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Invited review

Current insights into the molecular genetic basis of dwarfism in livestock

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ABSTRACT

Impairment of bone growth at a young age leads to dwarfism in adulthood. Dwarfism can be categorised as either proportionate, an overall size reduction without changes in body proportions, or disproportionate, a size reduction in one or more limbs, with changes in body proportions. Many forms of dwarfism are inherited and result from structural disruptions or disrupted signalling pathways. Hormonal disruptions are evident in Brooksville miniature Brahman cattle and Z-linked dwarfism in chickens, caused by mutations in *GH1* and *GHR*. Furthermore, mutations in *IHH* are the underlying cause of creeper achondroplasia in chickens. Belgian blue cattle display proportionate dwarfism caused by a mutation in *RNF11*, while American Angus cattle dwarfism is caused by a mutation in *PRKG2*. Mutations in *EVC2* are associated with dwarfism in Japanese brown cattle and Tyrolean grey cattle. Fleckvieh dwarfism is caused by mutations in the *GON4L* gene. Mutations in *COL10A1* and *COL2A1* cause dwarfism in pigs and Holstein cattle, both associated with structural disruptions, while several mutations in *ACAN* are associated with bulldog-type dwarfism in Dexter cattle and dwarfism in American miniature horses. In other equine breeds, such as Shetland ponies and Friesian horses, dwarfism is caused by mutations in *SHOX* and *B4GALT7*. In Texel sheep, chondrodysplasia is associated with a deletion in *SLC13A1*. This review discusses genes known to be involved in these and other forms of dwarfism in livestock.

Introduction

Height, or stature, is determined by a variety of genetic factors and heritability of stature varies between breeds. In cattle, heritability of height is estimated at 0.71 in Holstein-Friesians and 0.83 in Angus cattle (Haile-Mariam et al., 2013; Nephawe et al., 2004; Northcutt and Wilson, 1993). In horses, heritability of height at the withers ranges from estimates of 0.25 in Trakehner horses to 0.72 in Franches-Montagnes horses and 0.89 in Shetland ponies (Pretorius et al., 2004; Signer-Hasler et al., 2012; Von Kaiser et al., 1991).

Although there is not a general definition applicable for all animal breeds, reduced height can be defined as dwarfism. Dwarfism, like height, can be heritable within breeds and can result from disturbances in growth processes. Examples of these growth processes are endochondral ossification, a process involving gradual replacement of cartilage by bone (Staines et al., 2013), and intramembranous ossification, a process involving the transition of mesenchymal cells into osteoblasts (Provot and Schipani, 2005).

Dwarfism can be categorised as either proportionate or disproportionate. In proportionate dwarfism, normal body proportions are maintained, while the overall height is reduced. An example of proportionate dwarfism is Laron type dwarfism in human beings (Woods, 2007). In disproportionate dwarfism there is a height reduction in one or several body parts. Body proportions are altered in disproportionate dwarfism.

There are several microevolutionary processes which underlie different genetic forms of dwarfism. Deliberate selection of dwarf animals occurs in breeds where dwarfism is a breed standard. In breeds such as the Chinese Banna miniature pig, dwarfism arises due to deliberate selection of dwarf animals for breeding (Deng et al., 2011). In livestock populations, balancing selection, or heterozygote advantage, is an important process in which causative genes for dwarfism are often linked to quantitative trait

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loci (QTL) for important production traits. Often, heterozygotes display a desired trait, while homozygotes display severe detrimental effects. This is visible in Nordic Red cattle, where heterozygotes for a deletion are associated with increased milk production rates, but where homozygotes for the same deletion are associated with embryonic lethality (Hedrick, 2015). Another process is genetic hitchhiking with a neighbouring gene variant that has an impact on a desirable single gene trait. The affected allele is located near to a gene undergoing a selective sweep for a desirable trait. Finally, in populations with a relatively small population size, genetic drift of a founder mutation can be responsible for genetic diseases, such as Ellis-van Creveld syndrome in Australian aboriginal populations (Goldblatt et al., 1992).

Phenotyping single gene dwarfism is straightforward. With the availability of high density single nucleotide polymorphism (SNP) arrays and whole genome sequencing, it is feasible to rapidly identify the genes and mutations underlying this condition, assuming well-phenotyped cases and controls are available. Simple PCR-based tests can then be developed for breeding management and elimination of the undesirable dwarfism traits in livestock. In this review article, we present an overview of heritable dwarfism caused by either signalling or structural disruptions. References to Online Mendelian Inheritance in Animals (OMIA),[1] a comparative knowledge base of genetic disorders in animals (Lenffer et al., 2006; Nicholas, 2003), and Online Mendelian Inheritance in Man (OMIM),[2] a comparative knowledge base of genetic disorders in human beings, will be provided where possible.

Signalling disruptions

Signalling disruptions include hormonal disruptions, disrupted signalling pathways or disrupted DNA regulation. The inherited forms of dwarfism in livestock caused by signalling disruptions are summarised in Table 1.

Dwarfism with a known causal mutation

Growth hormone 1 and growth hormone receptor

Brooksville miniature Brahman cattle display a proportionate form of dwarfism (OMIA001473-9913), with decreased growth hormone receptor (GHR) expression in the liver (Liu et al., 1999). These findings are similar to those of Laron-type dwarfism in human beings (MIM262500) (McCormack et al., 2009; Woods, 2007). Analysis of the growth hormone 1 gene (*GH1*) in affected animals has revealed a T200M mutation as the most likely cause of dwarfism in Brooksville miniature Brahman cattle (Liu et al., 1999). The threonine residue at position 200 is highly conserved in vertebrates and is one of eight amino acids that form salt bridges in the GH-GHR binding protein interface. In Laron-type dwarfism in human beings, a T175A *GH1* mutation reduces GH activity by 40% (Millar et al., 2003); similarly, a 40% reduction in GH activity is also evident in affected Brahman cattle. Decreased expression of (*GHR*) in the liver can be explained by a reduction in GH activity, which leads to reduced activity signal transducer and activator of transcription 5 activation (STAT5), leading in turn to lower levels of expression of *GHR* type 1A mRNA, a *GHR* mRNA transcript specifically expressed in the liver (McCormack et al., 2009; Radcliff et al., 2003). Since the causal mutation has been identified, implementing breeding strategies and PCR-based tests to prevent carrier matings can prevent further outbreaks of this recessive form of dwarfism.

A Z-linked recessive form of dwarfism, which is commercially important, occurs in chickens (OMIA000309-9031). In contrast to the mammalian XY sex determination system, where males are the heterogametic sex (XY), in the avian ZW sex determination system the female is the heterogametic sex (ZW). This form of Z-linked dwarfism in chickens is caused by at least two mutations in the *GHR* gene located on the Z-chromosome. Affected animals require less space and a smaller amount of food, which makes the mutant broiler breeder lines of economic value. In the Connecticut chicken strain, the causal mutation is a 1773 base pair (bp) deletion including the stop codon and the last 27 codons that encode a conserved amino acid sequence at the 3′ end of the *GHR* gene (Agarwal et al., 1994). However, in the Leghorn chicken strain, there is evidence against this deletion, indicating there are at least two mutations in the *GHR* gene (Hull et al., 1993).

The dwarf phenotype is subject to deliberate selection. Dwarf chickens have been widely used in cross breeding of broilers and laying hens (Huang et al., 2016). Egg production in laying hens can be improved by reducing body size. Although feed restriction is usually practised to improve egg production, the dwarfing mutation reduces feed intake and body size without the use of feed restriction, while egg production is maintained (Tona et al., 2003). Therefore, deliberate selection of the dwarf genotype can improve egg production without compromising animal welfare.

Ring finger protein 11

A form of proportionate dwarfism, or growth retardation, exists in the heavily muscled Belgian blue cattle (OMIA 001686-9913). In around 40% of animals with this type of growth retardation, it is caused by a splice site mutation, c.124-2A > G, in the gene encoding ring finger protein 11 (*RNF11*). This protein is highly conserved, ubiquitously expressed, and complexes with the A20 enzyme, also known as tumour necrosis factor (TNF) α-induced protein 3 (TNFAIP3). This complex ensures transient activation of inflammatory signalling pathways, such as downregulating nuclear factor κ light chain-enhancer of activated B cells (NF-κB) signalling (Shembade et al., 2009). Approximately one third of homozygous GG mutants die before 6 months of age owing to infection. When homozygous individuals survive, they exhibit stunted growth and are culled. Taking this into account, the carrier frequency (~26%) is puzzlingly high. Carriers may exhibit a favourable trait in comparison with non-carriers or homozygous animals, resulting in heterozygote advantage at the causative locus and thus positive selection of carriers (Sartelet et al., 2012a).

Heterozygote advantage is also visible in crooked tail syndrome (CTS) in Belgian blue cattle. CTS is caused by two mutations in the gene for mannose receptor C type 2 (*MRC2*). Both mutations in *MRC2* are associated with desired traits, such as enhanced muscularity (Fasquelle et al., 2009; Sartelet et al., 2012b). Although genetic forms of dwarfism are nearly always allelically homogeneous and are therefore relatively easy to map, breeders will select for heterozygotes if a mutation renders a selective advantage to carriers. This process tends to be further accelerated by animal breeding programmes, particularly artificial insemination, allowing excessive use of popular sires (Sartelet et al., 2012b).

The exact causative process remains unclear. The *RNF11* mutation may cause growth retardation secondary to inflammation, but the gene is highly expressed during osteogenesis in bone cells, another process that is possibly disturbed in dwarfs. Also, RNF11 may be a modulator of transforming growth factor β and epidermal growth factor receptor signalling, two processes involved in bone growth (Gao et al., 2005). Elimination of the dwarfism phenotype is relatively easy using PCR-based gene tests and breeding programmes. However, knowledge of the causative

[1] See: http://omia.angis.org.au (accessed 22 May 2017).
[2] See: https://omim.org (accessed 22 May 2017).

Table 1
Dwarfism in livestock due to hormonal disruptions or other disruptions of signalling pathways.

Subtype	Gene	Species and breed	Mutation	Phenotype	Type	Gene function	Inheritance pattern	Cross species comparison	References
Hormonal/ hormone receptor disruptions	*GH1*[a]	Brooksville miniature Brahman cattle	T200M mutation	Dwarfism, mild	Proportionate	*GH1* is important for growth, shows 60% of normal function in affected animals	Autosomal recessive	Human—Laron-type dwarfism with the same 40% GH reduction due to a T175A mutation	McCormack et al. (2009)
	GHR[b]	Chickens	Varies depending on strain: 1773 bp deletion in connecticut chicken strain	Z-linked dwarfism	Proportionate	*GHR* encodes a receptor which binds growth hormone	Z-linked, recessive	Phenotype present in several dwarf chicken strains	Agarwal et al. (1994)
Disrupted signalling pathways	*RNF11*[c]	Belgian blue cattle	A > G splice site mutation	Dwarfism with pathogen resistance	Proportionate	The encoded RING finger protein 11 complexes with the A20 enzyme, which has a role in down-regulating NF-κβ	Autosomal recessive	No resemblance known	Sartelet et al. (2012a)
	PRKG2[d]	American Angus cattle	C > T nonsense mutation, truncating 85 amino acid residues	Dwarfism, with vertebral abnormalities	Disproportionate	*PRKG2* down-regulates type II collagen synthesis	Autosomal recessive	Phenotype resembles dwarfism in Charolais calves	Koltes et al. (2009)
	EVC2[e]	Japanese brown cattle	Two mutations: (1) C > T transition causing a 56 bp deletion; (2) CA > G frameshift mutation	Bovine chondrodysplastic dwarfism	Disproportionate	*EVC2* may have a direct or indirect effect on proliferating chondrocytes and perhaps a role in osteogenesis and/or Ca^{2+} homeostasis	Autosomal recessive	Diseases involving *EVC2*: 1) Dwarfism in Tyrolean grey cattle 2) Ellis-van Creveld syndrome and Weyers acrofacial dysostosis in human beings	Takeda et al. (2002)
	EVC2[e]	Tyrolean grey cattle	2 bp (AC) deletion	Chondrodysplastic dwarfism, seven calves in the summer of 2013	Disproportionate	*EVC2* may have a direct or indirect effect on proliferating chondrocytes and perhaps a role in osteogenesis and/or Ca^{2+} homeostasis	Autosomal recessive	Diseases involving *EVC2*: 1) Dwarfism in Japanese brown cattle 2) Ellis-van Creveld syndrome and Weyers acrofacial dysostosis in human beings	Murgiano et al. (2014)
	IHH[f]	Chickens	11,896 bp deletion	Creeper achondroplasia	Disproportionate	*IHH* has significant roles in bone formation, gut development and skeletal morphogenesis	Autosomal semi-dominant	Possible human homologs: 1) Brachydactyly type A1 2) Acrocapitofemoral dysplasia	Jin et al. (2016)
Suspected disrupted DNA regulation	*GON4L*[g]	Fleckvieh cattle	1 bp (C) deletion	Dwarfism	Proportionate	*GON4L* has roles in transcriptional repression, compromising cell-cycle progression and regulating DNA damage	Autosomal recessive	Phenotype resembles primordial dwarfism in human beings	Schwarzenbacher et al. (2016)
Suspected mutations	Suspected *GH*[a] or *GHR*[b]	Chinese Banna miniature pig	Unknown	Dwarfism	Proportionate	*GH1* is important for growth; *GHR* encodes a receptor which binds growth hormone	Inheritance pattern unknown	Phenotype resembles proportionate dwarfism in Miniature Brahman cattle and Holstein cattle	Deng et al. (2011)
	Suspected *IGF1R*[h] reduction or *GHR*[b] reduction	Holstein cattle	Unknown	Dwarfism	Proportionate	*IGF1R* encodes insulin-like growth factor 1 receptor; *GHR* encodes a receptor which binds growth hormone	Autosomal incompletely dominant	Phenotype resembles proportionate dwarfism in Australian Angus and Miniature Brahman cattle	Blum et al. (2007)

[a] GH1, growth hormone 1.
[b] GHR, growth hormone receptor.
[c] RNF11, ring finger protein 11.
[d] PRKG2, cGMP-dependent protein kinase type II.
[e] EVC2, EvC ciliary complex subunit 2.
[f] IHH, Indian hedgehog.
[g] GON4L, gon-4 like.
[h] IGF1R, insulin growth factor-1 receptor.

mutation may increase heterozygote frequency, since assisted selection will make it possible to avoid risk matings, while still allowing selection for the desired heterozygote trait (Druet et al., 2014).

cGMP-dependent protein kinase type II

Dwarfism in American Angus cattle is an autosomal recessive form of achondroplasia and presents as disproportionate dwarfism (OMIA001485-9913). Endochondral ossification is reduced at the growth plates, with protrusion of the alar wing of the basisphenoid bone into the cranial cavity, abnormalities of the ventral vertebral bodies and curvature of the vertebral processes (Mishra and Reecy, 2003). A region spanning from 0.8 to 2.8 cM on bovine chromosome 6 (BTA6) was discovered to be critical. Of five candidate genes identified, only one contained a coding mutation; this was a C > T mutation in the cGMP-dependent protein kinase type II gene (*PRKG2*), which introduced a premature stop codon, leading to truncation by 85 amino acid residues (Koltes et al., 2009).

The protein encoded by *PRKG2* downregulates type II collagen synthesis by activating SRY-box 9 (SOX9) (Chikuda et al., 2004). It is hypothesised that the kinase domain of mutant PRKG2 may be unable to downregulate type II collagen, resulting in impaired regulation of SOX9 levels. It is notable that type II and type X collagen are increased in the growth plate cartilage of dwarfs (Koltes et al., 2009). The function of PRKG2 remains unclear; however, it is an important element in signal transduction pathways in the brain, growth plate cartilage, jejunum, kidney, lung and pancreas. The causative mutation in *PRKG2* is presumably in linkage disequilibrium with one or several neighbouring QTL for production traits in cattle. Genetic hitchhiking with this neighbouring gene variant has increased homozygosity for that region. In addition, there was a certain period in history during which animals were selected for a stocky and short-legged phenotype (Koltes et al., 2009).

EvC ciliary complex subunit 2

Two mutations in the EvC ciliary complex subunit 2 gene (*EVC2*) are associated with an autosomal recessive form of dwarfism in Japanese brown cattle known as bovine chondrodysplastic dwarfism (OMIA000187-9913). Affected animals display disproportionate dwarfism with short limbs, joint abnormalities and ateliosis. Endochondral ossification is insufficient, with irregular chondrocyte arrangement and abnormal cartilaginous matrix formation (Takeda et al., 2002).

Two mutations have been identified in the *EVC2* gene occur on the distal short arm end of BTA6; these are a single nucleotide substitution and a 1 bp deletion. The first mutation, a C > T transition at position 1356 of the coding DNA sequence, introduces a cryptic splice donor site into exon 11, which causes a deletion of 56 nucleotides and thus a frameshift in the mRNA. The second mutation, a CA > G mutation at position 2054–2055, causes a frameshift that introduces a premature stop codon. The resulting protein is shortened by 42%. Affected calves are either homozygous for the CA > G deletion or compound heterozygous for the C > T transition and CA > G deletion (Takeda et al., 2002).

In mice, the *EVC2* gene is expressed in the cranial bones, long bones, kidneys and heart, and in embryos. In mouse embryos at embryonic day 17, the gene is strongly expressed in proliferating chondrocytes, but weakly expressed in other zones of the epiphyseal growth plates (Takeda et al., 2002). The *EVC* gene is responsible for Ellis-van Creveld syndrome in human beings; affected individuals exhibit short limbs and ribs, polydactyly, orofacial abnormalities, and dysplastic nails and teeth (MIM225500) (Ruiz-Perez et al., 2000). *EVC2* and *EVC* are arranged in a head-to-head genomic configuration in cattle, human beings and mice, with similar expression patterns, and mutations in these genes are responsible for short limb disorders.

Recessive mutations in the *EVC* gene are associated with Ellis-van Creveld syndrome in human beings and have also been found in Tyrolean grey cattle with dwarfism (OMIA000187-9913). Calves are born with abnormally short limbs, rotated and arched, with pronounced joint laxity; the most severely shortened bones are the femur and humerus (Murgiano et al., 2014). Cases have also exhibited abdominal cryptorchidism and heart defects, including cardiomegaly and myxomatous valvular degeneration (Muscatello et al., 2015). On histopathology, there are irregular growth plates in long bones and vertebrae, with premature closure of the growth plates and disorganisation of chondrocyte columns. The genital tracts of females were fully mature when examined at 2 months of age (Murgiano et al., 2014). A critical region on BTA6 was identified by homozygosity mapping and a 2 bp (AC) deletion was found in exon 19 of *EVC2*, corresponding to positions 2993–2994 of the mRNA. The allele frequency of the deletion was 15% in the Italian population of Tyrolean grey cattle. The mutation is predicted to cause a frameshift that introduces a premature stop codon, likely leading to a physiologically inactive protein (Murgiano et al., 2014).

The phenotypes of Japanese brown and Tyrolean grey cattle with dwarfism are similar to each other, but less severe than the corresponding human phenotype. Human patients with Ellis-van Creveld syndrome have abnormal genitalia, whereas this feature is only evident in female Tyrolean grey calves (D'asdia et al., 2013; McKusick et al., 1964; Murgiano et al., 2014).

The two cattle breeds are affected by different mutations that are 939 bp apart; a 1 bp deletion in Japanese brown cattle and a 2 bp deletion in Tyrolean grey cattle both lead to a shortened protein. Japanese brown cattle are also affected by a second, previously mentioned, C > T substitution which leads to a frameshift (Takeda et al., 2002). The Tyrolean grey breed has a relatively small effective population size. Therefore, genetic drift of a founder mutation is a likely cause for this recessive form of dwarfism. With the use of genotyping and next generation sequencing, it is feasible to develop a PCR-based genetic test to prevent further risk mating, thereby eliminating the disease.

Indian hedgehog

Creeper achondroplasia is described in chickens (OMIA000006-9031) and is associated with short, stunted legs, chondrodystrophy and a reduction in body size (Elmer, 1968). It is determined by an autosomal dominant lethal gene; homozygous mutations are lethal during embryonic development, whereas heterozygotes exhibit the creeper phenotype (Jin et al., 2016). The mutation is a deletion of 11,896 bp on GGA7 across the Indian hedgehog gene (*IHH*).

IHH has an important role in skeletal morphogenesis and IHH expression is reduced in affected chickens during cartilage development. There are two possible human homologues caused by single point mutations in *IHH*: type A1 brachydactyly and acrocapitofemoral dysplasia. Type A1 brachydactily is caused by a heterozygous mutation on chromosome 2q35 (MIM112500), a 298G-A transition in *IHH* found in several unrelated families (Giordano et al., 2003; McCready et al., 2002). However, there is a mild form of type A1 brachydactily caused by a single nucleotide deletion (Lodder et al., 2008). Acrocapitofemoral dysplasia (MIM607778), a form of skeletal dysplasia characterised by short stature, is caused by homozygous missense mutation, a 137C-T transition, in the N-terminal signalling region of *IHH* (Hellemans et al., 2003).

Gon-4-like

Proportionate dwarfism in Fleckvieh cattle is characterised by low birth weights (~15 kg) and craniofacial abnormalities, such as

brachygnathia inferior and spinal distortions (OMIA001985-9913). Other abnormalities, including wrinkled skin and a disproportionately large head, become visible during further growth. This form of dwarfism has an autosomal recessive pattern of inheritance and the causal mutation is a 1 bp C deletion in exon 20 of the Gon-4-like gene (*GON4L*). This mutation causes a frameshift, leading to a premature translation termination codon at position 1492, thus shortening the Gon-4-like protein by 33%. Use of a carrier bull for artificial insemination has caused an accumulation of calves homozygous for the deleterious mutation (Schwarzenbacher et al., 2016).

Gon-4-like protein has transcriptional repressor activity and may play a role in compromising cell cycle progression and DNA damage. Gon-4-like protein also has a role in B cell differentiation. Although the exact mechanism behind this form of dwarfism in Fleckvieh cattle is unknown, DNA damage response processes are essential for embryonic development (Schwarzenbacher et al., 2016). Dwarfism in Fleckvieh cattle resembles human primordial dwarfism resulting from DNA repair disorders (Harley et al., 2016; Woods, 1998). Defective DNA damage responses might be involved in affected Fleckvieh animals. It should be possible to prevent the birth of homozygous calves by identifying carrier animals through genotyping assays and genome-based breeding strategies to avoid carrier matings (Schwarzenbacher et al., 2016).

Dwarfism with suspected mutations

In some instances, dwarfism is part of the breed standard and thus is the result of deliberate selection. Mutations in *GH1* are associated with proportionate dwarfism as a breed standard in Chinese Banna miniature pigs. In this breed, five mutations have been observed in the *GH1* gene; three mutations are non-synonymous and correspond to the amino acid substitutions A9V, R22Q and S104P (Deng et al., 2011). The substitutions at positions nine and 22 affect the signal peptide, whereas the substitution at position 104 is located in the mature GH protein. Nine mutations occur in the *GHR* gene; four out of nine mutations are non-synonymous (E381D, A409S, L556V and A580G), any of which may influence downstream signal transduction by the GHR. It is very likely that all documented variants are almost certain to be fixed in the Chinese Banna miniature pig population (Deng et al., 2011). Further studies are required to elucidate the relationship between these mutations and dwarfism.

In Holstein cattle, there are reports of dwarfs with retarded proportionate growth (OMIA000308-9913). A study involving three affected animals, four unaffected half-siblings and four unrelated controls revealed reduced GHR expression in the liver, but not in the muscles of the affected animals. Insulin-like growth factor 1 receptor gene (*IGF1R*) mRNA levels in liver and muscle were higher in half siblings and controls than in dwarfs. IGF1R protein levels in muscle and liver tissues were also higher in half siblings than in dwarfs. Although the genetic cause remains unknown, there is an indication that a reduction in IGF1R levels causes this form of dwarfism in Holstein calves (Blum et al., 2007).

Dwarfism with no known cause

Several reports describe dwarfism due to a founder mutation. A mild form of dwarfism with an autosomal recessive pattern of inheritance was reported in four Jersey cows, all descendants of one sire (OMIA000308-9913) (Mead et al., 1942). More than 20 Charolais calves, again the progeny of one bull, were affected by dwarfism with an incomplete autosomal dominant pattern of inheritance (Gregory and Spahr, 1979). There are several documented cases of proportionate dwarfism in European cattle breeds, including the Brown Swiss, Simmental, German black and German red, with anomalies such as hydrocephalus, cryptorchidism, microphthalmia and ventricular septal defect (Herzog et al., 1982). Another example is a proportionate form of dwarfism in Australian Angus cattle that exhibits an autosomal dominant pattern of inheritance with incomplete penetrance (Fig. 1) (Latter et al., 2006).

Structural disruptions

Structural disruptions affect bone and cartilage development and extracellular matrix components. The genetic forms of dwarfism associated with structural disruptions characterised to date are summarised in Table 2.

Dwarfism with a known causal mutation

α1 Chain of type X collagen

In domestic pigs, there is a form of dwarfism that develops over time after birth (OMIA001718-9825). Affected animals exhibit dwarfism and metaphyseal chondrodysplasia. Bones are shorter in length, but their diameter is increased. The physes and metaphyses of long bones, the metacarpal and metatarsal bones, the ribs and costochondral junctions are affected. There is radiodense striation of the metaphysis on radiography, indicative of mineralised osteoid deposition. In general, there is excessive cartilage and reduced bone in the metaphyses. There are no changes in the phalanges or spine. Histological analysis demonstrates abnormal zones of hypertrophy with disorganised chondrocyte columns; hyperplastic chondrocytes are irregular and varied in size (Nielsen et al., 2000). Type X collagen is expressed during endochondral ossification by hypertrophic chondrocytes.

The mutation found in pigs is a G590R mutation in the signal C-terminal domain of the α1 chain of type X collagen gene (*COL10A1*). It has an autosomal dominant pattern of inheritance. The mutation leads to impairment of trimerisation of type X collagen. This decreases the availability of functional trimers, which is in turn an indication that the growth plate abnormalities are the result of a reduction in type X collagen (Nielsen et al., 2000).

Schmid metaphyseal chondrodysplasia (SMCD) is a mild disorder of skeletal development in human beings characterised by dwarfism and abnormalities in the growth plate (MIM156500). The causative mutation lies in the *COL10A1* gene (Warman et al., 1993). Several studies (Chan et al., 1995, 1996, 1998) indicate that there is a reduced amount of functional collagen chains in individuals with SMCD. The causative mutation in type X collagen disturbs long bone growth as a result of this reduction; this

Fig. 1. Proportionate dwarfism in Australian Angus cattle (Latter et al., 2006); a 1-day-old Angus dwarf calf is shown on the right and a normal calf is shown on the left. Reproduced with permission from Latter et al. (2006).

Table 2
Dwarfism due to structural disruptions.

Subtype	Gene	Species	Mutation	Phenotype	Type	Gene function	Inheritance pattern	Cross species comparison	References
Bone/ cartilage development	*COL10A1*[a]	Domestic pigs	G590R mutation in C-terminal domain	Dwarfism	Disproportionate (relatively mild)	*COL10A1* encodes type X collagen	Autosomal dominant	*COL10A1* mutations are associated with Schmid metaphyseal chondrodysplasia (SMCD) in human beings	Nielsen et al. (2000)
	SHOX[b]/ *CRLF2*[c]	Shetland ponies	Two mutations: (1) ~80 kb deletion; (2) ~160 kb deletion	Skeletal atavism	Disproportionate	*SHOX* regulates elements of growth and development (e.g. chondrocyte function in growth plate, cell cycle regulator); *CRLF2* has roles in haematopoietic cell development and bone metabolism	Autosomal recessive	Similar to skeletal atavism in American miniature horses and dwarfism in Friesian horses. *SHOX* mutations are associated with Léri-Weill dyschondrosteosis and idiopathic short stature in human beings	Rafati et al. (2016)
Extracellular matrix components	*ACAN*[d]	Dexter cattle	Two mutations: (1) C > T transition introducing a new start codon; (2) GGCA insertion, frameshift mutation	Bulldog-type dwarfism	Disproportionate	Aggrecan: large proteoglycan of cartilage (provides structure)	Suspected: autosomal recessive, but heterozygotes display mild form of dwarfism	Diseases associated with *ACAN* mutations: (1) Cartilage matrix deficiency in mice; (2) Nanomelia in chickens; (3) Kimberly-type spondyloepiphyseal dysplasia in human beings	Harper et al. (1998), Cavanagh et al. (2007)
	ACAN[d]	American miniature horses	Four frameshift mutations: (1) 1 bp deletion in exon 2; (2) G > A transition in exon 6; (3) 1 bp deletion in exon 11: (4) 21 bp deletion in exon 15	Two forms of dwarfism: (1) Chondrodysplasia-like dwarfism; (2) Skeletal atavism	Disproportionate	Aggrecan; large proteoglycan of cartilage (provides structure)	Autosomal recessive; genetic cause for skeletal atavism unknown	*D1* allele phenotype is similar to bulldog-type dwarfism in Dexter cattle; Skeletal atavism is similar to dwarfism seen in Friesian horses (see diseases involving *ACAN* under Dexter cattle above)	Eberth (2013)
	COL2A1[e]	Holstein cattle	G > A missense mutation	Bulldog-type dwarfism	Disproportionate	*COL2A1* encodes the α1 chain of type II Collagen	Autosomal dominant mutation, but the sire to which the cases could be traced back was mosaic for the mutation	Resembles achondrogenesis type II in human beings	Daetwyler et al. (2014)
	B4GALT7[f]	Friesian horses	C > T missense mutation	Dwarfism	Disproportionate	*B4GALT7* encodes an enzyme for glycosylation	Autosomal recessive	Similar to skeletal atavism in American miniature horses and Shetland ponies; diseases associated with mutations in *B4GALT7*: (1) Ehlers-Danlos syndrome in human beings; (2) Larsen of Reunion Island syndrome	Orr et al. (2010), Leegwater et al. (2016)
	SLC13A1[g]	Texel sheep	1 bp (T) deletion	Chondrodysplasia (wide stance, varus deviation, tracheal collapse)	Disproportionate severe (death within 4 months of birth)	*SLC13A1* encodes a sodium/sulphate transporter with several roles in cellular metabolism and bone and cartilage formation	Autosomal recessive	No resemblance known	Thompson et al. (2005), Zhao et al. (2012)

[a] COL10A1, type X collagen.
[b] SHOX, short stature homeobox.
[c] CRLF2, cytokine receptor-like factor 2.
[d] ACAN, aggrecan.
[e] COL2A1, type II collagen.
[f] B4GALT7, beta-1,4-galactosyltransferase 7.
[g] SLC13A1, solute carrier family 13 member 1.

hypothesis is supported by the lack of α1 chains in the growth plates of patients with SMCD (Nielsen et al., 2000). The radiodense striation of the metaphysis is typical of SMCD; human patients with SMCD exhibit striation in the physes and metaphyses of the long bones and ribs (Rimoin et al., 1976). Affected pigs also show abnormally developed thoracic vertebrae, scapulae and metatarsal and metacarpal bones; this difference may be explained by differences in growth rate and skeletal bone load (Nielsen et al., 2000).

Short stature homeobox

Skeletal atavism in Shetland ponies (OMIA002013-9796) is associated with two mutations in the pseudoautosomal region of the X/Y chromosome that delete a large region of the short stature homeobox gene (*SHOX*) and regions of the cytokine receptor-like factor 2 gene (*CRLF2*). The phenotype is similar to osteochondrodysplasia in Friesian horses and skeletal atavism in American miniature horses. There are two deletions, one a ~160 kbp deletion in conjunction with the *SHOX* gene and the other a ~80 kbp deletion overlapping the *SHOX* gene. Both mutations delete a downstream region of the *CRLF2* gene. The distal part of the larger deletion appears to correspond to the smaller deletion (Rafati et al., 2016). Mutations in *SHOX* have also been associated with short stature in human beings; for example, a 47 kbp deletion downstream of *SHOX* is the causative mutation of Léri-Weill dyschondrosteosis and idiopathic short stature in human beings (Benito-Sanz et al., 2012).

SHOX is essential during development as a cell cycle regulator and as a transcriptional activator in osteoclasts and osteoblasts (Rao et al., 2001). CRLF2 is a cytokine receptor with roles in haematopoietic cell development and bone metabolism (Al-Shami et al., 2004; Li, 2013). Heterozygotes did not exhibit a difference in height, indicating that there is no association between the mutations and height (Rafati et al., 2016). A PCR-based genetic test could be used to eliminate skeletal atavism from the Shetland pony breed.

Aggrecan

Bulldog-type dwarfism is reported in Dexter cattle (OMIA001271-9913); in these animals, the disorder is caused by abnormal cartilage development. Affected individuals are usually aborted at 7 months of gestation. The phenotype is one of extreme disproportionate dwarfism, with a short vertebral column, micromelia and a large abdominal hernia. The head is relatively large, with a retruded muzzle, cleft palate and protruding tongue (Fig. 2A), while the legs are short (Fig. 2B).

The causative mutations comprise a C > T transition and a GGCA insertion in the aggrecan gene (*ACAN*). The C > T transition is predicted to introduce a new start codon located 199 bp upstream of the original start codon. The GGCA insertion causes a frameshift mutation and a premature stop codon in exon 11 (Cavanagh et al., 2007). Normal aggrecan consists of 2327 amino acids, whereas mutated aggrecan consists of 91 amino acids. Both mutations account for all the animals tested, including a compound heterozygote animal and homozygous animals for both mutations. Aggrecan is a large aggregating proteoglycan present in cartilage. It is essential for providing the structure of cartilage by, for example, resisting compression (Cavanagh et al., 2007).

Bulldog-type dwarfism in Dexter cattle is a likely example of heterozygote advantage. The desired Dexter phenotype features short legs, a feature predominantly displayed by heterozygous animals. Artificial selection has favoured this Dexter phenotype above the wild-type Dexter cattle, thus maintaining a very high frequency of a lethal allele (Cavanagh et al., 2007).

The American miniature horse is also affected by dwarfism (OMIA001271-9796). Affected animals have a severely shortened stature, with shortened limbs relative to overall body size. Their forelegs are bowed and their neck is shortened. The cranium is disproportionately large and affected individuals have flat faces with large, bulging eyes. The nasal bridge is low, the muzzle is retruded, the palate is cleft and they have a protruding tongue. These animals also have severe mandibular brachygnathia and may have a large abdominal hernia (Eberth, 2013).

In general, there are two types of dwarfism in the American miniature horse. The first type is a chondrodysplasia-like dwarfism and involves malformations of the cartilage and subsequent bone formed during foetal development and growth. Four different mutations in *ACAN* are likely to cause chondrodysplastic dwarfism in the American miniature horse, namely *ACAN-D1*, *ACAN-D2*, *ACAN-D3* and *ACAN-D4*. The *D1* mutation is a 1 bp deletion in exon 2, which seems to be a recessive lethal allele in the homozygous state (*D1/D1*) and compound heterozygous states (*D1/D2*, *D1/D3*, *D1/D4*). The *D1* phenotype comprises abortion of foetuses with extremely short stature and severe malformations, similar to bulldog-type dwarfism in Dexter cattle (Fig. 3A and B). The *D2* mutation is a G > A transition in exon 6. Affected animals display dwarfism, with a shortened, barrel-like appearance (Fig. 3C). The *D3* mutation is a 1 bp deletion in exon 11. The accompanying dwarfism phenotype is less severe (Fig. 3D and E). The *D4* mutation is a 21 bp deletion in exon 15. Affected animals display a more pronounced form of dwarfism, with kyphosis and a short neck (Fig. 3F and G). All four mutations result in frameshifts which cause (complete) loss of expression of ACAN or alter the function of ACAN through amino acid substitution (Eberth, 2013).

The second type of dwarfism in American miniature horses is dwarfism without chondrodysplasia-like characteristics. These

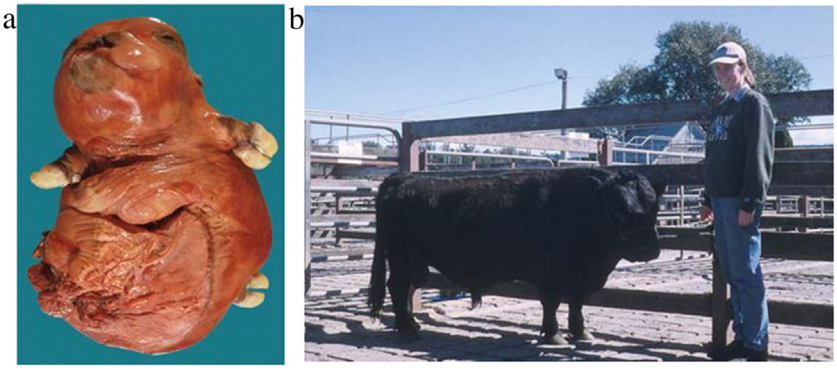

Fig. 2. Bulldog-type dwarfism in Dexter cattle (Cavanagh et al., 2007). (A) Homozygous Dexter calf with bulldog-type dwarfism, aborted mid-gestation. Extreme dwarfism is evident, with micromelia, a short vertebral column and a large abdominal hernia. (B) Heterozygous Dexter bull displaying disproportionate dwarfism, predominantly featuring short legs. Reproduced with permission from Cavanagh et al. (2007).

Fig. 3. Disproportionate dwarfism in American miniature horses (Eberth, 2013). (A) Foetus homozygous for the *D1* allele. (B) Foetus of genotype *D1*/*D2*. (C) Horse homozygous for the *D2* allele. (D) Foal of genotype *D3*/*D4*. (E) Horse of genotype *D2*/*D3*. (F) Horse of genotype *D2*/*D4*. (G) Horse of genotype *D4*/*D3*. Reproduced with permission from Eberth (2013).

individuals exhibit a slightly enlarged head and shortened upper limb bones, but have normal lower limb length and a normal body size and neck length. This form is called skeletal atavism and is characterised by abnormal bone growth restricted to the upper limb bones, similar to skeletal atavism in Shetland ponies and dwarfism in Friesian horses (Back et al., 2008; Rafati et al., 2016; Tyson et al., 2004). Skeletal atavism has been observed in American miniature horses with a normal *N*/*N* genotype, which suggests that the genetic cause does not lie in the *ACAN* gene (Eberth, 2013).

Diseases involving *ACAN* are also recognised in other animals and in human beings. Cartilage matrix deficiency in mice is associated with a 7 bp deletion in exon 5 of *ACAN* (Watanabe et al., 1994). A nonsense transversion in exon 12 of *ACAN* is recognised in chickens and is responsible for nanomelia, a disorder with

disproportionately small limbs (OMIA000702-9031) (Primorac et al., 1994; Vertel et al., 1994). Spondyloepiphyseal dysplasia type Kimberley, a dysplasia characterised by a shortened trunk and shortened limbs, is caused by a 1 bp insertion in exon 12 (Gleghorn et al., 2005). Identification of the causative mutation and DNA tests in Dexter cattle and American miniature horses should be implemented in current breeding programmes to prevent further births of affected animals.

α1 Chain of type II collagen

Chondrodysplasia is a disease known in Holstein-Friesians (OMIA001926-9913). This is a dominant genetic disorder but the sire to which all cases could be traced back was mosaic for the mutation. The phenotype is lethal and has features similar to aggrecan-type dwarfism in Dexter cattle and American miniature horses. Affected animals exhibit prominent disproportionate dwarfism, with a shortened axial skeleton and bilateral limb malformation. Severe splanchnocranial dysplasia and palatoschisis are also evident. The epiphyseal plates are irregular and disorganised (Agerholm et al., 2004). Next-generation sequencing recently identified the causal mutation in the Friesian breed as a G > A missense mutation in the α1 chain of type II collagen gene (*COL2A1*) on BTA5 (Daetwyler et al., 2014). The clinical signs and causal mutation in *COL2A1* indicate that the disorder is homologous to type II achondrogenesis in human beings (MIM200610) (Daetwyler et al., 2014; Körkkö et al., 2000).

In Danish Holstein cattle, there is another mutation causing lethal chondrodysplasia ('bulldog' syndrome). The mutation is a splice site variant G > A mutation in *COL2A1*. The sire of the affected calves was shown to be somatic mosaic. This is most likely due to an early embryonic mutation affecting both germinal and somatic cells (Agerholm et al., 2016). It is rather challenging to eliminate paternal dominant germ cell mutations which may occur without inbreeding from a cattle population. Once fast detection of affected calves and genetic investigation have determined the cause, the causative sire should be omitted from breeding (Agerholm et al., 2016).

β-1,4-Galactosyltransferase 7

Dwarfism also occurs in the Friesian horse, a Dutch breed (OMIA002068-9796) (Fig. 4). Affected individuals show disproportionate dwarfism, with shortened limbs, a relatively large head and a long back. Affected animals are approximately 25% smaller in height and they weigh around 50% less than normal Friesian horses. The fetlock joints are hyperextended. The first phalanges of dwarf foals and adults are the same length, although both are 25% smaller than those of a healthy Friesian foal; the first phalanx of dwarf Friesian horses only increases in breadth rather than length. Tendon laxity does not recover after birth, which normally happens in healthy foals, but instead increases. As a result, the affected animals have an abnormal gait, with extreme outward rotation of the elbows and hocks. The degree of hyperextension varies between individuals and also between the forelimbs and hind limbs (Back et al., 2008).

Fig. 4. Disproportionate dwarfism in the Friesian horse. A dwarf Friesian horse (left 1.12 m in height) next to two unaffected Friesian horses (middle 1.54 m and right 1.66 m in height).

Closer examination reveals abnormally shortened long bones and a distorted ribcage, with enlarged and widened costochondral junctions. The ribcage is somewhat S-shaped at thoracic vertebrae T10–T16 and the rib cartilage is overdeveloped inwards. Histologically, there are irregular metaphyseal growth zones, with a hypertrophic zone of increased width. The chondrocyte columns are irregular and thickened. There is a degree of cartilage retention in the primary spongiosa and large numbers of osteoblasts and osteoclasts line the bony trabeculae (Back et al., 2008).

The incidence of dwarfism in the Friesian horse is estimated at 0.25% and it is assumed to have an autosomal recessive pattern of inheritance. Orr et al. (2010) published a genome-wide association study on 10 affected dwarf animals and 10 controls that identified an associated region on ECA14 (3.16–5.7 Mb). They proposed several candidate genes, including PROP paired-like homeobox 1 (*PROP1*), zinc finger protein 346 (*ZNF346*), collagen type XXIII alpha 1 (*COL23A1*) and β-1,4-galactosyltransferase 7 (*B4GALT7*). *PROP1* causes dwarfism via disruption of the GH axis; however, involvement of this gene was excluded (Graaf-Roelfsema et al., 2009; Orr et al., 2010). ZNF346 has a role in apoptosis, which is important for the cartilage-to-bone transition. COL23A1 and B4GALT7 have roles in collagen-network formation. B4GALT7 is involved in glycosylation, has a role in connective-tissue disorders and is related to disturbed fibril organisation and proteoglycan synthesis (Orr et al., 2010).

A causal mutation for autosomal recessive dwarfism in the Friesian horse was recently identified in the *B4GALT7* gene using next generation sequencing (Leegwater et al., 2016). The mutation, a C > T transition, changes an arginine codon to a lysine codon. It also affects the last nucleotide of exon 1 of *B4GALT7*. This results in improper RNA splicing, which causes a 30-fold reduction in gene expression. The encoded enzyme, xylosylprotein β-1,4-galactosyltransferase 7, functions in the formation of the linker that connects core proteins with glycosaminoglycans in proteoglycans (Tsutsui et al., 2013). B4GALT7 is highly expressed in the growth plate, especially in the proliferative zone (Guo et al., 2013), explaining the irregular and thickened chondrocyte columns seen in the growth plates of affected horses.

Mutations in *B4GALT7* are associated with Ehlers-Danlos syndrome, a disorder of connective tissue affecting the skeletal system and the skin (MIM130070), and Larsen of Reunion Island syndrome in human beings, a syndrome characterised by joint dislocations, short stature and other deformities (Cartault et al., 2015; Faivaz-Ul-Haque et al., 2004; Okajima et al., 1999). Similarities between these conditions and dwarfism in Friesian horses include ribcage deformities, impaired growth and hypermobile joints. However, in contrast to Friesian horses, human patients display facial abnormalities, loose skin and proportional impaired growth (Cartault et al., 2015; Guo et al., 2013).

Starting from a small census populations size and a low effective genetic population size, the Friesian horse breed has increased considerably in population size during the last 40 years (Boerma et al., 2011). The microevolutionary process behind dwarfism in the Friesian horse breed therefore is likely to be genetic drift of a founder mutation. Given its recessive pattern of inheritance, it should be possible to eradicate the disorder from the breed by preventing crosses between carriers, a strategy

currently implemented in breeding management of the Friesian horse.

Solute carrier family 13 member 1

Texel sheep are affected by a type of chondrodysplasia characterised by dwarfism, which manifests as a wide stance and a stocky appearance, with varus deviation and tracheal collapse (OMIA001400-9940). Affected animals die within four months of birth (Thompson et al., 2005). A 1 bp deletion of T in the solute carrier family 13 member 1 gene (*SLC13A1*) causes this type of dwarfism in Texel sheep. *SLC13A1* encodes a renal sodium/sulphate cotransporter, involved in sulphate homeostasis. Sulphate is essential during several processes, ranging from cellular metabolism to growth; sulphated proteoglycans are essential for maintaining normal structure during bone and cartilage formation (Zhao et al., 2012).

In Suffolk and Hampshire sheep, another mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*) causes spider lamb syndrome, a form of chondrodysplasia characterised by increased long bone length (OMIA001703-9940). Heterozygote advantage may have led to the high allele frequency for spider lamb syndrome, since heterozygous animals display increased size (Beever et al., 2006). It may be that a similar selection process has occurred for chondrodysplasia in Texel sheep.

Dwarfism with no known cause

There is a relatively large number of cases of dwarfism that are known to be genetic, but for which the causative mutations have yet to be identified. Examples include snorter dwarfism (OMIA000310-9913), a form of dwarfism combined with breathing difficulties and susceptibility to bloat in cattle (High et al., 1959), stumpy dwarfism in Shorthorn cattle (OMIA000311-9913) and an autosomal recessive form of dwarfism observed in a pig herd (OMIA000299-9825) (Jensen et al., 1984). Llama syndrome, a form of chondrodysplasia characterised by short legs and jaws, and a relatively long neck, is recognised in Suffolk sheep (OMIA001616-9940) (Thompson et al., 2007). Dwarfism has also been reported in Nigerian dwarf goats (OMIA000299-9925) (Sponenberg et al., 1988). Until its extinction, there was a dwarf sheep breed, the Ancon sheep (OMIA000302-9940), which exhibited dwarfism with an autosomal recessive inheritance pattern (Landauer and Chang, 1949). In Cabugi sheep, a hair sheep of north-eastern Brazil, there is a form of skeletal dysplasia with craniofacial deformities and disproportionate dwarfism that may have an autosomal incompletely dominant pattern of inheritance (OMIA001903-9940) (Dantas et al., 2014). Chickens with a form of dwarfism had an unknown inheritance pattern and an unknown causative gene (OMIA000303-9031); involvement of the high mobility group AT-hook 2 gene (*HMGA2*) and *IGF1* have been ruled out (Ruyter-Spira et al., 1998).

Conclusions

Genetic forms of dwarfism can be grouped according to their causes as the result of signalling disruptions or structural disruptions. On the basis of phenotype, dwarfism can be either proportionate or disproportionate. The proportionate dwarfism phenotypes discussed in this review are caused by signalling disruptions; that is, they are either hormone-related or involve signalling pathways. Examples are Z-linked dwarfism in chickens and dwarfism in Brooksville miniature Brahman cattle. Disproportionate forms of dwarfism can be caused by either signalling abnormalities or structural disruptions. Examples are dwarfism in American Angus cattle and bulldog-type dwarfism in Dexter cattle.

Dwarfism phenotypes can be similar, even when the causative mutations are different. The dwarfism phenotype observed in Tyrolean grey and Japanese brown cattle is similar and is caused by mutations in *EVC2* in both animals, but the mutations are not identical. Chondrodysplastic dwarfism caused by the *D1* allele in American miniature horses and bulldog-type dwarfism in Dexter cattle are phenotypically similar but not identical, although both mutations are within the *ACAN* gene. Another form of dwarfism in the American miniature horse, skeletal atavism, is not caused by any of the mutations in *ACAN* but it resembles *SHOX* associated skeletal atavism in Shetland ponies. The phenotype is also quite similar to the dwarfism seen in Friesian horses.

Using high-density SNP arrays and genome sequencing, causative genes can be rapidly detected if well-phenotyped cases and controls are available. By using PCR-based tests, undesirable dwarfism traits can be eliminated in livestock. However, the underlying microevolutionary processes should also be considered. Deliberate selection of the dwarfism phenotype plays an important role in the Chinese Banna miniature pig and in Z-linked dwarfism in chickens. Elimination of dwarfism in Z-linked dwarfism is not feasible, because the phenotype is of economic value. Heterozygote advantage is likely to underlie dwarfism in Belgian blue cattle, since the causative gene appears to be linked to an important QTL and heterozygotes exhibit a favourable trait. For heterozygote advantage, PCR-based tests will prevent further outbreaks of dwarfism, but will not decrease heterozygote frequency, since selection for the heterozygote phenotype is still possible. This may also be a problem when genetic hitchhiking with a neighbouring gene variant is present. Thus, further research is needed to identify other genetic causes of dwarfism, but also to determine the underlying microevolutionary processes.

Conflict of interest statement

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

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