CMHD Pathology Report

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Mouse Genetics Project
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ReportID: Report Date: June 12, 2013
Pathologist: Dr. H. Adissu

CMHD LabID: N13-248

Relevant History:
Phenotypes:

Abnormal tail morphology
abnormal head morphology
broad head
bulging abdomen
abnormal external male genitalia morphology
enlarged testis
decreased body length
decreased body weight
decreased lean body mass
decreased bone mineral content
vertebral fusion
increased sacral vertebrae number
abnormal vertebrae morphology
scoliosis
abnormal spine curvature
vertebral transformation
abnormal humerus morphology
abnormal joint morphology
abnormal tibia morphology
abnormal ulna morphology
abnormal pelvic girdle bone morphology
abnormal thoracic cage shape
abnormal cranium morphology
decreased body weight
hypoalbuminemia
decreased circulating total protein level
decreased energy expenditure
increased energy expenditure
increased oxygen consumption
abnormal behavior
hypoactivity
impaired glucose tolerance
increased T cell number
increased CD8-positive T cell number
abnormal corneal endothelium morphology
abnormal corneal epithelium morphology
abnormal descemet membrane
partial lethality
chromosomal instability

AnimalID: M00559212 (Male)
Histopathology Findings:

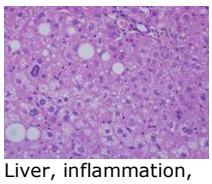
liver (MA:0000358)

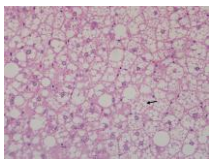
Histopath Description:
Moderate multifocal lipidosis with prominent large lipid vacuoles expanding many hepatocytes in midzonal regions (suspected to be Ito cells/hepatic stellate cells). Hepatocytes in the rest of the liver have microvesicular lipidosis. There are cluseters of neutrophils and occasional lymohocytes in portal areas. Rare clusters of foamy and granular macrophages are also noted. Occasional hepatocytes are large (2x normal) and have enlarged hyperchromatic nuceli (karyomegaly). Numerous binucleated and occasional trinucleated hepatocytes are present.

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

Definitive Diagnosis:
Mild chronic active inflammation; Ito cell hyperplasia; moderate hepatocellular lipidosis; hepatocellular megalocytosis , karyomegaly and multinucleation

Histopathology Comments:
Mild active inflammation is evident in this liver. The hepatocellular megalocytosis and Ito cell hyperplasia are likely reparative responses. Hepatocellular Megalocytosis occurs when hepatocytes are stimulated to divide, usually following a regenerative stimulus, when there is inhibition of mitosis but not DNA synthesis. Hepatocellular megalocytosis is routinely seen in rodent liver with increased severity as animals age.They are more notable than we routinely see in the controls at this age. This should be evaluated in view of the the gene function (Cenpj). Ito cells are hepatic stellates cells are responsive to hepatic injury induced by a variety of hepatic necrogenic agents.


Liver, inflammation, lipidosis, Ito cell hyperplasia, and cytomegaly, 40x, HE

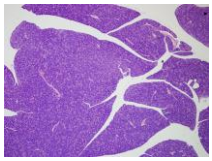

Liver, WT, control_normal, 40x, HE

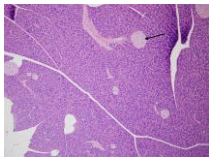
pancreatic islet (MA:0000127)

Histopath Description:
There are fewer pancreatic islets in this mouse compared to WT controls.

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

Definitive Diagnosis:
Pancreatic islet hypoplasia (number and size)


Pancreas, islet hypoplasia, 10x, HE

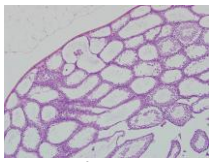

Pancreas, WT_control, normal, 10x, HE

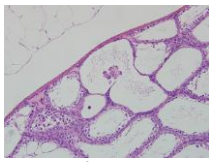
testis (MA:0000411)

Histopath Description:
There is severe vacuolar degeneration and atrophy of the seminiferous tubule affecting 50% of the testis.

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** severe;

Definitive Diagnosis:
Testicular degeneration and atrophy


Testis , degeneration and atrophy, 10x, HE


Testis , degeneration and atrophy, 20x, HE

brain (MA:0000168)

Histopath Description:
There is mild dilation of the lateral ventricles

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

Definitive Diagnosis:
Dilation of the brain ventricles

Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004).

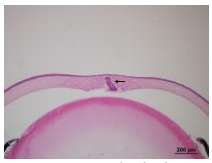
cornea (MA:0000266)

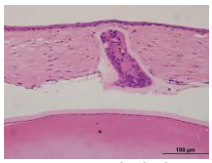
Histopath Description:
There is a focal epithelial inclusion within the middle cornea; there is a mild midstromal fibrosis surrounding this inclusion.

Morphological Diagnosis:
Distribution: focal; **MPATH Diagnosis:** cyst MPATH:62

Definitive Diagnosis:
Corneal epithelial cyst with mild dysplasia

Histopathology Comments:
This lesion was likely caused by an abberant epithelial migration and proliferation secondary to partial thickness penetrating injury of the cornea.


Cornea, epithelial inclusion, 10x, HE


Cornea, epithelial inclusion, 40x, HE

brain (MA:0000168)

Histopath Description:
There is moderate dilation of the lateral ventricles; there is rarefaction of the periventricular neuropile

Morphological Diagnosis:
Distribution: bilateral; **Severity:** moderate;

Definitive Diagnosis:
Dilation of the brain ventricles with vacuolation of the periventricular neuropil

Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004). The changes in this line are more severe.

AnimalID: M00559219 (Male)

Histopathology Findings:

liver (MA:0000358)

Histopath Description:
Moderate lipidosis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate;

Definitive Diagnosis:
Lipidosis

salivary gland (MA:0000346)

Histopath Description:
There are multifocal perivascular mononuclear inflammatory cell aggregates.

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

Definitive Diagnosis:
Interstitial inflammatory aggregates

brain (MA:0000168)

Histopath Description:
There is moderate dilation of the lateral ventricles; there is rarefaction of the periventricular neuropile

Morphological Diagnosis:
Distribution: bilateral; **Severity:** moderate;

Definitive Diagnosis:
Dilation of the brain ventricles with vacuolation of the periventricular neuropil

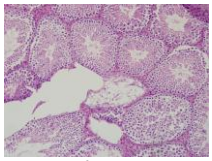
Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004). The changes in this line are more severe.

testis (MA:0000411)

Histopath Description:
There is a focal vacuolar degeneration and atrophy of the seminiferous tubule.

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

Definitive Diagnosis:
Testicular degeneration and atrophy


Testis , degeneration and atrophy, 20x, HE

retina (MA:0000276)

Histopath Description:
Involving one eye, there are clusters of external nuclear structures within the internal plexiform layer.

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

Definitive Diagnosis:
Retinal dysplasia

stomach (MA:0000353)

Histopath Description:
moderate neutrophilic gastritis

Morphological Diagnosis:
Distribution: multifocal to coalescing; **Severity:** moderate;

Definitive Diagnosis:
Gastrits, neutrophilic

AnimalID: M00559214 (Female)

Tissue Preservation and Staining:
Thyroid not available

Histopathology Findings:

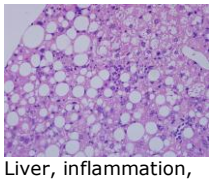
liver (MA:0000358)

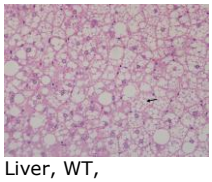
Histopath Description:
Moderate multifocal lipidosis with prominent large lipid vacuoles expanding many hepatocytes in midzonal regions (suspected to be Ito cells/hepatic stellate cells). Hepatocytes in the rest of the liver have microvesicular lipidosis. There are cluseters of neutrophils and occasional lymohocytes in portal areas. Rare clusters of foamy and granular macrophages are also noted. Occasional hepatocytes are large (2x normal) and have enlarged hyperchromatic nuceli (karyomegaly). Numerous binucleated and occasional trinucleated hepatocytes are present. Rare single dead hepatocytes are noted (see image)

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

Definitive Diagnosis:
Mild chronic active inflammation; Single hepatocellular necrosis, Ito cell hyperplasia; moderate hepatocellular lipidosis; hepatocellular megalocytosis , karyomegaly and multinucleation

Histopathology Comments:
Mild active inflammation and single hepatocellular necrosis is evident in this liver. The hepatocellular megalocytosis and Ito cell hyperplasia are likely reparative responses. Hepatocellular Megalocytosis occurs when hepatocytes are stimulated to divide, usually following a regenerative stimulus, when there is inhibition of mitosis but not DNA synthesis. Hepatocellular megalocytosis is routinely seen in rodent liver with increased severity as animals age.They are more notable than we routinely see in the controls at this age. This should be evaluated in view of the the gene function (Cenpj). Ito cells are hepatic stellates cells are responsive to hepatic injury induced by a variety of hepatic necrogenic agents.


Liver, inflammation, lipidosis, Ito cell hyperplasia, and cytomegaly, 40x, HE


Liver, WT, control_normal, 40x, HE

brain (MA:0000168)

Histopath Description:
There is moderate dilation of the lateral ventricles; there is rarefaction of the periventricular neuropile

Morphological Diagnosis:
Distribution: bilateral; **Severity:** moderate;

Definitive Diagnosis:
Dilation of the brain ventricles with vacuolation of the periventricular neuropil

Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004). The changes in this line are more severe.

AnimalID: M00559213 (Female)

Histopathology Findings:

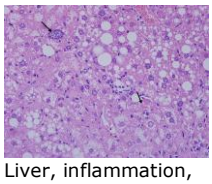
liver (MA:0000358)

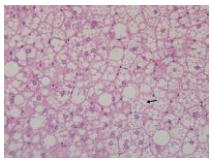
Histopath Description:
Moderate multifocal lipidosis with prominent large lipid vacuoles expanding many hepatocytes in midzonal regions (suspected to be Ito cells/hepatic stellate cells). Hepatocytes in the rest of the liver have microvesicular lipidosis. There are cluseters of neutrophils and occasional lymohocytes in portal areas. Rare clusters of foamy and granular macrophages are also noted. Occasional hepatocytes are large (2x normal) and have enlarged hyperchromatic nuceli (karyomegaly). Numerous binucleated and occasional trinucleated hepatocytes are present. Rare single dead hepatocytes are noted (see image)

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

Definitive Diagnosis:
Mild chronic active inflammation; Single hepatocellular necrosis, Ito cell hyperplasia; moderate hepatocellular lipidosis; hepatocellular megalocytosis , karyomegaly and multinucleation

Histopathology Comments:
Mild active inflammation and single hepatocellular necrosis is evident in this liver. The hepatocellular megalocytosis and Ito cell hyperplasia are likely reparative responses. Hepatocellular Megalocytosis occurs when hepatocytes are stimulated to divide, usually following a regenerative stimulus, when there is inhibition of mitosis but not DNA synthesis. Hepatocellular megalocytosis is routinely seen in rodent liver with increased severity as animals age.They are more notable than we routinely see in the controls at this age. This should be evaluated in view of the the gene function (Cenpj). Ito cells are hepatic stellates cells are responsive to hepatic injury induced by a variety of hepatic necrogenic agents.


Liver, inflammation, lipidosis, Ito cell hyperplasia, and cytomegaly, 40x, HE


Liver, WT, control_normal, 40x, HE

brain (MA:0000168)

Histopath Description:
There is moderate dilation of the lateral ventricles; there is rarefaction of the periventricular neuropile

Morphological Diagnosis:
Distribution: bilateral; **Severity:** moderate;

Definitive Diagnosis:
Dilation of the brain ventricles with vacuolation of the periventricular neuropil

Histopathology Comments:
Mild dilation of the lateral ventricles is a background condition in mice of C57BL/6N background (Brayton et al., 2004). The changes in this line are more severe.

Report Summary and Recommendation:
Testicular degeneration and atrophy is present in both males (M00559212 and M00559219), with a more severe lesion seen in the former. Note that similar but uniform and complete testicular hypoplasia and infertility was observed in mcph1 line submitted from WTSI.

Three mice showed mild chronic active inflammation and single cell necrosis in the liver accompanied by hepatocellular cytomegaly and presumed Oto cell hyperplasia (both considered a reparative/regenerative response). The cause of hepatitis is not certain but Helicobacteriosis is a suspect. However, the hepatocellular cytomegaly and karyomegally was quite marked hence should be viewed in light of the role of the gene in genomic instability and the chromosomal instability documented during clinical phenotyping.

There is moderate ventricular dilation in the brain (the changes are more severe than usually seen in controls of this strain). The hippocampus appears to be compressed by the dilated ventricles.

Line summary: 1. Testicular degeneration and atrophy (2/2); 2. Hepatitis with karyomegaly and cytomegaly (3/4); 3. More marked ventricular dilation (brain) (4/4)