Chapter

Interspecies Translation: Bovine Marbling to Human Muscular Dystrophy

Jose L. Valenzuela, Sally S. Lloyd, Edward J. Steele, Francis L. Mastaglia and Roger L. Dawkins

Abstract

There are interesting similarities and differences when comparing the histopathology of bovine marbling and human muscular dystrophy. At the simplest level, both conditions are characterized by genetically controlled and more or less inexorable replacement of muscle fibers with fat cells. At issue is whether an improved understanding of these two processes can lead to better outcomes for patients. There are many forms of dystrophy that differ in their genetics and their histopathology. There are also many forms of "marbling" ranging from the coarse to fine, epimysial, perimysial to endomysial and even to total replacement or steatosis. A detailed examination of marbling will provide a framework for further investigation of human dystrophy. Ultimately, the many genetic factors involved can be addressed through a better understanding of the metabolic pathways involved in marbling.

Keywords: synteny, muscular dystrophy, bovine marbling, adipogenesis

1. Introduction

The purpose of this review is to compare the genetics and histopathology of bovine marbling and human muscular dystrophy. Surprisingly, in spite of similarities, the literature suggests that marbling is a function of extreme adipogenesis whereas dystrophy is a consequence of fundamental defects in muscle itself. In fact, completely independent studies, as summarized here, reveal that similar genes have been implicated in some selected situations. Further, it is clear that the histopathology of some forms of dystrophy can resemble some forms of bovine marbling.

2. Marbling

Marbling is the term used to describe the presence of macroscopically visible fat within muscle (**Figures 1** and **2**). Coarse marbling refers to white areas of fat through and around muscle bundles, generally as continuous bands arising from the subcutaneous adipose tissue. By contrast, fine or "snowflake" marbling is characterized by more even white flecks resulting in pink rather than red muscle.

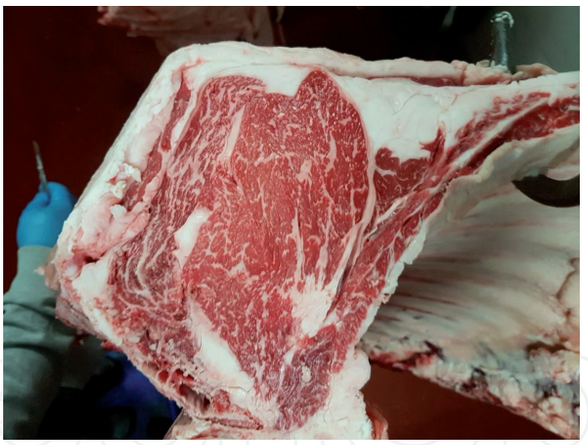

Figure 1.
Loin at the eleventh intercostal level of carcass of Melaleuka Stud steer M508 (wy63 ak25 dx13), MSA MB 1100, DOF 471. There are extensive areas of fine marbling as indicated by pink muscle with fine flecks. Note 88% Wagyu (63% black, 25% red). See also ***Figure 5*** *for microscopic features.*

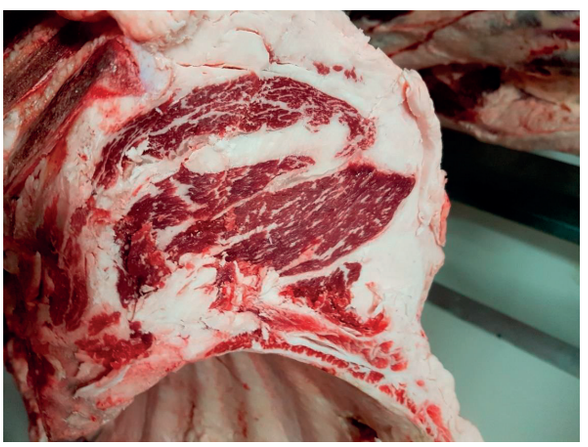

Figure 2.
Loin at the eleventh intercostal level of carcass of Melaleuka Stud heifer M621 (wy75 dx25), MSA MB 920, DOF 443. There is a predominance of fat arborizing from the subcutaneous tissue and creating coarse marbling. The muscle areas are dark red in comparison to ***Figure 1****. Note lower MSA MB of 920 but similar days on feed (DOF).*

These two forms may coexist but can be distinguished and quantified by skilled observers. Fine marbling is associated with improved taste and tenderness [1]. Further, it has been shown to relate to a preferred fatty acid profile. Accordingly, there is copious funding and now a substantial understanding of the environmental and genetic factors which favor fine rather than coarse.

3. Interspecies translation

Interspecies translation from cattle to man has unrecognized potential. Firstly, cattle are close to humans in evolutionary time and fall within that window of 50–100 million years of separation (or last common ancestor) which is characterized by very similar proteins but vastly different regulations of expression. The same window may explain the fact that the two species have synergized over some 40,000 years of contact and at least 7000 years of domestication. As one example, infections can be similar and, in some cases, are transmissible from one to the other, but close exposure to cattle is generally innocuous implying some form of immunity. As for example in the case of pox and tuberculosis. We argue that cattle are both relevant and relatively safe for translational studies.

Secondly, domestic cattle are well maintained, closely observed, and very well understood. There are huge databases and DNA banks which have been in existence for 50 years. Innumerable breeds can be compared often under different environmental conditions. Many of these breeds have been closed for hundreds of years and then intentionally crossed with each other. There is great potential for meaningful studies of population genetics and family and haplotype associations and, even more so, for structure-function genomics. Metabolic and inflammatory pathways are relatively well understood and are supported by inestimable funding available to ensure future supplies of meat, milk, cheese, butter, leather, and fertilizer.

Thirdly, cattle are plentiful and even more so than humans. Because the generation time and life expectancy are much shorter, there are excellent opportunities to study and treat genetically determined diseases prospectively [2].

4. Other instances of translation

White muscle disease or selenium/vitamin E deficiency occurs quite commonly in livestock raised on leached soils. The pathology resembles dystrophy in some respects. A mutation in the selenoprotein N gene (SEPN1) is responsible for some types of congenital muscular dystrophies and myopathies [3]. Kakulas [4] demonstrated that dystrophy-like changes explained the weakness observed in quokkas on Rottnest Island. Importantly, the condition could be corrected by treating the deficiency raising the possibility that human dystrophies could be reversible if the basic defect could be corrected.

5. Genomic approach

The term genome is used here to refer to the architecture of DNA sequences, whereas others have come to use the term in the context of single-nucleotide polymorphisms wherever they occur. The difference is fundamental to the discovery of gene clusters with coherent cis and trans interactions between conserved sequences known as ancestral haplotypes [5–9]. Many studies have shown that the SNP approach in livestock and humans fails to identify these critical sequences and can be misleading at best [10]. SNPs are neutral markers of parentage rather than functionally important [11].

One major benefit of ancestral haplotypes as opposed to SNPs is that it is possible to use interspecies translation. During mammalian evolution, polymorphic frozen blocks have diverged to some extent although the functionally important sequences tend to be conserved.

As shown in **Figure 3** and **Table 1**, there are similarities between genomic regions on Hosa 17 and Bota 19. Although there have been architectural changes such as insertions and transversions, the gene content has been preserved.

Bota 19 was chosen as the reference because of its critical role in determining the degree of marbling between individuals of a breed, F1 crosses and between breeds [5, 12–14].

Hosa 17 was chosen for comparison because it contains some of the same genes such as TCAP. Further analysis revealed an extraordinary degree of preservation or synteny in spite of an evolutionary separation time of at least 50 million years and therefore millions of generations. Implicit is that there are functional reasons for similarities in genomic architecture.

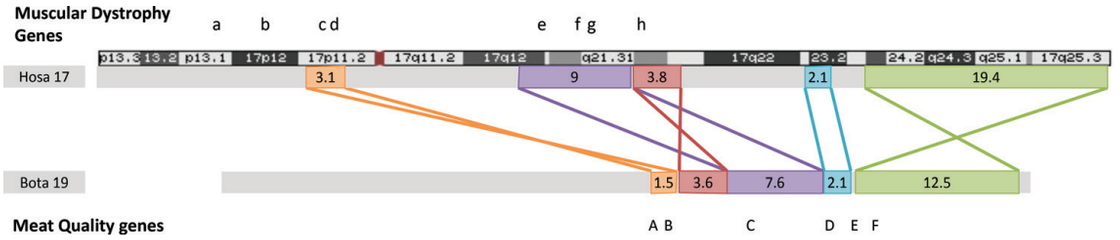

Figure 3.
Marbling and muscular dystrophy are syntenic on bovine chromosome 19 (Bota 19) and human chromosome 17 (Hosa 17). Colored boxes represent segments with the same gene content. Crossed joining lines indicate inverted translocations. Numbers represent Mb. Synteny was determined by the positions of homologous genes in the human assembly Hg 38 and bovine assembly BosTau8 located using the UCSC genome browser. Inverted sections and the exact location of boundaries between blocks were determined by dotplots comparing the two sequences. Adapted from: [13] Locations of ***Muscular Dystrophy Genes****: (a) MYH2, (b) PMP22, (c) TRPV2, (d) SREBF1, (e) TCAP, (f) CAVIN1, (g) BECN1, (h) SGCA and* ***Meat Quality Genes*** *(A)SREBF1, (B) MPRIP, (C) TCAP, (D) GH, (E) UTS2R, (F) FASN shown here. See* ***Table 1*** *for more information about these genes.*

Gene location	Description	Human muscular dystrophy	Meat quality trait
MYH2 Hosa 17p13.1 Bota chr19: 30.13Mb	MYH2 encodes the myosin heavy chain isoform that is expressed in fast type 2A muscle fibers	Proximal myopathy and ophthalmoplegia is caused by heterozygous, compound heterozygous, or homozygous mutation in MYH2 leading to a lack of type 2a fibres [18]	In pork, IMF, water holding capacity, and meat color [19]
PMP22 Hosa 17p12 Bota chr19: 33.35Mb	Peripheral myelin protein-22	Duplication of peripheral myelin protein 22 causes Charcot-Marie-Tooth disease type 1A [20]	
TRPV2 Hosa 17p11.2 Bota chr19: 33.816Mb	Transient receptor potential cation channel, V2: responds to heat and cations	Muscular dystrophy is ameliorated in dystrophin-deficient mdx mice by dominant-negative inhibition of TRPV2 [21]	
SREBF1 Hosa 17p11.2 Bota chr19: 35.23Mb	Sterol regulatory element-binding protein-1 controls cholesterol homeostasis by stimulating transcription of sterol-regulated genes	Mutations of LMNA that cause Emery-Dreifuss muscular dystrophy (EDMD2-AD) and familial partial lipodystrophy (FPLD2) result in less binding of lamin A to SREBP1 [22]	SREBF1 is involved in adipogenesis and polymorphisms are associated with fatty acid composition of Japanese Black Cattle [23]
MPRIP Hosa 17p11.2 Bota chr19: 35.557Mb	Myosin phosphatase rho-interacting protein targets myosin phosphatase to regulate the phosphorylation of myosin light chain [24]		Haplotypes diffentiated by polymorphsims in MRIP are associated with differences in intramuscular fat development in Wagyu [25]
SGCA Hosa 17q21.33 Bota chr19: 37.11Mb	Sarcoglycan, alpha Sarcoglycans form part of the dystrophin-glycoprotein complex	Mutations in SGCA cause limb-girdle muscular dystrophy type 2D. SGCB, SGCD, and SGCG are associated with LGMD types 2E, 2F, and 2C, respectively [26]	
TCAP Hosa 17q12 Bota chr19: 40.69Mb	Titin-cap (telethonin) is a sarcomeric protein localized to the periphery of Z discs that define the border of the sarcomere as a structural anchor and signaling center	Limb-girdle muscular dystrophy type 2G (LGMD2G) is caused by mutations in the TCAP gene [27]	A polymorphism of TCAP is associated with IMF content and fatty acid composition of beef [13, 28]

Gene location	Description	Human muscular dystrophy	Meat quality trait
CAVIN1 Hosa 17q21.2 Bota chr19: 43.14Mb	Cavin is an essential factor in the biogenesis of caveolae	Congenital generalized lipodystrophy, type 4; (CGL4) is caused by mutations in CAVIN1 that result in CAV 3 deficiency [29]	
BECN1 Hosa 17q21.31 Bota chr19: 43.47Mb	Beclin-1 participates in the regulation of autophagy	Expression of BECN1 was reduced in patients with muscular dystrophies BTHLM1 and UMCD1 which were caused by COL6A1 mutations [30]	Involved in proteolysis and beef aging [31]
GH1 Hosa 17q23.3 Bota Chr19: 48.77Mb	Growth Hormone		A polymorphism of growth hormone is associated with fatty acid composition of Wagyu beef [32]
FASN Hosa 17q25.3 Bota Chr19: 51.38 Mb	Fatty Acid Synthase the key enzyme of de novo lipogenesis to produce saturated fatty acids		Fatty Acid Synthase is highlighted in GWAS for fatty acid content and composition of Wagyu and Hanwoo beef [33, 34]
UTS2R Hosa17q25.3 Bota Chr19: 50.81 Mb	A receptor abundant in heart and pancreas and responsive to Urotensin II which has potent vasoactive properties		A polymorphism of UTS2R is associated with IMF content of Wagyu x Holstein beef [39]

Table 1.
Details of relevant genes in Bota 19 and Hosa 17.

Yet further analysis suggests some explanations for the co-location of similar genes. Irrespective of cis and trans interactions between the protein products, there is evidence of co-regulation (see, e.g., SREBP). In this context, we conclude that, although products and their regulating transcription factors are preserved, separation has permitted the insertion of species-specific elements, which control the quantitative differences between humans and cattle.

Importantly, as shown in **Figure 3** and **Table 1**, Hosa 17 contains multiple candidates for involvement in human muscular dystrophy. There is even more complexity in explaining the multiple candidates as shown in **Tables 2** and **3**.

Thus, syntenic analysis has suggested a novel approach to identification of operative elements in marbling and in some forms of dystrophy.

Gene location	Description	Human muscular dystrophy	Meat quality trait
MSTN Hosa 2q32.2 Bota chr2: 6.21Mb	Myostatin	Muscle hypertrophy was caused by a homozygous mutation in myostatin [35]	Mutations in myostatin cause double muscling in several cattle breeds [36]
CAPN3 Hosa 15q15.1 Bota chr10: 37.8Mb	Calpains are nonlysosomal intracellular cysteine proteases. CAPN3 is a muscle-specific large subunit	Limb-girdle muscular dystrophy type 2A (LGMD2A) is caused by homozygous or compound heterozygous mutation in CAPN3	SNPs within CAPN3 are associated with tenderness in *Bos Indicus* cattle [37]

Gene location	Description	Human muscular dystrophy	Meat quality trait
CAPN1 Hosa 11q13.1 Bota chr29: 44.06Mb	m-Calpain		Two CAPN1 genetic markers are associated with tenderness in Brahman beef [38]
DMD Hosa Xp21.2-.1 Bota chrX: 115.34Mb	Dystrophin maintains the structural integrity of myofibrils	Duchene muscular dystrophy	
LAMA2 Hosa 6q22.33 Bota chr9: 67.96Mb	LAMA2 gene encodes the alpha-2 chain of laminin-2 Laminin-2 (merosin) is the main laminin found in muscle fibers	Congenital merosin-deficient muscular dystrophy type 1A; MDC1A	
MYOT Hosa 5q31.2 Bota chr7: 50.94Mb	Myotilin directly binds F-actin and efficiently cross-links actin filaments and prevents filament disassembly	LGMD1A is caused by heterozygous mutation in the MYOT. It is characterized by adult-onset muscle weakness, progressing from the hip to the shoulder girdle	SNPs in MYOT correlate with loin muscle area and intramuscular fat in Qinchuan cattle[39]
CAV3 Hosa 3p25.3 Bota chr22: 17.83Mb	Caveolin 3	Muscular dystrophy, limb-girdle, type 1C; LGMD1C	
SGCD Hosa 5q33.2-.3 Bota chr7: 69.59Mb	Sarcoglycan, delta is expressed in skeletal and heart muscles and to a lesser extent in smooth muscle. Delta-sarcoglycan is localized at the sarcolemma	Muscular dystrophy, limb-girdle, type 2F; LGMD2F	
SGCE Hosa 7q21.3 Bota chr4: 11.84Mb	Epsilon-sarcoglycan	Myoclonus-dystonia is a genetically heterogeneous disorder characterized by myoclonic jerks affecting mostly proximal muscles	
SGCB Bota chr6: 69.53Mb	Beta-sarcoglycan		
SGCG at Bota chr12: 34.92Mb			
COL6A1 COL6A2 21q22.3	Collagen, type VI, alpha-1, and alpha-2 Members of the collagen VI family form distinct networks of microfibrils in connective tissue and interact with other extracellular matrix components	Ullrich congenital muscular dystrophy 1 Bethlem myopathy 1	
COL6A3 2q37.3	COLLAGEN, TYPE VI, ALPHA-3	Ullrich congenital muscular dystrophy 1, Bethlem myopathy 1 Dystonia 27	

Gene location	Description	Human muscular dystrophy	Meat quality trait
ITGA7 12q13.2	The alpha-7 integrin is a specific cellular receptor for the basement membrane proteins laminin-1, laminin-2, and laminin-4. The alpha-7 subunit is expressed mainly in skeletal and cardiac muscles and may be involved in differentiation and migration processes during myogenesis	Congenital muscular dystrophy	
EMD Xq28	Emerin is found along the nuclear rim of many cell types and is a member of the nuclear lamina-associated protein family	Emery-dreifuss muscular dystrophy 1, X-LINKED; EDMD1	
ATP2A1 (SERCA-1) 16p11.2	Calcium-transporting ATPase lower cytoplasmic Ca(2+) concentration by pumping Ca(2+) to luminal or extracellular spaces. ATP2A1 is the ATPase type found in fast twitch muscles	Brody myopathy	
DES 2q35	Desmin is the muscle-specific member of the intermediate filament (IF) protein family. It is one of the earliest myogenic markers, both in the heart and somites, and is expressed in satellite stem cells and replicating myoblasts	Myopathy, myofibrillar, 1	
PLEC 8q24.3	Plectin-1 is one of the largest polypeptides known and is believed to provide mechanical strength to cells and tissues by acting as a cross-linking element of the cytoskeleton	Epidermolysis bullosa with muscular dystrophy Limb-girdle type 2Q	

Table 2.
Details of relevant genes outside of Hosa 17/Bota 19.

Absent protein	Dystrophy type	Gene location
Dystrophin	Xp21 muscular dystrophies (Duchenne, Becker)	DMD Hosa Xp21.2-p21.1 Bota chrX: 115,342,323-117,606,340
Sarcoglycans	Limb-girdle muscular dystrophies 2C-F	SGCA Hosa 17q21.33 Bota 19 SGCB Bota chr6 SGCD Hosa 5q33.2 Bota 7 SGCE Hosa 7q21.3 Bota 4 SGCG Bota chr12
Dysferlin	Limb-girdle muscular dystrophy 2B	DYSF Hosa 2p13.2
Caveolin-3	Limb-girdle muscular dystrophy 1a, rippling muscle disease, hyperCKemia	CAV3 Hosa 3p25.3 Bota 22 CAVIN1 Hosa 17q21.2 Bota 19
Telethonin	Limb-girdle muscular dystrophy 2G	TCAP Hosa 17q12 Bota 19
Laminin a2	MDC1A ("merosin"-deficient congenital muscular dystrophy)	LAMA2 Hosa 6q22.33, Bota 9
Collagen VI	Ullrich congenital muscular dystrophy	COL6A1&2 Hosa 21q22.3 COL6A3 Hosa 2q37.3
Integrin alpha7	Mild congenital dystrophy/myopathy	ITGA7 Hosa 12q13.2

Absent protein	**Dystrophy type**	**Gene location**
Calpain-3 (easier to assess on immunoblots than sections)	Limb-girdle muscular dystrophy 2A	CAPN3 Hosa 15q15.1 Bota 10
Emerin	X-Linked emery-dreifuss muscular dystrophy	EMD Hosa Xq28
SERCA 1	Brody disease	***ATP2A1 Hosa 16p11.2***
Plectin	Epidermolysis bullosa with muscular dystrophy, limb-girdle dystrophy 2Q	PLEC Hosa 8q24.3
LAMP-2	Danon disease	LAMP2 Xq24
Accumulating protein	**Dystrophy type**	**Gene location**
Actin	Congenital actin myopathy/nemaline myopathy	ACTA1 Hosa 1q24.13 TPM3 Hosa 1q23
Myosin	Myosin storage myopathy	MYH7 Hosa 14q11
Myotilin	Myotilin-related myofibrillar myopathy	MYOT Hosa 5q31.2
Desmin	Desmin myopathy	DES Hosa 2q35 SEPN1 Hosa 1p36
(Adapted from [15] Table 6.3 dystrophy related protein changes detectable with immunohistochemistry).		

Table 3.
Protein accumulations and deficits in dystrophy.

6. Histopathological approach

The substantial range of changes found in the human dystrophies is illustrated in the study of Dubowitz et al. [15].

We are fortunate in having histological muscle samples from cattle with degrees of marbling [14]. Some of these changes are illustrated in **Figures 4–8** from three animals (M508, M621, and M129) fed a standard ration for 471, 443, and 481 days respectively. The macroscopic measure of marbling (MSA MB) ranged from high to moderate (1100, 920 and 820, respectively) as expected in high content Wagyu (88, 75, and 63%, respectively). A common feature is the invasion of adipose tissue between intact muscle fascicles (**Figure 4**). For the most part, the process extends along the perimysium leading to variation in fiber size, staining of myofibers (**Figures 5** and **6**), and the formation of residual islands of myofibers (**Figure 7**), which suggests an explanation for fine (see **Figure 1**) rather than coarse (see **Figure 2**) marbling; fine is due to more aggressive invasion reflecting quantitative differences in gene regulation.

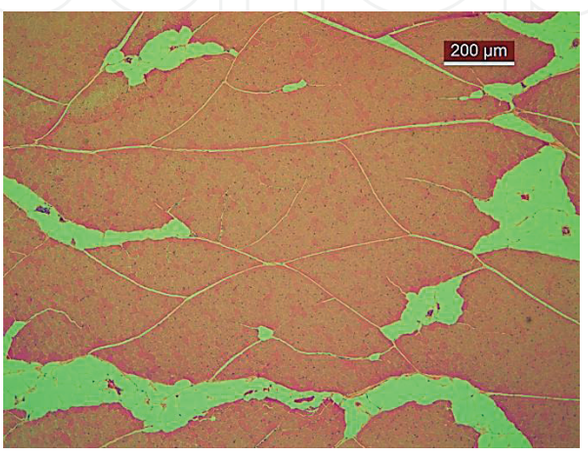

Figure 4.
Highly marbled loin muscle shows a pattern of fat arborization and invasion with adipocytes predominantly in the perimysium, between muscle fascicles. Note extensive vascularization centrally within the fat. M508 (wy63 ak25 dx13), MSA MB 1100, DOF 471. See also ***Figure 1****.*

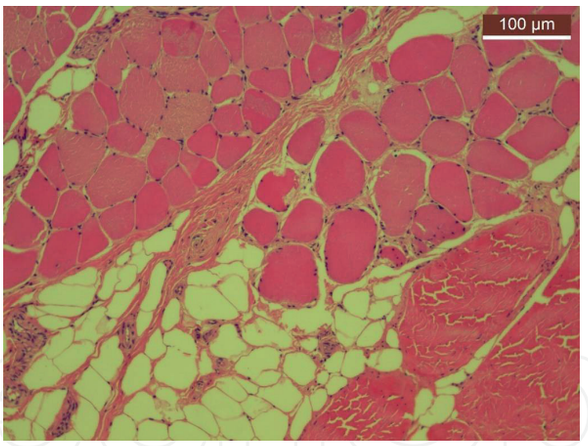

Figure 5.
Histological section of Sacrocaudalis dorsalis medialis of a highly marbled, high Wagyu content (88%) steer M508 (wy63 ak25 dx13), showing variation of fiber size, with the presence of rounded fibers, internal nuclei, abundant perimysial connective tissue, and considerable adipose tissue. Formalin-fixed H & E, MSA MB 1100, DOF 471. CYO lab number Ch18/110G. See also ***Figure 1*** *for macroscopic comparison.*

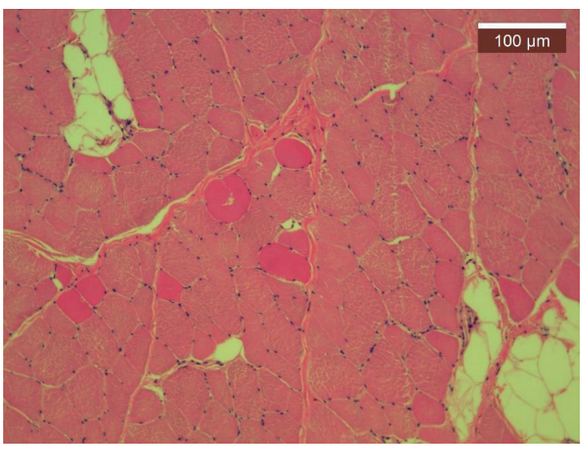

Figure 6.
Histological section of Sacrocaudalis dorsalis medialis of a highly marbled, high Wagyu content (75%) heifer M621 (wy75 dx25). Field selected to show eosinophilic rounded fibers of variable size, with abundant perimysial connective tissue in their proximity. Formalin-fixed H & E, MSA MB 820, DOF 471. CYO lab number Ch18/109Y. See also ***Figure 2*** *for macroscopic features such as coarse marbling.*

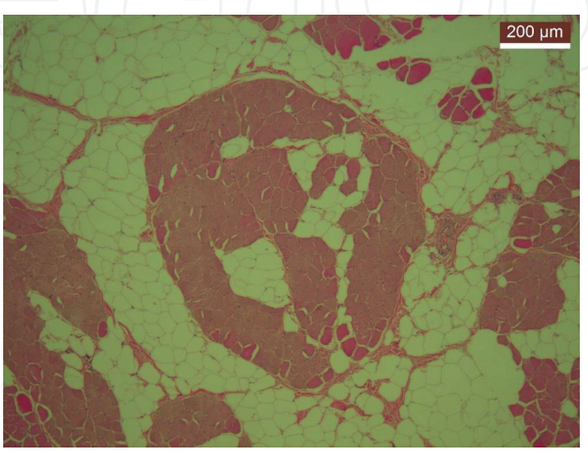

Figure 7.
Histological section of Sacrocaudalis dorsalis medialis of a highly marbled, high Wagyu content steer (88%) (wy63 ak25 dx13), showing aggressive adipose invasion, with abundant perimysial connective tissue and the generation of island-like areas of fibers with evident architectural changes including shrinkage of fibers as the front advances. Formalin-fixed H & E, MSA MB 1100, DOF 471. CYO lab number Ch18/110G. See also ***Figures 1, 4****, and* ***5****.*

In some fields, there are collections of nuclei including intracytoplasmic (**Figure 8**).

These observations have led us to the conclusion that the extent and type of marbling is a function of the aggressive extension of the advancing adipocytes with secondary loss of myocytes.

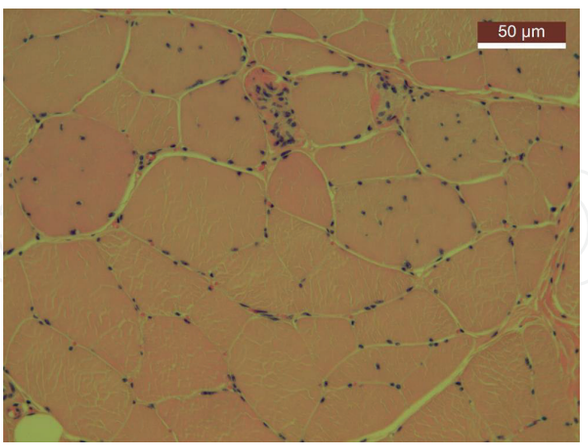

Figure 8.
Histological section of Sacrocaudalis dorsalis medialis of a highly marbled, high Wagyu content steer (63%), M129 (wy63 dx13). Higher power selected to illustrate variability of fiber size, affinity for eosin, and the presence of intracytoplasmatic and interstitial nuclei. Formalin-fixed H & E, MSA MB 880, DOF 481. CYO lab number Ch18/135Z.

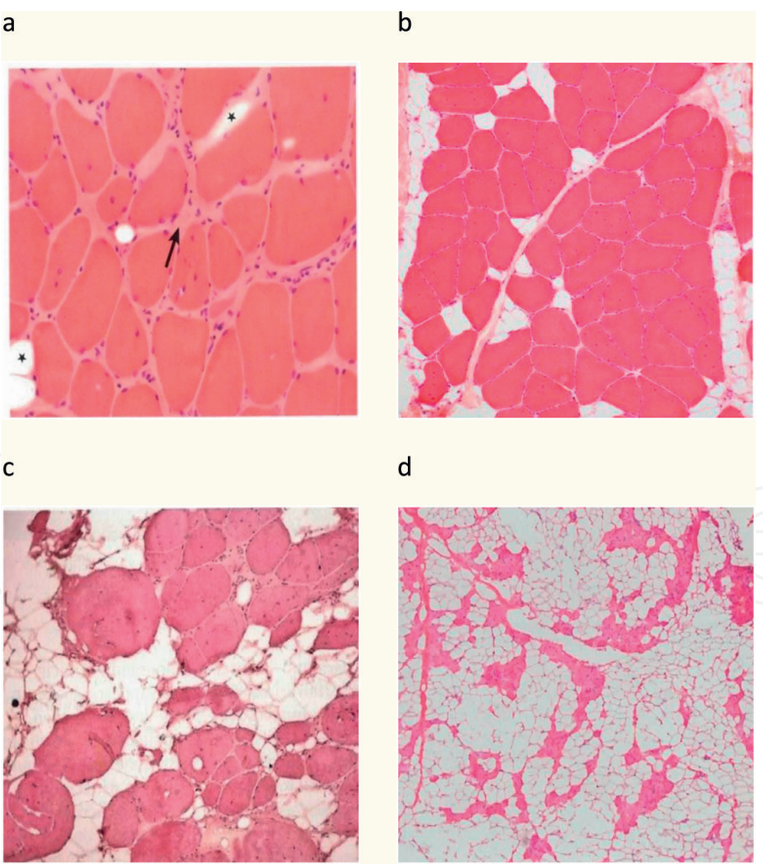

Figure 9.
Examples of adipocyte intrusion in human muscular dystrophy. (a) Case of limb-girdle muscular dystrophy showing most fibers surrounded by endomysial connective tissue with some adipocytes (*) ([15], Figure 11.4b). (b) From the deltoid muscle of a patient with ophthalmoplegia associated with a MYH2 mutation showing fatty infiltration, mild fiber atrophy, fibers with internal nuclei, an irregular myofibrillar network, and lobulated fibers ([15], Figure 15.27). (c) From the quadriceps of a patient with facioscapulohumeral dystrophy at 42 years showing pronounced proliferation of connective tissue and fat with a wide variation of muscle cell size and many internal nuclei ([15], Figure 14.1b). (d) Low power view of a biopsy from a case of congenital muscular dystrophy showing only islands of fibers in a vast amount of adipose tissue ([15], Figure 4.30).

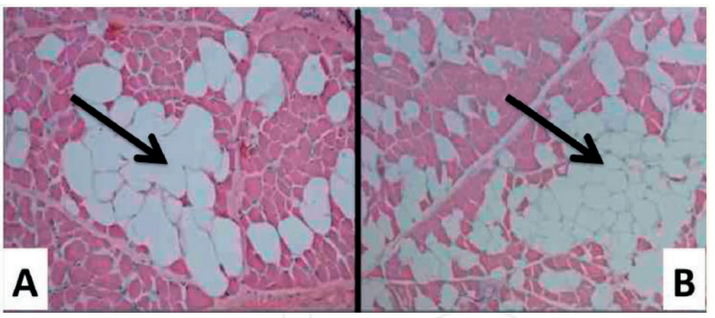

Figure 10.
Muscle samples taken from carcasses where steatosis was observed macroscopically at slaughter. Fat infiltration occurs within the muscle fascicle, there are few adipocytes within the perimysium. Used with permission from [17].

Some forms of human dystrophy have very similar histopathology, for example, congenital myopathies as illustrated by Dubowitz et al. [15] and reproduced here in **Figure 9**.

As in human dystrophies, there can be different degrees depending upon the muscle group and the field selected. Here, we focus on *Sacrocaudalis dorsalis medialis*, because it is convenient to biopsy, whereas the loin can only be accessed readily post-mortem.

Accordingly, it will be possible to undertake detailed time course studies so as to monitor sequential changes and eventually responses to therapy. Future studies should also address bovine steatosis. The pathology [16, 17] is different from marbling. Adipocytes occur within rather than around fascicles (**Figure 10**) suggesting that the process may be a function of differentiation of stem cells, rather than invasion [1].

7. Conclusion

In spite of similarities in pathology and genomics, there is more to learn before precise translation is possible. However, there are strong indications that such approaches could have important implications for human dystrophies and other muscle diseases. Moreover, a better understanding of the control factors and signals responsible for determining the relative proportions of muscle and adipose tissue in bovine muscles, and how they are coordinated, is fundamental and will be crucial to understanding more fully the significance of adipose tissue replacement in human dystrophies and to developing new therapeutic strategies for these diseases.

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Conflict of interest

Collectively, the authors associated with the CY O'Connor ERADE Village Foundation have an interest in the work described in this manuscript as it forms part of the foundation's intellectual property.

Author details

Jose L. Valenzuela[1,2], Sally S. Lloyd[1,2], Edward J. Steele[1,3], Francis L. Mastaglia[4] and Roger L. Dawkins[1,2*]

1 CY O'Connor ERADE Village Foundation, North Dandalup, Australia

2 Centre for Innovation in Agriculture, Murdoch University, Murdoch, Australia

3 Melville Analytics Pty Ltd, Melbourne, VIC, Australia

4 Queen Elizabeth II Medical Centre, Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia

*Address all correspondence to: rldawkins@cyo.edu.au

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