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Review

Neurodegeneration in the elderly – When the blood type matters: An overview of the McLeod syndrome with focus on hematological features

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ABSTRACT

Multisystem deterioration occurs mainly in older individuals and may be related to physiological tissue degeneration. However, genetic predisposition may be unmasked by inappropriate functional and structural system deficiencies. McLeod syndrome (MLS) is a rare, multisystem disease which is X-chromosomal inherited and belongs to the neuroacanthocytosis syndromes (NAS). The main clinical manifestations contain progressive neuro-psychiatric and cognitive deterioration, choreatic movement disorder, as well as myopathy, sensory motor axonal neuropathy and cardiomyopathy. In addition, MLS patients have red blood cell abnormalities including immune-hematological, morphological and functional impairments of red blood cells. In large deletions, contiguous gene syndrome may arise, including Duchenne muscular dystrophia, cellular immunodeficiency or retinitis pigmentosa. Hematological abnormalities such as blood group abnormalities in Kell- and XK blood group system, formation of anti-public red blood cell alloantibodies, acanthocytosis and elevated creatinine phosphokinase may precede clinical disease manifestation for decades and provide tools for early diagnosis. Patients with unexplained neuro-muscular deterioration and/or neuro-psychological pathologies accompanied with hematological abnormalities should be investigated for MLS.

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McLeod syndrome (MLS) is part of the Neuroacanthocytosis syndromes (NAS)

NAS are defined as progressive neurodegenerative diseases affecting mainly basal ganglia including nucleus caudatus and putamen in association with red blood cell acanthocytosis. Additional hematological abnormalities e.g. morphological, functional and serological aberrations of red blood cells (RBC) are part of disease defining clinical features [1–3]. Four different diseases with overlapping clinical manifestations account for the NA syndromes: Choreoacanthocytosis (ChAc) and the McLeod syndrome (MLS) constitute the core NAS and are caused by mutations of the *VPS13A* gene on chromosome 9q21 and the *XK* gene on *Xp21.1*, respectively. The more rare diseases such as Huntington-like2 disease (HDL2) and the pantothenate kinase 2 disease (PKAN) complete the group of NAS. Affected genes and proteins, mechanism of inheritance and clinical as well as laboratory phenotypes are summarized in Table 1.

Usually, the MLS is diagnosed in patients with progressive neuro-psychiatric deficiencies and having excluded other pathologies such as Huntington's disease, Tourette's syndrome and familial hemolytic anemia. The clinical picture reflects a neuro-hematological disorder [4] where the subtle hematological findings may precede the neurological deficiencies for decades and remain unrecognized until neuro-psychiatric alterations prompt invasive assessment. The patients suffer on premature dementia, intellectual and cognitive impairment, depression, personality changes, social retraction and in some cases they may suffer of movement disorders such as choreatic movement disorder and dystonia as well as generalized epileptic seizures [1,2,5–12]. In all MLS patients examined up to date creatinine phosphokinase (CPK) is elevated, without signs of acute myocardial and muscular cell necrosis or renal insufficiency. The diagnostic key feature is the prototypic McLeod blood group phenotype comprising weakened or absent Kell blood group antigens and negativity for the Kx antigen on the red blood cell membrane. This blood group abnormality is highly

specific for MLS and separates the disease from other NAS. In many patients with MLS the blood group peculiarity goes along with acanthocytosis of variable degree and compensated hemolytic anemia. However, several individuals have been described with exclusive McLeod RBC phenotype without other hematological, neuro-psychiatric and neuromuscular symptoms [13,14]. Mostly, these cases are recognized when being blood group phenotyped for KEL antigens while serving as blood donors. In fact, the first case discovered with the prototypic RBC phenotype was the healthy blood donor Mr. McLeod, who engaged into blood donation as a dentist student and was diagnosed with “a new phenotype (McLeod) in the Kell blood group system” [15] because of weakened expression of several Kell antigens as compared to his parents.

Peculiarity of blood group antigens on McLeod erythrocytes

The MLS is the only NAS with distinct blood group abnormality affecting the KEL (ISBT 06) as well as the XK (ISBT 019) blood group system. The Kell glycoprotein (CD238) is a type II single-pass transmembrane red blood cell protein containing 732 amino acids and functions as an endopeptidase which cleaves big-endothelin3 into the active endothelin3, that acts as a potent vasoconstrictor [16,17]. It expresses at least 35 recognized blood group antigens, including 5 antithetical pairs exerting clinical relevance [18]. From these, the K/k pair (Kell/Cellano) is the most important one [19]. The single amino acid exchange of methionine replacing threonine at position 193 (Met193Thr) eliminates a N-glycosylation site of the Kell protein constituting the K (KEL1) and k (KEL2) epitopes, respectively. Alloantibodies against K and k may cause severe hemolytic transfusion reactions as well as life-threatening morbus hemolyticus neonatorum [19,20].

The XK protein, encoded by the *XK* gene at *Xp21.1*, is a 444 amino acid multipass red blood cell membrane peptide, forming a heterodimer with the Kell glycoprotein and expresses the single blood group antigen Kx [21,22]. The

Table 1

Genetic and somatic deficiencies in NA syndromes. Various genetic defects with distinct inheritance and overlapping clinical manifestation constitute the NA syndromes.

Adapted from Jung et al. [2].

Disorder phenotype	ChAc	MLS	HDL2	PKAN
Gene/Chromosome	<i>VPS13A</i> /9q21	<i>XK</i> / <i>Xp21.1</i>	<i>JPH3</i> /16q24.3	<i>PANK2</i> /20p13
Protein	Chorein	XK protein	Junctophilin-3	Pantothenate kinase 2
Inheritance	Autosomal/recessive	X-linked/recessive	Autosomal/dominant	Autosomal/recessive
Hemolytic anemia	None	Yes (not always)	None	None
Acanthocytes	+++	++	+/-	+/-
Serum CK	Increased	Increased	Normal	Normal
Neuroimaging abnormalities	Striatal	Striatal	Striatal/cortical	Striatal “Eye of the tiger”
Age of onset	20–30	25–60	20–40	<16
Chorea	+++	+++	+++	+++
Other movement disorders	Dystonia lip biting Parkinsonism	Vocalization	Dystonia, Parkinsonism	Dystonia Parkinsonism spasticity
Seizures	Yes	Yes	None	None
Neuromuscular defects	Areflexia atrophy	Areflexia atrophy	None	None
Cardiac affection	None	Arrhythmias cardiomyopathia sudden cardiac death	None	None

ChAc: choreoacanthocytosis, MLS: McLeod syndrome, HDL2: Huntington-like2 syndrome, PKAN: Pantothenatekinase 2 disease.

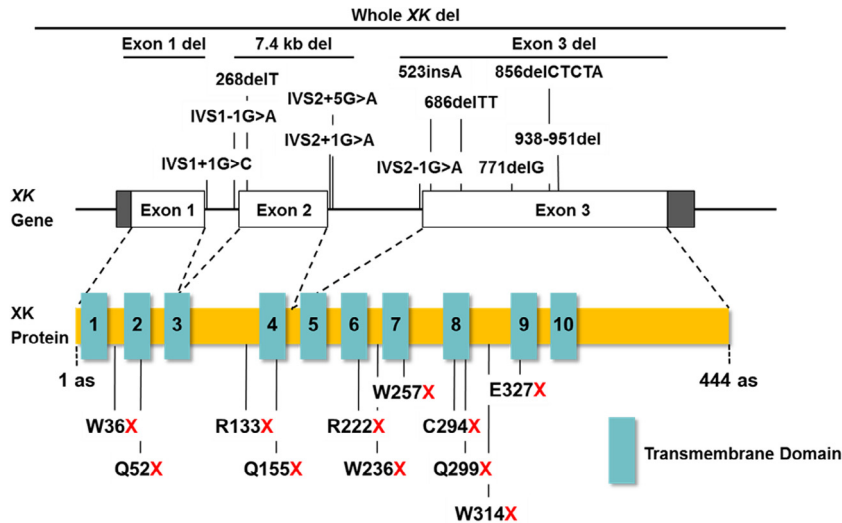


Fig. 1. The XK gene with its three exons and the corresponding red blood cell multipass membrane protein XK are shown. All three exons may be affected by stop and missense mutations leading to shortened or missing protein at the red cell surface. Also splice site mutation as well as partial and complete gene deletion mutations may cause absence of XK protein. Whole XK gene deletions extending to telomeric and centromeric coding regions may lead to the contiguous gene syndrome. X: Marks premature termination of XK protein assembly due to stop codon.

antigen Kx is located at the fifth extracellular loop of the XK peptide in close proximity to the disulfide bond $\text{XK}^{\text{Cys}347}$ – $\text{Kell}^{\text{Cys}72}$, covalently linking and stabilizing the Kell–XK heterodimer [22]. In most ethnicities, the frequency of the Kx antigen is >99% and may therefore be considered as “the public Kx phenotype” [19]. Individuals with the McLeod phenotype characteristically lack the Kx antigen, which is due to a complete absence or a drastically shortened XK protein and may rise anti-public red blood cell antibodies such as anti-Kx and anti-Km upon immunizing events, such as transfusion. These alloantibodies will react with most of the homologous blood donations and may therefore generate substantial problems in the supplementation with correctly matched, e.g. Kx negative blood [4,13,23]. In Kx negative individuals, the observed weakened agglutination of Kell antigens serves as surrogate for the McLeod phenotype and needs to be distinguished from a modified Kell antigen expression in Kmod and Knull phenotypes. These equally rare variants of *KEL* alleles lead to modified Kell protein expression [24,25] without molecular, phenotypic and clinical signs of MLS. The red blood cells of Kmod and Knull phenotypes express the Kx antigen [24,26,27] and will therefore not develop anti-public antibodies in the Kx blood group system.

Genetic defects at Xp21.1 lead to the absence or truncation of the XK protein causing both the reduced or complete absence of the Kell antigen in the erythrocyte membrane, as well as the absence of the Kx blood group antigen (Kx-) [5]. At least 29 different mutations at Xp21.1 are recognized as molecular mechanism for the Kx- phenotype [5,18]. These are missense and stop mutations anywhere in the three exons of the coding sequence as well as splice site and insertion/deletion mutations leading to erroneous translation and transcription of the gene, respectively [5]. In cases of large deletional defects, neighbor genes of *XK* may also be affected and give rise to the “contiguous

gene syndrome” [28], of which the clinical phenotype is dominated by the co-affected gene(s) [29]. Most important are deletions affecting DMD, a gene located telomeric to *XK*, leading to Duchenne muscular dystrophy [28] or deletions affecting the centromeric *CYBB* gene, leading to X-linked granulomatous disease (X-CGD) [30,31]. Figure 1 gives an overview on some of the molecular defects at Xp21.1 and the consequences for the XK protein.

Distinct morphology of McLeod erythrocytes

Patients suffering on MLS or ChAc usually present with various degrees of acanthocytosis in circulating blood, which may be visualized by light microscopy of a blood smear. The abnormally shaped RBCs (acanthocytes) are characterized by few irregular membrane protrusions [32]. They are different from echinocytes which show many, more regular and shorter membrane bulges. However, although the morphological variants are distinct, these RBC abnormalities are interchangeable and in most cases acanthocytes are accompanied by echinocytes [33]. Since the lipid composition of altered RBC is normal, the acanthocytic shape change results from impaired interaction of the membrane multiprotein complexes (MMPC) with the cytoskeleton of red blood cell [33]. The major RBC anion exchanger protein, band 3 (B3), one of the most abundant membrane protein, is organized either as a tetrameric B3-ankyrin complex, a dimeric B3-protein 4.1R complex (also called “junctional complex”) or as a free B3 protein [34,35]. The B3 multimeric entities are attached to various other transmembrane proteins such as glycophorin A and C, Rh protein/Rh associated glycoprotein (RhAG), Kell, XK and Duffy proteins as well as CD47 and Landstein–Wiener (LW) glycoproteins and thereby constitute the MMPC. The MMPC interact with the RBC cytoskeleton by recruiting linker proteins such as protein 4.2/ankyrin (ankyrin complex) and protein 4.1R/adducin (4.1R

complex) [36–38]. The MMPC-cytoskeleton network controls the RBC discocytic shape and determines RBC deformability, rheological, adhesive and functional properties [37,39,40]. Deficiencies in one or several proteins of MMPC impairing the MMPC-cytoskeleton interaction were found to cause inherited RBC membranopathies such as hereditary elliptocytosis, ovalocytosis, stomatocytosis and spherocytosis [37,41–49]. Moreover, the cytoplasmic part of B3 as well as of other attached membrane proteins control a variety of metabolic pathways in RBC by binding to aldolases, kinases, oxidases and phosphatases [50–58].

However, not only deficiencies or dysfunction of RBC membrane proteins may lead to acanthocytosis. Also, hereditary disorders of lipid metabolism such as apolipoprotein A and vitamin E deficiency [59,60] as well as a number of acquired conditions such as acute and chronic anemia, hepatitis, alcoholic liver cirrhosis, hypopituitarism, hypothyroidism, malabsorption syndromes and malnutrition may be associated with acanthocytic shape change of RBC [61].

Acanthocytic RBCs are a typical finding in NAS especially in patients with MLS and ChAc. However, the finding is neither specific nor sensitive enough for clinical diagnosis [13,14]. Moreover, the in vitro diagnosis of acanthocytes is technically demanding and prone of false positive testing [62]. Therefore, Storch et al. suggested a modified technique to assess peripheral blood smears for acanthocytes. According to Storch et al., quantification of acanthocytes needs to be done using wet smear of diluted blood sample and by applying dark field microscopy [62]. Due to technical demanding procedure and the low disease specificity of acanthocytes, this test has lost its diagnostic power. Nevertheless, functional impairment of transmembrane ion transport [58,63–65], impaired formation of endovesicles by acanthocytes in NAS [66] and the findings by DeFranceschi et al. who described 14 kinases constituting a mutual phospho-tyrosine sub-network in acanthocytes of NAS [51] suggested common pathways for acanthocyte formation and neurodegeneration in NAS. Therefore, acanthocytes of MLS may provide an easy accessible substrate to be investigated for patho-mechanism of disease and may paste new avenues of treatment options for patients suffering on NAS.

MLS is a multisystem disorder

Although the genetic alteration in MLS was precisely located at Xp21.1 [67] the genotype–phenotype correlation is weak and most mutation carriers are discovered while being assessed for a wide spectrum of subtle to severe central nervous system or neuromuscular affection occurring together with pathological changes of red blood cells (acanthocytosis, coombs-negative, hemolytic anemia) [1–3,68]. The molecular characterization of underlying genetic defects in NAS allows unambiguous distinction between the four different entities of NAS (Table 1). Molecular defect identification has therefore become the key tool for diagnosis [1,69]. In MLS, the disorder is caused by the affection of the XK protein, which is expressed ubiquitously in body tissues [70] and most likely functions as a membrane transporter [71,72] with so far not precisely

defined substrate. In the RBC membrane the XK protein is co-expressed with the Kell protein and forms a heterodimer [22,27,70,73]. In contrast, non-hematopoietic cells express the XK protein independently of the Kell protein which may not even be present [70]. Therefore, XK may act as a universal gatekeeper by direct or indirect control of substrate exchange between different subcellular compartments [70,72]. Several groups have shown that in the absence of XK or other RBC membrane proteins, the RBC shape and transmembrane ion transport may be severely altered. Active ion transport channels including the Ca²⁺ dependent K⁺ transport (Gardos channel) as well as the transporters of Mg²⁺, Cl⁻, SO₄⁻ and other ions are negatively affected [58,63,65,66,74]. Especially, the proper function of Gardos channel is pivotal for the integrity and function of RBCs [75–78]. Gardos channels are ubiquitously expressed in body tissue [79] and their functionality may depend on intact XK protein. In line with this assumption, disruption of XK may therefore lead to multisystem deficiencies by impairment of Gardos functionality which could explain the chief affected cardiac and neuronal tissues in MLS [79–83] (see Table 1).

Molecular MLS assessment

As detailed earlier, the NAS are monoallelic deficiency syndromes, perfectly suited for molecular defect analysis. The genetic defects of MLS always involve *XK*, the gene encoding the XK protein and its Kx antigen, which is located at Xp21.1. The genetic lesions may be point mutations leading to amino acid exchanges and stop codons, splice site mutations and small insertional and deletional aberrations (indels), as well as large X-chromosomal deletions involving up to approximately 5 Mio bp, as reported as of yet. A listing of all currently known *XK*-null alleles, e.g. *XK**N01 to *XK**N29, may be retrieved from the homepage of the ISBT terminology committee [18]. The mode of inheritance of MLS is X-chromosomal recessive, implying carrier status with no, or abrogated clinical disease manifestation in mothers, sisters and daughters of affected males. To exclude a disease caused by a molecular defect at Xp21.1, we designed a systematic approach to investigate the regions, telomeric and centromeric to *XK* for the unique identification of contiguous gene defects. In brief, the X-chromosome is investigated in between *OTC* (Ornithine Carbamoyltransferase at Xp11.4, OMIM*300461) and *DMD* (Duchenne Muscular Dystrophy, Dystrophin 1 at Xp21.2, OMIM*300377), by 36 equally distanced positional PCRs also co-amplifying sequences of the Human Growth Hormone 1 (*GH1* at 17q23.3, OMIM*139250), which serve as positive amplification controls. The X-chromosomal distance investigated by this approach covers more than 8.8 Mio base pairs (bp) in total and includes *XK*, 0.7 Mio bps from its centromeric end (McLeod syndrome associated *XK* at Xp21.1, OMIM*314850), as well as *CYBB* (Cytochrome b(-245) subunit associated with X-CGD at Xp11.4, OMIM*300481) and *RPGR* (Retinitis Pigmentosa GTPase Regulator at Xp11.4, OMIM*312610). In case of large X-chromosomal deletions, certain positional PCRs will fail to amplify. The indicated gap is then narrowed down by additional positional PCRs until the breakpoint of the deletion may be bridged by one single PCR.

Consequently, this case specific PCR product is then sequenced and allows for the exact definition of the breakpoint position, and may itself already be used as highly accurate diagnostic tool for the detection of a carrier status in mothers, sisters and daughters of affected males. In case no large X-chromosomal deletion is observed, all three XK exons, also including some sequences of the promoter and at least 50 bp of each flanking intron will be sequenced to reveal point mutations within the gene, potentially causative of an XK inactivating effect. The effect of such point mutations may be clearly evident, e.g. when nonsense mutations lead to the creation of stop codons in the predicted XK peptide, or be less informative and of questionable meaning, e.g. when exchanged amino acids share in between no, and up to similar physiochemical properties, then called “radical” and “conservative missense mutations”, respectively. Using this approach we were able to describe five intragenic XK mutants, with only one of them already known and listed as XK^{*N.20} by the ISBT terminology committee [18], the others, with as yet undescribed nonsense (n = 1), frame shift (n = 1) and radical missense mutation (n = 1) and two large X-chromosomal deletions, respectively. All carriers had different MLS phenotypes including neuropsychiatric disorder associated with hereditary sudden death syndrome, severe choreatic movement disorder and X-linked CGD, in one case (manuscript in preparation).

Clinically guided MLS diagnosis

Most of the MLS mutations described so far were discovered in patients being investigated for neuro-psychiatric or choreatic movement disorders or in cases with immune deficiency syndromes [5]. Normally, the patients suffer from unspecific neuro-psychiatric symptoms for years without having assigned clear diagnosis. Sometimes, MLS is diagnosed in asymptomatic mutation carriers, most often when routinely phenotyped for KEL antigens while serving as blood donors [13–15]. These blood donors may develop clinical MLS later on and available data indicate a high penetrance of the disorder with a possible onset in the sixth and seventh decades [84]. However, in patients with unexplained neuropsychiatric problems or choreatic movement disorders with onset in the third or fourth decade it might be important to exclude MLS as the underlying disease causing condition. The findings may have important implications usually for the male patient as well as for his family members. Although the disease progression cannot be stopped, early supportive measures such as seizure protection, psychiatric treatment as well as prevention of mutilating involuntary movements may provide desired palliation of disease associated disabilities. Importantly, early recognition of orofacial dystonia may be pivotal to prevent feeding impairment and secondary wasting disease [85]. Also, the recognition of private blood type (Kx-) is crucial when it comes to transfusion support. By timely searching for Kx- blood donors from international donor registries or alternatively, by use of cryopreserved autologous blood units the formation of anti-public antibodies can be prevented [23]. Finally, cardiac complications such as fatal

arrhythmia may be prevented by implantation of a cardiac pacemaker [86].

For genetic counseling of MLS patient's family members, it is important to identify the exact genetic defect which can then be followed for segregation in the relatives of the patient. Finally, in X-linked CGD patients, the exclusion of mutations at Xp21.1 is pivotal in planning and exertion of CGD treatment which often includes stem cell transplantation and transfusion support [87,88].

We established an algorithm to comprehensively assess patient's samples for suspected McLeod mutations (Fig. 2). Firstly, the patient's RBCs are examined for expression of the Kx antigen as well as several antithetical Kell antigens (e.g. K, k, Kp^b) by conventional serology techniques. It is important to emphasize that IgG coating of patient's RBCs needs to be excluded by negative direct antiglobuline test in order to validate serological antigen determination. Also, genetic investigation for inherited Kell antigens by commercial genotyping kits helps to confirm serological findings. In case the Kx antigen is absent and the inherited Kell antigens show weakened or missing expression, the McLeod red cell phenotype is proven. In such cases, the blood smear is assessed for the presence of acanthocytes and the extracted genomic DNA will be searched for disease causing mutations (see discussion earlier). Identified mutations will then be used to design a molecular protocol to follow the segregation of the disease specific mutation in consanguineous family members. In order to complete an individual McLeod assessment, we further recommend to perform an expression study of the KEL protein by flow cytometry as described earlier [13]. Flow cytometric investigation of KEL protein expression by using commercially available anti-Kell antibodies (e.g. BRIC18, BRIC68, BRIC203, provided by IBGRL, Bristol/UK) allows for a quantification of the circulating McLeod RBCs admixed to normal RBCs. Double RBC populations with normal and depressed KEL protein expression is a typical finding in female McLeod carriers [4,7]. All individuals with confirmed McLeod RBC phenotype need to be assessed for the presence of red blood cell alloantibodies, since anti-public alloantibodies may have substantial consequences for transfusion support of MLS patients.

Conclusion

MLS is a rare multisystem disease which affects mainly male adults. Neuro-psychiatric, neuromuscular, cardiac and hematologic affection dominate the clinical picture and may vary substantially in individual patients. Early diagnosis in patients with suggestive clinical symptoms is crucial for guiding the patient's management in order to prevent cardiac and hematologic sequelae and to palliate clinical and social consequences of disease. Diagnostic cornerstones are red blood cell phenotyping in the XK- and KEL system, appropriate molecular analysis of underlying genetic defect and quantification of circulating acanthocytes. The molecular mutation analysis also provides insights into multi gene defects (contiguous gene syndrome) which is most important in cases with juvenile X-linked granulomatous disease, retinitis pigmentosa and Duchenne muscular dystrophy.

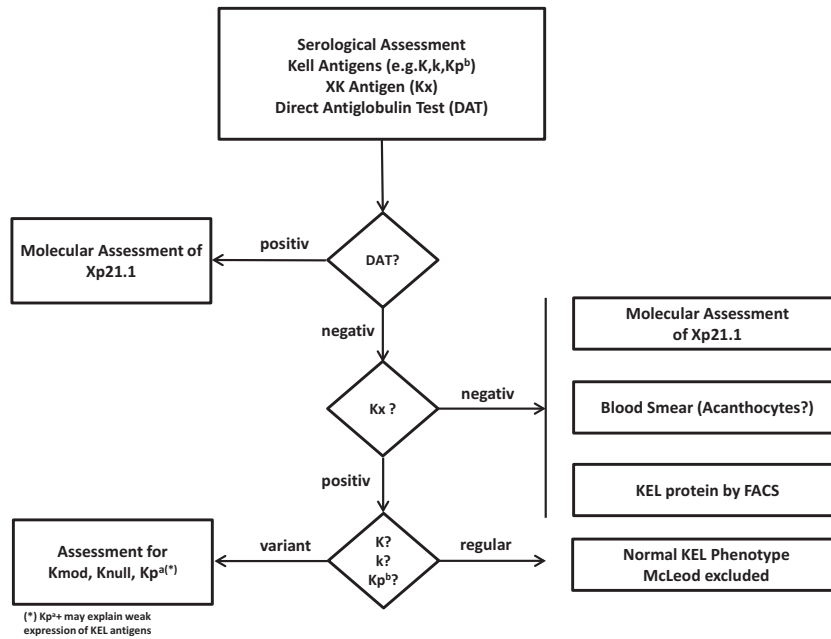


Fig. 2. Delineates the systematic analysis of patient samples suspected for the presence of a McLeod mutation. The assessment always starts with the serological evaluation for KEL and Kx antigen expression, which are expected to be either negative or weakened. The antigen expression pattern needs to be validated by negative direct antiglobuline test. In case of positive DAT, the antigens might be determined false positive. Kx antigen expression pattern will then guide further evaluation performed. If Kx is negative, an assumed molecular defect directly encoded by the XK gene itself, or alternatively a large deletion affecting the expanded XK locus at Xp21.1 is checked for. Respective X-chromosomal mutations may then establish the diagnosis of McLeod syndrome and also explain the secondary weakened Kell antigen expression. If Kx reacts positive, the MLS is excluded and other reasons for weakened KEL expression might be checked for (K_{mod}, K_{null}, Kp³). In MLS, further diagnostic steps may be taken, e.g. detailed FACS analysis of weakened Kell antigen expression, or a microscopic investigation for the presence of acanthocytes. DAT: direct antiglobuline test. FACS: fluorescence activated cell sorting.

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