Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.
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.
Table of Contents

List of Figures............................................................................................................ix
List of Tables..............................................................................................................xi
Glossary.....................................................................................................................xii

1 Introduction, literature review and study objectives................................................1
  1.1 Introduction ......................................................................................................2
  1.2 Composition and function of cartilage..............................................................3
    1.2.1 Extracellular structure...............................................................................3
    1.2.2 Sulphation of matrix proteoglycans...........................................................7
    1.2.3 Endochondral ossification.........................................................................8
    1.2.4 Structure of articular cartilage..................................................................9
    1.2.5 Structure of physeal cartilage.................................................................10
    1.2.6 Chondrodysplasias in human beings ......................................................13
    1.2.7 Defects in extracellular structural proteins...............................................14
      Defects of type II collagen......................................................................14
      Defects of type IX collagen.....................................................................16
      Defects of type X collagen......................................................................17
      Defects of type XI collagen......................................................................17
      Defects of cartilage oligomeric matrix protein (COMP)........................17
      Defects in other extracellular structural proteins.................................18
    1.2.8 Defects in metabolic pathways.................................................................18
      Defects of the diastrophic dysplasia sulphate transporter (DTDST)....18
      Defects in other metabolic pathways....................................................20
    1.2.9 Defects in the folding and degradation of macromolecules....................21
    1.2.10 Defects in hormones and signal transduction mechanisms.................22
      Fibroblast growth factor receptor 3 (FGFR3).......................................22
      Defects in the PTH/PTHrP receptor.....................................................23
      Others.....................................................................................................24
    1.2.11 Defects in nuclear proteins and transcription factors...........................24
    1.2.12 Defects in RNA and DNA processing and metabolism.........................24
    1.2.13 Defects in cytoskeletal elements............................................................25
    1.2.14 Chondrodysplasias of unknown aetiology.............................................25
      Chondrodysplasia punctata group........................................................26
      Short rib polydactyly syndromes...........................................................26
      Spondylometaphyseal dysplasias..........................................................26
  1.3 Chondrodysplasias of animals.........................................................................27
    1.3.1 Animals as models for human disease..................................................27
1.3.2 Sheep
"Spider lamb syndrome"
Ancon mutant
Lethal dwarfism
Texel chondrodysplasia
South Down dwarfism
Ectrodactyly

1.3.3 Cattle
Brachycephalic "snorter"
Dexter bulldog
Complex vertebral malformation (CVM)

1.3.4 Dogs
Alaskan malamute chondrodysplasia
Canine GM-1 gangliosidosis
Canine MPS I
Canine MPS VII
English pointer enchondrodystrophy
Miniature poodle pseudoachondroplasia
Oculoskeletal dysplasias
Norwegian Elkhound chondrodysplasia
Great Pyrenees chondrodysplasia
Irish Setter chondrodysplasia
Multiple epiphyseal dysplasia of beagles
Bull terrier osteochondrodysplasia

1.3.5 Cats
Feline MPS VI
Feline MPS VII
Scottish Fold osteochondrodysplasia

1.3.6 Pigs
Dwarfism
Danish Landrace chondrodysplasia
Hereditary dwarfism

1.3.7 Deer

1.3.8 Goats

1.3.9 Mice
Achondroplasia (cn)
Brachymorphic mouse
Cartilage matrix deficient (cmd) mice

1.3.10 Rabbits

1.3.11 Birds

1.3.12 Non-human primates
1.4 Nutritional chondrodysplasia
  1.4.1 Manganese deficiency
  1.4.2 Plant toxicity
1.5 Conclusion and study objectives

2 Pathology of chondrodysplasia in Texel sheep
  2.1 Introduction
  2.2 Materials and methods
    2.2.1 Animals used and samples collected
    2.2.2 Tissue processing and analysis
    2.2.3 Immunohistochemistry
    2.2.4 Electron microscopy
  2.3 Results
    2.3.1 Clinical signs
    2.3.2 Gross pathology
    2.3.3 Histological findings
    2.3.4 Histomorphometry
    2.3.5 Immunohistochemistry
    2.3.6 Electron microscopy
  2.4 Discussion
  2.5 Summary

3 Morphometric studies
  3.1 Introduction
  3.2 Materials and methods
    3.2.1 Animals used and measurements taken
    3.2.2 Analysis
  3.3 Results
    3.3.1 Overview
    3.3.2 Whole body growth
    3.3.3 Thoracic growth
    3.3.4 Mandibular growth
    3.3.5 Forelimb bone growth
    3.3.6 Hindlimb bone growth
    3.3.7 Allometry
      Bone lengths in relation to crown-rump length
      Relative limb bone lengths
  3.4 Discussion
| Figure 1.1 | Microarrangement of major collagens within hyaline cartilage matrix | 5 |
| Figure 1.2 | Proteoglycan aggregate structure of hyaline cartilage | 6 |
| Figure 1.3 | Sulphate transport and activation in chondrocytes | 8 |
| Figure 1.4 | Structure of articular cartilage showing the arrangement of cells and matrix components of the various zones | 10 |
| Figure 1.5 | The organisation of physeal cartilage showing the arrangement of cells and matrix components of the various zones | 12 |
| Figure 1.6 | Diagram outlining some of the pathways involved in the regulation of endochondral ossification | 13 |
| Figure 1.7 | Sulphation of cartilage proteoglycans in control and chondrodysplastic Texel sheep | 31 |
| Figure 2.1 | Chondrodysplastic Texel lambs | 56 |
| Figure 2.2 | Chondrodysplasia in Texel sheep | 57 |
| Figure 2.3 | Trachea from a chondrodysplastic Texel lamb | 58 |
| Figure 2.4 | Thoracic cavities from 3-4-month-old control and chondrodysplastic lambs | 59 |
| Figure 2.5 | Enlarged costochondral junctions in chondrodysplasia of Texel sheep | 59 |
| Figure 2.6 | Joint lesions in chondrodysplasia of Texel sheep | 60 |
| Figure 2.7 | Hydronephrosis in chondrodysplasia of Texel sheep | 61 |
| Figure 2.8 | High-power view of control and chondrodysplastic hyaline cartilage | 62 |
| Figure 2.9 | Articular cartilage from the proximal humerus of a 30-day-old chondrodysplastic lamb | 63 |
| Figure 2.10 | Costochondral junctions of normal and chondrodysplastic lambs 6-7 weeks of age | 64 |
| Figure 2.11 | Physis of control and month-old chondrodysplastic lambs | 65 |
| Figure 2.12 | Sagittal sections of 3rd-4th lumbar vertebral bodies and intervertebral disc from 3-4-month-old control and chondrodysplastic Texel lambs | 66 |
| Figure 2.13 | Tracheal cartilage from normal and chondrodysplastic lambs | 67 |
| Figure 2.14 | Immunohistochemical staining of types II and VI collagen in articular-epiphyseal cartilage from control and chondrodysplastic Texel sheep | 70 |
| Figure 2.15 | Articular cartilage chondrocytes and pericellular matrix from control and chondrodysplastic Texel lambs | 71 |
| Figure 2.16 | High power views of pericellular and interterritorial matrix of cartilage from control and chondrodysplastic Texel lambs | 71 |
| Figure 3.1 | Serial measurements taken from control and chondrodysplastic Texel lambs | 84 |
| Figure 3.2 | Crown-rump length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals | 87 |
Figure 3.3   Shoulder-rump length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals.......................88
Figure 3.4   Thoracic width and rate of increase in thoracic width in control and chondrodysplastic Texel lambs at different age intervals.......................89
Figure 3.5   Thoracic depth and rate of increase in thoracic depth in control and chondrodysplastic Texel lambs at different age intervals.......................90
Figure 3.6   Mandible length and growth rate of control and chondrodysplastic Texel lambs at different age intervals......................................................91
Figure 3.7   Humeral length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals......................................................92
Figure 3.8   Ulnar length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals................................................................93
Figure 3.9   Metacarpal length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals......................................................93
Figure 3.10   Femoral length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals......................................................95
Figure 3.11   Tibial length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals................................................................95
Figure 3.12   Tarsal-metatarsal length and rate of growth in control and chondrodysplastic Texel lambs at different age intervals.......................96
Figure 3.13   Relative bone lengths in the forelimb of chondrodysplastic and control Texel lambs at 21-30 days of age.............................................................99
Figure 3.14   Relative bone lengths in the hindlimb of chondrodysplastic and control Texel lambs at 31-40 days of age.............................................................99
Figure 3.15   The change in relationship between tibial and tarsal-metatarsal length in chondrodysplastic and control Texel lambs......................................100
Figure 3.16   Comparison of lengths of equivalent bones in fore and hind limbs of chondrodysplastic and control Texel lambs..........................................100
Figure 4.1   Fibroblast sulphate uptake in chondrodysplastic and control Texel sheep........................................................................................................111
Figure 5.1   Amplification scheme for fluorescently labelled universal primers.....120
Figure 5.2   Typical chromatogram showing amplified microsatellite sequence....122
Figure 5.3   Chi-squared test results for differences between control and chondrodysplastic Texel sheep in heterozygosity, allele frequency and genotype of microsatellite markers.........................................................123
Figure 6.1   Typical electropherogram of chondroitin disaccharides from ovine articular cartilage....................................................................................131
Figure 6.2   Ratios of ∆di-mono4S to ∆di-mono6S in chondrodysplastic and control Texel sheep of different ages.................................................................132
List of Tables

Table 2.1  Chondrocyte density expressed as cells per 400X field in cartilage of chondrodysplastic and control Texel lambs............................................68
Table 2.2  Cartilage thickness of chondrodysplastic and control Texel lambs........69
Table 3.1  ANOVA models fitted for the comparison of lengths of limb bones between control and chondrodysplastic Texel lambs..............................85
Table 3.2  Influences other than chondrodysplasia on body length...................88
Table 3.3  Influences other than chondrodysplasia on thoracic dimensions...........90
Table 3.4  Influences other than chondrodysplasia on mandibular length.............91
Table 3.5  Influences other than chondrodysplasia on forelimb bone length..........94
Table 3.6  Influences other than chondrodysplasia on hindlimb bone length..........97
Table 3.7  Bone length and body dimensions influenced by sex, dam, rank, birthweight or status when crown-rump length is a covariate...............98
Table 5.1  List of microsatellite markers chosen for amplification, together with nearby genes related to cartilage or skeletal development......................118
Table 5.2  Optimal annealing temperatures for microsatellite primers...............119
Table 5.3  Half-sib regression interval mapping results for microsatellite data from chondrodysplastic and control Texel sheep.................................123
Table 6.1  Concentrations of chondroitin sulphate disaccharides from chondrodysplastic and control Texel sheep of varying ages.........................132
# Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>alcian blue, histological stain</td>
</tr>
<tr>
<td>Abluminal</td>
<td>pertaining to the outer portion of a tubular structure</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>a form of skin hyperpigmentation</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>specific term for failure of cartilage growth, also commonly used to refer to a common form of dwarfism in humans</td>
</tr>
<tr>
<td>Acromesomelia</td>
<td>shortening of the middle and distal parts of the limbs</td>
</tr>
<tr>
<td>Alympatic</td>
<td>lacking lymphatic vessels</td>
</tr>
<tr>
<td>Anauxetic</td>
<td>without growth</td>
</tr>
<tr>
<td>Aneural</td>
<td>lacking innervation</td>
</tr>
<tr>
<td>Anisospondyly</td>
<td>different abnormal shapes of vertebral bodies</td>
</tr>
<tr>
<td>Ankylosis</td>
<td>bony fusion of a joint</td>
</tr>
<tr>
<td>Anlage</td>
<td>an embryonic precursor to a structure</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>Appositional growth</td>
<td>growth by the addition of external layers (c.f. interstitial growth)</td>
</tr>
<tr>
<td>APS</td>
<td>adenosine phosphosulphate</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>joint disease</td>
</tr>
<tr>
<td>Articular-epiphyseal complex</td>
<td>the epiphyseal cartilage of young animals consisting of both an articular surface and a zone of growth</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>Avascular</td>
<td>lacking blood vessels</td>
</tr>
<tr>
<td>Basophilic</td>
<td>a tissue that stains with a basic dye, such as haematoxylin</td>
</tr>
<tr>
<td>Blepharophimosis</td>
<td>abnormally narrow palpebral fissure (gap between eyelids)</td>
</tr>
<tr>
<td>BMP</td>
<td>bone morphogenic protein</td>
</tr>
<tr>
<td>Bossing</td>
<td>swelling</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>having a short (broad) head</td>
</tr>
<tr>
<td>Brachydactyly</td>
<td>short fingers</td>
</tr>
<tr>
<td>Brachygnathia</td>
<td>shortened mandible or jaw</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>flexural deformity of interphalangeal joints</td>
</tr>
<tr>
<td>Cancellous bone</td>
<td>has a latticed structure (c.f. compact bone)</td>
</tr>
<tr>
<td>CATSHL syndrome</td>
<td>a syndrome featuring camptodactyly, tall stature, scoliosis and hearing loss</td>
</tr>
<tr>
<td>CDMP-1</td>
<td>cartilage derived morphogenic protein-1</td>
</tr>
<tr>
<td>CE</td>
<td>capillary electrophoresis</td>
</tr>
<tr>
<td>CHILD syndrome</td>
<td>congenital hemidysplasia with ichthyosiform erythroderma and limb defects</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>Chondroblasts</td>
<td>immature cartilage cells</td>
</tr>
<tr>
<td>Chondrocalcin</td>
<td>the C-propeptide of type II collagen</td>
</tr>
</tbody>
</table>
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 color 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
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrillogenesis</td>
<td>formation of fibrils</td>
</tr>
<tr>
<td>Fibrocartilage</td>
<td>contains bundles of type I collagen within the matrix</td>
</tr>
<tr>
<td>Genu valgum</td>
<td>valgus deformity at the knees, &quot;knock-knees&quot;</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>increased intraocular pressure</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>haematoxylin &amp; eosin, common histological stain</td>
</tr>
<tr>
<td>Haploinsufficiency</td>
<td>occurs when a single functional gene is unable to produce enough product to maintain a wild type (normal) phenotype</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>enlarged liver and spleen</td>
</tr>
<tr>
<td>HEPES</td>
<td>N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid</td>
</tr>
<tr>
<td>Homeobox genes</td>
<td>highly conserved genes that regulate bodily segmentation during embryonic development</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>Hyaline cartilage</td>
<td>has a homogeneous, amorphous matrix</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>dilatation of the cerebral ventricles</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>in chondrocytes is a stage late in maturation with increased cell size</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>widely-spaced eyes</td>
</tr>
<tr>
<td>Hypocellular</td>
<td>having decreased cell density</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>incomplete development of an organ or tissue</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>decreased tone of skeletal muscles</td>
</tr>
<tr>
<td>IBD</td>
<td>identical by descent</td>
</tr>
<tr>
<td>Ichthyosiform</td>
<td>resembling scaly skin</td>
</tr>
<tr>
<td>Ihh</td>
<td>Indian hedgehog</td>
</tr>
<tr>
<td>Inclusion</td>
<td>abnormal aggregation of substance, e.g. within a cell</td>
</tr>
<tr>
<td>Interstitial growth</td>
<td>growth by internal expansion, e.g. division of cells already within the tissue (c.f. appositional growth)</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>abnormal curvature of the spine both dorsoventrally and sagittally</td>
</tr>
<tr>
<td>Lacuna</td>
<td>the space surrounding chondrocytes caused by an artefact of fixation</td>
</tr>
<tr>
<td>Lamellar bone</td>
<td>mature bone with a lamellar arrangement of collagen fibres</td>
</tr>
<tr>
<td>LD</td>
<td>linkage disequilibrium</td>
</tr>
<tr>
<td>Lordosis</td>
<td>inward curvature of part of the spine</td>
</tr>
<tr>
<td>MATN3</td>
<td>the gene encoding matrilin-3, a protein involved in the homeostasis of cartilage and bone</td>
</tr>
<tr>
<td>Megalocephaly</td>
<td>abnormally enlarged head</td>
</tr>
<tr>
<td>Membranous bones</td>
<td>growing or developing as a result of direct differentiation of osteoblasts from mesenchyme without a cartilaginous anlage</td>
</tr>
<tr>
<td>Mesenchyme</td>
<td>embryonic cells capable of developing into connective tissues or vasculature</td>
</tr>
<tr>
<td>Metachromasia</td>
<td>the staining of a tissue a different colour from that of the dye used</td>
</tr>
<tr>
<td>Metaphysis</td>
<td>the junction between the physis and diaphysis, containing abundant trabecular bone and a relatively thin cortex</td>
</tr>
<tr>
<td>Microdontia</td>
<td>abnormally small teeth</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>abnormally small jaw or mandible</td>
</tr>
<tr>
<td>Micromelia</td>
<td>abnormally small limbs</td>
</tr>
</tbody>
</table>
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-spondylometaphyseal dysplasia
Ossification - the process of bone formation
Osteoblasts - immature bone cells
Osteochondrodysplasia - 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
∆di-mono4S - chondroitin 4-sulphate disaccharide
∆di-mono6S - chondroitin 6-sulphate disaccharide