CMHD Pathology Report

CMHD Pathology Core
Toronto Centre for Phenogenomics
25 Orde St. 3rd fl.
Toronto, Ont. M5T 3H7
Tel.(416) 586-8375
Fax (416) 586-5993

contact: Dr. Susan Newbigging
email: newbigging@lunenfeld.ca

Principle Investigator: Dr. Jacqui White
Institute: Wellcome Trust Sanger Institute
Address: Attn: Linda Read Wellcome Trust Genome Campus Hinxton Cambridge CB10 1SA, UK

Mouse Genetics Project
Wellcome Trust Sanger Institute
Wellcome Trust Genome Campus
Hinxton, Cambridge
CB10 1SA
UK

email: MGPenquiries@sanger.ac.uk
Mouse Portal
Europhenome

ReportID: Report Date: August 20, 2013
Pathologist: Dr. H. Adissu

CMHD LabID: N13-491

Relevant History:
Phenotypes:

abnormal behavior
abnormal cornea morphology
increased mean platelet volume
decreased circulating alanine transaminase level
decreased circulating amylase level
decreased circulating aspartate transaminase level
vertebral transformation
increased mature B cell number
increased regulatory T cell number
increased susceptibility to bacterial infection
closed eyes
abnormal corneal endothelium morphology
corneal vascularization
increased corneal stroma thickness
iris synechia
abnormal brainstem auditory evoked potential
partial lethality
abnormal fertility/fecundity

AnimalID: M00723890 (Male)

Histopathology Findings:

liver (MA:0000358)

Histopath Description:
The overall hepatic lobular architecture is normal. Diffusely, hepatocytes contain intracytoplasmic clear vacuoles (lipid). The lipid vacuoles within the midzonal and periacinar regions are small (2-3 um in diameter) and surround a central nucleus (interpreted as microvesicular lipid). The lipid vacuoles within the portal areas are large (8-12 um in diameter) and displace the nucleus to the margin (macrovesicular lipid).

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** lipid deposition MPATH:42

Definitive Diagnosis:
Hepatic lipidosis

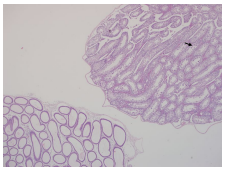
Histopathology Comments:
Hepatocellular vacuolar change of variable degree suggestive of lipidosis is present in all mice from WTSI, consistent with high lipid diet.

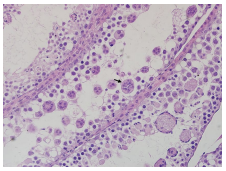
testis (MA:0000411)

Histopath Description:
Seminiferous tubules contain numerous large cells that are up to 50 um in diameter. The cells are multinucleated containing up to 30 nuclei that are mostly located centrally. Some of these multinucleated cells have foamy cytoplasm and some contain pyknotic nuclei (apoptotic). The rest of the seminiferous tubule is vacuolated spermatids and spermatocytes are low in number and maturing spermatids are absent. The epididymal ducts are devoid of spermatocytes.

Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme;

Definitive Diagnosis:
vacuolar degeneration of seminiferous tubule with giant multinucleated spermatids; epididymal aspermia


Testis and epididymis, note small testis and empty epididymal duct, 4x, HE


Testis, vacuolar degeneration of seminiferous tubule with giant multinucleated spermatids, note absence of spermatogenesis, 40x, HE

lymph node (MA:0000139)

Histopath Description:
The mesenteric lymph node is markedly enlarged (greater than four fold). The medulla is particularly expanded by chords and sheets of plasmatoid cells. There are promient germinal centers within the medulla

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** hyperplasia MPATH:134

Definitive Diagnosis:
Lymphoid hyperplasia

Histopathology Comments:
The changes in the mesenteric lymph node are suggestive of draining of a regional inflammatory process. However, such a process was not observed in the tissues examined. Early maginal center lymphoma is suspected.

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, testis, epididymis, seminal vesicle, and prostate.

AnimalID: M00698323 (Male)

Histopathology Findings:

liver (MA:0000358)

Histopath Description:
The overall hepatic lobular architecture is normal. Diffusely, hepatocytes contain intracytoplasmic clear vacuoles (lipid). The lipid vacuoles within the midzonal and periacinar regions are small (2-3 um in diameter) and surround a central nucleus (interpreted as microvesicular lipid). The lipid vacuoles within the portal areas are large (8-12 um in diameter) and displace the nucleus to the margin (macrovesicular lipid).

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** lipid deposition MPATH:42

Definitive Diagnosis:
Hepatic lipidosis

Histopathology Comments:
Hepatocellular vacuolar change of variable degree suggestive of lipidosis is present in all mice from WTSI, consistent with high lipid diet.

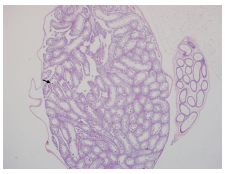
testis (MA:0000411)

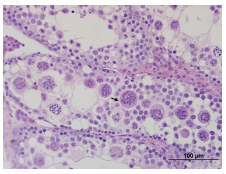
Histopath Description:
Seminiferous tubules contain numerous large cells that are up to 50 um in diameter. The cells are multinucleated containing up to 30 nuclei that are mostly located centrally. Some of these multinucleated cells have foamy cytoplasm and some contain pyknotic nuclei (apoptotic). The rest of the seminiferous tubule is vacuolated spermatids and spermatocytes are low in number and

maturing spermatids are absent. The epididymal ducts are devoid of spermatocytes.

Morphological Diagnosis:
Distribution: diffuse; **Severity:** extreme;

Definitive Diagnosis:
vacuolar degeneration of seminiferous tubule with giant multinucleated spermatids; epididymal aspermia


Testis and epididymis, note small testis and empty epididymal duct, 4x, HE

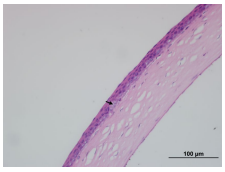

Testis, vacuolar degeneration of seminiferous tubule with giant multinucleated spermatids, note absence of spermatogenesis, 40x, HE

eye (MA:0000261)

Histopath Description:
The basal layer of the corneal epithelium is multifocally disorganized and contains large non-polarized vacuolated cells. Occasional apoptotic cells are noted.

Morphological Diagnosis:
Distribution: multifocal; **Severity:** mild;

Definitive Diagnosis:
Corneal epithelial dysplasia, mild


Eye cornea, epithelial dysplasia, mild, 40x, HE

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, testis, epididymis, seminal vesicle, and prostate.

AnimalID: M00723893 (Female)

Histopathology Findings:

liver (MA:0000358)

Histopath Description:
The overall hepatic lobular architecture is normal. Diffusely, hepatocytes contain intracytoplasmic clear vacuoles (lipid). The lipid vacuoles within the midzonal and periacinar regions are small (2-3 um in diameter) and surround a central nucleus (interpreted as microvesicular lipid). The lipid vacuoles within the portal areas are large (8-12 um in diameter) and displace the nucleus to the margin (macrovesicular lipid).

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** lipid deposition MPATH:42

Definitive Diagnosis:
Hepatic lipidosis

Histopathology Comments:
Hepatocellular vacuolar change of variable degree suggestive of lipidosis is present in all mice from WTSI, consistent with high lipid diet.

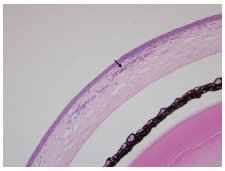
eye (MA:0000261)

Histopath Description:
Unilateral mild neutrophilic inflammation with mid stromal vascularization; mild diroganization and hyperplasia of corneal epithelium

Morphological Diagnosis:
Duration: subacute; **Distribution:** multifocal; **Severity:** mild;

Definitive Diagnosis:
Keratitis, neutrophilic

Histopathology Comments:
Lesion may explain ocular morphology



Eye, cornea, keratitis with dysplastic epithelial regererative hyperplasia. 20x

lymph node (MA:0000139)

Histopath Description:
The mesenteric lymph node is markedly enlarged (greater than four fold). The medulla is particularly expanded by chords and sheets of plasmatoid cells. There are promient germinal centers within the medulla

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** hyperplasia MPATH:134

Definitive Diagnosis:
Lymphoid hyperplasia

Histopathology Comments:
The changes in the mesenteric lymph node are suggestive of draining of a regional inflammatory process. However, such a process was not observed in the tissues examined. Early maginal center lymphoma is suspected.

parathyroid gland (MA:0000128)

Histopath Description:
The parathyroid gland is partially replaced by a lymphoid tissue reminiscent of thymic tissue.

Morphological Diagnosis:
Distribution: multifocal;

Definitive Diagnosis:
Ectopic thymic tissue

Histopathology Comments:
incidental

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, uterus, oviduct, and ovary, and mammary gland.

AnimalID: M00698327 (Female)

Histopathology Findings:

liver (MA:0000358)

Histopath Description:
The overall hepatic lobular architecture is normal. Diffusely, hepatocytes contain intracytoplasmic clear vacuoles (lipid). The lipid vacuoles within the midzonal and periacinar regions are small (2-3 um in diameter) and surround a central nucleus (interpreted as microvesicular lipid). The lipid vacuoles within the portal areas are large (8-12 um in diameter) and displace the nucleus to the margin (macrovesicular lipid).

Morphological Diagnosis:
Distribution: Diffuse; **Severity:** moderate; **MPATH Diagnosis:** lipid deposition MPATH:42

Definitive Diagnosis:
Hepatic lipidosis

Histopathology Comments:
Hepatocellular vacuolar change of variable degree suggestive of lipidosis is present in all mice from WTSI, consistent with high lipid diet.

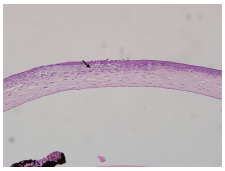
eye (MA:0000261)

Histopath Description:
Unilateral mild neutrophilic infiltartes in mid corneal stroma. The epithelium is hyperplastic with marked epithelial cell hypetrophy and disorganization. There is mild mid-stromal vascularization.

Morphological Diagnosis:
Duration: subacute; **Distribution:** focally extensive; **Severity:** mild;

Definitive Diagnosis:
Keratitis, with dysplastic epithelial regererative hyperplasia.

Histopathology Comments:
Lesion may explain ocular morphology



Eye, cornea, keratitis with dysplastic epithelial regererative hyperplasia. 20x

Organ/Tissue Analyzed:
Histopathology examination included the following organs and tissues: brain, trigeminal ganglion, eyes, salivary glands, trachea, lungs, heart, thymus, thyroid gland, parathyroid gland, exocrine and endocrine pancreas, oesophagus, stomach, small intestine, large intestine, liver, gall bladder, spleen, kidneys, adrenal gland, lymph nodes, spinal cord, bone marrow, sternum, femur and tibia with associated skeletal muscles, brown fat, pinna, skin, uterus, oviduct, and ovary, and mammary gland.

Report Summary and Recommendation:
Corneal inflammation and dysplastic regenerative response was observed in two females. One of the male mice has a mild dysplastic changes in the cornea. There is no accompanying corneal inflammation in this male; hence primary corneal epithelial dysplasia can not be ruled out.

Both males have a unique testicular lesion characterized by presence of multinucleated spermatids. We have observed rare (1-2) multinucleated spermatids in WT mice with no apparent effect on the level of spermatogenesis. The lesion in this line is extreme and is accompanied by other degenerative and apoptotic changes, absence of spermatogenesis, and epididymal aspermia.

Interestingly, increased numbers of giant rounded spermatids was documented in sterile Pink-Eyed Mutant Mouse (Hunt and Johnson, 1971; Bryan 1977). Note that the current line also has some eye abnormalities.

Multinucleated germ cells are often seen in the seminiferous tubules of fertile males from a number of species of rodents (Bryan, 1977). They can be present as spontaneous age associated lesions (Gordon et al., 1996), or are caused by various insults including ligation of the efferent duct (Singh and Abe, 1987), chemicals (Chinoya et al., 2005) and radiation toxicity associated with tritium (Bhatia, 1985). Ultrastructural studies suggest that the giant cells are formed as a result of the fusion of spermatids due to alterations in the intercellular bridges (Singh and Abe, 1987) or from degenerate spermatocytes or spermatids (Gordon et al., 1996). These cells are also reported as spontaneous finding in young beagle dogs (Goedken et al. 1998)

Line summary: Eye: Corneal epithelial dysplasia with or without keratitis (3/4); Testis: Semiferous degeneration and atrophy with numerous giant multinucleated spermatids.

References:
Bhatia AL. (1985). Tritium Toxicity: Age-dependent Radiosensitivity of Mouse Testes. Bull. Environ. Contam. Toxicol. 34:803-808 Bryan JHD (1987). Spermatogenesis Revisited III. The Course of Spermatogenesis in a Male-Sterile Pink-Eyed Mutant Type in the Mouse. Cell Tiss. Res. 180, 173-186. Chinoya NJ et al. (2005). Fluoride+aluminium induced toxicity in mice testis with giant cells and its reversal by vitamin c. fluoride 38:109–114 Gordon LR, Majika JA, and Boorman GA (1996). Spontaneous Nonneoplastic and neoplastic lesions and experimentally induced neoplasms of the testes and accessory sex glands. In Pathobiology of the Aging Mouse. Mohr U et al (ed). Vol 1. ILSI, P422. Singh SK, Abe K.

(1987). Light and electron microscopic observations of giant cells in the mouse testis after efferent duct ligation. Arch Histol Jpn. 50:579-85. Goedken MJ et al. (2008).Spontaneous and age-related testicular findings in beagle dogs.Toxicol Pathol. 36(3):465-71.