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# **Chondrodysplasia of Texel Sheep**

A thesis presented in partial fulfillment  
of the requirements for the degree of

Doctor of Philosophy

*at*

Massey University,

Palmerston North,

New Zealand

Susan Amanda Piripi

2008

# 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.

# Acknowledgements

I would like to express my extreme gratitude to my chief supervisor, Keith Thompson, for his enduring support, guidance and patience throughout my studies. My co-supervisors, Hugh Blair and Elwyn Firth also assisted me greatly, and were able to offer valuable new perspectives in many areas.

My studies were facilitated by financial support from Meat and Wool New Zealand, Muriel Caddie scholarships in veterinary science, the Rose C. and George W. Hopkins Memorial Fellowship for Veterinary Pathology Research, and the IVABS Postgraduate Research Fund. For this assistance, I am most grateful.

I would like to thank my Mum, Joan Ellicott, for her sustained support and interest in my studies, and I would also like to recognise Ian Muir for inspiring my passion for biological science, all those years ago.

The efforts of Graeme Poole and Tim Byrne in the establishment and maintenance of the experimental flock were most appreciated, along with the sheep-wrangling skills of Richard Carter, Tim White, Chris Ellicott, Gillian Gibb, Steve Youngblood and others. My thanks to Dianne Knight, Laryssa Howe, Jane Candy, John Cockrem, Sarah Dorling and Trish McLenachan, for their advice, assistance, and the use of their laboratories and equipment, and to Kathryn Stowell for her useful suggestions. I am most grateful Mike Hogan for his helpfulness in the post-mortem room, along with Pat Davey, Evelyn Lupton and Mary Gaddam for their skills in specimen preparation for histology, Tony Poole for his expertise and assistance in immunohistochemistry, and Aaron Hicks, Moira Brennan and Doug Hopcroft for their technical work in electron microscopy. I would also like to express my appreciation to James Koltes and Jim Reecy for so warmly welcoming me into their department in Ames and for looking after me while I was away from home, to Martin Williams for his enthusiasm and his technical and interpretative skills in capillary electrophoresis, and to many others not listed here, for their support and good wishes.

Thankyou so much to my wonderful husband, Morore Piripi, for his assistance in the field, the lab and at home, for cooking countless dinners, providing endless cups of tea, and for all his advice and encouragement.

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# Glossary

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

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

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

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



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