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McLeod Neuroacanthocytosis Syndrome

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Summary

Clinical characteristics

McLeod neuroacanthocytosis syndrome (designated as MLS throughout this review) is a multisystem disorder with central nervous system (CNS), neuromuscular, cardiovascular, 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. Cardiac manifestations include dilated cardiomyopathy, atrial fibrillation, and tachyarrhythmia. 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 affected male 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 established in a male proband with suggestive clinical, laboratory, and neuroimaging studies; a family history consistent with X-linked inheritance; and identification on molecular genetic testing of either a hemizygous *XK* pathogenic variant (90% of affected males) or a hemizygous deletion of Xp21.1 involving *XK* (10% of affected males).

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Management

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

Agents/circumstances to avoid: Blood transfusions with Kx antigens should be avoided in males with MLS. Kx-negative blood or, if possible, banked autologous blood should be used.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of any age in order to identify as early as possible those who would benefit from: (1) detailed blood compatibility information to prevent transfusion of Kx+ homologous blood products, and (2) possible prophylactic cryopreservation of autologous blood for use in future transfusions.

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 heterozygous, the chance of transmitting the *XK* pathogenic variant in each pregnancy is 50%. Males who inherit the *XK* variant will be affected; females who inherit the *XK* variant will be heterozygous and will usually not be affected. Affected males pass the *XK* pathogenic variant to all of their daughters and none of their sons. Once the *XK* pathogenic variant has been identified in an affected family member, carrier testing for at-risk females, prenatal testing for a pregnancy at increased risk, and preimplantation genetic diagnosis are possible.

Diagnosis

Suggestive Findings

The diagnosis of McLeod neuroacanthocytosis syndrome (MLS) **should be suspected/considered** in an individual with the following clinical and laboratory findings and family history.

Clinical Findings

CNS manifestations

- Progressive chorea syndrome similar to that seen in Huntington disease including the clinical triad of movement disorder, cognitive alterations, and psychiatric manifestations
- Seizures, mostly generalized

Neuromuscular manifestations (often subclinical or mild)

- Sensorimotor axonopathy
- Neurogenic muscle atrophy, including unexplained elevation of creatine phosphokinase
- Myopathy

Cardiomyopathy

- Echocardiography may demonstrate congestive cardiomyopathy or dilated cardiomyopathy [Mohiddin & Fananapazzir 2004].

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

Family history consistent with X-linked inheritance

Laboratory/Electrophysiologic Findings

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 [Jung et al 2007, Roulis et al 2018]. Serologically absent Kx erythrocyte antigen and serologically weakened or absent Kell antigens are 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 Kell antigens, thus differentiating the phenotype from individuals with *KEL*-null (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 [Jung et al 2007, Roulis et al 2018].

Red blood cell studies

- **RBC acanthocytosis** is found in virtually all males with MLS. 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%. Repeat testing may be required, as the findings of acanthocyte determinations may fluctuate over time. Proven presence of acanthocytes, however, is not a necessary precondition to make the diagnosis of the McLeod neuroacanthocytosis syndrome. Note: No data regarding the age at which acanthocytosis develops are available.

  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. While these anti-public antibodies do not contribute to the auto-hemolysis in MLS, they need to be considered in homologous transfusion.
- Exclusion of autoimmune hemolytic anemia by negative direct antiglobulin test
- Investigation for biochemical markers of hemolysis (LDH, haptoglobin, bilirubin, reticulocytes) and muscle disorder (CPK, CPK-MB)

Neuromuscular studies

- **Muscle enzymes.** All males with MLS examined to date have had elevated serum creatine phosphokinase (CK) concentrations reaching values up to 4,000 U/L [Danek et al 2001a, Jung et al 2001a].
- **Electromyography** may demonstrate neurogenic and myopathic changes [Danek et al 2001a].
- **Nerve conduction studies** may demonstrate axonal damage of variable degree [Danek et al 2001a].

- **Muscle computed tomography (CT)** 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].

Central Nervous System Studies

Neuroimaging

- 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, brain MRI demonstrated extended T_2-weighted hyperintense white matter alterations [Danek et al 2001a, Nicholl et al 2004].
- 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].

Establishing the Diagnosis

Male proband. The diagnosis of McLeod neuroacanthocytosis syndrome **is established** in a male proband with suggestive clinical and laboratory findings, neuroimaging studies, and family history, as well as **one of the following** identified on molecular genetic testing (see Table 1):

- A hemizygous pathogenic variant involving *XK* (~90% of affected individuals) [Dotti et al 2000, Danek et al 2001a, Jung et al 2001b, Jung et al 2003]
- A hemizygous deletion of Xp21.1 involving *XK* (10% of affected individuals) [Kawakami et al 1999, El Nemer et al 2000, Danek et al 2001a, Wendel et al 2004]

  Note: Deletions involving *XK* vary in size from intragenic to larger multigene deletions. Failure to generate *XK* sequence in a male proband is consistent with a deletion; however, other techniques are needed to define the breakpoints of the deletion (see Table 1).

Female proband. The diagnosis of McLeod neuroacanthocytosis syndrome **is usually established** in a female proband with one of the following: (1) detection by flow cytometry of two populations of RBC, one with normal expression of Kell antigens and one with reduced expression, or (2) detection of a heterozygous pathogenic variant in XK by molecular genetic testing.

Note: Based on published cases, heterozygous females do not have RBC acanthocytosis or elevated CK serum levels.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

There are three options for establishing the diagnosis of McLeod neuroacanthocytosis syndrome:

- **Option 1.** Determination of the McLeod blood group phenotype followed by CMA for individuals with findings suggestive of a contiguous-gene deletion
- **Option 2.** Determination of the McLeod blood group phenotype followed by single-gene testing for those in whom McLeod blood group phenotyping supports the diagnosis

- **Option 3.** Multigene panel or comprehensive genomic testing for symptomatic individuals in whom the diagnosis of McLeod neuroacanthocytosis syndrome has not been considered

Option 1

(Determination of the McLeod blood group phenotype followed by CMA for individuals with findings suggestive of a contiguous-gene deletion)

Chromosomal microarray analysis (CMA). For individuals with suggestive clinical features of McLeod neuroacanthocytosis syndrome and one or more of the disorders observed in contiguous-gene deletions that include *XK*, CMA should be performed first to detect large deletions that cannot be detected by sequence analysis or gene-targeted deletion/duplication analysis. These other disorders and their causative genes include Duchenne muscular dystrophy (*DMD*), X-linked chronic granulomatous disease (*CYBB*), X-linked retinitis pigmentosa (*RPGR*), and ornithine transcarbamylase deficiency (*OTC*). See Genetically Related Disorders, **Contiguous-gene rearrangements**.

Note: Alternatively, next-generation sequencing (NGS), such as exome sequencing or genome sequencing, may identify a large deletion involving *XK*, particularly in a male; however, detection of a deletion by NGS must be confirmed by an orthogonal (i.e., statistically independent) method.

Option 2

(Determination of the McLeod blood group phenotype followed by single-gene testing for those in whom McLeod blood group phenotyping supports the diagnosis)

Single-gene testing. When the phenotypic and laboratory findings (specifically McLeod blood group phenotyping) support the diagnosis of McLeod neuroacanthocytosis syndrome [Frey et al 2015], perform sequence analysis of *XK* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Note: (1) Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis. (2) Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected in an affected female by these methods and may require CMA (see Option 1).

Option 3

(For symptomatic individuals in whom the diagnosis of McLeod neuroacanthocytosis syndrome has not been considered)

When the diagnosis of McLeod neuroacanthocytosis syndrome has not been considered in a symptomatic individual, the options are a multigene panel or comprehensive genomic testing.

A multigene panel that includes *XK* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other

non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing involves either e**xome sequencing** or **genome sequencing**. If exome sequencing is not diagnostic, exome array (when clinically available) needs be considered to detect (multi)exon deletions or duplications that cannot be detected by exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in McLeod Neuroacanthocytosis Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
XK	Sequence analysis [3, 4]	~60% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	~40% [5, 6, 8]
	Chromosomal microarray analysis [9]	~30% [6, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants 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.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Roulis et al [2018]
6. A current list of XK pathogenic variants is maintained here: IBST (scroll down; select **Blood Group Allele Terminology**, then **XK**).
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (see Genetically Related Disorders, **Contiguous-gene rearrangements**) may not be detected by these methods.
8. Note that most reported deletions and duplications are large enough to likely be detected by CMA; however, gene-targeted deletion/duplication analysis does have a higher resolution.
9. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *XK*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xp21.1 region. CMA designs in current clinical use target the Xp21.1 region.

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 manifestation 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, manifestations 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 feature 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 initially 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 manifestation 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 manifestation 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]. 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]. Comparable histologic findings were observed in the heart of the only individual with MLS who has undergone cardiac transplantation [Laurencin et al 2018].

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 findings at the time of initial diagnosis of the blood group abnormalities and are only recognized during routine workup 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 manifestations, intellectual disability, and/or cardiomyopathy.

The interval between reported disease onset and death ranges from seven to 51 years, and the mean age of death is 53 years (range: 31 to 69 years) [Danek et al 2001a, Jung et al 2001a, Hewer et al 2007, Walker et al 2019]. Mean disease duration from diagnosis to death was 21 years [Walker et al 2019]. Cardiac problems, in particular tachyarrhythmia, appear to be a major cause of premature death in MLS; other causes of death included pneumonia, seizure, suicide, and sepsis [Walker et al 2019].

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

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 [Øyen 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].

Other Studies

Serum concentrations of LDH, AST, and ALT may also be elevated [Danek et al 2001a, Jung et al 2001a]. These elevated values reflect muscle cell pathology and should not be misinterpreted as hepatic pathology.

Magnetic resonance spectroscopy (MRS). ^{1}H-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 [Dydak et al 2006].

Nuclear medicine. SPECT studies using ^{123}I-IMP and ^{123}I-IBZM revealed reduction of striatal perfusion and striatal D2-receptor density, respectively, in some males with MLS [Danek et al 1994, Oechsner et al 2001].

Using [^{18}F]-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].

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 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].

Postmortem motor and sensory nerve examinations demonstrated axonal motor neuropathy [Hewer et al 2007].

Brain pathology. Data from four individuals with MLS (3 males and 1 manifesting female heterozygote) 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.

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 2007a].

Only three pathogenic *XK* missense variants have a possible genotype-phenotype correlation. Although rare, they are potentially useful in the elucidation of structural and functional relationships. For more details, see Table 6.

- 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].
- An individual with the c.664C>G variant did not show significant neurologic or systemic abnormalities [Walker et al 2007b].
- 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 2007b].

Penetrance

In males, the penetrance of neurologic and neuromuscular manifestations of MLS is high – perhaps even complete – after age 50 years. Available data indicate that most males with the McLeod blood group phenotype will develop clinical manifestations 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 manifestations may be absent or only minor even after long-term follow up [Jung et al 2003, Walker et al 2007b].

In the past, many reports (including that of the index case) described only hematologic findings, and no neurologic or neuroimaging workup was performed in these individuals [Allen et al 1961, Symmans et al 1979, Bertelson et al 1988, Lee et al 2000]. However, in many of these individuals neurologic manifestations were identified 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" (named after the first proband, Hugh McLeod) 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 250 cases known worldwide. The prevalence is estimated at 1:10,000,000 [Walker et al 2019].

Genetically Related (Allelic) Disorders

No other phenotypes are known to be caused by pathogenic variants in *XK* alone.

Contiguous-gene rearrangements. Other genes that lie in close proximity to *XK* at Xp21.1 and the disorders caused by their deletion include the following [Peng et al 2007]:

- 5' of *XK* on Xp21.1: *DMD* (Duchenne muscular dystrophy)
- 3' of *XK* on Xp21.1:
  - *CYBB* (X-linked chronic granulomatous disease)
  - *RPGR* (*RPGR*-related retinitis pigmentosa)
  - *OTC* (ornithine transcarbamylase deficiency)

Note: Concurrent deletion of *CYBB* and *XK* is the most common; deletion of all five genes is exceedingly rare.

Differential Diagnosis

Table 2. Other Genes of Interest in the Differential Diagnosis of McLeod Neuroacanthocytosis Syndrome (MLS)

Gene	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MLS	Distinguishing from MLS
HTT	Huntington disease (HD)	AD	• May appear indistinguishable from MLS • Progressive choreatic movement disorder • Cognitive & psychiatric disturbances	• Anticipation • Absence of seizures, myopathy, & cardiomyopathy
Neuroacanthocytosis syndromes [1] assoc w/lipid malabsorption primarily affecting spinal cord, cerebellum, & PNS [2]				
ANGPTL3	Hypobetalipoproteinemia type 2 (OMIM 605019) [2]	AR	• Acanthocytosis • Dysarthria • Neuropathy • Areflexia	• Pigmentary retinopathy • Absence of basal ganglia involvement
APOB	Hypobetalipoproteinemia type 1 (OMIM 615558) [2]	AR		
MTTP	Abetalipoproteinemia (Bassen-Kornzweig disease) [2]	AR		
Neuroacanthocytosis syndromes predominantly affecting CNS (esp basal ganglia) [3]				

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MLS	Distinguishing from MLS
JPH3	HDL2	AD	• Progressive course • Dystonia • Presentation w/chorea or parkinsonism may change w/ evolution of the disease	• Almost all affected individuals reported to date have been of African ancestry • RBC acanthocytes not substantiated [5]
PANK2	PKAN; including HARP [4] (see also Neurodegeneration with Brain Iron Accumulation Disorders Overview)	AR	• Progressive dystonia • Dysarthria • Rigidity • In ~25% of individuals: "atypical" presentation w/ onset age >10 yrs, prominent speech defects, psychiatric disturbance, & more gradual disease progression • In ≥8%: acanthocytosis	• Usually childhood or adolescent onset • Basal ganglia iron deposition • "Eye of the tiger" sign on MRI characteristic • Pigmentary retinopathy
PRNP	HDL1 (OMIM 603218)	AD	Phenotype may be indistinguishable from HD.	• Rapidly progressive course • No hematologic, neuromuscular, or cardiac manifestations
VPS13A	Chorea-acanthocytosis (ChAc)	AR	• Progressive movement disorder (primarily chorea) • Subclinical myopathy → progressive distal muscle wasting & weakness • Mental changes • Seizures • Progressive cognitive & behavioral changes that resemble a frontal lobe syndrome • Dystonia affecting trunk & esp oral region & tongue → dysarthria & serious dysphagia w/resultant weight loss	• May present w/a parkinsonian syndrome • Habitual tongue & lip biting characteristic
Other disorders				
ATN1	DRPLA	AD		
ATP7B	Wilson disease	AR		
ATXN3	SCA3	AD		
CP	Aceruloplasminemia	AR		Aceruloplasminemia could be considered a neurodegeneration w/ brain iron accumulation. [6]
DYT3	X-linked dystonia-parkinsonism (DYT3, DYT-TAF1, Lubag)	XL		
FTL	Neuroferritinopathy	AD		
HPRT1	Lesch-Nyhan syndrome	XL		

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MLS	Distinguishing from MLS
NKX2-1	Benign hereditary chorea (see *NKX2-1*-Related Disorders)	AD		
PLA2G6	*PLA2G6*-associated neurodegeneration (infantile neuroaxonal dystrophy; Karak syndrome)	AR		
TBP	SCA17	AD		

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DRPLA = dentatorubral-pallidoluysian atrophy; HDL = Huntington disease-like; MOI = mode of inheritance; PKAN = pantothenate kinase-associated neurodegeneration; PNS = peripheral nervous system; SCA = spinocerebellar ataxia; XL = X-linked

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

2. Neurologic findings include:

a. A progressive spinocerebellar degeneration with gait ataxia, dysmetria, and dysarthria;

b. A demyelinating sensorimotor and axonal peripheral neuropathy with hyporeflexia and diminished vibration and position sense;

c. Rarely, pyramidal tract signs; and

d. Rarely, cranial nerve involvement [Kane & Havel 1995, Tarugi & Averna 2011].

3. Results in a chorea syndrome resembling Huntington disease

4. HARP syndrome (*h*ypoprebetalipoproteinemia, *a*canthocytosis, *r*etinitis pigmentosa, and *p*allidal degeneration) is allelic with PKAN [Ching et al 2002, Houlden et al 2003]. The continued use of this term is discouraged particularly since "hypoprebetalipoproteinemia" is not a meaningful entity.

5. Anderson et al [2017]

6. Kassubek et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with McLeod neuroacanthocytosis syndrome (MLS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with McLeod Neuroacanthocytosis Syndrome

System/Concern	Evaluation	Comment
Neurologic	For movement disorder	Choreiform movements; head drops; apply unified Huntington Disease Rating Scale (UHDRS) & perform brain MRI
	For seizures	Usually generalized seizures; perform EEG [1]
	For neuromuscular involvement	Absent DTRs, muscle weakness or atrophy; determine serum CK, ALT, AST, & LDH levels; EMG & NCV studies
Cognitive	To include motor, speech/language evaluation, & general cognitive skills	Frontotemporal & executive deficits; perform formal neuropsychological evaluation &/or Montreal cognitive assessment
Psychiatric	For frontal-type deficits; personality disorder, anxiety, depression, obsessive-compulsive disorder, bipolar disorder, schizo-affective disorder	Perform standardized psychiatric assessment; evaluation of symptom-oriented psychotherapeutic & psychopharmacologic interventions. Contact w/a patient advocacy organization may provide additional benefit. [2]

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Feeding	Feeding/nutritional assessment	Feeding dystonia; consider clinical &/or fiberoptic feeding evaluation
Cardiac	Dilated cardiomyopathy, atrial fibrillation, tachyarrhythmia	Usually develop over time [1]; perform echocardiography &Holter-ECG
Hematologic	Immunohematologic evaluation: erythrocyte phenotyping for Kell & Kx antigens; expression of Kell protein by flow cytometry, search for anti-public alloantibodies, direct antiglobulin test [3]	↑ risk of transfusion reactions w/repetitive blood transfusions; consider autologous blood banking when planned surgery may require blood transfusions.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

DTRs = deep tendon reflexes; EEG= electroencephalogram

1. Early recognition and treatment of cardiac manifestations and seizures are important, as these potential complications may be severe and could cause premature death [Danek et al 2001a, Hewer et al 2007, Walker et al 2019].

2. Irvine & Irvine [2013]

3. Frey et al [2015]

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with McLeod Neuroacanthocytosis Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Chorea	• Dopamine antagonists incl tiapride, clozapine, or quetiapine • Dopamine depletor: tetrabenazine	Avoid use of typical neuroleptics (e.g., haloperidol) because of risk of extrapyramidal adverse events.
Seizures	Antiepileptic drugs [1]	Avoid long-term use of benzodiazepines because of possible negative effect on neuromuscular system.
Neuromuscular	• Physiotherapy • Sufficient supplementation of calories & protein • Supplementation of vitamins D & B_{12} if needed	• Endurance exercise as tolerated may be helpful. • Avoid strength exercises, in particular of the eccentric type.
Cognitive	Cognitive training is probably rarely indicated.	Consider counseling as needed based on daily living &/or work-related requirements, incl job alternatives.
Psychiatric	Standard treatment according to manifestation	Extended & continuous multidisciplinary psychosocial support for affected individuals & families
Cardiac	Standard treatment according to clinical &/or ECG presentation	
Hematologic	Avoid transfusion of Kx+ homologous blood products.	Avoid repetitive blood transfusions; Consider cryopreservation of Kx- autologous blood for future use.

1. When epilepsy is suspected, EEG should be performed and AED treatment considered (based on standard guidelines including the monitoring of medication-specific laboratory parameters and serum concentrations). Because of the increased risk of rhabdomyolysis, treatment with neuroleptics – in particular clozapine – should be carefully monitored, both clinically and with serum CK measurements.

Surveillance

Table 5. Recommended Surveillance for Individuals with McLeod Neuroacanthocytosis Syndrome

System/Concern	Evaluation	Frequency
Cardiac	Cardiac examinations (Holter ECG & echocardiography)	Initially every 2-3 yrs; more frequently if abnormal clinical findings &/or cardiac examinations
Seizures	EEG	Whenever new-onset seizures are suspected
Muscle (rhabdomyolysis)	Serum CK concentration	Regularly, in particular when under neuroleptic treatment

Agents/Circumstances to Avoid

Blood transfusions with Kx antigens should be avoided in males with the McLeod blood group phenotype. Kx-negative blood or, if possible, banked autologous blood should be used for transfusions. Note that because heterozygous females have both Kx+ and Kx- red blood cells, they can be transfused with Kx+ homologous blood products.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of any age in order to identify as early as possible those who would benefit from: (1) detailed blood compatibility information to prevent transfusion of Kx+ homologous blood products, and (2) possible prophylactic cryopreservation of autologous blood for use in future transfusions.

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.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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 a male proband

- The father of an affected male will not have the disease nor will he be hemizygous for the *XK* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novoXK* pathogenic variant, in which case the mother is not a carrier. One *de novoXK* pathogenic variant has been described in MLS [Supple et al 2001].
- If a woman has more than one affected son and the *XK* pathogenic variant cannot be detected in her leukocyte DNA, she may have germline mosaicism. No data regarding germline mosaicism in MLS are available to date.

Sibs of a male proband. The risk to sibs depends on the genetic 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 heterozygotes and will usually not be affected. Significant interfamilial phenotypic variability has been observed in MLS (see Clinical Description).

  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 proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *XK* pathogenic variant to:

- All of their daughters who will be heterozygotes and usually will not be affected (see Clinical Characteristics, Females);
- None of their sons.

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

Heterozygote (Carrier) Detection

Identification of female heterozygotes requires either (a) prior identification of the *XK* pathogenic variant in the family or, (b) if an affected male is not available for testing, either molecular genetic testing first by sequence analysis, and if no *XK* pathogenic variant is identified, by gene-targeted deletion/duplication analysis or flow cytometric analysis of Kx and Kell erythrocyte antigens.

Note: Heterozygous females may very rarely develop clinical manifestations such as chorea or late-onset cognitive decline [Sveinsson et al 2018].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early identification of those who would benefit from detailed blood compatibility information to prevent transfusion of Kx+ homologous blood products.

Considerations in families with an apparent *de novo* pathogenic variant. When the mother of a male proband with an X-linked condition does not have the pathogenic variant identified in the proband, the pathogenic

variant is likely *de novo*. However, non-medical explanations including alternate maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of genetic 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 heterozygotes, or are at risk of being heterozygotes.

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 and Preimplantation Genetic Diagnosis

Once the *XK* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for MLS are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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**
  39 Coleherne Court
  London SW5 0DN
  United Kingdom
  Phone: 44 (0) 20 7460-8874
  Email: ginger@naadvocacy.org; Jen@naadvocacy.org
  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

- **European Huntington's Disease Network (EHDN)**
  Germany
  www.ehdn.org

- **Huntington's Disease Society of America (HDSA)**
  www.hdsa.org
- **Neuroacanthocytosis Database (Registry)**
  Prof. Adrian Danek
  Neurologische Klinik
  POB 701260
  Germany
  Phone: 49 (89) 4400-76676
  Email: adrian.danek@med.uni-muenchen.de
  www.euro-hd.net/html/na/registry

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

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
XK	Xp21.1	Membrane transport protein XK	XK @ LOVD	XK	XK

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

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

300842	MCLEOD SYNDROME; MCLDS
314850	KELL BLOOD GROUP PROTEIN, MCLEOD SYNDROME-ASSOCIATED; XK

Molecular Pathogenesis

XK encodes XK, a red blood cell antigen. The XK protein has ten transmembrane domains and the structural characteristics of a membrane transport protein [Ho et al 1994]. The XK protein attaches to the Kell glycoprotein, encoded by *KEL* on chromosome 7, by a single disulfide bond (XK p.Cys347- Kell p.Cys72) when they are coexpressed [Russo et al 1998]. In the red cell membrane, the heterodimeric protein-complex XK-KEL is part of the larger membrane multiprotein complex subunit 4.1 (MMPC4.1) containing Band3 glycoprotein, glycophorin C, Rh protein, Rh associated glycoprotein, and Duffy protein, which supports red cell cytoskeleton stability [Frey et al 2015, Lux 2016]. XK may also be important for transmembrane exchange of divalent cations (Ca++, Mg++) and Gardos channel function [De Franceschi et al 2005, Rivera et al 2013].

XK and Kell are predominantly coexpressed 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 [Russo et al 2000, Camara-Clayette et al 2001, Jung et al 2001b]; however, 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 in non-erythroid tissue differs from that of XK in combination with Kell.

Mechanism of disease causation. McLeod neuroacanthocytosis syndrome occurs through a loss-of-function mechanism.

***XK*-specific laboratory technical considerations.** A naming convention for abnormal *XK* alleles has been established by the International Society of Blood Transfusion (IBST; scroll down and select **Blood Group Allele Tables**, then **XK**). The XK protein reference allele is defined as XK*01. Alleles associated with MLS are defined as XK*N.# beginning with 01, with N indicating null and # being assigned to each reported abnormal allele (e.g., c.664C>G [p.Arg222Gly] is designated XK*N.27).

Note: Stepwise partitioning of Xp21 has been used as an alternative method to define the exact breakpoints of contiguous-gene deletions [Gassner et al 2017, Sveinsson et al 2018].

Notable *XK* variants. All three of the reported 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 p.Glu327 and p.Arg222 residues may be involved in the basic structure of *XK* rather than in its function; the p.Cys294 residue, which is conserved specifically in the *XK* family, may be critical for normal function [Walker et al 2007b].

Table 6. Notable *XK* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_021083.2 NP_066569.1	c.664C>G	p.Arg222Gly (XK*N.27)	The 3 reported *XK* missense variants are predicted to disrupt either structure or function [Walker et al 2007b].
	c.880T>C	p.Cys294Arg (XK*N.28)	
	c.979G>A	p.Glu327Lys (XK*N.29)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

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