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Neuroacanthocytosis Syndromes: The Clinical Perspective

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Abstract

The two very rare neurodegenerative diseases historically known as the "neuroacanthocytosis syndromes" are due to mutations of either *VPS13A* or *XK*. These are phenotypically similar disorders that affect primarily the basal ganglia and hence result in involuntary abnormal movements as well as neuropsychiatric and cognitive alterations. There are other shared features such as abnormalities of red cell membranes which result in acanthocytes, whose relationship to neurodegeneration is not yet known. Recent insights into the functions of these two proteins suggest dysfunction of lipid processing and trafficking at the subcellular level and may provide a mechanism for neuronal dysfunction and death, and potentially a target for therapeutic interventions.

Keywords

VPS13A, XK, acanthocytosis, chorea, lipid, BLTP

Introduction

VPS13A disease (chorea-acanthocytosis) and *XK* disease (McLeod syndrome) are the currently recognized "core neuroacanthocytosis syndromes" (Jung et al., 2021; Peikert et al., 2023). These two genetically distinct disorders share remarkable phenotypic similarities, resulting in significant diagnostic confusion, even after the identification of their respective causative genetic mutations (Walker and Danek, 2021). These two disorders were initially thought to constitute a single disease entity ("neuroacanthocytosis" or "Levine-Critchley syndrome"); intriguingly it now appears likely that the involved proteins are functionally linked, suggesting that a common mechanism at the subcellular level may be the cause of the remarkable phenotypic resemblance (Park and Neiman, 2020; Peikert et al., 2022a; Peikert and Danek, 2023).

The descriptive name for these disorders refers to the thorny red blood cells, known as acanthocytes, whose appearance is a diagnostic clue, however, these are neither specific nor obligatory for diagnosis (Peikert et al., 2022b). While acanthocytes can be seen in other conditions, including in disorders of lipid absorption (such as abetalipoproteinemia), their presence in combination with the specific neurologic symptoms seen here is a useful, although not invariable, clue to diagnosis.

Increased awareness of these disorders over the past two decades has resulted in improvements in diagnosis and management, with a growing appreciation for their protean manifestations, both neurological and nonneurological (see "Red Flags Findings," Figure 1). Patients with these disorders might present initially to psychiatrists, hematologists, cardiologists, transfusion medicine specialists, gastroenterologists, or others, in addition to neurologists from a variety of subspecialties, including neuromuscular, epilepsy, behavior, sleep, or movement disorders.

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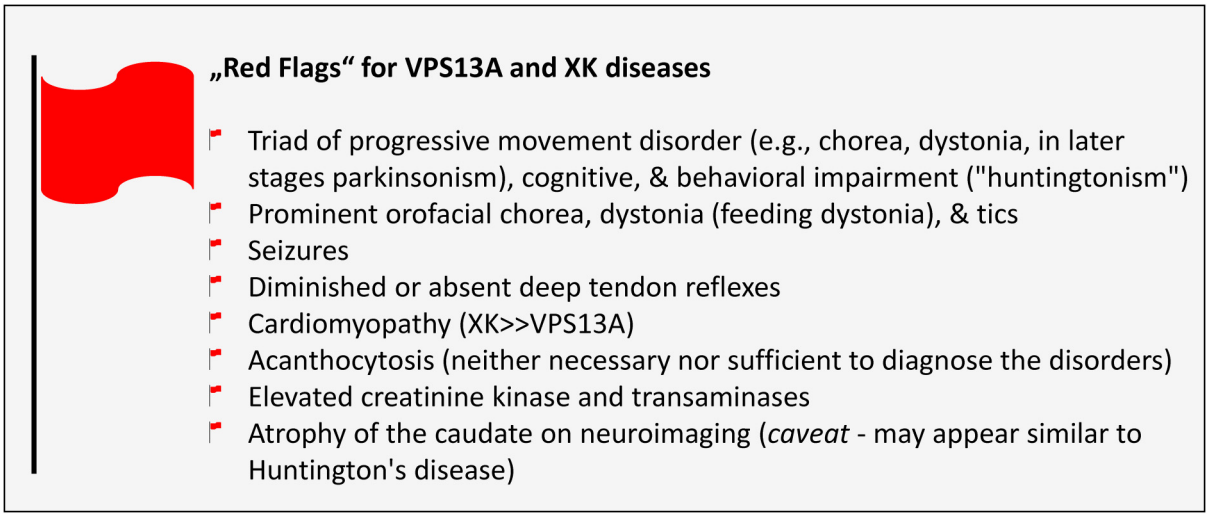

Figure 1. "Red Flags findings" for *VPS13A*and *XK* diseases.

Nomenclature

The history of the taxonomy of "neuroacanthocytosis syndromes" might be said to reflect the evolution of identification, diagnosis, and nomenclature of genetic disorders in the 20th and 21st (Walker and Danek, 2021) (Figure 2). In the 1960s, Irvine Levine (Estes et al., 1967; Levine et al., 1968) and Edmund Critchley (Critchley et al., 1967, 1968), each identified families with a novel syndrome with features of erythrocyte acanthocytosis and basal ganglia neurodegeneration resulting in a spectrum of movement disorders, which was termed "neuroacanthocytosis" (NA). This syndrome was well-recognized in Japan (later identified as *VPS13A* disease due to a founder mutation; Ueno et al., 2001), and at the time was believed to be a single disease, and was given the eponym "Levine-Critchley syndrome." This term was used interchangeably with the term "neuroacanthocytosis," most notably in the seminal work published by Hardie in 1991 (Hardie et al., 1991). However, molecular investigation of the subjects in this series determined that they carried mutations causative of several disorders, namely VPS13A, XK, and pantothenate kinase-associated neurodegeneration (PKAN; Gandhi et al., 2008).

In 2011, descendants of Critchley's original family from eastern Kentucky were found to carry mutations in VPS13A (Velayos-Baeza et al., 2011), while more recently descendants of Levine's family have been found to carry mutations in *XK* (Walker, Danek, Westhoff, and Vege, personal observations). This pleasing symmetry, and the association of the two genetically distinct disorders under a single term, appears to be further validated by the apparent functional relationship of the affected proteins, VPS13A and XK, in membranes (Park and Neiman, 2020; Guillén-Samander et al., 2022; Park et al., 2022; Ryoden et al., 2022; Sakuragi and Nagata, 2023).

Given the presence of acanthocytosis in PKAN, and the presence of an individual with this disorder in Hardie's series, we initially included PKAN under the umbrella of "neuroacanthocytosis syndromes," however, it is now clear that the cellular pathophysiology is divergent from that of the other disorders. For a number of years now PKAN has been more appropriately described as the prototypical "neurodegeneration with brain iron accumulation" disorder. In Hardie's series, the individual carried the diagnosis of hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP), which has transpired to be allelic with PKAN (Ching et al., 2002).

Huntington's disease-like 2 was also included in this grouping, however, this disease is also now excluded from the group in light of recent reports showing the absence of acanthocytosis in 12 of 12 investigated HDL2 patients (Anderson et al., 2017).

Current usage of NA is understood to encompass the diseases caused by mutations in the genes *VPS13A* and *XK*. Biallelic mutations in *VPS13A* cause what has been termed "chorea-acanthocytosis" or "choreoacanthocytosis" or sometimes just "neuroacanthocytosis". Mutations in *XK* cause McLeod syndrome, named after the initial propositus, a Harvard dental student who was found incidentally to carry the rare blood group caused by this mutation (Allen et al., 1961).

In this review, we address these two distinct genetic disorders, which have remarkable phenotypic overlap, in addition to some distinguishing features.

It has been noted that acanthocytes can be absent or appear late in either disorder (Malandrini et al., 1993; Sorrentino et al., 1999; Klempír et al., 2008; Bayreuther et al., 2010) and that the hyperkinetic movement disorder known as "chorea" can be absent in *VPS13A* disease (Peluso et al., 2017), thus in line with current trends in the

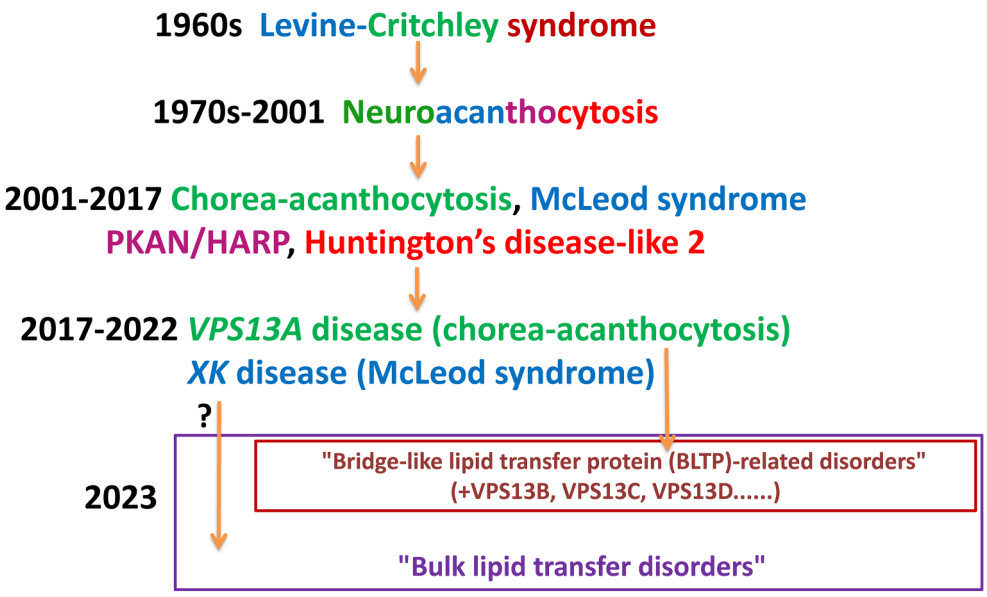

Figure 2. The evolution of nomenclature of neuroacanthocytosis syndromes. *VPS13A* disease can now be included in the group of disorders due to mutations of genes encoding for other VPS13 family members (bridge-like lipid transfer protein [BLTP]-related disorders), and possibly other related proteins. Further research will determine whether disruption of bulk lipid transfer indeed underlies the pathophysiology of these and other disorders, including *XK* disease, and whether "bulk lipid transfer disorders" is indeed an appropriate term.
Note. HARP = hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration; PKAN = pantothenate kinase-associated neurodegeneration.

nomenclature of mono-genetic disorders from hereon we identify these disorders based upon their genetic cause.

The Relationship Between VPS13A and XK Proteins and Related Diseases

The locations and functions of the hitherto little-known VPS13 protein family (A–D) have only been recently unraveled. The development of Alphafold provided critical insights into protein structure, and hence potential functions. Located at membrane contact sites (MCS), the VPS13 protein family members act as conduits for nonvesicular bulk lipid transfer (Bean et al., 2018; Kumar et al., 2018; Yeshaw et al., 2019; Dziurdzik and Conibear, 2021; Leonzino et al., 2021) and belong to the newly recognized superfamily of "bridge-like lipid transfer proteins (BTLPs)" (Braschi et al., 2022; Levine, 2022; Neuman et al., 2022). The corresponding human genes are of considerable interest as mutations in each lead to a hereditary neurological disease: *VPS13A* disease (Rampoldi et al., 2001; Ueno et al., 2001), *VPS13B* disease (Cohen syndrome; Kolehmainen et al., 2003), *VPS13C* disease (familial parkinsonism with Lewy bodies; Lesage et al., 2016; Smolders et al., 2021) or *VPS13D* disease (various ataxic-spastic conditions, formerly classified as SCAR4/SCA24/SCASI; Gauthier et al., 2018; Seong et al., 2018). To date, acanthocytosis has not been identified in these clinically distinct syndromes apart from *VPS13A* disease. Further insights into pathophysiology in diseases due to mutations of these other members of the VPS13 protein family, other BTLPs, and proteins related by a common function, such as XK, may indicate that these are all part of a group of disorders with a common mechanism of impaired bulk lipid transport (Figure 2).

The VPS13A protein resides at MCS between the endoplasmic reticulum (ER) and various organelles; mitochondria, lipid droplets, endosomes, or plasma membrane. At these sites, the protein is arranged with its N-terminus in contact with the ER and the C-terminus near the second organelle (Kumar et al., 2018; Muñoz-Braceras et al., 2019; Yeshaw et al., 2019). Together with adaptor proteins, such as VAP, VPS13A has been described to form a "bridge" or "tunnel" with a hydrophobic groove enabling bulk phospholipid transfer between the respective organelle membranes (Figure 3; Leonzino et al., 2021; Dall'Armellina et al., 2023). While selectivity, direction, and functional consequences of this transfer need to be further investigated, this process seems to be important for expansion (e.g., autophagosome formation) or modification of lipid composition of membranes (Leonzino et al., 2021; Dabrowski et al., 2023). At the plasma membrane, VPS13A interacts with the scramblase XK (Guillén-Samander et al., 2022; Park et al., 2022; Ryoden et al., 2022), while a putative ER-sided scramblase is as yet undefined (Figure 3). This complex may be involved in the transport of lipids between the ER and plasma membrane and lipid scrambling between the two leaflets of the plasma membrane (Guillén-Samander et al., 2022) as has

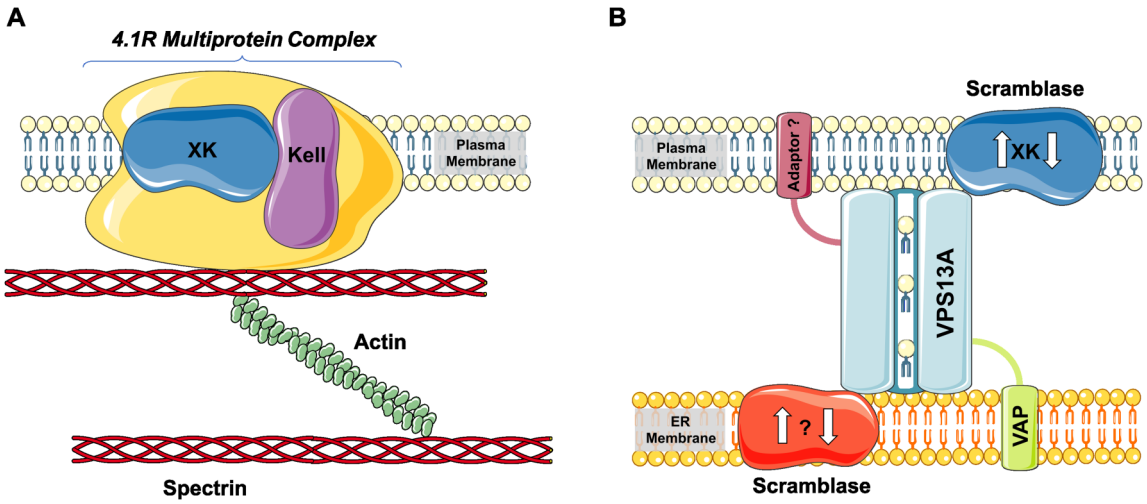

Figure 3. VPS13A, XK, and their interaction partners. The XK and VPS13A proteins have various interacting proteins. (A) The scramblase XK binds to Kell in the 4.1R multiprotein complex of red cell membranes (drawn simplistically) and (B) interacts with VPS13A at membrane contact sites between the endoplasmic reticulum (ER) and plasma membranes. VPS13A is a bridge-like lipid transfer protein residing at various membrane contact sites where it forms a "tunnel" enabling bulk lipid transfer and where it interacts with adaptor proteins, such as VAP as the ER-sided adaptor (the opposite adaptor is as yet undefined as is a speculative scramblase at the ER side). Reproduced with permission (Creative Commons CC-BY-NC license) from Sage Journals 2023 from Peikert and Danek (2023). (This figure contains modified images from Servier Medical Art [https://smart.servier.com] licensed by a Creative Commons Attribution 3.0 Unported License).

been shown in CD25+ CD4+ T-cells. Here, VPS13A-XK plays a role in ATP-induced phosphatidylserine exposure (by an unidentified P2X7-dependent signal) and subsequent necrotic cell death (Ryoden et al., 2022). The exact role of this process in neurons anf other cell types involved in "neuroacanthocytosis" is the subject of further research. Nevertheless, the XK–VPS13A interaction most likely represents the mechanistic basis for the phenotypic similarities between the respective diseases (Peikert and Danek, 2023).

VPS13A Disease

This progressive neurodegenerative disorder is caused by biallelic mutations and typically appears in early adulthood (Peikert et al., 2023). Prevalence is estimated at 1:1,000,000, but underrecognition is likely. Signs and symptoms are consistent with the involvement of the basal ganglia, in particular, the head of the caudate nucleus (Walterfang et al., 2011; Liu et al., 2018). Psychiatric features such as obsessive-compulsive behaviors, tics, or psychosis can be early and confounding features. In addition to the sometimes bizarre appearance of involuntary movements, these can lead to a diagnosis of a functional neurologic disorder (Peikert et al., 2023).

The movement disorders that can develop include dystonia, tics, chorea, and—typically more prevalent in the later disease stages—parkinsonism. There is a predilection for involvement of the lower face, mouth, and oropharynx, thus speech and swallowing are often affected relatively early in the disease course, in comparison to Huntington's disease (HD), which otherwise has similar features (Peikert et al., 2023). Feeding dystonia with involuntary tongue protrusion is an occasional characteristic phenomenon associated with *VPS13A* disease (Bader et al., 2010).

Other features that distinguish *VPS13A* disease from disorders that solely affect the basal ganglia, such as HD, include seizures, which can be a presenting feature, and peripheral neuropathy and myopathy. Involvement of skeletal, and possibly cardiac, muscle appears generally to be milder in *VPS13A* disease than in *XK* disease, although at times it can be clinically significant. Additionally, the liver and spleen can often be enlarged, with elevation of liver enzymes, and there can be cardiac involvement, albeit typically mild (Quick et al., 2021).

The course of *VPS13A* disease is one of slow progression over several decades, although there can be sudden death, likely related to seizures or autonomic dysfunction (Walker et al., 2019).

Laboratory features such as elevation of creatine kinase (CK) and liver enzymes can lead to presymptomatic diagnosis by whole exome sequencing (Walker, personal observations). Other potential biomarkers include a reduced erythrocyte sedimentation rate (Darras et al., 2021) and elevated serum neurofilament light chain (Peikert et al., 2020), although the latter finding is a common sign of central and peripheral nervous system damage. In addition to genetic testing, diagnosis can be made by Western blot of peripheral red blood cells to look for the absence of VPS13A (chorein; Dobson-Stone et al., 2004). There appear to be rare cases, likely due to missense mutations, in which VPS13A is present on Western blot but dysfunctional.

When acanthocytosis is present in a significant percentage of red blood cells on peripheral blood smear (ideally performed as per Storch et al., 2005), this is supportive of the diagnosis, however, this is not a consistent finding and can be absent (Malandrini et al., 1993; Sorrentino et al., 1999; Bayreuther et al., 2010; Peikert et al., 2022b). The relationship between this observation and neurodegeneration remains unclear, and there is not a clear correlation between disease severity or progression and this laboratory finding.

Neuropathological reports have been strikingly uninformative to date, revealing primarily marked neuronal loss and astrogliosis primarily affecting the basal ganglia, most prominently the head of the caudate nucleus (Liu et al., 2018). The latter is in contrast to HD, where neuropathologic changes are more obvious in the caudal region of the neostriatum (Vonsattel et al., 1985). However, recent lipidomic analysis of postmortem human brain tissue is supportive of dysfunctional lipid metabolism (Miltenberger-Miltenyi et al., 2023; Figure 4), as are our observations of apparent lipid accumulation in neurons (Figure 5; Ditzel et al., 2023). Similar lipidomic changes have been reported in Parkinson's disease and various VPS13 model systems, and are discussed in detail elsewhere (Miltenberger-Miltenyi et al., 2023).

XK Disease

Symptoms of X-chromosomal *XK* disease typically appear in middle-aged men, although similar to *VPS13A* disease, identification of elevated CK and transaminases, the latter sometimes misinterpreted as of hepatic origin, can lead to diagnosis in earlier life (Tian et al., 2019). Affected subjects may also be identified if they undergo blood-typing, as they have an atypical pattern of erythrocyte antigen expression, namely absent Kx antigen and weakened Kell antigens, known as the "McLeod blood group phenotype" (Redman and Marsh, 1993; Redman et al., 1999). The protein product of the *XK* gene, XK, is expressed on the surface of erythrocytes and presents an antigen, known as Kx (Redman and Marsh, 1993; Russo et al., 1998; Redman et al., 1999). Most mutations of *XK* result in absent or dysfunctional (and hence mislocated) XK and hence Kx; additionally XK is linked to another protein, Kell, in the erythrocyte membrane within the 4.1R multiprotein complex, thus when XK is absent, expression of Kell antigens is markedly reduced (Peikert and Danek, 2023; Figure 3).

As with *VPS13A* disease, acanthocytes can be an informative feature when present, but can be absent (Klempír et al., 2008).

XK disease appears to be even rarer than *VPS13A* disease, with an estimated prevalence of 1:10,000,000, although again, underdiagnosis is likely a factor. Symptoms of *XK* disease are generally very similar to those of *VPS13A* disease, although there can be much more variation in presentation, severity, and rate of disease progression. In addition, symptom onset is usually later and some patients may manifest as late as their 60s (Jung et al., 2021; Peikert et al., 2022a). Milder symptoms appear to be related to mutations that result only in dysfunctional, rather than absent, XK (Walker et al., 2007). Severe involvement of speech and swallowing is a less consistent feature. The other most striking feature is the involvement of cardiac muscle, which can result in significant morbidity and mortality (Oechslin et al., 2009; Walker et al., 2019; Quick et al., 2021). Cardiac involvement can be the presenting feature, and can even require cardiac transplantation (Laurencin et al., 2018). Myopathy of skeletal muscle and peripheral neuropathy can also be significant and a cause of morbidity (Jung and Brandner, 2002; Hewer et al., 2007; Vaisfeld et al., 2021). Sleep disturbances, such as sleep apnea and periodic limb movements, have recently been recognized and may compound other issues (Lim et al., 2022).

Similar to *VPS13A* disease, neuropathological evaluation demonstrates neuronal loss and gliosis in the basal ganglia (Deutschländer et al., 2022).

Management

Management of these two disorders, in common with other neurodegenerative disorders at the time of writing, is directed at controlling symptoms (Walker, 2015) and preventing future complications, for example, by annual monitoring for cardiac complications (Jung et al., 2021; Peikert et al., 2023). Neurologic symptoms are managed as in other diseases with similar manifestations; this principle extends to deep brain stimulation which has been employed in a number of patients, primarily with *VPS13A* disease, with at least short-term benefits. Weight loss can be significant, and placement of a feeding tube can be a valuable strategy (unlike in Alzheimer's disease, where it is not found to improve life expectancy or quality).

Similar to other neurodegenerative diseases affecting the basal ganglia, such as HD, in both of these disorders behavioral issues can be very challenging to manage and can be a major determinant of functioning and quality of life. The involvement of a psychiatrist can be valuable.

In *XK* disease, affected patients are encouraged to bank their blood in case of future need, to avoid the possibility of a transfusion reaction. Regular screening for potential heart involvement regardless of the presence of specific symptoms is recommended.

Ongoing multidisciplinary care involving therapists of all modalities, including physiotherapy, speech, occupational, and psychological, is recommended.

Potential Disease-Modifying Strategies

Based on preclinical evidence of Lyn kinase hyperactivity with subsequent perturbation of autophagy, impaired

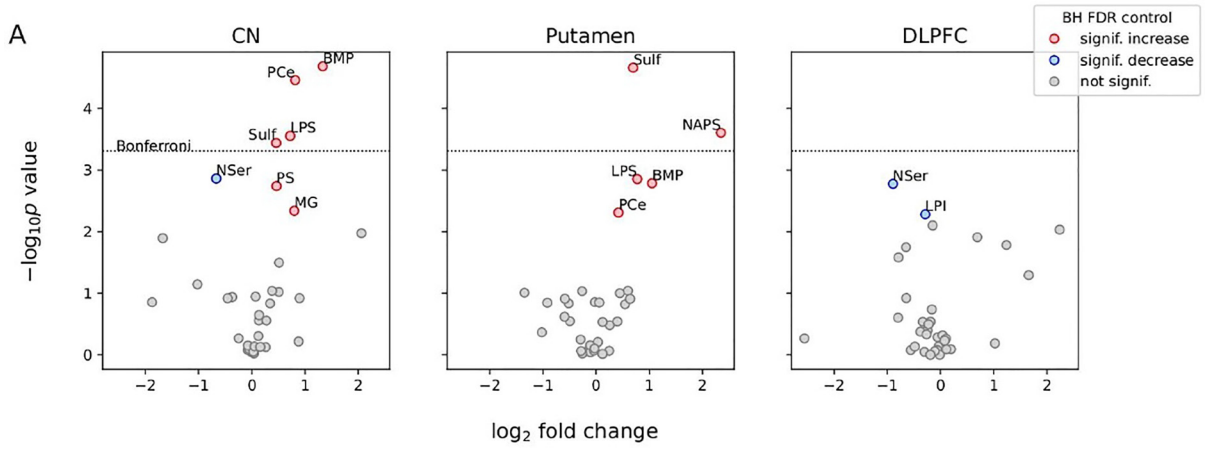

Figure 4. Lipid-level alterations in the brain extracts of ChAc, compared with non-ChAc, patients. (A) The *x*-axis of the volcano plots shows the log-transformed fold change in the expression of lipid groups in ChAc relative to non-ChAc patients. The shared *y*-axis of the volcano plots shows the minus log-transformed *P* values for the null hypothesis of no lipid-level change in patients with ChAc relative to control patients in a given brain region. *P* values were obtained from linear mixed models controlling for brain region, age at death, and subject-to-subject variability. Labeled red/blue symbols mark lipid groups with significantly increased/ decreased levels in ChAc, respectively, after 5% FDR control with the BH procedure (BH FDR, in the legend). The horizontal dotted line shows the threshold for the more conservative Bonferroni procedure. See reference for methodological details. In summary, there was increased BMP, sulfatide, LPS, and PCE in the caudate nucleus and putamen, but not in the DLPFC; increased PS and MG in the caudate nucleus and increased NAPS in the putamen; decreased NSer in the caudate nucleus and DLPFC and decreased LPI in the DLPFC; of note, there was no single outlier case driving significance. Reproduced with permission © Wiley 2023 from Miltenberger-Miltenyi et al. (2023).
Note. BH = Benjamini–Hochberg; BMP = bis(monoacylglycerol)phosphate; ChAc = chorea-acanthocytosis; DLPFC = dorsolateral prefrontal cortex; FDR = false discovery rate; LPI = lysophosphatidylinositol; LPS = lysophosphatidylserine; MG = monoacylglycerol; NAPS = N-acyl phosphatidylserine; NSer = N-acyl serine; PCE = phosphatidylcholine ether; PS = phosphatidylserine..

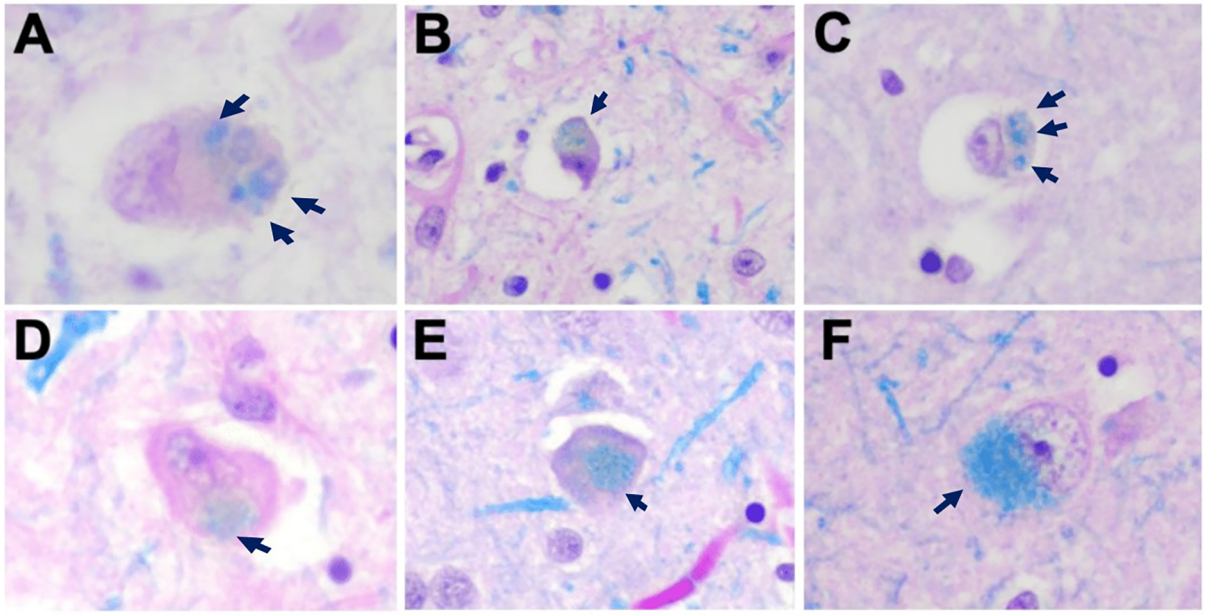

Figure 5. Lipid inclusions. Examples of lipid accumulation morphologies in *VPS13A* disease (chorea-acanthocytosis). Sections stained with Luxol fast blue (LFB) showed variable patterns of lipid accumulation (arrows) with (A, B, C) puncta, (D, E) single cytoplasmic, or (F) diffuse patterns. 20× magnification for all images. Reproduced with permission © Wiley 2023 from Ditzel et al. (2023).

protein phosphorylation of red cell membrane proteins and neuronal hyperexcitability in *VPS13A* disease (De Franceschi et al., 2011; Lupo et al., 2016; Stanslowsky et al., 2016), three subjects were given the protein kinase inhibitor dasatinib (Peikert et al., 2021b). Although target engagement in red blood cells was achieved, clinical

parameters remained essentially unchanged. Follow-up studies suggested failure of central nervous system penetrance by orally administered dasatinib (Peikert et al., 2021a), which indicated that, based on current knowledge, this approach cannot be generally recommended to treat *VPS13A* disease patients.

Future Directions

Further studies are required to expand our findings in *VPS13A* disease and to extend our observations by performing lipidomics and neuropathology in *XK* disease. In addition, further studies are needed to demonstrate that disordered lipid transfer at MCS due to loss of protein function and subsequent neuronal dysfunction is the proximate cause of neurodegeneration, prior to this being the focus for the development of potential therapy targets.

The cause of the abnormal red cell membrane structure that results in acanthocytosis is not known, although there is evidence of abnormal protein phosphorylation in red cell membranes (De Franceschi et al., 2011) and of depolymerized cortical actin (Foller et al., 2012). These cells do not contain nuclei or subcellular organelles once they are in the peripheral circulation, however, it is possible that abnormal lipid metabolism and organellar transfer during maturation (erythropoiesis) affects their membrane composition.

In order to achieve "clinical trial readiness" once a disease-modifying strategy/compound has been identified, it is essential to identify potential study subjects (at the international level, given the rarity of these diseases), and to further characterize disease natural history and biomarkers.

Conclusions

Recent insights into the group of proteins involved in bridge-like lipid transfer have elucidated mechanisms of subcellular lipid processing. Mutations of *VPS13A* result in rather localized neurodegeneration and dysfunction of lipid metabolism, thus providing a tantalizing indication that this dysfunction might be a target for therapeutic intervention. Mutations resulting in loss or dysfunction of the scramblase XK, which interacts with VPS13A, produce a remarkably similar disease, potentially suggesting a common mechanism, and hence a shared pathway to intervention.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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