Summary

Clinical characteristics. McLeod neuroacanthocytosis syndrome (designated as MLS throughout this review) is a multisystem disorder with central nervous system (CNS), neuromuscular, and hematologic manifestations in males. CNS manifestations are a neurodegenerative basal ganglia disease including (1) movement disorders, (2) cognitive alterations, and (3) psychiatric symptoms. Neuromuscular manifestations include a (mostly subclinical) sensorimotor axonopathy and muscle weakness or atrophy of different degrees. Hematologically, MLS is defined as a specific blood group phenotype (named after the first proband, Hugh McLeod) that results from absent expression of the Kx erythrocyte antigen and weakened expression of Kell blood group antigens. The hematologic manifestations are red blood cell acanthocytosis and compensated hemolysis. Allo-antibodies in the Kell and Kx blood group system can cause strong reactions to transfusions of incompatible blood and severe anemia in newborns of Kell-negative mothers. Females heterozygous for XK pathogenic variants have mosaicism for the Kell and Kx blood group antigens but usually lack CNS and neuromuscular manifestations; however, some heterozygous females may develop clinical manifestations including chorea or late-onset cognitive decline.

Diagnosis/testing. The diagnosis of MLS is based on findings on clinical examination, immunohematologic testing, and flow cytometry. XK is the only gene in which pathogenic variants are known to cause MLS. Contiguous gene deletions involving XK may also include CYBB (causing X-linked chronic granulomatous disease); DMD (Duchenne muscular dystrophy); and RPGR (X-linked retinitis pigmentosa).

Management. Treatment of manifestations: Dopamine antagonists (e.g., tiapride, clozapine, quetiapine) and the dopamine depletory (tetrabenazine) may be used to ameliorate chorea; treatment of psychiatric problems, cardiac abnormalities, and seizures are based on the clinical findings; long-term and continuous multidisciplinary psychosocial support is needed for affected individuals and their families.

Prevention of secondary complications: Kx-negative blood or banked autologous blood for transfusions when possible.

Surveillance: Holter ECG and echocardiography every two to three years in those without known cardiac complications; consider placement of prophylactic cardiac pacemaker; monitor for seizures; monitor serum CK
concentrations for evidence of rhabdomyolysis if excessive movement disorders are present or if neuroleptic medications are being used.

**Genetic counseling.** MLS is inherited in an X-linked manner. If the mother of an affected male is a carrier, the chance of transmitting the \( \textit{XK} \) pathogenic variant in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be carriers and will usually not be affected. Affected males pass the pathogenic variant to all of their daughters and none of their sons. Prenatal testing for pregnancies at increased risk is possible through laboratories offering either testing for the gene of interest or custom testing.

**Diagnosis**

**Clinical Diagnosis**

Diagnosis of McLeod neuroacanthocytosis syndrome (MLS) is established in individuals with the following combination of manifestations:

- The McLeod blood group phenotype
- A family history consistent with X-linked inheritance AND any combination of the following:
  - CNS manifestations
    - Progressive chorea syndrome similar to that seen in Huntington disease including the clinical triad of movement disorder, cognitive alterations, and psychiatric symptoms
    - Seizures, mostly generalized
  - Neuromuscular manifestations (often subclinical or mild)
    - Sensorimotor axonopathy
    - Neurogenic muscle atrophy
    - Myopathy
  - Dilated cardiomyopathy and arrhythmias

**Testing**

**Hematologic Testing**

**McLeod blood group phenotype**

- In affected males the diagnosis of the McLeod blood group phenotype is based on the immunohematologic determination of absent expression of the Kx erythrocyte antigen and reduced expression of the Kell blood group antigens using human anti-Kx and monoclonal anti-Kell antibodies, respectively [Allen et al 1961, Lee et al 2000b, Jung et al 2007]. Serologically weakened or absent Kell antigens, along with documented presence of \( \textit{KEL} \) and related genes in genomic DNA and in conjunction with serologically absent Kx erythrocyte antigen, is pathognomonic for the McLeod blood group phenotype.

- McLeod blood group phenotype is established by showing negativity for Kx erythrocyte antigen and weakened or absent expression of at least two to three antithetic pairs of Kell antigens (Kell/Cellano, Kpa/b, Jsa/b), thus differentiating the phenotype from individuals with \( \textit{KEL} \)-null (\( \textit{K}_0 \)) phenotype, which is characterized by strong expression of Kx. Expression of Kx / Kell protein complex on red blood cell membrane can also be evaluated by flow cytometry.

- In heterozygous females mixed red blood cell populations may be identified with flow cytometric analysis of Kx and Kell RBC antigens on red blood cell membrane [Oyen et al 1996, Kawakami et al 1999, Jung et al 2001a, Singleton et al 2003, Jung et al 2007].
Red Blood Cell Studies

**RBC acanthocytosis** is found in virtually all males with MLS; repeat testing may be required. Note: No data regarding the age at which acanthocytosis develops are available.

Accurate determination of RBC acanthocytosis is challenging. The best procedure requires diluting whole blood samples 1:1 with heparinized saline followed by incubation for 60 minutes at room temperature; wet cell monolayers are then prepared for phase-contrast microscopy. When all RBCs with spicules (corresponding to type AI/AII acanthocytes and echinocytes) are counted, normal controls show less than 6.3% acanthocytes/echinocytes [Storch et al 2005]. Acanthocyte count in MLS may vary considerably but usually ranges between 8% and 30%.

Confirmation of erythrocyte morphology by scanning electron microscopy (if available) may be helpful.

**Compensated hemolysis** (i.e., hemolysis without anemia) is found in virtually all males with MLS. The following can be used to evaluate for hemolysis:

- Assessment for allo-antibodies against high frequency antigens (anti-public antibodies) such as anti-Kx, anti-K20, and anti-Km antibodies
- Exclusion of autoimmune hemolytic anemia by negative direct antiglobulin test (DAT)
- Investigation for biochemical markers of hemolysis (LDH, haptoglobin, bilirubin, reticulocytes) and muscle disorder (CPK, CPK-MB)

Neuromuscular and Cardiac Studies

**Muscle enzymes.** All males with MLS examined to date have had elevated serum creatine phosphokinase (CK) concentrations reaching values up to 4000 U/L [Danek et al 2001a, Jung et al 2001a]. Serum concentrations of LDH, AST, and ALT may also be elevated [Danek et al 2001a, Jung et al 2001a].

**Clinical electroneuromyography**

- Electromyography may demonstrate neurogenic and myopathic changes [Danek et al 2001a].
- Electroneurography may demonstrate axonal damage of variable degree [Danek et al 2001a].

**Muscle CT.** Computed tomography (CT) scan of muscle may reveal a selective pattern of fatty degeneration of lower-leg muscles preferentially affecting the vastus lateralis, biceps femoris, and adductor magnus muscles, and sparing the gracilis, semitendinosus, and lateral head of the gastrocnemius muscle [Ishikawa et al 2000].

**Muscle biopsy** shows myopathic as well as neurogenic alterations, which were predominant in most studies:

- Several studies demonstrated fiber type grouping, type 1 fiber predominance, type 2 fiber atrophy, increased variability in fiber size, and increased central nucleation [Swash et al 1983, Jung et al 2001b].
- In a series of ten individuals with MLS, including the original index patient, all had abnormal muscle histology: four had clear but nonspecific myopathic changes; however, all had neurogenic changes of variable degree consistent with predominant neurogenic muscle atrophy [Hewer et al 2007].
- One individual with an XK pathogenic missense variant had normal histologic and immunohistochemical findings [Jung et al 2003].
- In muscle of healthy individuals, Kell antigen was located in the sarcoplasmic membranes and Kx immunohistochemistry revealed a type 2 fiber-specific intracellular staining most probably confined to the sarcoplasmic reticulum. Muscle in males with MLS revealed no expression of Kx or Kell [Jung et al 2001b].

**Nerve histology.** Nerve biopsy may demonstrate a chronic axonal neuropathy with prominent regenerative activity and selective loss of large myelinated fibers [Dotti et al 2004].

Post-mortem motor and sensory nerve examinations demonstrated axonal motor neuropathy [Hewer et al 2007].

**Cardiac studies**
• Echocardiography may demonstrate congestive cardiomyopathy or dilated cardiomyopathy [Mohiddin & Fananapazzir 2004].

• Electrocardiography (ECG) may demonstrate atrial fibrillation or tachyarrhythmia [Mohiddin & Fananapazzir 2004].

• In seven males with MLS, one presented with a cardiomyopathy and died from sudden cardiac death in the absence of any cardiovascular risk factors. Autopsy demonstrated eccentric hypertrophy and mild left ventricular dilatation. Histopathology was not specific and revealed focal myocyte hypertrophy, slight variation of myofiber size, and patchy interstitial fibrosis [Witt et al 1992, Oechslin et al 2009].

Central Nervous System Studies

Neuroimaging

• In asymptomatic heterozygous females and early in the disease course in affected males, neuroimaging findings may be normal [Jung et al 2001a, Jung et al 2003].

• In affected males, CT and magnetic resonance imaging (MRI) of the brain may demonstrate atrophy of the caudate nucleus and putamen of variable degree [Danek et al 2001a, Jung et al 2001a]. Basal ganglia volumes are inversely correlated with disease duration [Jung et al 2001a]. A follow-up study of three individuals with MLS over seven years using an automated subcortical segmentation procedure demonstrated decreasing caudate volumes [Valko et al 2010].

• In two males with MLS, cerebral MRI demonstrated extended T2-hyperintense white matter alterations [Danek et al 2001a, Nicholl et al 2004].

Magnetic resonance spectroscopy (MRS). 1H-MRS demonstrates pathologic NAA/(Cr+Cho) ratios in frontal, temporal, and insular areas with an individual pattern in males with MLS who have predominant psychiatric or neuropsychological manifestations [Dydk et al 2006].

Nuclear medicine. SPECT studies using 123I-IMP and 123I-IBZM, respectively, revealed reduction of striatal perfusion as well as striatal D2-receptor density in some males with MLS [Danek et al 1994, Oechsner et al 2001]. Using [18F]-FDG (2-fluoro-2-deoxy-glucose) PET, bilaterally reduced striatal glucose uptake was found in all symptomatic individuals with MLS [Jung et al 2001a, Oechsner et al 2001]. Quantitative FDG-PET also demonstrated reduced striatal glucose uptake in asymptomatic males with the McLeod blood group phenotype and in female heterozygotes [Jung et al 2001a, Oechsner et al 2001]. The degree of reduction of striatal glucose uptake also correlated with disease duration [Jung et al 2001a].

Brain pathology. Data from four individuals with MLS (3 males and 1 manifesting female carrier) are available [Hardie et al 1991, Danek et al 2008, Geser et al 2008]:

• In the manifesting female carrier, marked striatal atrophy was noted, corresponding to nonspecific loss of nerve cells and reactive astrocytic gliosis with predominant alterations in the head of the caudate nucleus [Hardie et al 1991].

• In two males similar alterations were found with severe atrophy of the striatum and (less pronounced) of the globus pallidus [Danek et al 2008, Geser et al 2008]. Marked neuronal loss and astrocytic gliosis were observed on histologic examination. Moderate focal subcortical and subtle cortical astrocytic gliosis, particularly in frontal areas, was noted.

• In contrast to chorea-acanthocytosis (ChAc), none of the four individuals with MLS demonstrated pathology in the thalamus or substantia nigra. Neither Lewy bodies nor definite abnormalities in other brain areas (e.g., the cortex) were observed.

Molecular Genetic Testing

Gene. XK is the only gene in which pathogenic variants are known to cause MLS.
**Research.** In males with an intragenic \(XK\) deletion, the X-chromosomal breakpoints can be located and characterized by DNA sequencing. To identify and determine the extent of a contiguous gene deletion, a chromosomal microarray analysis may be performed.

**Table 1.**

Summary of Molecular Genetic Testing Used in McLeod Neuroacanthocytosis Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test Method</th>
<th>Pathogenic Variants Detected</th>
<th>Variant Detection Frequency by Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>(XK)</td>
<td>Sequence analysis</td>
<td>Sequence variants</td>
<td>Probably &gt;95% 4,5</td>
</tr>
<tr>
<td></td>
<td>Deletion/duplication analysis</td>
<td>Exon and whole-gene deletion/duplication</td>
<td>Probably &gt;95%</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. Examples of pathogenic variants detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Lack of amplification by PCR prior to sequence analysis can suggest a putative deletion of one or more exons or the whole gene on the \(X\) chromosome in affected males; confirmation may require additional testing by deletion/duplication analysis.
6. Sequence analysis of genomic DNA cannot detect deletion of one or more exons or the entire \(X\)-linked gene in a heterozygous female.
7. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

An overview of all currently known \(XK\) pathogenic variants, including large X-chromosomal deletions is available at the Blood Group Antigen Gene Mutation Database (dbRBC); see Table A.

**Testing Strategy**

To establish the diagnosis of MLS in a male proband with a Huntington disease-like disorder and elevated CK levels:

- Establish McLeod blood group phenotype by immunohematologic methods. Note: The presence of the McLeod blood group phenotype establishes the diagnosis of MLS.
- Quantify acanthocytes in freshly prepared wet blood smear using phase-contrast microscopy (supportive of the diagnosis but not mandatory).

To confirm the diagnosis of MLS in a male proband, use molecular genetic testing to identify a pathogenic \(XK\) variant.

**Contiguous gene rearrangements.** Large deletions involving multiple genes at Xp21.1 may cause other disorders in individuals with MLS (see Contiguous Gene Rearrangements). To determine the genes involved in a contiguous gene deletion, chromosomal microarray analysis can be performed

**Carrier testing for at-risk female relatives** requires one of the following: (a) flow cytometric analysis of Kx and Kell erythrocyte antigens; (b) prior identification of the pathogenic variant in the family; or (c) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and then, if no pathogenic variant is identified, by deletion/duplication analysis.

Note: Heterozygous females may develop clinical manifestations such as chorea or late-onset cognitive decline.
**Predictive testing** for at-risk asymptomatic adult family members requires determination of the McLeod blood group phenotype in at-risk males, flow cytometric analysis of Kx and Kell RBC antigens in at-risk heterozygote females, and/or prior identification of the pathogenic variant in the family.

**Genotype-phenotype correlations.** Molecular characterization of individual genetic defect may give evidence of clinical disease manifestation: to date, three XK pathogenic missense variants that may result in a milder phenotype have been described [Russo et al 2002, Jung et al 2003, Walker et al 2007a] (see Table 4).

**Prenatal diagnosis and preimplantation genetic diagnosis (PGD)** for at-risk pregnancies require prior identification of the pathogenic variants in the family.

**Contiguous Gene Rearrangements**

Other genes that lie in close proximity to XK at Xp21.1 include the following [Peng et al 2007]:

- **CYBB** encoding the cytoplasmic subunit of phagocyte NADPH oxidase (phox) protein termed gp91phox
- **RPGR** encoding retinitis pigmentosa GTPase regulator
- **OTC** encoding ornithine transcarbamylase
- **DMD** encoding the protein dystrophin

Large deletions in Xp21.1 can therefore cause the following disorders in individuals with MLS. Note: Concurrent deletion of CYBB with XK is the most common; deletion of all five genes is exceedingly rare.

- X-linked chronic granulomatous disease (X-linked CGD) (deletion of CYBB) is a primary immunodeficiency disorder of phagocytes (neutrophils, monocytes, macrophages, and eosinophils). Impaired killing of bacteria and fungi result in severe recurrent bacterial and fungal infections and dysregulated inflammatory response that causes granuloma formation and other inflammatory disorders such as colitis.
- **RPGR**-related retinitis pigmentosa (**RPGR**; previously **RP3**)
- Ornithine transcarbamylase deficiency (**OTC**) leading to urea cycle defects
- Duchenne muscular dystrophy (**DMD**)

**Clinical Characteristics**

**Clinical Description**

McLeod neuroacanthocytosis syndrome (MLS) is a multisystem disorder with central nervous system (CNS), neuromuscular, and hematologic manifestations in males. CNS manifestations of MLS resemble Huntington disease. Symptoms comprise the prototypic triad of a progressive neurodegenerative basal ganglia disease including (1) movement disorder, (2) cognitive alterations, and (3) psychiatric symptoms [Danek et al 2001a, Jung et al 2007]. It should be noted that each sign and symptom may develop in isolation or in variable combinations.

Choreiform movements are the presenting symptom in about 30% of individuals with MLS, and develop in up to 95% of individuals over time [Danek et al 2001b, Jung et al 2001a, Hewer et al 2007]. Some individuals with MLS develop head drops, feeding dystonia, and gait abnormalities, symptoms formerly believed to be specific to another type of neuroacanthocytosis, the autosomal recessive chorea-acanthocytosis [Chauveau et al 2011, Gantenbein et al 2011].

Cognitive alterations are not a major presenting symptom of MLS; however, frontal-type cognitive deficits are eventually found in at least 50% of individuals during the course of the disease [Danek et al 2001a, Jung et al 2001a, Danek et al 2004, Hewer et al 2007].

About 20% of individuals manifest psychiatric abnormalities including personality disorder, anxiety, depression, obsessive-compulsive disorder, bipolar disorder, or schizo-affective disorder. Psychopathology develops in about 80% of individuals over time [Danek et al 2001a, Jung et al 2001a, Jung & Haker 2004, Walterfang et al 2011].

Seizures are the presenting symptom in about 20% of individuals. Up to 40% of individuals with MLS eventually have seizures, usually described as generalized seizures.
Neuromuscular manifestations are not a common presenting symptom of MLS. However, almost all individuals with MLS have absent deep tendon reflexes as an indication of a (mostly subclinical) sensorimotor axonopathy [Danek et al 2001a, Jung et al 2001a]. About 50% of individuals develop clinically relevant muscle weakness or atrophy of a neurogenic nature during the disease course. Deterioration rate is slow, and few individuals develop severe weakness [Kawakami et al 1999, Danek et al 2001a, Jung et al 2001a, Hewer et al 2007].

Cardiac manifestations including dilated cardiomyopathy, atrial fibrillation, and tachyarrhythmia are rarely presenting signs and symptoms of MLS. About 60% of individuals develop cardiac manifestations over time [Witt et al 1992, Danek et al 2001a, Oechslin et al 2009].

Hepatosplenomegaly, most probably resulting from compensated hemolysis, occurs in about one third of males with MLS [Danek et al 2001a].

About 30% of males with the McLeod blood group phenotype do not have neuromuscular or CNS symptoms at the time of initial diagnosis of the blood group abnormalities and are only recognized during routine work up in blood banks or in the course of family evaluations [Danek et al 2001a, Jung et al 2001a, Jung et al 2007]. However, most males with the McLeod blood group phenotype developed neurologic manifestations during long-term follow-up [Danek et al 2001a, Hewer et al 2007]. The age of onset of neurologic manifestations ranges from 18 to 61 years; the majority of individuals become symptomatic before age 40 years. Almost all clinical observations indicate a slowly progressive disease course [Danek et al 2001a, Jung et al 2001a, Valko et al 2010]. Because of difficulty in determining the exact onset of disease, few reliable data regarding disease duration are available. Activities of daily living may become impaired as a result of the movement disorder, psychiatric symptoms, intellectual disability, and/or cardiomyopathy.

The interval between reported disease onset and death ranges from seven to 51 years [Danek et al 2001a, Jung et al 2001a, Hewer et al 2007]. Mean age of death is 53 years, ranging from 31 to 69 years [Danek et al 2001a, Jung et al 2001a, Hewer et al 2007]. Cardiac problems, in particular tachyarrhythmia, appear to be a major cause of premature death in MLS. Cardiovascular events, epileptic seizures, and aspiration pneumonia may be the major causes of death in older individuals [Danek et al 2001a, Jung et al 2001a, Hewer et al 2007].

Females who are heterozygous for an XK pathogenic variant have mosaicism for the Kell system blood group and RBC acanthocytosis by virtue of X-chromosome inactivation [Oyen et al 1996, Kawakami et al 1999, Jung et al 2001a, Singleton et al 2003, Jung et al 2007]. Some heterozygous females may develop clinical manifestations such as chorea or late-onset cognitive decline.

The most probable reason for the following clinical manifestations observed in female heterozygotes is skewed X-chromosome inactivation, in which the X chromosome with the normal XK allele is by chance inactivated in a disproportionately large number of cells [Ho et al 1996]. Pertinent observations are:

- One female heterozygote developed the typical MLS phenotype [Hardie et al 1991].
- A female heterozygote had acanthocytosis, a bimodal pattern of Kell blood group antigens on flow cytometry, elevated serum creatine kinase concentrations, and a tic-like movement disorder [Kawakami et al 1999].
- In one family, female heterozygotes had slight cognitive deficits and reduced striatal glucose uptake in the absence of an obvious movement disorder [Jung et al 2001a].

Genotype-Phenotype Correlations

Data presently available are insufficient to draw conclusions about genotype-phenotype correlations in McLeod neuroacanthocytosis syndrome [Danek et al 2001a]. MLS shows considerable phenotypic variability, even between family members with identical XK variants [Danek et al 2001b, Walker et al 2007b].

Only three pathogenic XK missense variants have been reported so far. Although rare, they are potentially useful in the elucidation of structural and functional relationships. See Molecular Genetics.

- The c.979G>A variant was associated with an isolated immunohematologic phenotype without evidence for muscular, central, and peripheral nervous system involvement [Jung et al 2003].
• Similarly, an individual with the c.664C>G variant did not show significant neurologic or systemic abnormalities [Walker et al 2007a].

• Also, a single base substitution in an intron near a splice junction (c.508+5G>A, resulting in alternative splicing and some degree of normal splicing) did not lead to any significant neurologic abnormalities [Walker et al 2007a].

• In contrast, an individual with the c.880T>C variant manifested the full McLeod neuroacanthocytosis syndrome [Danek et al 2001a].

Penetrance
In males, the penetrance of neurologic and neuromuscular manifestations of MLS is high after age 50 years, perhaps even complete. Available data indicate that most males with the "McLeod blood group phenotype" will develop clinical symptoms of McLeod neuroacanthocytosis syndrome [Bertelson et al 1988, Hardie et al 1991, Danek et al 2001a, Jung et al 2001b]. In a few individuals, however, neurologic and neuromuscular symptoms may be absent or only minor even after long-term follow up [Jung et al 2003, Walker et al 2007a].

In the past, many reports (including that of the index case) described only hematologic findings, and no neurologic or neuroimaging work up was performed in these individuals [Allen et al 1961, Symmans et al 1979, Bertelson et al 1988, Lee et al 2000a]. In many of these individuals neurologic manifestations were noted during long-term follow-up [Bertelson et al 1988, Danek et al 2001a].

Nomenclature
The term "neuroacanthocytosis" refers to several genetically and phenotypically distinct disorders [Danek et al 2004, Danek et al 2005]; see Differential Diagnosis.

The term "McLeod blood group phenotype" describes the immunohematologic abnormalities consisting of absent expression of Kx RBC antigen and reduced expression of Kell RBC antigens in the index case originally described by Allen et al [1961].

The terms "Kell blood group precursor" and "Kell blood group precursor substance" for the XK protein or the Kx RBC antigen, respectively, are incorrect and no longer in use.

Prevalence
The prevalence of MLS cannot be determined based on the data available from the approximately 150 cases known worldwide.

Genetically Related (Allelic) Disorders
No other phenotypes are known to be caused by mutation of XK alone.

Differential Diagnosis
Huntington disease (HD). HD is the prototypic hereditary chorea syndrome and manifests with progressive movement disorder and cognitive and psychiatric disturbances. The mean age of onset of HD ranges from 35 to 44 years, and the median survival is 15 to 18 years after onset. The symptoms of HD and MLS may appear indistinguishable. However, autosomal dominant inheritance and anticipation in HD and the presence of seizures, elevated serum CK concentrations, and myopathy in MLS may help distinguish the two conditions. Diagnosis of HD rests on the detection of an expansion of the CAG trinucleotide repeat in HTT.

Other neuroacanthocytosis syndromes. Neurologic disorders associated with RBC acanthocytosis have been summarized as neuroacanthocytosis syndromes [Danek et al 2004, Danek et al 2005, Jung et al 2011].

One group of neuroacanthocytosis syndromes is associated with lipid malabsorption and primarily affects the spinal cord, cerebellum, and peripheral nervous system. The neurologic findings include: (1) a progressive spinocerebellar degeneration with gait ataxia, dyssmetria, and dysarthria; (2) a demyelinating sensorimotor and axonal peripheral neuropathy with hyporeflexia and diminished vibration and position sense; (3) rarely, pyramidal tract signs; and (4)
rarely, cranial nerve involvement [Kane & Havel 1995, Tarugi & Averna 2011]. These disorders include the following:

- Hypobetalipoproteinemia type 1 (FHBL1)
- Hypobetalipoproteinemia type 2 (FHBL2)
- Abetalipoproteinemia (ABL, Bassen-Kornzweig disease)

FHBL1, FHBL2, ABL, and MLS share the findings of acanthocytosis, dysarthria, neuropathy, and areflexia but differ in that ABL and HBL have pigmentary retinopathy and do not have basal ganglia involvement. ABL and HBL are caused by mutation of the gene encoding the microsomal triglyceride transfer protein causing vitamin E deficiency. ABL is inherited in an autosomal recessive manner. HBL has clinical manifestations in both the homozygous and heterozygous states.

A second group of neuroacanthocytosis syndromes predominantly affects the central nervous system, in particular the basal ganglia, resulting in a chorea syndrome resembling Huntington disease (Table 2). These disorders include the following:

- **Chorea-acanthocytosis (ChAc)** is characterized by a progressive movement disorder and an often subclinical myopathy, mental changes, and seizures. Seizures are observed in almost half of affected individuals and can be the initial manifestation. Progressive cognitive and behavioral changes resemble a frontal lobe syndrome. Myopathy results in progressive distal muscle wasting and weakness. The movement disorder is mostly chorea. In contrast to MLS, some individuals present with a Parkinsonian syndrome. In addition, dystonia is common and affects the trunk and in particular the oral region and the tongue, causing dysarthria and serious dysphagia with resultant weight loss. Habitual tongue and lip biting are characteristic. Mean age of onset is about 35 years, although ChAc can develop as early as the first decade or as late as the seventh decade. ChAc runs a chronic progressive course and may lead to major disability within a few years; life expectancy is reduced. Diagnosis of ChAc rests on the presence of typical clinical and MRI findings and molecular genetic testing if available. Testing for RBC expression of chorein, the \( VPS13A \) product, is a useful alternative [Dobson-Stone et al 2004]. Inheritance is autosomal recessive.

- **Huntington disease-like 2 (HDL2)** manifests in the third to fourth decade and has a progressive course over ten to 15 years [Margolis et al 2001]. Phenotypic variation is marked. Dystonia is a frequent finding, and presentation with chorea or parkinsonism may change with evolution of the disease. With the exception of one Mexican pedigree, all affected individuals reported to date have been of African ancestry [Margolis et al 2001, Stevanin et al 2002, Walker et al 2003]. RBC acanthocytes have been noted in only a few individuals with HDL2. Diagnosis of HDL2 rests on detection of an expansion of the CTG trinucleotide repeat in \( JPH3 \). Inheritance is autosomal dominant.

- **Pantothenate kinase-associated neurodegeneration (PKAN)** (neurodegeneration with brain iron accumulation [NBIA], formerly Hallervorden-Spatz syndrome) is characterized by progressive dystonia and basal ganglia iron deposition with onset usually before age ten years. Dysarthria, rigidity, and pigmentary retinopathy are common. About 25% of individuals have an "atypical" presentation with onset after age ten years, prominent speech defects, psychiatric disturbance, and more gradual progression of disease [Swaiman 2001, Zhou et al 2001]. Acanthocytosis is observed in at least 8% of individuals. The so-called 'eye of the tiger' sign on MRI is characteristic [Hayflick et al 2003]. Diagnosis of PKAN rests on the presence of typical clinical and MRI findings, and molecular genetic testing of \( PANK2 \). Inheritance is autosomal recessive.

See also Neurodegeneration with Brain Iron Accumulation Disorders Overview.

- **HARP syndrome** (hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) is allelic with PKAN [Ching et al 2002, Houden et al 2003]. The continued use of this term is discouraged particularly since "hypobetalipoproteinemia" is not a meaningful entity.

Table 2 summarizes the diseases in the differential diagnosis of MLS.
### Table 2.
Differential Diagnosis of McLeod Neuroacanthocytosis Syndrome

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Chromosomal Locus</th>
<th>Protein</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington disease</td>
<td><em>HTT</em></td>
<td>4p16.3</td>
<td>Huntingtin</td>
<td>143100</td>
</tr>
<tr>
<td>HDL1 (Huntington disease-like 1)</td>
<td><em>PRNP</em></td>
<td>20pter-p12</td>
<td>Major prion protein</td>
<td>603218</td>
</tr>
<tr>
<td>HDL2 (Huntington disease-like 2)</td>
<td><em>JPH3</em></td>
<td>16q24.3</td>
<td>Junctophilin-3</td>
<td>606438</td>
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<tr>
<td>Dentatorubral-pallidoluysian atrophy</td>
<td><em>ATN1</em></td>
<td>12p13.31</td>
<td>Atrophin-1</td>
<td>125370</td>
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<td>Neuroferritinopathy</td>
<td><em>FTL</em></td>
<td>19q13.3-q13.4</td>
<td>Ferritin light chain</td>
<td>606159</td>
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<tr>
<td>Spinocerebellar ataxia type 3</td>
<td><em>ATXN3</em></td>
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<td>Ataxin-3</td>
<td>109150</td>
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<td>Spinocerebellar ataxia type 17</td>
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<td>14q-13.1</td>
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<td><strong>Autosomal Recessive</strong></td>
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<td>Chorea-acanthocytosis</td>
<td><em>VPS13A</em></td>
<td>9q21</td>
<td>Chorein</td>
<td>200150</td>
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<tr>
<td>HDL3 (Huntington disease-like 3)</td>
<td><em>HDL3</em></td>
<td>4p15.3</td>
<td>Protein not identified</td>
<td>604802</td>
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<tr>
<td>Wilson disease</td>
<td><em>ATP7B</em></td>
<td>13q14.3-q21.1</td>
<td>Copper transporting ATPase 2</td>
<td>277900</td>
</tr>
<tr>
<td>Aceruloplasminia</td>
<td><em>CP</em></td>
<td>3q23-q24</td>
<td>Ceruloplasmin</td>
<td>604290</td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration, including HARP</td>
<td><em>PANK2</em></td>
<td>20p13-p12.3</td>
<td>Pantothenate kinase 2</td>
<td>234200</td>
</tr>
<tr>
<td><em>PLA2G6</em>-associated neurodegeneration (PLAN) (infantile neuroaxonal dystrophy; Karak syndrome)</td>
<td><em>PLA2G6</em></td>
<td>2q13.1</td>
<td>85-kd calcium-independent phospholipase A2</td>
<td>256600 (610217)</td>
</tr>
<tr>
<td><strong>X-Linked</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked dystonia-parkinsonism syndrome (Lubag)</td>
<td><em>DYT3</em></td>
<td>Xq13.1</td>
<td>Multiple transcript system DYT3</td>
<td>314250</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td><em>HPRT1</em></td>
<td>Xq26-q27.2</td>
<td>Hypoxanthine guanine phosphoribosyl-transferase 1</td>
<td>300322</td>
</tr>
</tbody>
</table>

### Management

**Evaluations Following Initial Diagnosis**

To establish the extent of disease in an individual diagnosed with McLeod neuroacanthocytosis syndrome (MLS), the following evaluations are recommended:

- Neurologic and neuropsychological examination
- Serum CK concentration and liver function tests
- Cardiac examination, including ECG, Holter ECG, and echocardiography
- Cerebral MRI and electroencephalography
- Medical genetics consultation
Treatment of Manifestations

The following are indicated:

- Dopamine antagonists including tiapride, clozapine, or quetiapine, as well as dopamine depletor tetrabenazine to ameliorate chorea
- Treatment of psychiatric problems according to the clinical presentation
- Treatment of cardiac abnormalities according to the clinical and/or ECG presentation
- Antiepileptic drugs (AEDs) for treatment of seizures
- Extended and continuous multidisciplinary psychosocial support for affected individuals and their families

Prevention of Secondary Complications

Transfusion hazards secondary to anti-Kx antibody production resulting from previous exposure to Kx antigens during homologous blood transfusion must be considered in:

- All males with the McLeod blood group phenotype [Russo et al 2000b], in particular males with X-linked chronic granulomatous disease resulting from a contiguous gene deletion of CYBB and XK (see Diagnosis, Contiguous Gene Rearrangements) [Holland 2005]; and
- Carrier females with the McLeod blood group phenotype.

Kx-negative blood or, if possible, banked autologous blood should be used for transfusions.

Surveillance

Early recognition and treatment of cardiac problems and seizures is important, as these potential complications may be severe and appear to cause premature death [Danek et al 2001a].

- If no pathologic findings are identified at initial evaluation, cardiac examinations (Holter ECG and echocardiography) should be repeated every two to three years.
- In the case of suspected epilepsy, EEG should be performed. If AED treatment is indicated, medication-specific laboratory parameters and serum concentrations should be followed.

One individual with MLS developed life-threatening rhabdomyolysis; thus, serum CK concentrations should be carefully monitored, in particular if excessive movement disorders are present or if neuroleptic medications are being used [Jung & Brandner 2002].

Agents/Circumstances to Avoid

Blood transfusions with Kx antigens should be avoided in males and females with the McLeod blood group phenotype. Kx-negative blood or, if possible, banked autologous blood should be used for transfusions.

Treatment with neuroleptics, in particular clozapine, should be carefully monitored.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In female heterozygotes, the probability of manifestations of the McLeod neuroacanthocytosis syndrome in the reproductive period is presumably very low; thus, no particular recommendations can be made. Of note, transfusion reactions have to be considered in female carriers who have the McLeod blood group phenotype (see Prevention of Secondary Complications).

No prenatal or perinatal neurologic manifestations of MLS are known; however, severe anemia can be observed in Kell-positive newborns born to sensitized Kell-negative mothers [Lee et al 2000b, Jung et al 2007].
Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

McLeod neuroacanthocytosis syndrome (MLS) is inherited in an X-linked manner.

Risk to Family Members

Parents of the proband

- The father of an affected male will not have the disease nor will he be a carrier of the pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a de novo pathogenic variant, in which case the mother is not a carrier. One de novo XK pathogenic variant has been described in MLS [Supple et al 2001].
- If a woman has more than one affected son and the pathogenic variant cannot be detected in DNA extracted from her leukocytes, she may have germline mosaicism. No data regarding germline mosaicism in MLS are available to date.
- Females heterozygous for XK pathogenic variants have mosaicism for the Kell and Kx blood group antigens but usually lack CNS and neuromuscular manifestations. However, some heterozygous females may develop clinical manifestations including chorea or late-onset cognitive decline.

Sibs of the proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant will be carriers and will usually not be affected.
- Females heterozygous for XK pathogenic variants have mosaicism for the Kell and Kx blood group antigens but usually lack CNS and neuromuscular manifestations. However, some heterozygous females may develop clinical manifestations including chorea or late-onset cognitive decline.
- If the pathogenic variant has not been identified in the mother's DNA, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of the proband. Affected males will pass the pathogenic variant to all of their daughters and none of their sons.

Other family members of the proband. The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending on their gender, may be at risk of being carriers or of being affected.

Carrier Detection

If the pathogenic variant in the family have been identified, carrier testing for at-risk family members may be available from a laboratory offering either testing of the gene of interest or custom testing. Carrier testing using immunohematologic techniques is possible.
Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the pathogenic variant has been identified in an affected family member, prenatal testing for at-risk pregnancies may be available from a laboratory offering either testing for the gene of interest or custom prenatal testing.

**Preimplantation genetic diagnosis (PGD)** may be an option for some families in which the pathogenic variant has been identified.

Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Advocacy for Neuroacanthocytosis Patients**
  
  32 Launceston Place  
  London W8 5RN  
  United Kingdom  
  
  **Phone:** 020 7409 0092  
  **Fax:** 020 7495 4245  
  **Email:** glenn@naadvocacy.org; ginger@naadvocacy.org  
  [www.naadvocacy.org](http://www.naadvocacy.org)

- **Cardiomyopathy UK**
  
  Chiltern Court  
  Asheridge Road  
  Unit 10  
  Chesham Buckinghamshire HP5 2PX  
  United Kingdom  
  
  **Phone:** 0800 018 1024 (UK only); 0800 018 1024 (UK only)  
  **Email:** info@cardiomyopathy.org  
  [www.cardiomyopathy.org](http://www.cardiomyopathy.org)

- **Huntington's Disease Society of America (HDSA)**
  
  *HDSA has material on their site to assist in caretaking issues for adult onset progressive neurologic diseases.*  
  [www.hdsa.org](http://www.hdsa.org)
Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.
McLeod Neuroacanthocytosis Syndrome: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>XK</td>
<td>Xp21.1</td>
<td>Membrane transport protein XK</td>
<td>XK @ LOVD Blood Group Antigen Gene Mutation Database (XK)</td>
<td>XK</td>
</tr>
</tbody>
</table>

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.
OMIM Entries for McLeod Neuroacanthocytosis Syndrome (View All in OMIM)

| 314850 | KELL BLOOD GROUP PROTEIN, MCLEOD SYNDROME-ASSOCIATED; XK |

Note: The terms "Kell blood group precursor" for the XK protein or the Kx RBC antigen, respectively, are incorrect and should no longer be used.

Molecular Genetic Pathogenesis

The XK protein is predicted to have ten transmembrane domains and the structural characteristics of prokaryotic and eukaryotic membrane transport proteins [Ho et al 1994]. The XK protein is linked to the Kell glycoprotein by a single disulfide bond (XK Cys\(^{347}\) - Kell Cys\(^{72}\)) when they are co-expressed, and the two proteins most probably form a functional complex [Russo et al 1998]. XK and Kell are predominantly expressed in erythroid tissues, but their expression in non-erythroid tissues differs. XK is ubiquitously expressed in many other tissues, especially in high amounts in skeletal muscle and brain. In contrast, Kell is expressed in very small amounts in different tissues including human brain and skeletal muscle. XK and Kell are both expressed in testis [Russo et al 2000a, Camara-Clayette et al 2001, Jung et al 2001b]. However, recent studies by in situ hybridization histochemistry (ISHH) and RT-PCR of mouse tissues indicate that Kell is not present in brain and skeletal muscle in that species. XK is expressed in various cerebral regions, with high amounts in pontine region, olfactory lobe, and cerebellum [Lee et al 2007].

It has been proposed that the function of isolated XK differs from that of XK in combination with Kell. The Kell protein (product of KEL on chromosome 7) is a member of M13 family of zinc endopeptidases and is an endothelin-3...
converting enzyme generating the bioactive endothelin-3 [Lee et al 1999, Lee et al 2000b]. Experimental studies have demonstrated that endothelin is a neurotrophic factor at low concentrations and a cytotoxic factor at high concentrations, suggesting that endothelin-related mechanisms could be implicated in neurodegeneration [Ehrenreich et al 2000]. However, no acanthocytosis or cerebral or neuromuscular signs and symptoms have been described in individuals with absent Kell membrane glycoproteins caused by the so-called KEL null (Ko)-phenotype [Lee et al 2000a; Kőrösi et al 2007].

**XK dysfunction may cause apoptosis** dysregulation, which should be considered a major cause of myopathy and striatal neurodegeneration in McLeod neuroacanthocytosis syndrome. The XK protein is a member of XK family that comprises XK, XPLAC, and XTES. Phylogenetic analysis has shown that XK and XPLAC are present in vertebrate fish while XTES is found only in primate testis [Calenda et al 2006]. In addition to the XK family, the phylogram contained five gene clusters distantly related to the XK and ced-8 gene clusters that are present in the nematode C. elegans. The ced-8 domain (FLxxxPQL[x]6WxxxxxxR[x]6HP) is a typical signature sequence found in all members of the XK-related gene clusters. The ced-8 protein of C. elegans shares a low homology with XK protein but the topologic structure is similar to XK. The ced-8 protein is reported to play a role as a cell death effector downstream of the caspase ced-3 [Stanfield & Horvitz 2000]. The human homologue of ced-3, caspase-8, plays a crucial role in the striatal neurodegeneration of Huntington disease [Hackam et al 2000, Gervais et al 2002].

**Gene structure.** XK comprises three exons. Only one splicing variant is known [Walker et al 2007a]. For a detailed summary of gene and protein information, see Table A, Gene.


Only three XK pathogenic missense variants have been reported to date (Table 4). Although rare, they are potentially useful in the elucidation of structural and functional relationships (see *Normal gene product*).

**Table 4.**

<table>
<thead>
<tr>
<th>Selected XK Pathogenic Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Nucleotide Change (Alias)</td>
</tr>
<tr>
<td>c.508+5G&gt;A</td>
</tr>
<tr>
<td>c.664C&gt;G (746C&gt;G)</td>
</tr>
<tr>
<td>c.880T&gt;C (962T&gt;C)</td>
</tr>
<tr>
<td>c.979G&gt;A (1061G&gt;A)</td>
</tr>
</tbody>
</table>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** XK is a 444-amino acid protein. The exact function of the XK protein is not known, but its predicted structure suggests that it is a membrane transport protein [Ho et al 1994].

All three of the pathogenic missense variants occurred in the transmembrane domains and on highly conserved amino-acid residues that are evolutionarily related to XK, suggesting possible important roles in structure or function. The
Glu327 and Arg222 residues may be involved in the basic structure of XK rather than in its function, and the Cys294 residue, which is conserved specifically in the XK family, may be critical for normal function [Walker et al 2007a].

Abnormal gene product. Most XK pathogenic variants predict an absent or truncated XK protein devoid of the Kell protein-binding site, suggesting a loss of function. For missense variants, see Normal gene product.

References

Literature Cited


Holland SM. Chronic granulomatous disease and MLS. Mov. Disord. 2005;20:1677.


Suggested Reading


Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. Orphanet J Rare Dis. 2011;6:68. [PMC free article: PMC3212896] [PubMed: 22027213]


Chapter Notes

Author Notes

Hans H Jung is a leading senior consultant at the Department of Neurology, University Hospital Zurich, Switzerland where he runs consultations for neurogenetic and neuromuscular disorders. His research focuses on the clinical, pathologic, and molecular basis of chorea syndromes, in particular the McLeod neuroacanthocytosis syndrome.

Adrian Danek, a professor of cognitive neurology at the University of Munich, has contributed to neuroacanthocytosis research since 1990. His interests also include functional brain anatomy, problem solving (Towers of Hanoi/London), the frontotemporal lobe degeneration syndromes (see www.ftld.de), and other familial dementias (see www.dian-info.org/de).

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Christoph Gassner specializes in molecular blood group genotyping. In the context of McLeod, his research has primarily focused on establishing reliable genetic methods for the detection of pathogenic variants in XK and large X-chromosomal deletions. He is also interested in KEL genetics, with special focus on KEL null and other variants.

Acknowledgments

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