017) amongst AMR will highlight genes known for their involvement in NCC development or in neurocristopathies.

Finally, we propose the generation of an extensive database of subterranean and fossorial rodents containing their digging mode and other relevant morphological and behavioural traits. Using this database in combination with statistical analysis corrected by phylogeny to avoid evolutionary relationships affecting the independence of the individual samples (Freckleton et al., 2002), it would be possible to test if the digging mode in subterranean rodents is associated with DS traits and with an increased social behaviour.

Discussion

We showed that the NMR presents a phenotype compatible with the DS when compared with solitary AMRs. We suggest that the DS could be beneficial for the evolution of life underground; and that the digging mode, determined by the properties of the soil, could create an evolutionary pressure on the NCC that generated the DS amongst AMRs. Furthermore, we highlighted some known mutations compatible with the evolution of a domestic phenotype and proposed experiments to test our hypothesis.

Taken all these together, we propose that the high degree of social tolerance necessary for the evolution of cooperative breeding and eusociality in AMRs might have occurred through self-domestication. Hard soils could impose an evolutionary pressure towards chisel-tooth digging, which requires a flatter face to increase the muscle attachments. If the muzzle reduction occurs through the selection of less active NCC, this could generate the pleiotropic effects seen in domestic animals and in neurocristopathies and might increase the social tolerance as a side effect. Moreover, the gathering of large number of individuals in subterranean tunnels generates a hypoxic environment which could lead to molecular adaptations that affect to the NCC development, further enhancing a self-domesticated phenotype.

An increased social tolerance associated with self-domestication could be beneficial for subterranean rodents because a colonial, cooperative lifestyle reduces the digging work carried out for any individual and increases the chances to find disperse food (Faulkes and Bennett, 2013). Therefore, combination of scarce resources in increasingly arid environments (Faulkes and Bennett, 2013, 2016), together with the constraints imposed by hard soils and the underground environment, could create selective pressures that directly and indirectly lead to the self-domestication of the AMR. Intriguingly, in this way, the properties of the soil could act simultaneously as a distal (Faulkes and Bennett, 2013) and proximal factors for the evolution of sociality. In other words, the evolution of sociality in subterranean rodents could be initiated as a side effect of the underground environment and properties of the soil.

Previously, neoteny has been used as a unifying biological explanation of the many distinctive NMR's morphological and physiological traits (Skulachev et al., 2017; Buffenstein et al., 2020). Nevertheless, it is unclear what evolutionary pressures guided the evolution of a neotenic phenotype or how neotenic traits relate to each other. Instead, we argue that the self-domestication hypothesis is a more comprehensive framework for the evolution of the NMR. In fact, neoteny is often associated with a domestic phenotype, and neotenic and DS traits can be confounded (Sánchez-Villagra et al., 2016). Our hypothesis offers a clear rationale to explain many NMR's attributes, how they relate to each other and pinpoints the evolutionary pressures that drove them.

The DS can be controversial due to the lack of a consistent definition of the traits amongst different publications (Lord et al., 2020). Under the mild neurocristopathy theory of domestication, the DS is seen as a collection of pleiotropic effects of variable penetrance produced by mutations affecting the NCC, as can be readily seen in human neurocristopathies (Wilkins et al., 2014; Vega-Lopez et al., 2018). Furthermore, in viable animals, the effects of the mutations affecting the NCC can be further confounded by compensatory mutations in some of the altered organs (Pavlicev and Wagner, 2012).

For example, all the components of the ear in the NMR show signs of degeneration and intraspecific variation (Mason et al., 2016), however the NMR accumulated positively selected mutations affecting the cochlear hair bundles (Pyott et al., 2020). A plausible interpretation is that the general ear degeneration produced by a mild-neurocrystopathy was later compensated by mutations that readapted the NMR hearing to the subterranean environment. In addition, some other traits associated with DS are neutral in the subterranean niche, and as such, they will not be compensated. This relaxed selective pressure in the underground environment could produce the exacerbation of certain traits, explaining perhaps the highly variable white forehead patch or the defects in the pain perception in the AMR family. Thus, the AMR could show how the combination of positive compensatory selection and relaxed selection can produce variations within the DS.

The study of the NCC could guide future research in the NMR as an animal model and provide new clues to understand its extraordinary biological traits. The recognition of self-domestication and its pleiotropic effects could lead to a deeper understanding of the interactions of social behaviour and the physical environment during evolution.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

GSN envisioned the project and wrote the first version of the manuscript. GSN and KK acquired, analysed the data, and revised and corrected the manuscript. KK carried out the phylogenetic

analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articless/10.3389/fevo.2022.987177/full#supplementary-material

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