Chondrodysplasia of Texel Sheep

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Abstract

Chondrodysplasia of Texel sheep is a newly described recessively inherited disorder distinct from other chondrodysplasias described in sheep. Phenotypically normal at birth, affected lambs develop microscopic lesions as early as 9 days of age, and usually demonstrate gross deformities and markedly reduced rates of bone growth by 2 to 3 weeks. Individual bone growth rates are most severely affected in the proximal bones of the forelimbs. Chondrodysplastic lambs typically have short stature, angular limb deformities, a barrel-shaped chest and a wide-based stance. Gross lesions include tracheal narrowing and contortion, enlarged costochondral junctions, and erosion of articular cartilage in major limb joints. Microscopic lesions are confined to hyaline cartilage, and are characterised by degeneration of the interterritorial matrix and dense perichondrocytic rings consisting predominantly of type VI collagen. These lesions are identical in appearance to those in achondrogenesis 1b and diastrophic dysplasia, two diseases caused by defects of the diastrophic dysplasia sulphate transporter (DTDST) in human beings.

An investigation to measure the uptake of radiolabelled sulphate by dermal fibroblasts *in vitro* did not provide evidence of a defect in the DTDST in chondrodysplastic Texel sheep. A linkage disequilibrium study of ovine chromosomes 1, 5, 6, 13 and 22 using microsatellite DNA markers was unable to identify evidence of a mutation causing this form of chondrodysplasia. Capillary electrophoresis of unsaturated chondroitin sulphate disaccharides demonstrated a relative reduction in the ratio of chondroitin 4-sulphate to chondroitin 6-sulphate in affected animals of all ages. This biochemical feature enables the potential determination of the phenotype of newborn lambs prior to the emergence of gross or microscopic lesions.

The pathology of the disease, combined with the findings of the genetic, biochemical and *in vitro* studies, suggest that a mutation may be present in the *CHST11* gene. This gene is a good candidate for future studies aimed at discovering the genetic defect in chondrodysplasia of Texel sheep and developing a test to identify heterozygous animals.

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Glossary

AB	-	alcian blue, histological stain
Abluminal	-	pertaining to the outer portion of a tubular structure
Acanthosis nigricans	-	a form of skin hyperpigmentation
Achondroplasia	-	specific term for failure of cartilage growth, also commonly used to refer to a common form of dwarfism in humans
Acromesomelia	-	shortening of the middle and distal parts of the limbs
Alymphatic	-	lacking lymphatic vessels
Anauxetic	-	without growth
Aneural	-	lacking innervation
Anisospondyly	-	different abnormal shapes of vertebral bodies
Ankylosis	-	bony fusion of a joint
Anlage	-	an embryonic precursor to a structure
ANOVA	-	analysis of variance
Appositional growth	-	growth by the addition of external layers (c.f. interstitial growth)
APS	-	adenosine phosphosulphate
Arthropathy	-	joint disease
Articular-epiphyseal complex	-	the epiphyseal cartilage of young animals consisting of both an articular surface and a zone of growth
ATP	-	adenosine triphosphate
Avascular	-	lacking blood vessels
Basophilic	-	a tissue that stains with a basic dye, such as haematoxylin
Blepharophimosis	-	abnormally narrow palpebral fissure (gap between eyelids)
BMP	-	bone morphogenic protein
Bossing	-	swelling
Brachycephaly	-	having a short (broad) head
Brachydactyly	-	short fingers
Brachygnathia	-	shortened mandible or jaw
Camptodactyly	-	flexural deformity of interphalangeal joints
Cancellous bone	-	has a latticed structure (c.f. compact bone)
CATSHL syndrome	-	a syndrome featuring camptodactyly, tall stature, scoliosis and hearing loss
CDMP-1	-	cartilage derived morphogenic protein-1
CE	-	capillary electrophoresis
CHILD syndrome	-	congenital hemidysplasia with ichthyosiform erythroderma and limb defects
CI	-	confidence interval
Chondroblasts	-	immature cartilage cells
Chondrocalcin	-	the C-propeptide of type II collagen

Chondrocytes - mature cartilage cells
Chondrodysplasia - an abnormality of cartilage growth or development
Chondrogenic tissue - contains cells with the potential to differentiate into cartilage-forming cells
Chondron - the functional unit of cartilage
CHST3 - the gene encoding chondroitin 6-sulphotransferase, adding sulphate to the 6-position of chondroitin
CHST11 - the gene encoding chondroitin 4-sulphotransferase, adding sulphate to the 4-position of chondroitin
Cisternae - cavities or reservoirs
COMP - cartilage oligomeric matrix protein
Compact bone - has a dense, laminar structure (c.f. cancellous bone)
Coxa vara - a hip deformity where the angle between the ball and shaft of the femur is reduced
cpm - counts per minute
Cyanosis - bluish colour of skin, mucous membranes, etc. due to lack of oxygenated haemoglobin in the blood
Dentigerous cysts - follicular tooth-based cysts
Diaphysis - the main shaft of a long bone
Diarthrodial - a free-moving form of joint articulation
Distal - (as in part of a limb) far from the body
DJD - degenerative joint disease
DMC - Dyggve-Melchior-Clausen dysplasia
DMEM - Dulbecco's modified Eagle's medium
Dolichocephaly - having a long head
DTDST - diastrophic dysplasia sulphate transporter
Dysmorphism - abnormality of shape
Dysplasia - abnormality of growth or development
Dyspnoea - breathing difficulty
Ectrodactyly - absence of one or more digits
Elastic cartilage - has elastic fibres and lamellae within the matrix
Endochondral bones - bones that grow or develop within cartilage
Epiphysis - the end of a long bone separated from the main part of the bone by the physis
Epitope - the part of a molecule to which an antibody may bind
Erythroderma - reddening of the skin
Erythrogenesis (erythropoiesis) - the formation of red blood cells
Exophthalmus - abnormal protrusion of the eyeball
FAM - 6-carboxy-fluorescine
Fenestrated - containing one or more openings
FGF - fibroblast growth factor
FGF2 - fibroblast growth factor-2
FGFR3 - fibroblast growth factor receptor-3

Fibrillogenesis	-	formation of fibrils
Fibrocartilage	-	contains bundles of type I collagen within the matrix
Genu valgum	-	valgus deformity at the knees, "knock-knees"
Glaucoma	-	increased intraocular pressure
H&E	-	haematoxylin & eosin, common histological stain
Haploinsufficiency	-	occurs when a single functional gene is unable to produce enough product to maintain a wild type (normal) phenotype
Hepato-splenomegaly	-	enlarged liver and spleen
HEPES	-	N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid
Homeobox genes	-	highly conserved genes that regulate bodily segmentation during embryonic development
HPLC	-	high performance liquid chromatography
Hyaline cartilage	-	has a homogeneous, amorphous matrix
Hydrocephalus	-	dilatation of the cerebral ventricles
Hypertrophy	-	in chondrocytes is a stage late in maturation with increased cell size
Hypertelorism	-	widely-spaced eyes
Hypocellular	-	having decreased cell density
Hypoplasia	-	incomplete development of an organ or tissue
Hypotonia	-	decreased tone of skeletal muscles
IBD	-	identical by descent
Ichthyosiform	-	resembling scaly skin
Ihh	-	Indian hedgehog
Inclusion	-	abnormal aggregation of substance, e.g. within a cell
Interstitial growth	-	growth by internal expansion, e.g. division of cells already within the tissue (c.f. appositional growth)
Kyphoscoliosis	-	abnormal curvature of the spine both dorsoventrally and sagittally
Lacuna	-	the space surrounding chondrocytes caused by an artefact of fixation
Lamellar bone	-	mature bone with a lamellar arrangement of collagen fibres
LD	-	linkage disequilibrium
Lordosis	-	inward curvature of part of the spine
MATN3	-	the gene encoding matrilin-3, a protein involved in the homeostasis of cartilage and bone
Megalocephaly	-	abnormally enlarged head
Membranous bones	-	growing or developing as a result of direct differentiation of osteoblasts from mesenchyme without a cartilaginous anlage
Mesenchyme	-	embryonic cells capable of developing into connective tissues or vasculature
Metachromasia	-	the staining of a tissue a different colour from that of the dye used
Metaphysis	-	the junction between the physis and diaphysis, containing abundant trabecular bone and a relatively thin cortex
Microdontia	-	abnormally small teeth
Micrognathia	-	abnormally small jaw or mandible
Micromelia	-	abnormally small limbs

Microphthalmia	-	abnormally small eyes
MPS	-	mucopolysaccharidosis
Mydriasis	-	excessive dilation of the pupil of the eye
Myopathy	-	disease of muscle tissue
Myopia	-	short-sightedness
Myotonia	-	increased muscle irritability or spasming
Odontoid hypoplasia	-	underdevelopment of the odontoid process, leading to cervical spine instability
OMIA	-	online mendelian inheritance in animals
OMIM	-	online mendelian inheritance in man
Organogenesis	-	the formation and development of bodily organs
OSMED	-	oto-spondylometa-epiphyseal dysplasia
Ossification	-	the process of bone formation
Osteoblasts	-	immature bone cells
Osteochondro-dysplasia	-	abnormal growth or development of cartilage and bone
Osteocytes	-	mature bone cells
Osteopenia	-	deficiency of bone tissue
Osteophyte	-	a small abnormal bony growth, especially at joint margins
Osteoprogenitors	-	cell with the potential to differentiate into bone-forming cells
Osteosclerosis	-	abnormal hardening of bone
PAP	-	phosphoadenosine-phosphate
PAPS	-	phosphoadenosine-phosphosulphate
PAPSS	-	phosphoadenosine-phosphosulphate synthase
PAS	-	periodic acid-Schiff, a technique used in histology to identify glycogen
PBS	-	phosphate-buffered saline
PCR	-	polymerase chain reaction
Pectus carinatum	-	protrusion of the sternum causing "pigeon-breast"
Pectus excavatum	-	retrusion of the sternum causing a "caved-in" chest
Perichondrium	-	dense connective tissue surrounding non-articular cartilage containing an outer fibrous layer and an inner chondrogenic layer
Periosteum	-	dense connective tissue surrounding bone containing an outer fibrous layer and an inner cambium layer containing osteoprogenitor cells
Peroxins	-	peroxisomal assembly proteins
Physis	-	the cartilaginous growth plate in an immature endochondral bone
Platyspondyly	-	having flattened vertebral bodies
Pleomorphic	-	having multiple forms
Polydactyly	-	the presence of more than five digits on hands or feet
Polymorphic	-	having many forms
Primary spongiosa	-	the initial trabecular network in the metaphysis immediately adjacent to the physis consisting of osteoid overlying calcified cartilage
Proximal	-	(as in part of a limb) close to the body
PTH	-	parathyroid hormone
PTHrP	-	parathyroid hormone-related protein

QTL	-	quantitative trait linkage
Rarefaction	-	thinning, becoming less dense
rER	-	rough endoplasmic reticulum
Retinopathy	-	disease of the retina
Rhizomelia	-	abnormally short proximal limb-bones
RHT	-	ruthenium hexammine trichloride
RMRP	-	RNA component of mitochondrial RNA processing endoribonuclease
ROX	-	6-carboxyl-X-rhodamine
SADDAN	-	severe achondroplasia with developmental delay and acanthosis nigricans
Sclerosis	-	hardening
Scoliosis	-	lateral curvature of the spine
SDS	-	sodium dodecyl sulphate
SDS-PAGE	-	sodium dodecyl sulphate polyacrylamide gel electrophoresis
Sedlin	-	endoplasmic reticulum protein with unknown function
SLC26A2	-	the gene encoding the DTDST
SNPs	-	single nucleotide polymorphisms
Spondylolisthesis	-	displacement of vertebrae or the vertebral column in relation to vertebrae below
Secondary spongiosa	-	persisting trabeculae of the primary spongiosa that have been remodelled to become lamellar bone
SHOX	-	short-stature homeobox
SLS	-	spider lamb syndrome
SMC	-	Smith-McCort dysplasia
Splanchnocranium	-	the part of the skull connected with the sense organs
Spondylo-	-	involving the spine
Spongiosa	-	cancellous bone consisting of a mesh of trabeculae
STAT	-	signal transducer and activator of transcription
Stenosis	-	abnormal narrowing of a tubular organ or structure
Synostosis	-	fusion of bone
Talipes equinovarus	-	flexural deformity causing "clubbed foot"
TB	-	toluidine blue, a histological stain
TD	-	thanatophoric dwarfism
TDT	-	transmission disequilibrium testing
TGF-β	-	transforming growth-factor-β
Tris	-	tris-(hydroxymethyl)-aminomethane
Valgus	-	abnormal lateral (outward) curvature of a bone or joint
Varus	-	abnormal medial (inward) curvature of a bone or joint
Woven bone	-	immature bone with a random arrangement of collagen fibres
Δdi-mono4S	-	chondroitin 4-sulphate disaccharide
Δdi-mono6S	-	chondroitin 6-sulphate disaccharide