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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 movement disorders, cognitive alterations, and 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. Alloantibodies 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. Although they usually lack CNS and neuromuscular manifestations, 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 either a hemizygous *XK* pathogenic variant

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(90% of affected males) or a hemizygous deletion of Xp21.1 involving *XK* (10% of affected males) identified on molecular genetic testing.

Management

Treatment of manifestations: The following recommendations apply to affected males (although symptomatic heterozygous females may undergo the same procedures, no scientific data are available): use of dopamine antagonists (e.g., tiapride, clozapine, quetiapine) and the dopamine depletory (tetrabenazine) to ameliorate chorea; assessment of cardiac involvement initially with cardiac MRI (if available), Holter electrocardiogram (EKG), echocardiography, cardiac biomarkers, and specialized electrophysiological investigations (if indicated); consideration of placement of prophylactic cardiac pacemaker / implantable cardioverter-defibrillator; treatment of psychiatric problems and seizures based on clinical findings; long-term and continuous multidisciplinary psychosocial support for affected individuals and their families.

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

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic male and female 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, (2) possible prophylactic cryopreservation of autologous or homologous blood for use in future transfusions, and (3) interventions to prevent sudden cardiac events.

Surveillance: For those with known cardiac involvement, follow up per treating specialist; for those without known cardiac involvement, Holter EKG, echocardiography, and cardiac biomarkers (e.g., troponin T/I, pro BNP) every two years; 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 testing 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.

CNS Manifestations

Clinical findings

- Progressive chorea syndrome, which also can be part of a clinical triad of movement disorders, cognitive alterations, and psychiatric symptoms ("Huntington-like syndrome")
- Seizures, mostly generalized

Neuroimaging studies

- **Males**
  - Brain CT and MRI may demonstrate variable atrophy of the caudate nucleus and putamen [Danek et al 2001a, Jung et al 2001a].
  - Brain MRI in two males demonstrated extended T_2-weighted hyperintense white matter alterations [Danek et al 2001a, Nicholl et al 2004].
- **Males and females.** Neuroimaging findings may be normal early in the disease course in affected males and in asymptomatic heterozygous females [Jung et al 2001a, Jung et al 2003].

Neuromuscular Manifestations

Clinical findings (often subclinical or mild)

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

Neuromuscular studies

- Muscle enzymes. All affected males examined to date have had elevated serum creatine phosphokinase (CK) concentration 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, Hewer et al 2007].
- Nerve conduction studies may demonstrate axonal damage of variable degree [Danek et al 2001a].
- Muscle CT and MRI 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].

Cardiac Manifestations

Clinical findings. Often dilated cardiomyopathy, atrial fibrillation, and tachyarrhythmia

Cardiac studies

- Echocardiography and cardiac MRI may demonstrate congestive cardiomyopathy or dilated cardiomyopathy with reduced left ventricular ejection fraction [Mohiddin & Fananapazzir 2004, Quick et al 2021].
- Electrocardiography may demonstrate atrial fibrillation or critical ventricular tachycardia [Mohiddin & Fananapazzir 2004, Quick et al 2021].
- Cardiac MRI may demonstrate focal late gadolinium enhancement [Quick et al 2021].
- Myocardial biopsy and cardiac MRI T_1-weighted mapping may reveal interstitial cardiac fibrosis [Oechslin et al 2009, Quick et al 2021].

Red Blood Cell Manifestations

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. 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.

  Accurate determination of RBC acanthocytosis is challenging. The recommendation to "send at least three blood smears" preferably of wet preparations of peripheral blood to an experienced laboratory [Balint & Lang 2020] has not been formally evaluated.

  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 fewer 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.

  Confirmation of erythrocyte morphology by scanning electron microscopy or confocal microscopy with 3D-rendering [Darras et al 2021] (if available) may be helpful.

- **Erythrocyte sedimentation rate** is significantly slowed and easily identified on a two-hour read-out [Darras et al 2021].

- **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 alloantibodies 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 autohemolysis 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)

Family History

Family history is consistent with **X-linked inheritance** (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

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, 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

Option 1 is the 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, **comprehensive genomic testing** such as exome sequencing or genome sequencing may identify a large deletion involving *XK*, particularly in a male; however, detection of a deletion by these methods must be confirmed by an orthogonal (i.e., statistically independent) method.

Option 2

Option 2 is the 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: 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 using these methods and may require CMA (see Option 1).

Option 3

Option 3 is 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 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  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]	~60% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~40% [4, 5, 7]
	Chromosomal microarray analysis [8]	~30% [5, 7]

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. 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. Roulis et al [2018]
5. A current list of *XK* pathogenic variants is maintained here: IBST (scroll down; select **Blood Group Allele Terminology**, then **XK**).
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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.
7. 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.
8. 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, cardiovascular, and hematologic manifestations in males. Heterozygous females 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.

Affected Males

CNS manifestations of MLS resemble Huntington disease. Symptoms comprise the prototypic triad of a progressive neurodegenerative basal ganglia disease including movement disorder, cognitive alterations, and 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 drop, 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.

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 predominantly neurogenic nature but also myopathic 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].

Obstructive sleep apnea, mentioned in a number of individuals with MLS, must be better characterized to qualify as a disease feature [Danek et al 2001a, Weaver et al 2019].

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, Quick et al 2021].

In a cardiac MRI study confirming the potentially malignant nature of cardiac involvement in MLS, four of five individuals with MLS had a dilated left ventricle, two of four a dilated right ventricle, and three of five a reduced left ventricular ejection fraction. Two of four individuals with MLS experienced ventricular tachycardia; Troponin T and CK values were elevated in all individuals for whom data were available [Quick et al 2021].

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].

McLeod blood group phenotype. About 30% of males with the McLeod blood group phenotype did not have neuromuscular or CNS findings at the time of initial diagnosis of the blood group abnormalities and were 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 hematologic manifestations are red blood cell acanthocytosis and compensated hemolysis. Alloantibodies 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.

Natural history. 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; the mean age of death is 53 years (range: age 31-69 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 include pneumonia, seizure, suicide, and sepsis [Walker et al 2019].

Heterozygous Females

Females 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:

- One heterozygous female developed the typical MLS phenotype [Hardie et al 1991, Ho et al 1996].
- A heterozygous female 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, heterozygous females had slight cognitive deficits and reduced striatal glucose uptake in the absence of an obvious movement disorder [Jung et al 2001a].
- The mother of a male with a contiguous-gene deletion of *XK* and *CYBB* developed impaired balance, mixed polyneuropathy, mild generalized chorea, and memory loss [Weaver et al 2019].

- Two deceased women from a larger pedigree (the mother of a male with proven MLS and her cousin – the mother of a proven heterozygous female) had shown involuntary movements according to family members [Sveinsson et al 2020].

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].

MRI volumetry. 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].

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].

[^{18}F]-FDG (2-fluoro-2-deoxy-glucose) PET revealed bilaterally reduced striatal glucose uptake 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 has shown 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, supporting the finding that XK forms a complex with VPS13A (see Molecular Pathogenesis). 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 heterozygote, 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, 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 among 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]. See Genotype-Phenotype Correlations.

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 [Walker & Danek 2021] (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 phenotypes other than those discussed in this *GeneReview* are known to be associated with germline 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

The two disorders of primary interest in the differential diagnosis of McLeod neuroacanthocytosis syndrome (MLS) are chorea-acanthocytosis and Huntington disease. These disorders – which may appear clinically indistinguishable from MLS – and other disorders in the differential diagnosis of MLS are summarized in Table 2.

Table 2. 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	AD	• May appear indistinguishable from MLS • Progressive choreatic mvmt disorder • Cognitive & psychiatric disturbances	• Anticipation • Absence of acanthocytes, seizures, myopathy, & cardiomyopathy • Normal CK
VPS13A	Chorea-acanthocytosis	AR	• Progressive mvmt 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 → weight loss	• May present w/a parkinsonian syndrome • Habitual tongue & lip biting characteristic • Cardiac disease less severe, if present
Other disorders				

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MLS	Distinguishing from MLS
ATN1	DRPLA	AD		
ATP7B	Wilson disease	AR		
ATXN3	SCA3	AD		
CP	Aceruloplasminemia [1]	AR		Acanthocytosis has been reported in 1 person w/aceruloplasminemia but this does not appear to be a consistent finding. [2]
DYT3	X-linked dystonia-parkinsonism (DYT3, DYT-TAF1, Lubag)	XL		
FTL	Neuroferritinopathy [1]	AD		
JPH3	Huntington disease-like 2	AD	• May appear indistinguishable from MLS • Progressive choreatic movement disorder • Cognitive & psychiatric disturbances	Acanthocytosis was initially reported; subsequent systematic studies have not validated that observation. [3]
HPRT1	Lesch-Nyhan disease	XL		
NKX2-1	Benign hereditary chorea (See *NKX2-1*-Related Disorders.)	AD		
PANK2	PKAN; incl HARP [1, 4]	AR	• Progressive dystonia • Dysarthria • Rigidity • In ~25% of persons: "atypical" presentation w/onset age >10 yrs, prominent speech defects, psychiatric disturbance, & more gradual disease progression • In ≥8%: acanthocytosis	• Chorea not observed • Usually childhood or adolescent onset • Basal ganglia iron deposition • "Eye of the tiger" sign on MRI characteristic • Pigmentary retinopathy
PLA2G6	*PLA2G6*-associated neurodegeneration [1] (infantile neuroaxonal dystrophy; Karak syndrome)	AR		
PRNP	Huntington disease-like 1 (See Genetic Prion Disease.)	AD	Phenotype may be indistinguishable from Huntingrton disease.	• Rapidly progressive course • No hematologic, neuromuscular, or cardiac manifestations
TBP	SCA17	AD		
Lipid malabsorption syndromes with acanthocytosis [5] affecting spinal cord, cerebellum, & PNS [6]				

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/MLS	Distinguishing from MLS
ANGPTL3	Hypobetalipoproteinemia type 2 (OMIM 605019) [6]	AR	• Acanthocytosis • Dysarthria • Neuropathy • Areflexia	• Pigmentary retinopathy • No basal ganglia involvement
APOB	*APOB*-related familial hypobetalipoproteinemia [6]	AR		
MTTP	Abetalipoproteinemia (Bassen-Kornzweig syndrome) [6]	AR		

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

1. See also Neurodegeneration with Brain Iron Accumulation Disorders Overview.

2. Kassubek et al [2017]

3. Anderson et al [2017]

4. HARP (*h*ypoprebetalipoproteinemia, *a*canthocytosis, *r*etinitis pigmentosa, and *p*allidal degeneration) syndrome 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 [Walker et al 2021].

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

6. Neurologic findings include [Kane & Havel 1995, Tarugi & Averna 2011]:

- A progressive spinocerebellar degeneration with gait ataxia, dysmetria, and dysarthria;
- A demyelinating sensorimotor and axonal peripheral neuropathy with hyporeflexia and diminished vibration and position sense;
- Pyramidal tract signs (rare);
- Cranial nerve involvement (rare).

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 mvmts; head drop • Apply 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 incl motor, speech/language eval, & general cognitive skills	• Executive deficits • Perform formal neuropsychological eval &/or Montreal cognitive assessment.
Psychiatric	For frontal-type deficits: personality disorder, anxiety, depression, OCD, bipolar disorder, schizo-affective disorder	• Perform standardized psychiatric assessment; eval of symptom-oriented psychotherapeutic & psychopharmacologic interventions. • Contact w/patient advocacy org may provide addl benefit. [2]

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Feeding	Feeding/nutritional assessment	• Feeding dystonia • Consider clinical &/or fiberoptic feeding eval
Cardiac	Dilated cardiomyopathy, atrial fibrillation, tachyarrhythmia	• Usually develop over time [1] • Perform echocardiography, Holter EKG, & cardiac biomarker analysis (e.g., Troponin T/I, pro-BNP). • If available, perform cardiac MRI & electrophysiologic investigations.
Hematologic	Immunohematologic eval: • 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. • Consider homologous blood banking for emergencies.
Liver	Abdominal ultrasound exam	Screening for hepatosplenomegaly
Genetic counseling	By genetics professionals [4]	To inform patients & families re nature, MOI, & implications of MLS in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources; • Social work involvement for caregiver support; • Home nursing referral.	

DTRs = deep tendon reflexes; EEG = electroencephalogram; EKG = electrocardiogram; OCD = obsessive-compulsive disorder; UHDRS = Unified Huntington Disease Rating Scale

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]

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

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	Anti-seizure medication [1]	Avoid long-term use of benzodiazepines because of possible negative effect on neuromuscular system.
Neuromuscular	• PT • Sufficient supplementation of calories & protein • Supplementation of vitamins D & B_{12} if needed	• Endurance exercise as tolerated may be helpful. • Avoid strength exercises, esp 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.

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Psychiatric	Standard treatment based on manifestation	Extended & continuous multidisciplinary psychosocial support for affected persons & families
Cardiac	Standard treatment based on clinical &/or EKG presentation	Consider: placement of prophylactic cardiac pacemaker/implantable cardioverter-defibrillator; heart transplant
Hematologic	Avoid transfusion of Kx+ homologous blood products.	• Avoid repetitive blood transfusions. • Consider cryopreservation of autologous or homologous blood for future use.
Family support & resources	Eval of needs every visit & involvement of respective local services when needed	Advocacy groups for neuroacanthocytosis in Europe & US may support affected persons & their caregivers.

EKG = electrocardiogram; PT = physical therapy
1. When epilepsy is suspected, EEG should be performed and anti-seizure medication 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	**W/cardiac involvement**	Per treating specialist	Per treating specialist
	W/o known cardiac involvement	Cardiac exams (at least Holter EKG, echocardiography & cardiac biomarkers)	• Every 2 yrs • When findings are abnormal, more frequently depending on cardiologist's eval
Seizures		EEG	Whenever new-onset seizures are suspected
Muscle (rhabdomyolysis)		Serum CK concentration	Regularly, esp when under neuroleptic treatment
Family support & resources		Eval of social, psychological, & financial situation	At each visit

EEG = electroencephalogram; EKG = electrocardiogram

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 or homologous 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 male relatives of any age in order to identify as early as possible those who would benefit from:

- Detailed blood compatibility information to prevent transfusion of Kx+ homologous blood products;
- Possible prophylactic cryopreservation of autologous or homologous blood for use in future transfusions; and

- Prevention of sudden cardiac events.

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, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise 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. Note: 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.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo XK* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.

  One *de novo XK* pathogenic variant has been described in MLS [Supple et al 2001].
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

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. Significant interfamilial phenotypic variability has been observed in MLS (see Clinical Description).
  - Females who inherit the pathogenic variant will be heterozygotes. Females who are heterozygous for an *XK* pathogenic variant 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. The typical MLS phenotype was reported in one female. (See Clinical Description, Heterozygous Females.)

- 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 presumed to be 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 will usually not be affected. Some heterozygous females may develop clinical manifestations such as chorea or late-onset cognitive decline (see Clinical Description, Heterozygous Females).
- None of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having an *XK* pathogenic variant.

Heterozygote 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: Some heterozygous females may develop clinical manifestations such as chorea or late-onset cognitive decline (see Clinical Description, Heterozygous Females).

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.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.

Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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**
  United Kingdom
  Phone: 44 (0) 20 7460-8874
  Email: ginger@naadvocacy.org
  www.naadvocacy.org
- **Neuroacanthocytosis Advocacy USA**
  2285 Harlock Road
  Melbourne FL 32934
  Email: susan@naadvocacyusa.org; joy@naadvocacyusa.org
  www.naadvocacyusa.org
- **Cardiomyopathy UK**
  United Kingdom
  Phone: 0800 018 1024 (UK only)
  Email: contact@cardiomyopathy.org
  cardiomyopathy.org
- **European Huntington's Disease Network (EHDN)**
  Germany
  www.ehdn.org
- **Huntington's Disease Society of America (HDSA)**
  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

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
XK	Xp21.1	Endoplasmic reticulum membrane adapter 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 forms a complex with VPS13A, a protein that acts as lipid transporter protein at different membrane contact sites, for example, between the mitochondria and the endoplasmic reticulum [Kumar et al 2018, Urata et al 2019, Yeshaw et al 2019, Park & Neiman 2020]. XK is involved in the relocalization of VPS13A (e.g., from lipid droplets to subdomains of the endoplasmic reticulum), and may act as a phospholipid scramblase, like other proteins of the XK family [Park & Neiman 2020]. Of note, pathogenic *VPS13A* cause autosomal recessive chorea-acanthocytosis (ChAc), which is phenotypically very similar to MLS. Hence, dysfunction of an XK-VPS13A complex may represent the common molecular basis for both MLS and ChAc – which is a possible explanation for their phenotypic similarities [Kumar et al 2018, Urata et al 2019, Yeshaw et al 2019, Park & Neiman 2020].

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]. 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].

Notable *XK* variants. All three of the pathogenic missense variants reported in Table 6 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.Arg222 and p.Glu327 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_021083.4 NP_066569.1	c.508+5G>A		Intronic substitution that results in alternative splicing w/ some normal transcript; not assoc w/significant neurologic abnormalities [Walker et al 2007b]
	c.664C>G	p.Arg222Gly (XK*N.27)	The 3 reported *XK* missense variants 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

Chapter Notes

Author Notes

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