VPS13A and XK bulk lipid transfer diseases

(formerly the now obsolete Levine-Critchley syndrome)

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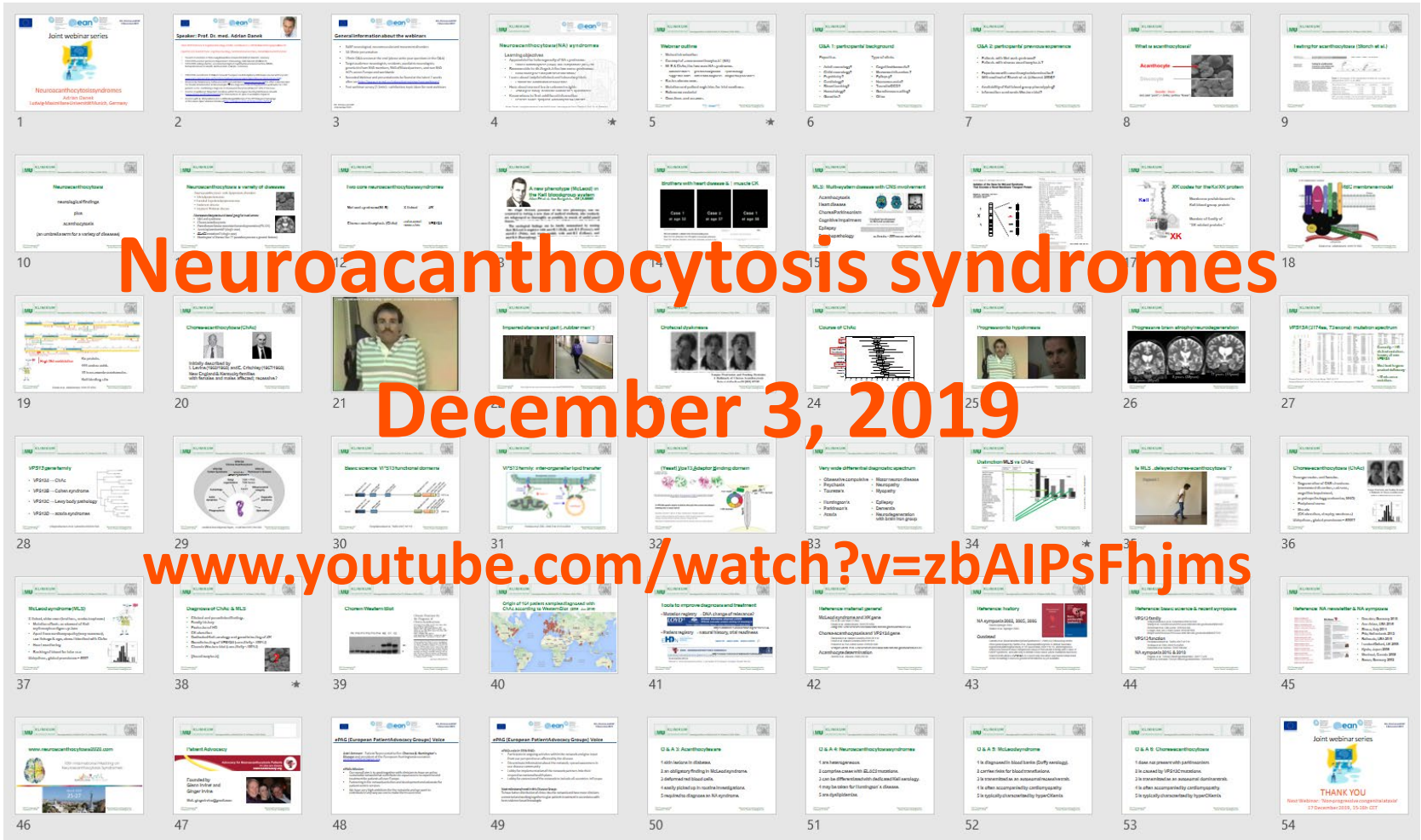

Neuroacanthocytosis syndromes

December 3, 2019

www.youtube.com/watch?v=zbAIPsFhjms

"Neuroacanthocytosis" – Overdue for a Taxonomic Update

Tremor and Other Hyperkinetic Movements

VIEWPOINT

ubiquity press

RUTH H. WALKER
ADRIAN DANEK
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ABSTRACT

The term "neuroacanthocytosis" (NA) is used for a spectrum of neurological disorders in which there are thorny red blood cells. While NA historically referred to disorders of lipoprotein absorption, we have promoted it as an overarching term for a group of basal ganglia disorders, with specific reference to two diseases that we defined as "core" NA syndromes. "Neuroacanthocytosis" has also been used to refer to a specific, now genetically-defined disease, otherwise known as "chorea-acanthocytosis". These various usages have resulted in diagnostic confusion, and in a number of cases have quite likely prevented the pursuance of precise, molecular, diagnosis. Disease nomenclature is an ever-evolving field, especially in the current era of expanding genetics, and naming proposals are often far from ideal. We, however, suggest that the term "neuroacanthocytosis" should no longer be generally used and if so, only with appropriate understanding of its limitations. Further, we propose that chorea-acanthocytosis be renamed as "*VPS13A* disease" in accordance with its genetic etiology.

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KEYWORDS:
neuroacanthocytosis; acanthocytosis; McLeod syndrome; chorea-acanthocytosis; VPS13A

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VPS13A and XK bulk lipid transfer diseases

Learning objectives

- Learn about current developments in „neuroacanthocytosis“ and „Levine-Critchley syndrome“
  bulk lipid transfer science, genetic diagnoses in historic families
- Understand proposal to change nomenclature
  - Chorea-acanthocytosis (ChAc) -> VPS13A disease
  - McLeod syndrome (MLS) -> XK disease
- Become able to distinguish the two diseases
  - Distinct clinical features, lab findings/biomarkers, molecular correlates
- Know where to find additional information
  - Reviews, books, symposia, patient advocacies

Webinar outline

- Mutual introduction
- Problems of „neuroacanthocytosis“/„Levine-Critchley syndrome“
- VPS13A and XK diseases (novel nomenclature)
  - clinical features - genetic background - diagnosis
- Bulk lipid transfer as recently discovered mechanism
- Reference material
- Questions and answers

Q&A 1 and 2: participants' background

1, Expertise:

- Adult neurology?
- Child neurology?
- Psychiatry?
- Cardiology?
- Blood bank/hematology?
- Genetics?
- Cell biology/biochemistry?
- Other

2, Type of clinic:

- Cognitive/dementia?
- Movement disorders?
- Epilepsy?
- Neuromuscular?
- Tourette/OCD?
- Mental retardation?
- Genetic counselling?
- Other

Webinar outline

- Mutual introduction
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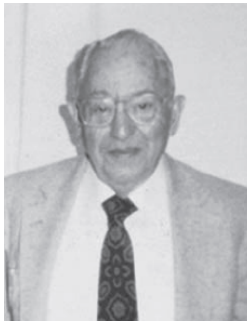

Levine et al. 1968

Hereditary Neurological Disease With Acanthocytosis

A New Syndrome

Irving M. Levine, MD; J. Worth Estes, MD; and Joseph M. Looney, MD, Boston

ACANTHOCYTOSIS has been characterized as a genetic disorder manifested by the appearance of spiny red cells in the peripheral blood smear, abnormal lipid metabolism usually involving absent β-lipoproteins, steatorrhea, retinitis pigmentosa, and alterations of the central and peripheral nervous systems including atrophy of certain muscle groups.[1] In 1966 a complete review of this disorder was published by Farquhar and Ways.[2]

In 1960 Levine et al[3] gave a preliminary report of the patient and family presented in this paper. The earlier report indicated that in 13 of 28 maternal relatives there were acanthocytes in the peripheral blood while 15 had none. At that time, 8 of 17 persons available for neurological examinations showed signs of neurological disease. Studies of the red blood cells (RBC) and serum lipids in the family were presented in a subsequent report (Estes et al).[4] A unique feature of the syndrome in this family is that there was no abnormality of serum lipids and no deficiency of tocopherol. The proband's brother was reported as a new case of acanthocytosis with schizophrenia in 1963.[5] The neurological disorder is similar in the two siblings.

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From the Veterans Administration Outpatient Clinic, Boston (Drs. Levine and Looney), Boston University School of Medicine (Drs. Levine, Estes, and Looney), Hematology Research Laboratory, Boston University Medical Center Hospital (Dr. Estes), and Tufts University School of Medicine (Drs. Levine and Looney).

Presented in part at the American Academy of Neurology, Denver, 1964, and at the Second International Congress of Neurogenetics and Neuro-ophthalmology of the World Federation of Neurology, Montreal, 1967.

Reprint requests to 17 Court St, Boston, 02108 (Dr. Levine).

Report of Cases

The proband, III-7 (Fig 1) is a 50-year-old white married engineer whose birth and early development are described as normal. However, at approximately the age of 15, he had a brief illness characterized by jaundice, gastric pain, dark urine, and questionably light-colored stools. Similar episodes were noted on four other occasions within the next seven years and once while in the army. No anemia was reported during the periods of jaundice. No more than an equivocal history of steatorrhea could be elicited. His symptoms have consisted essentially of progressive weakness and cramps in his legs, involuntary movements of all limbs, grand mal seizures, and failing memory and efficiency. This resulted in his premature retirement.

The patient entered the army in 1943 at the age of 27. During basic training he experienced, for the first time, slight weakness in his legs. For about a year there was some progression of this weakness, and he developed an irregular gait and involuntary "jerky" movements of his limbs.

Following return to civilian life, there was gradual increase in weakness, choreiform movements, incoordination, disturbance of gait, and difficulty in articulation. In 1956 he experienced a grand mal seizure for the first time and was admitted to the hospital. No additional neurological abnormalities were disclosed during this hospitalization nor were any abnormalities of the blood revealed. Seizures have been fairly well controlled with diphenylhydantoin and phenobarbital. In the past ten years his chorea has increased considerably but with less progression of his neuromuscular disorders. He has not had visual disturbances other than minor refractive errors which have been corrected with eyeglasses. Dementia, highlighted by intellectual impairment, paranoid ideation, and negativism, has advanced rapidly in the past five years resulting in medical retirement from his job in January 1967. He has usually eaten a well balanced diet, without apparent excesses or restrictions such as fat or gluten.

General Physical Examination.—A somewhat thin man of stated age had blood pressure of 130/80; his heart, lungs, and abdomen were normal. Mentally, the patient was alert and cooperative but somewhat preoccupied and anxious. He was correctly oriented in all spheres. He denied hallucinations, illusions or delusions, although he expressed subtle ideas of reference and definite ideas of persecution. Insight was poor and judgement was shallow. He was very forgetful and kept notes of matters he wished to discuss with the examiner.

Neurological Examination.—Corrected visual acuity in the right eye of 20/25 and in the left eye of 20/20 was noted. There was no evidence of inflammation, palsy, or nystagmus. The right palpebral fissure was 1 mm larger, and the right eyeball protruded ½ mm more than that of the left eye. Both of these were within normal limits of variation between the eyes. The pupils were round, equal, and reactive. The lenses in each eye as seen with the slit lamp exhibited multiple tiny discrete white opacities in the anterior and posterior cortex. The ocular fundi revealed no edema, hemorrhage, atrophy, or unusual pigmentation. Esophoria of two prism diopters was elicited with the Maddox red glass for far and near (normal). Fair convergence was present. Good depth perception was demonstrated in the cardinal position of gaze. The central and peripheral visual fields were within normal limits. Tonometry (Schiøtz) disclosed a pressure of 17.3 mm in each eye (normal). Despite the patient's complaint of intermittent diplopia, no true palsy of the muscles could be demonstrated, and it was probably attributable to fatigue or emotional tension or both. Corneal sensitivity and reflexes were normal and equal.

There was no facial weakness or asymmetry; however, there were frequent facial grimaces and occasional chomping movements. The uvula moved in midline; there were no swallowing difficulties. The tongue protruded in the midline but was interrupted by side to side and seem to be any loss in overall intellectual or memory function. In 1966 a Wechsler Bellevue Intelligence Scale revealed a verbal IQ of 115, his involuntary movements prevented further testing.

Several members of the family have acanthocytosis and neuromuscular weakness somewhat similar to that of the proband (Fig 1). The proband is married and has two children, a son and a daughter. Although both children are described as well by the parents, the daughter has both hematological and neurological disorders. His brother's behavior and mental status are similar to those described in the proband.[5]

In September 1958 two sisters of our patient were found to have acanthocytes in peripheral blood, as noted by M. Yettra, MD (written communication, July 1959). This was discovered when one of the sisters having suspected anemia for many years, went to her physician for a periodic checkup. At this time it was reported that neither sister had any neurological disability, although evidence of neurological deficit in one of them was found two years later by one of us (I.M.L.). Soon after the discovery of acanthocytes in the blood smears of these two sisters, similar cells were found in the peripheral blood smear of our proband. These events initiated this study.

This family has been unusually cooperative in constructing the pedigree seen in Fig 1, as well as in clinical and laboratory participation. It soon became evident that the disorder involved the maternal side of the family. Blood smears of seven paternal relatives in two generations were examined and were found to be normal. The entire family is distributed over many states as well as outside of the continental United States so that it has been impossible to examine most of the family members living beyond the New England area.

On the basis of available documented data, it has been shown that two unrelated people of English descent married in 1643, but in their progeny three generations hence there was marriage of second cousins in 1754, the only available evidence of consanguinity. The maternal relatives investigated extended through four generations and totaled 32 persons, 16 males and 16 females.

The youngest person with neurological abnormality was a 2-year-old girl, while the oldest was a 78-year-old woman. The youngest person in whose peripheral blood smear acan-

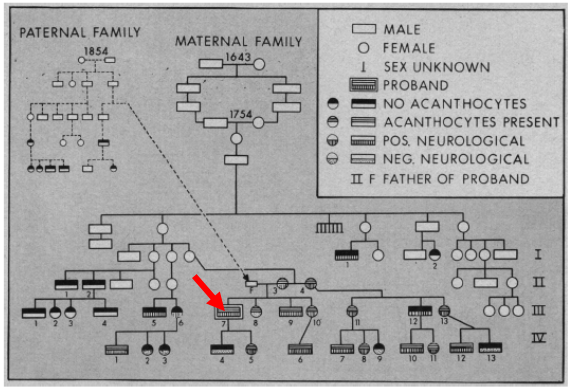


Fig 1.—Pedigree of family with hereditary neurological disorder and acanthocytosis.

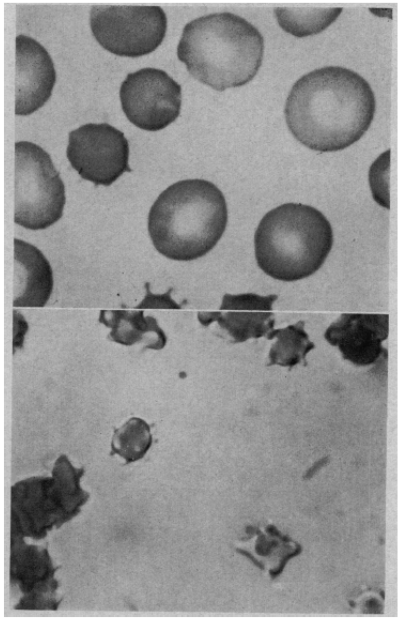


Fig 2.—Top, Peripheral blood smear of proband, patient III-7, showing spiny acanthocytes (Wright's stain, × 1,280). Bottom, 2% plasma suspension of proband's RBC (unstained, × 1,000).

Arch Neurol—Vol 19, Oct 1968
Arch Neurol—Vol 19, Oct 1968

Index patient

Levine et al. 1968, follow-up reports and NIH files

By age 25 years dragging his right leg. Leg weakness was progressive; subsequently developed leg cramps, limb chorea, and a gait disturbance.

At age 40 first generalized seizures and paranoid ideation, age 47: generalized areflexia, leg muscle atrophy/weakness and distal hypalgesia/pallhypesthesia.

Age 50: gait *"lurching in character with long strides and somewhat ataxic because of quick involuntary knee buckling movements."* Difficulty with serial subtractions. Generalized chorea, involuntary tongue movements at rest and dysarthria. *"Frequent facial grimaces and occasional chomping movements"* but no dysphagia. Tonic extension of great toes.

CK elevated. EMG: lower motor neuron. Quadriceps Bx: neuropathy and/or myopathy.

Pneumencephalography: moderately dilated ventricles.

Advancing *"intellectual impairment, paranoid ideation and negativism"*, died at age 54.

Critchley et al. 1968

Acanthocytosis and Neurological Disorder Without Betalipoproteinemia

E. M. R. Critchley, BM, MRCP; David B. Clark, MD; and Abraham Wikler, MD, Lexington, Ky

IN THE Bassen-Kornzweig syndrome,[1-6] thorny malformation of the erythrocytes (acanthocytes), a disease which begins in childhood, is associated with progressive ataxia; atypical retinitis pigmentosa; muscle wasting; steatorrhea, which may appear only in early life; and biochemical abnormalities. The serum levels for cholesterol, carotenoids, vitamin A, and phospholipids are invariably depressed, and the β-lipoprotein moiety is absent. This syndrome appears to be the expression of an autosomal recessive gene.

The family described in this paper is not the first in which acanthocytosis in an adult has been reported in conjunction with neurological disease, but the neurological manifestations are dissimilar to those of the Bassen-Kornzweig syndrome, and the biochemical abnormalities of that syndrome are not present. Kuo and Bassett in 1962[7] reported steatorrhea, acanthocytosis, and neuropathy in a man aged 41, but the nature of the neuropathy was not commented upon. Kahan et al, 1963,[8,9] found "acquired" acanthocytosis in a patient with Eales' disease and also reported two families in which hereditary vitreo-retinal degeneration (degeneratio hyaloideoretinalis) was associated with acanthocytosis. It is still not certain[10] whether the cells described in Kahan's patients were acanthocytes or crenated erythrocytes. More recently, Lewis et al[11] and Mars et al[12] from Cleveland have reported the biochemical abnormalities and the neurological findings in a 38-year-old patient with a pattern of disease quite dissimilar to that of the present family. The salient clinical features found in their patient were fat intolerance, impaired sphincter control, cerebellar incoordination, hyperactive reflexes, and hypobetalipoproteinemia.

Submitted for publication June 10, 1967; accepted June 24.

From Department of Neurology, University of Kentucky Medical Center, Lexington.
Reprint requests to Department of Neurology, University of Kentucky Medical Center, 800 Rose St, Lexington 40506 (Dr. Critchley).

Report of Cases

Neurologically affected members of this family lie within two generations. The proband (I, 10), a 29-year-old white man from eastern Kentucky who belongs to the first generation, was seen some 2½ years ago and exhibited at that time involuntary movements and a grossly swollen, raw, bitten tongue (Fig 1). He had had 15 to 20 similar episodes of tongue, lip, and cheek biting, which often occurred at night. The episodes had begun six year earlier on a background of increasing general weakness, nervousness, "fits and jerks," and had increased in frequency and severity. The involuntary movements included finger-snapping, grimacing, dystonic and choreiform movements, hyperextension of the trunk, sucking noises, plosive sounds, and drooling. Coprolalia, seen in the Gilles de la Tourette syndrome, was not evident. There had been times when he could not speak plainly; "the inside of his mouth would draw", he would "snap at his lips, and his stomach would stick." When he ate, his tongue would involuntarily push his food out onto his plate. Since 1962 he had preferred to retire to a separate room to eat his food.

He was alert, well-oriented, had no gross memory defects or psychotic behavior, and was disturbed by his own repulsive appearance. He slurred and stuttered a little when talking and had occasional inappropriate laughter. Despite the frequent involuntary movements, there was no ataxia of gait, and finger-nose, finger-finger, and heel-shin coordination tests were intact. He had generalized hypotonia, flexor plantar responses, and loss of deep tendon reflexes.

His symptoms conformed, for the most part, to the tentative diagnosis of Huntington's chorea. His full-scale intelligence quotient was 72 (Weckaler Adult Intelligence Scale (WAIS), verbal 81, and performance 61. The electro-

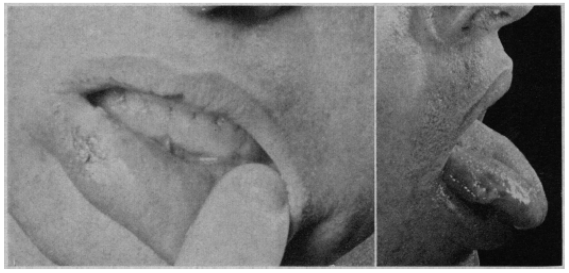
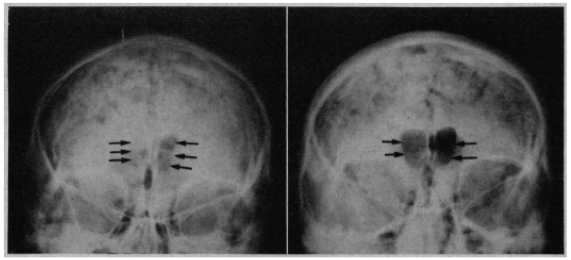


Fig 1.—Lip and cheek of proband (I,10) when first admitted.

Fig 2.—Pneumoencephalographs to show increase of air over cortex and lessening of caudate bulges into lateral ventricles (left, December 1964; right, June 1966).



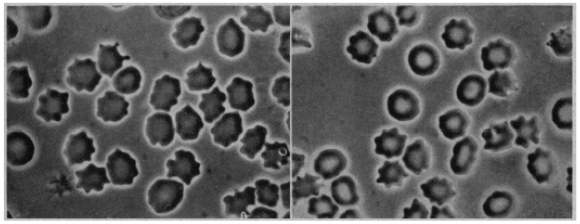


Fig 3.—Peripheral blood from proband with significant acanthocytosis. Wet preparation, phase contrast microscopy.

encephalogram contained a slight excess of bioccipital theta activity. Cerebrospinal fluid, muscle and nerve biopsy, nerve conduction velocities, electrocardiogram, and skull x-ray film were normal, but comparison of serial pneumoencephalograms taken 18 months apart showed increased air over the cortex and lessening of the caudate bulges into the lateral ventricles (Fig 2).

Hematologic data (Table 1), total fecal fat, cholesterol, tocopherol, triglycerides, and fractionated lipoproteins were all within normal limits. However, 30% to 40% of the red blood cells (RBC) seen in wet preparations examined by phase contrast and in dry films (Wright's stain), were acanthocytes (Fig 3). The slightly raised reticulocyte and bilirubin levels and the depression of haptoglobins were suggestive of mild hemolysis.

The main findings were involuntary tic-like and choreiform movements, areflexia, dilatation of the lateral ventricles, and acanthocytosis in the presence of normal serum lipids. His involuntary movements failed to respond to diphenylhydantoin sodium, phenobarbital, diazepam and hydroxyzine hydrochloride. Trihexyphenidyl hydrochloride (Artane) had a minimally beneficial effect, and, more recently, haloperidol has been used with apparently favorable results—though whether or not the improvement observed is due to this drug is uncertain since the reduction in frequency of tics continued for about two months after its cessation.

Fig 4.—Family Tree I: Immediate family.

Generation I

Immediate Family.—The proband was the youngest of ten children. When his mother died of uterine carcinoma at the age of 43 his father remarried and had five more children. Neither parent nor siblings were known to have had any neurological disease, but three of the patient's full siblings had had "spells," had become psychotic, and had died in mental institutions. Another sibling, who was believed to have been unaffected, was murdered when aged 38. Two siblings, aged 49 and 39, have acanthocytes but show no evidence of neurological disease (Fig 4).

The first sibling affected (I, 2) died at 31 years of age after an illness beginning with seizures when aged 25. Although she never actually lost consciousness, she bit her tongue and cheek, had involuntary limb movements, dropped things, and became forgetful. In the last two years of her life, she became emaciated and had violent shaking of her hands.

The second (I, 4) died at 26 years of age after an illness of two years' duration. His tongue began rejecting food, and he retreated into another room to eat. He had "passing-out spells" during which he would tear or pull on things. He did not lose weight or have violent hand movements.

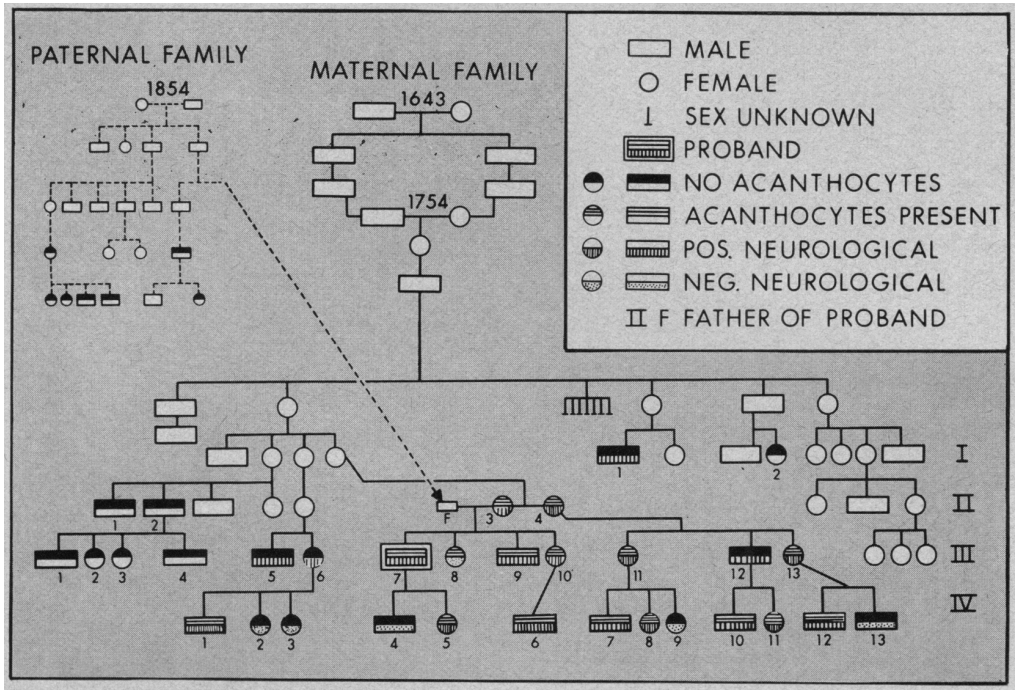
The third (I, 5) also died at 26 years of age. She bit her tongue, lips, and cheeks, and had involuntary limb movements, weight loss, and

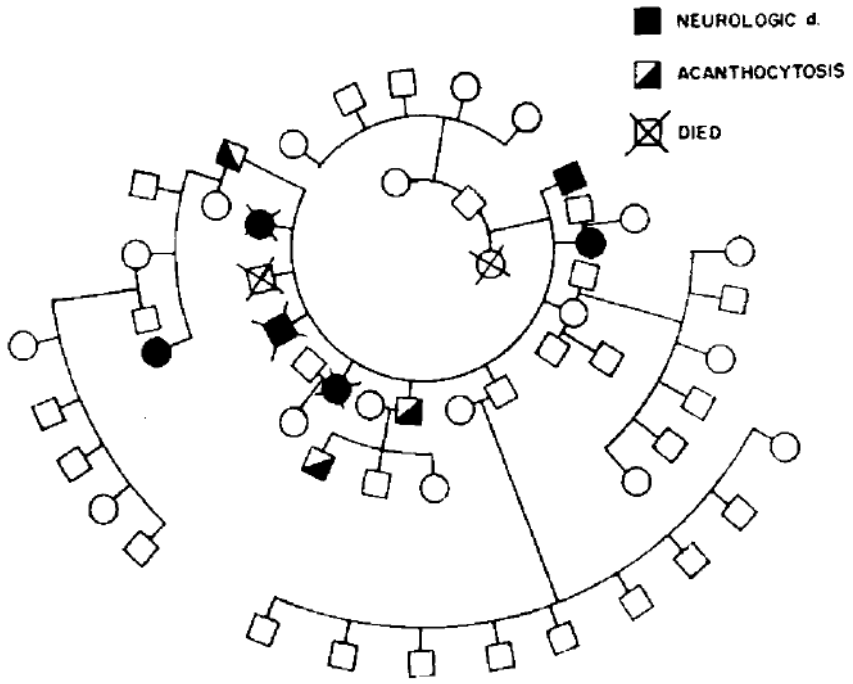
Index patient „Terry“

Critchley et al. 1968

“When first seen at the age of 26, he exhibited involuntary movements and had a grossly swollen, raw, bitten tongue. .. The involuntary movements included finger-snapping, grimacing, dystonic and choreiform movements, hyperextension of the trunk, twisting movements of his shoulders, sucking noises, plosive sounds and drooling. .. When he ate, his tongue would involuntarily push food out on to his plate.”

Levine families Critchley





Acanthrocytosis: defined in Bassen-Kornzweig cases

BLOOD *The Journal of Hematology*
JUNE, 1952 VOL. VII, NO. 6

Acanthrocytosis

A Genetic Erythrocytic Malformation

By Karl Singer, M.D., Ben Fisher, M.D. and Meyer A. Perlstein, M.D.

In 1950 Bassen and Kornzweig[1] reported observations on an 18 year old girl who, after having been afflicted with celiac disease in early childhood, exhibited (1) atypical retinitis pigmentosa, (2) diffuse involvement of the nervous system (particularly the spino-cerebellar tracts) and (3) a hitherto undescribed malformation of the circulating erythrocytes. The latter showed an unusual degree of "crenation" characterized by protoplasmic projections of varying sizes and shapes, which gave the cells a bizarre appearance simulating small crabs, beetles or stars. In the film, many of these erythrocytes were small and deeply stained, thus resembling spherocytes with buds or pseudopods. The hypotonic fragility was slightly decreased. There was only a mild anemia (Hgb 11.3 Gm.; RBC 3.9 M.). No data were reported to indicate whether a hemolytic process existed. A younger brother of the patient had almost identical changes of the eye grounds and red cells, but no neuropathy. The parents were first cousins.

In the present communication, observations on a 13½ year old boy are reported. He shows an analogous malformation of his red cells associated with a similar diffuse, progressive neurologic disease. However, retinal changes are *not* apparent. The patient also had suffered from a celiac syndrome in his early years of life. His parents are second cousins.

Since the most conspicuous feature of these abnormal erythrocytes is their distorted "thorny" appearance in wet preparations and in the film, we have called them *acanthrocytes* (*akantha*, thorn in Greek). The occurrence of these misshapen red cells together with diffuse progressive neuropathy, on the basis of consanguinity of the parents, is unlikely to be merely coincidental and may be characteristic of a new hereditary syndrome.

Report of Case

History

The patient is a 13½ year old Jewish boy, whose father and mother are second cousins. His parents and two sisters, aged 17 and 6, are living and well. The child was apparently

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In view of these findings, the patient appeared to have a progressive neuropathy with involvement of the cerebellum and/or its tracts, the basal nuclei, and the dorsal columns.

Laboratory Examinations

(1) The electroencephalogram and electrocardiogram were normal, as were X-rays of the chest and skeleton. (2) Urine: albumin and sugar were absent. Urobilinogen was not increased. A test for phenylpyruvic acid was negative. (3) The feces were formed, of firm consistency and contained no unusual amounts of fat and no occult blood. The serum proteins were 7.0 Gm. per cent with 4.6 Gm. albumin and 2.4 Gm. globulin. The bromsulfalein, thymol turbidity and intravenous glucose tolerance tests gave normal results. Serum calcium, phosphorus and bilirubin were within normal limits.

(4) Blood: Hgb. 11.7 Gm.; RBC 3.75 M. Reticulocytes 0.5 per cent, hematocrit (Wintrobe) 37 per cent, MCV: 38 cu. μ, MCHgb 31.2 $\mu\mu$, MCHgbC 31.6 per cent; WBC 6100/cu.

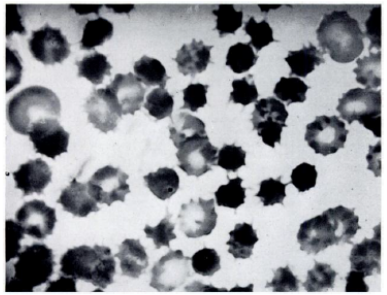


Fig. 1.—Acanthrocytes in the blood film.

mm. with a normal differential count: neutrophils segmented 50 per cent, nonsegmented 3 per cent, lymphocytes 37 per cent, monocytes 10 per cent. Platelet count (method of Dameshek[3]) 529,200/cu. mm. A great number of the red cells in the counting chamber as well as in the film, showed a peculiar "crenated" appearance. Many of these abnormally shaped erythrocytes were relatively small and deeply stained and exhibited several irregularly spaced protuberances, thus resembling crenated spherocytes (fig. 1). These "acanthrocytes," as we suggest they be called, did not form rouleaux in the wet preparation. An aspiration from the sternum revealed a cellular marrow of the following composition (1,000 nucleated cells counted): myeloblasts 0.6 per cent, promyelocytes 1.2 per cent; neutrophils: myelocytes 2 per cent, metamyelocytes 10.1 per cent, nonsegmented granulocytes 11.7 per cent, segmented 8.9 per cent; eosinophils: myelocytes 0.8 per cent, metamyelocytes 0.9 per cent, nonsegmented granulocytes 0.7 per cent, segmented granulocytes 0.9 per cent; basophilic granulocytes 0.1 per cent. Red cell series: pronormoblasts 2.4 per cent, basophilic normoblasts 6.9 per cent, polychromatic normoblasts 9.6 per cent, orthochromatic normoblasts 11.4 per cent, normoblasts in mitosis 0.4 per cent; reticulum cells 1.4 per cent; lymphocytes 30 per cent. The nucleated hemoglobinized red cells did not show any abnormality in shape. The erythrocytic:granulocytic ratio was 1:1.2, suggesting a moderate erythrocytic hyperplasia. Megakaryocytes were present in normal numbers.

ance of the abnormal red cells definitely antedated the clinical onset of the neuropathy. Whether the erythrocyte malformation was already present at birth or evolved later in life cannot be stated.

Retinitis pigmentosa which was present in Bassen and Kornzweig's case is a typical example of an abiotrophic disorder.[40] The concept of abiotrophy implies an hereditary disease which may remain latent for many years and develops in tissues with apparently normal functions during this latent period.[40] Similarly, some neuropathies (Friedreich's ataxia, Marie's ataxia, other hereditary ataxias, Huntington's chorea, etc.) also belong to the category of abiotrophic diseases. The literature contains several pedigrees of families showing simultaneous occurrence of retinitis pigmentosa and hereditary ataxia.[41–44] Since the presenting

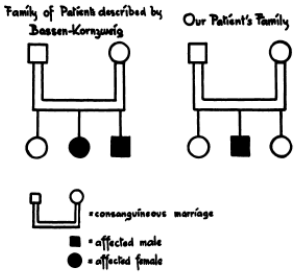


Fig. 5.—Pedigrees of families showing acanthrocytosis.

condition in both patients with acanthrocytosis was ataxia, and since acanthrocytosis may easily be overlooked, it is possible that this syndrome may not be too uncommon. Whether this is so can only be elucidated by a systematic survey of numerous patients afflicted with evidence of abiotrophic neuropathy. Such a project has been started in our clinic. At this moment, the available data are insufficient to permit consideration of possible linkage of pathologic genes for the various abnormalities observed in the patients showing acanthrocytosis.

3. *Clinical Aspects*

A very puzzling feature common to both families with acanthrocytosis is the reported "celiac syndrome." It started early in life, causing severe anemia and malodorous, fatty stools, and disappeared after a few years on standard dietary, vitamin and folic acid therapy. Unfortunately, no adequate data are at hand for establishing the exact nature of these intestinal disturbances, which preceded the neuropathy. The problem arises whether the nervous disease appearing later

Bassen-Kornzweig: Abetalipoproteinemia!

Schwartz et al. (1961). **Bassen-Kornzweig syndrome**. Neuromuscular disorder resembling Friedreich's ataxia associated with retinitis pigmentosa, acanthocytosis, steatorrhea, and an **abnormality of lipid metabolism**. Trans Am Neurol Assoc 86, 49–53

Salt et al. (1960). On having no beta-lipoprotein. A syndrome comprising **a-beta-lipoproteinaemia**, acanthocytosis, and steatorrhoea. Lancet 276, 325–329

What to call a condition where serum lipids are normal but acanthocytosis are seen?

Adrian Danek - danek@lmu.de

What to call a condition where serum lipids are normal but acanthocytosis are seen?

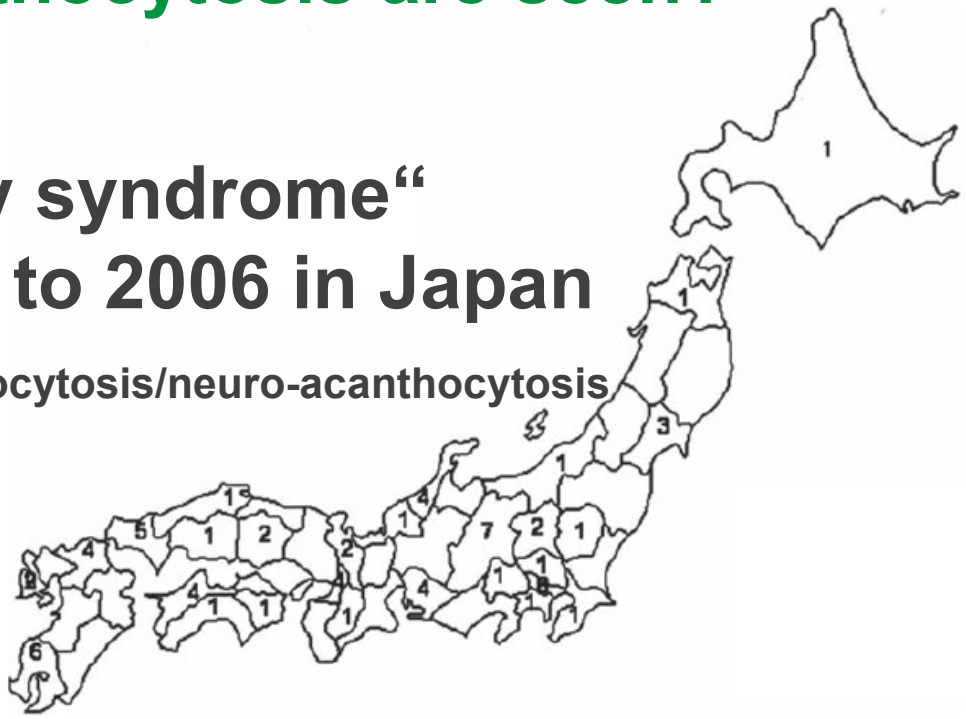
Acanthocytosis and Neurological Disorder
Without Betalipoproteinemia

E. M. R. Critchley, BM, MRCP;
David B. Clark, MD; and
Abraham Wikler, MD, Lexington, Ky

What to call a condition where serum lipids are normal but acanthocytosis are seen?

-> „Levine-Critchley syndrome“
71 cases from 1974 to 2006 in Japan

also known as chorea-acanthocytosis/neuro-acanthocytosis



From Levine-Critchley syndrome to

Neuroacanthocytosis: Hardie et al. 1991

NEUROACANTHOCYTOSIS

A CLINICAL, HAEMATOLOGICAL AND PATHOLOGICAL STUDY OF 19 CASES

by R. J. HARDIE,[1] H. W. H. PULLON,[3]* A. E. HARDING,[1] J. S. OWEN,[5] M. PIRES,[2] G. L. DANIELS,[4] Y. IMAI,[5] V. P. MISRA,[6] R. H. M. KING,[6] J. M. JACOBS,[2] P. TIPPETT,[4] L. W. DUCHEN,[2] P. K. THOMAS[1,6] *and* C. D. MARSDEN[1]

(From the [1]University Department of Clinical Neurology and [2]Department of Neuropathology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, the [3]Department of Haematological Medicine, King's College Hospital School of Medicine and Dentistry, the [4]Medical Research Council Blood Group Unit, University College London, and the [5]Departments of Academic Medicine and [6]Neurological Science, Royal Free Hospital School of Medicine, London, UK)

SUMMARY

Nineteen cases are described, including 12 cases from three different families and 7 nonfamilial cases, in which multisystem neurological disease was associated with acanthocytosis in peripheral blood and normal plasma lipoproteins. Mild acanthocytosis can easily be overlooked, and scanning electron microscopy may be helpful. Some neurologically asymptomatic relatives with significant acanthocytosis were identified during family screening, including some who were clinically affected.

The mean age of onset was 32 (range 8–62) yrs and the clinical course was usually progressive but there was marked phenotypic variation. Cognitive impairment, psychiatric features and organic personality change occurred in over half the cases, and more than one-third had seizures. Orofaciolingual involuntary movements and pseudobulbar disturbance commonly caused dysphagia and dysarthria that was sometimes severe, but biting of the lips or tongue was rarely seen. Chorea was seen in almost all symptomatic cases but dystonia, tics, involuntary vocalizations and akinetic-rigid features also occurred. Two cases had no movement disorder at all. Computerized tomography often demonstrated cerebral atrophy. Caudate atrophy was seen less commonly, and nonspecific focal and symmetric signal abnormalities from the caudate or lentiform nuclei were seen by magnetic resonance imaging in 3 out of 4 cases.

Depression or absence of tendon reflexes was noted in 13 cases and neurophysiological abnormalities often indicated an axonal neuropathy. Sural nerve biopsies from 3 cases showed evidence of a chronic axonal neuropathy with prominent regenerative activity, predominantly affecting the large diameter myelinated fibres. Serum creatine kinase activity was increased in 11 cases but without clinical evidence of a myopathy.

Postmortem neuropathological examination in 1 case revealed extensive neuronal loss and gliosis affecting the corpus striatum, pallidum, and the substantia nigra, especially the pars reticulata. The cerebral cortex appeared spared and the spinal cord showed no evidence of anterior horn cell loss.

Two examples of the McLeod phenotype, an X-linked abnormality of expression of Kell blood group antigens, were identified in a single family and included 1 female. The genetics of neuroacanthocytosis are unclear and probably heterogeneous, but the available pedigree data and the association with the McLeod phenotype suggest that there may be a locus for this disorder on the short arm of the X chromosome.

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* Present address: Haematology Department, Palmerston North Hospital, Private Bag, Palmerston North, New Zealand.

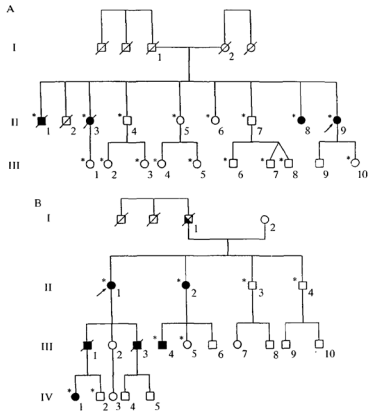


FIG. 1. Pedigree of families H (A) and L (B). Arrow = index case, circle = female, square = male, filled symbols indicate neurological disease, * = examined by us, open symbols unaffected, half-filled = probably affected by history, open with * indicates neurologically normal on examination by us and no acanthocytes on blood film.

Methods

Haematology

Blood was collected into tubes containing ethylene-diamine-tetracetic acid (EDTA) and in addition, where possible, a blood film was made from fresh blood without EDTA contact. When this was not possible, blood films were made from EDTA-containing samples within 1 h of collection. Each sample was processed by a Coulter S-Plus JR or STKR and the blood count parameters obtained. The dried blood films were stained with May-Grunwald Giemsa stain at pH 6.8 and subsequently examined by light microscopy at ×1000 magnification under oil immersion. Care was taken to examine them at a point where the film was only one cell thick and with minimal space between the cells. In each case 500 cells were counted and the proportions of acanthocytes and echinocytes estimated.

For the purposes of this study an acanthocyte was defined as a dense, slightly contracted red cell which had a number of irregularly spaced thorny surface projections, often with terminal bulbs (Brecher and Bessis, 1972). Echinocytes also have an abnormal cell surface, but with more abundant and evenly distributed surface projections that have a much broader base in relation to their length. We regarded an acanthocyte count of >3% as significant.

TABLE I. CLINICAL FEATURES OF AFFECTED CASES

Case	Sex	Age (yrs) of onset	Age (yrs) at last examination (or death*)	Dementia	Seizures	Psychiatric features	Orofacial dyskinesia	Dysphagia	Dysarthria	Movement disorder	Tendon reflexes
Family H											
1	M	37	61*	+	+	+	O	+	+	P	O
2	F	39	61*	+	O	+	+	+	+V	CP	R
3	F	40	49	+	O	O	O	+	+V	CDPT	R
4	F	44	47	+	O	+	O	O	+V	CPT	O
Family L											
5	F	51	57	+	+	+	+	O	+	CT	O
6	F	–	56	O	O	O	O	O	O	C	+
7	M	24	31*	O	+	+	O	O	O	C	O
8	M	22	31*	O	+	O	O	O	O	O	O
9	M	–	27	O	O	O	O	O	O	CT	O
10	F	–	14	O	O	O	O	O	O	O	R
Family B											
11	F	12	24	+	O	+	+B	O	+	DPT	+
12	M	8	23	+	O	+	O	O	+	D	+
Sporadic cases											
13	M	44	51	+	+	+	+	+	+V	CP	O
14	M	62	67	+	O	+	+	O	+V	CDPT	+
15	F	22	25	+	+	+	+B	+	+V	CDT	+
16	F	28	36	+	+	+	+B	+	+V	CDT	R
17	M	8	18	+	O	O	+	+	+	D	+
18	M	33	36	O	O	O	+	+	+V	D	R
19	M	39	44	O	+	O	+	+	+V	D	R

B = tongue/lip biting; V = vocalizations; C = chorea; D = dystonia; P = parkinsonism; T = tics; O = absent; R = reduced; + = present.

Webinar outline

- Mutual introduction
- Problems of „neuroacanthocytosis“/„Levine-Critchley syndrome“
- **XK and VPS13A diseases (novel nomenclature)**
  - **clinical features - genetic background - diagnosis**
- Bulk lipid transfer as recently discovered mechanism
- Reference material
- Questions and answers

Wimer et al. 1977

British Journal of Haematology, 1977, **36**, 219.

Haematological Changes Associated with the McLeod Phenotype of the Kell Blood Group System

B. M. Wimer, W. L. Marsh, H. F. Taswell and W. R. Galey

Lovelace-Bataan Medical Center, Albuquerque, New Mexico; New York Blood Center, New York, New York; Mayo Clinic, Rochester, Minnesota; and University of New Mexico School of Medicine, Albuquerque, New Mexico

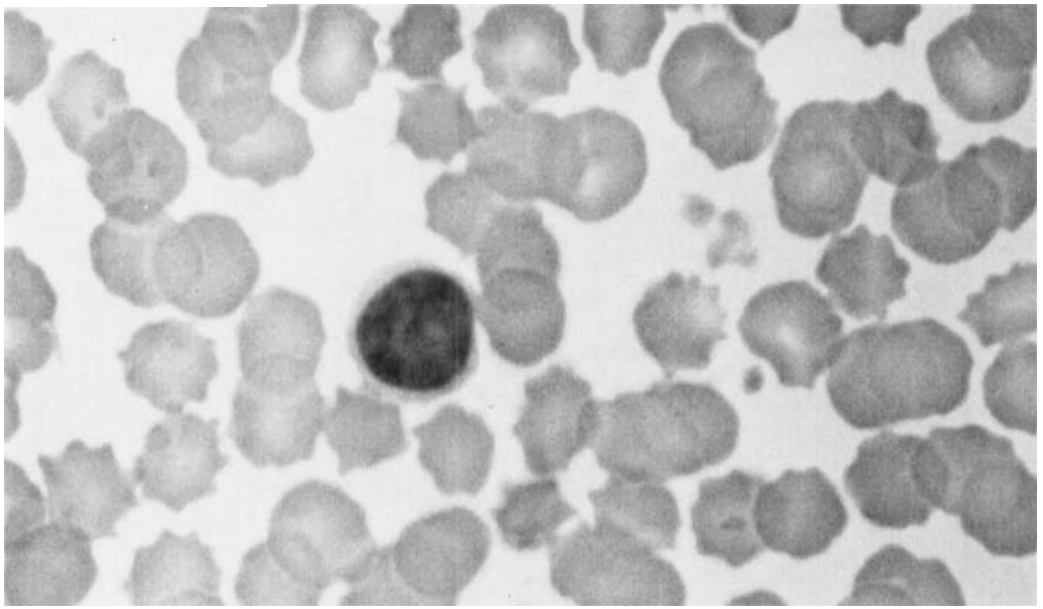
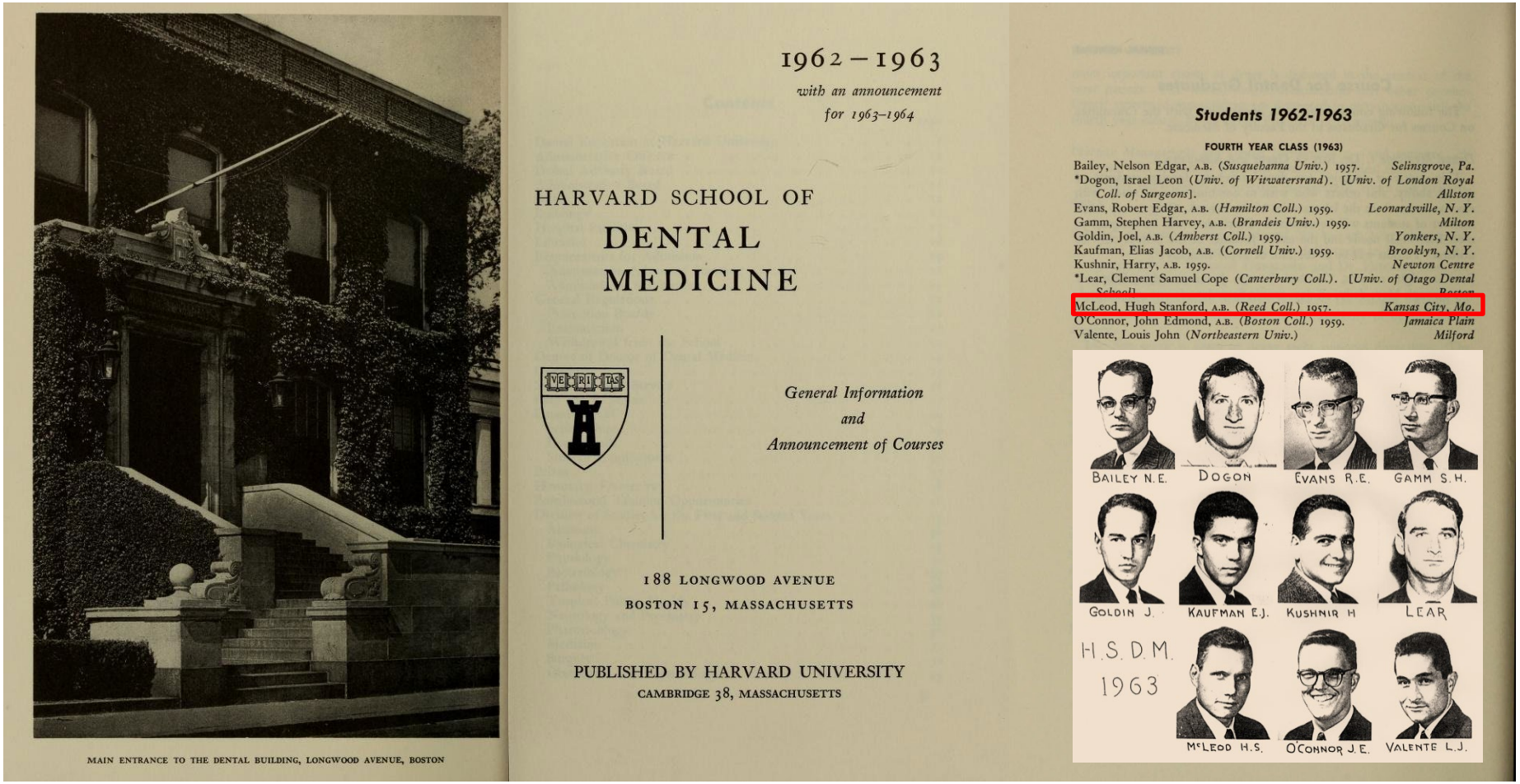


Fig 1. Peripheral blood film of McLeod phenotype red cells showing characteristic acanthocytosis.



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FOURTH YEAR CLASS (1963)

Bailey, Nelson Edgar, A.B. (*Susquehanna Univ.*) 1957. *Selinsgrove, Pa.*
*Dogon, Israel Leon (*Univ. of Witwatersrand*). [*Univ. of London Royal Coll. of Surgeons*]. *Allston*
Evans, Robert Edgar, A.B. (*Hamilton Coll.*) 1959. *Leonardsville, N. Y.*
Gamm, Stephen Harvey, A.B. (*Brandeis Univ.*) 1959. *Milton*
Goldin, Joel, A.B. (*Amherst Coll.*) 1959. *Yonkers, N. Y.*
Kaufman, Elias Jacob, A.B. (*Cornell Univ.*) 1959. *Brooklyn, N. Y.*
Kushnir, Harry, A.B. 1959. *Newton Centre*
*Lear, Clement Samuel Cope (*Canterbury Coll.*). [*Univ. of Otago Dental School*] *Boston*
McLeod, Hugh Stanford, A.B. (*Reed Coll.*) 1957. *Kansas City, Mo.*
O'Connor, John Edmond, A.B. (*Boston Coll.*) 1959. *Jamaica Plain*
Valente, Louis John (*Northeastern Univ.*) *Milford*

Hugh McLeod's blood cells Allen et al. 1961

Vox Sang. 6: 555–560 (1961)

A New Phenotype (McLeod) in the Kell Blood-group System*

FRED H. ALLEN, JR., SISSEL M. R. KRABBE and PATRICIA A. CORCORAN

The Blood Grouping Laboratory of Boston

Until 1957, there were two known antibodies in the Kell blood-group system, and three phenotypes. Three new antibodies were then found in rapid succession [1, 2, 5], and four new phenotypes [1, 2, 4]. It is the purpose of this paper to describe an eighth phenotype. The notation to be used has been presented in a separate communication [3] and is shown in Table I.

Mr. *Hugh McLeod*, possessor of the new phenotype, was encountered in testing a new class of medical students, who routinely are subgrouped as thoroughly as possible, in search of useful panel donors. He was originally thought to be of Peltz type [4], lacking all antigens of the Kell series, and his blood was distributed as such to other laboratories as a reference blood. Immediate responses from several laboratories, and our own subsequent investigations, proved that his cells gave weak reactions with both anti-Kp^b and with anti-k and that these reactions were not non-specific, or due to contaminating antibodies in the reagents.

The mode of inheritance of the new phenotype is not revealed by tests of the family. Both parents are type K: –1, 2, –3, 4, 5 (phenotype 2 in Table I). The parents are not related.

Serological Data

(1) *Direct tests of McLeod cells.* Tests with anti-K1 (Kell), anti-K3 (Penney), and anti-K5 (Peltz) were consistently negative. These were confirmed by absorption tests. Tests with various anti-K4 (Rautenberg) serums consistently gave weak reactions. Direct tests with anti-K2 (Cellano) serums gave variable reactions; some were weak, others were negative. The red cells of the parents gave negative

TABLE I

Notation for the Kell Blood-group System

	New notation	*Old notation*
Antibodies:		
	Anti-K1 (Kell)	Anti-K
	Anti-K2 (Cellano)	Anti-k
	Anti-K3 (Penney)	Anti-Kp^a
	Anti-K4 (Rautenberg)	Anti-Kp^b
	Anti-K5 (Peltz)	Anti-Ku
Phenotypes:*		
1.	K:1, 2,–3, 4, 5 (Kell+)	K+k+Kp(a–b+)Ku+
2.	K:–1,2,–3,4,5 (Kell–)	K–k+Kp(a–b+)Ku+
3.	K:1,–2,–3,4,5 (Cellano–)	K+k–Kp(a–b+)Ku+
4.	K:–1,2,3,4,5 (Penney+)	K–k+Kp(a+b+)Ku+
5.	K:1,w2,3,4,5 (Kell+, Penney+)	K+k+(weak), Kp(a+b+)Ku+
6.	K:–1,w2,3,–4,5 (Rautenberg–)	K–k+(weak),Kp(a+b–)Ku+
7.	K:–1,–2,–3,–4,–5 (Peltz type)	K–k–Kp(a–b–)Ku–
8.	K:–1,w2,–3,w4,–5 (McLeod type)	K–k+(weak),Kp(a–b+weak)Ku–
Allelic genes:		
1.	$K^{1,-2,-3,4,5}$	K^b, KKp^b
2.	$K^{-1,2,-3,4,5}$	k^b, kKp^b
3.	$K^{-1,w2,3,-4,5}$	k^a, kKp^a
4.	k	K°

* Numbers used in phenotype names refer to the various antibodies used. Use of the number unmodified indicates a positive reaction. Use of minus sign before number indicates no reaction. Use of "w" before the number indicates weak or variant reaction. In recording results of tests with a single antibody, such as anti-K2, one may write K2+ or K2–, or, alternatively, K:2 or K:–2.

TABLE II

Reactions of McLeod Family with Anti-K2 and Anti-K4

Serum	Test Cells	Dilution of serum, and results* 1	2	4	8	16	32
Anti-K2 (Cellano)-(Nir.)	H. M.	0	1	2	1	0	0
»	father	4	4	4	4	3	1
»	mother	4	4	4	3	3	1
Anti-K4 (Rautenberg)-(Rau.)	H. M.	1	1	3	3	2	1
»	father	4	4	4	4	4	4
»	mother	4	4	4	4	4	4

reactions with anti-K1 (Kell) and anti-K3 (Penney), and normally strong reactions with anti-K2 (Cellano), anti-K4 (Rautenberg) and anti-K5 (Peltz). Results of titrations of anti-K2 and anti-K4 serums are shown in Table II. Anti-K2 serum (Nir.) was one that had been classified as a weak reactor with H. M. red cells. The prozones were confirmed by repeated tests.

(2) *Absorptions.* With every example of anti-K4 (Rautenberg), regardless of the strength of the direct reaction, all antibody was removed by the cells of Hugh McLeod, almost as rapidly as by absorption with ordinary K4+ red cells. Repeated absorptions of anti-K5 ("triple eluate" prepared from serum of Mrs. Peltz [5]) consistently failed to remove the antibody, confirming that H. M. is K5–. Absorptions with McLeod cells and anti-K1, anti-K2, and anti-K3 are shown in Table III. Preliminary work had shown that

TABLE III

Absorptions Done with Red Cells of McLeod on Selected Serums

Serum	Number of absorptions with McLeod red cells	Test Cells	Dilutions of serums before and after absorptions. Testing done by indirect Coombs method* 1	2	4	8	16	32	64	128
Anti-K1 (Kek.) (anti-Kell)	0	K:1,2,–3,4,5	4	4	4	4	4	4	3	2
	8**	»	4	4	4	4	4	4	3	1
	16	»	4	4	4	4	4	3	2	0
	24	»	4	4	4	4	4	3	3	±
Anti-K2 (Gig.) (anti-Cellano)	0	»	4	4	4	4	4	4	3	2
	8	»	4	4	4	3	3	1	0	0
	16	»	0	0	0	0	0	0	0	0
Anti-K2 (Mar.) (anti-Cellano)	0	»	4	4	4	3	3	1	0	0
	8	»	3	3	2	3	1	±	0	0
	16	»	1	1	1	1	±	0	0	0
	24	»	±	0	0	0	0	0	0	0
Anti–K3 (Mes.) (anti-Penney)	0	K:–1,2,3,4,5	4	4	3	2	0	0	0	0
	8	»	4	4	3	2	±	0	0	0
	16	»	4	4	2	1	0	0	0	0
	24	»	4	4	3	1	0	0	0	0

* All readings done "blind". 4 = ++++, 3 = +++, etc.

** 8 parts of packed red cells to 1 part of serum: all absorptions in this series done in this way. Packed red cells used for all absorptions were washed and centrifuged in small aliquots, then pooled and mixed:

MLS: Multi-system disease with CNS involvement

- Acanthocytosis
- Heart disease
- Chorea/Parkinsonism
- Cognitive impairment
- Epilepsy
- Psychopathology

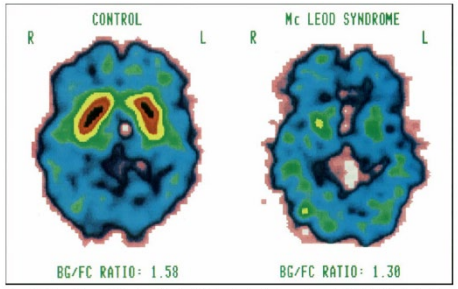


Figure 2. Pattern of accumulation of a radioactively labeled D_2-selective dopamine agonist (^{123}I-IBZM) in horizontal SPECT brain images of a normal control (left) and a patient with McLeod syndrome (right). Reduced striatal dopamine

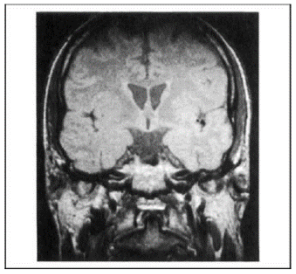


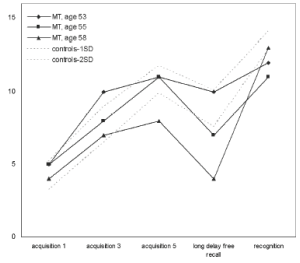
Figure 1. Proton-density-weighted MRI in a 52-year-old patient with chorea and the McLeod erythrocyte phenotype discloses slight atrophy of the caudate nucleus

Cerebral involvement in McLeod syndrome

A. Danek, MD; I. Uttner, MSc; T. Vogl, MD; K. Tatsch, MD; and T.N. Witt, MD

Article abstract—McLeod syndrome is an Xp21-linked Kell blood group variant due to lack of erythrocyte protein Kx with associated RBC membrane dysfunction such as acanthocytosis. A man with this syndrome developed chorea and slight neuropsychological impairment. He had caudate atrophy on cerebral imaging and reduced striatal dopamine D_2-receptor binding on single-photon emission computed tomography. Since Xp21 was partly deleted in the patient, the missing gene product (possibly Kx) may be essential for the integrity of the striatum.

NEUROLOGY 1994;44:117-120



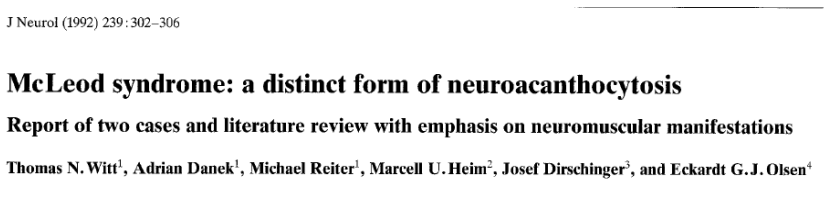
estimate: <300 cases world-wide

Brothers with heart disease & ↑ muscle CK

Case 1 at age 52

Case 2 at age 57

Case 1 at age 58

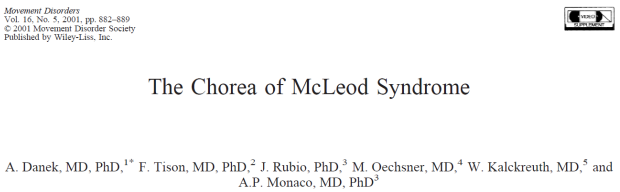


J Neurol (1992) 239 : 302–306

McLeod syndrome: a distinct form of neuroacanthocytosis

Report of two cases and literature review with emphasis on neuromuscular manifestations

Thomas N. Witt[1], Adrian Danek[1], Michael Reiter[1], Marcell U. Heim[2], Josef Dirschinger[3], and Eckardt G. J. Olsen[4]



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The Chorea of McLeod Syndrome

A. Danek, MD, PhD,[1*] F. Tison, MD, PhD,[2] J. Rubio, PhD,[3] M. Oechsner, MD,[4] W. Kalckreuth, MD,[5] and A.P. Monaco, MD, PhD[3]

McLeod gene XK (1994)

Cell, Vol. 77, 869–880, June 17, 1994, Copyright © 1994 by Cell Press

Isolation of the Gene for McLeod Syndrome That Encodes a Novel Membrane Transport Protein

Mengfatt Ho,* Jamel Chelly,* Nick Carter,† Adrian Danek,‡ Paul Crocker,* and Anthony P. Monaco*
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Institute of Molecular Medicine
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D-81366 München 70
Federal Republic of Germany

Summary

McLeod syndrome is an X-linked multisystem disorder characterized by abnormalities in the neuromuscular and hematopoietic systems. We have assembled a cosmid contig of 360 kb that encompasses the McLeod gene locus. A 50 kb deletion was detected by screening DNA from patients with radiolabeled whole cosmids, and two transcription units were identified within this deletion. The mRNA expression pattern of one of them, designated as *XK*, correlates closely to the McLeod phenotype. *XK* encodes a novel protein with structural characteristics of prokaryotic and eukaryotic membrane transport proteins. Nucleotide sequence analysis of *XK* from two unrelated McLeod patients has identified point mutations at conserved splice donor and acceptor sites. These findings provide direct evidence that *XK* is responsible for McLeod syndrome.

Introduction

Neurological impairment that occurs with erythrocyte acanthocytosis has been broadly classified under the term neuroacanthocytosis, comprising at least three neurological syndromes (Hardie, 1989). McLeod syndrome is a distinct condition defined on the basis of abnormal expression of the Kell blood group antigens. The neurological defects in this syndrome have a typically insidious onset in the fourth decade of life, presenting initially as areflexia and gradually progressing to dystonic and choreiform movements (Witt et al., 1992; Redman and Marsh, 1993). Neuroimaging findings of McLeod patients reveal a striking similarity with those of early Huntington's disease (HD), with caudate nucleus atrophy seen on a cranial computed tomographic scan and magnetic resonance imaging. In addition, neuropsychological assessment demonstrates cognitive deterioration with deficits in information processing, in attention and planning, and in encoding and retrieval processes (Danek et al., 1994). As in HD, there is decreased binding of striatal dopamine D2 receptors as assessed by single photon emission computed tomography with [^{123}I]iodobenzamide. This finding is indicative of dysfunction of cells in the striatum or reduction of their number. The biochemical basis underlying these neurological defects is currently unknown.

McLeod syndrome is also associated with a late-onset form of muscular dystrophy and cardiomyopathy, characterized by elevated levels of serum creatine kinase and carbonic anhydrase III (Marsh et al., 1981; Swash et al., 1983; Witt et al., 1992). Muscle biopsies of patients show features of active muscle fiber necrosis and regeneration with subsarcolemmal and sarcoplasmic calcium deposition in abnormal muscle fibers (Swash et al., 1983; Danek et al., 1990; Carter et al., 1990). Similar findings have been observed in muscle biopsies of Duchenne muscular dystrophy (DMD) patients (Bradley and Fulthorpe, 1978; Carpenter and Karpati, 1979), which suggest that membrane defects are involved in McLeod syndrome. Involvement of dystrophin in McLeod syndrome has been ruled out by immunological and DNA analysis (Carter et al., 1990; Danek et al., 1990)

The hematological abnormalities in McLeod syndrome are characterized by red blood cells with acanthocytic morphology, reduced in vivo survival, weakened Kell antigens, and the absence of an antigen, Kx (Wimer et al., 1977). The precise mechanism of acanthocytosis in McLeod red cells is unknown. Although grossly irregular in shape, there is no evidence of any abnormality or deficiency in membrane proteins or phospholipids (Galey et al., 1978; Kuypers et al., 1985). Absence of the Kx antigen is the most prominent biochemical defect in McLeod syndrome, and its absence is associated with a marked reduction of all Kell antigens (Marsh and Redman, 1987). Immunoprecipitation experiments using human alloimmune anti-Kx serum have established that Kx is a 37 kDa protein found on the surface of red blood cells (Redman et al., 1988), but its distribution in other tissues has not been determined. To date, Kx remains uncharacterized owing to the rarity of the human alloimmune anti-Kx, the inability to produce antibodies to Kx in animals, and the extremely small amounts of Kx present in red blood cells (Redman and Marsh, 1993).

Family studies of McLeod syndrome suggest there is no genetic heterogeneity, and the different cellular defects in McLeod syndrome are likely to be due to a single X-linked gene (Symmans et al., 1979; Swash et al., 1983). The locus for McLeod syndrome has been mapped, by deletion analysis, to a region between the gene loci for DMD and chronic granulomatous disease (CYBB) (Bertelson et al., 1988). A novel marker, *DXS709*, was recently isolated from cloning the breakpoint of a DMD patient with a 6 Mb deletion. Pulsed-field gel electrophoresis (PFGE) mapping using *DXS709* and *CYBB* as markers has further defined the gene locus to a region of less than 380 kb (Ho et al., 1991).

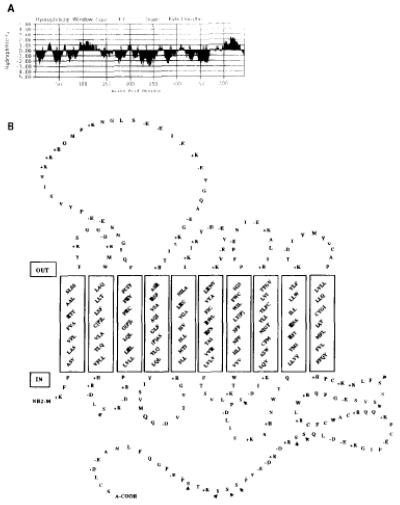


Figure 8. Inferred Structural Features and Proposed Model of the XK Encoded Protein

(A) Hydropathy profile of the XK-encoded protein according to the algorithm of Kyte and Doolittle, (1982) using a window of 11 amino acids. Negative values indicate hydrophobic residues. Putative transmembrane α helices are numbered from 1 to 10.

(B) Schematic representation of the XK-encoded protein, showing the proposed topology in the plasma membrane. The single letter amino acid code is used, and rectangles indicate potential membrane-spanning α helices. Within TM helices, negatively charged residues (aspartate and glutamate) and positively charged residues (arginine, lysine, and histidine) are outlined. Outside the TM segments, charged residues are denoted by their respective plus or minus signs. All the proposed extracellular loops (except loop 1) have net neutral charge, whereas all the cytoplasmic loops (except loop 2) and the amino and carboxyl termini have net positive charges. Proline residues located within TM domains are boxed, and putative phosphorylation sites for various serine protein kinases are indicated by an arrow if they are predicted to be cytoplasmic.

presence of a relatively large number of potential phosphorylation sites and a large extracellular hydrophilic loop linking TM segments 3 and 4. Remarkably, an identical topographical arrangement is predicted from the hydrophobicity plots of a glutamate transporter from rabbit and rat (Kanai and Hediger, 1992; Pines et al., 1992), human noradrenaline transporter (Pacholczyk et al., 1991), rat dopamine transporter (Shimada et al., 1991), rat brain γ-aminobutyric acid transporter (Guastella et al., 1990), and rat brain serotonin transporter (Blakely et al., 1991). These transporters belong to an expanding family of Na^+-/Cl^--dependent neurotransmitter transporters (Uhl, 1992; Uhl and Hartig, 1992; Amara, 1993). The protein encoded by *XK* bears the closest resemblance to the rabbit Na^+-dependent glutamate transporter in having the same number of TM segments, a large putative second extracellular loop, and multiple consensus phosphorylation site motifs. However, this topographical similarity is not complemented by substantial similarity of primary amino acid sequence, which suggests that the XK protein may define a novel family of transport proteins.

To investigate the substrate specificity of XK protein, fresh red blood cells from patient MT and two healthy individuals were assayed for the uptake of various substrates, with and without the relevant inhibitors, according to a previously described method (Kirk et al., 1994). Preliminary findings did not reveal significant differences between red blood cells from controls and from McLeod patient MT in the uptake of various radiolabeled L-amino acids tested (arginine, alanine, glutamine, glutamate, glycine, tryptophan, and valine). Nor were there any differences in the unidirectional influx of monovalent cations K^+ and choline, the uncharged nucleoside adenosine, monovalent anions L-lactate and Cl^-, and divalent anion, SO_4^{2-} based on radioisotope uptake measurements of $^{86}Rb^+$, [^{14}C]choline, [^{14}C]adenosine, L-[^{14}C]lactate, $^{36}Cl^-$, and $^{35}SO_4^{2-}$, respectively (K. Kirk and C. Ellory, unpublished data). To avoid difficulties in obtaining fresh red blood cells, future analysis to determine the substrate specificity of XK protein will be performed in a Xenopus oocyte expression system. A more diverse repertoire of substrates, such as neutral amino acids, oligopeptides, neuropeptides, and neurotransmitters, will be tested as candidates for transport by the XK protein.

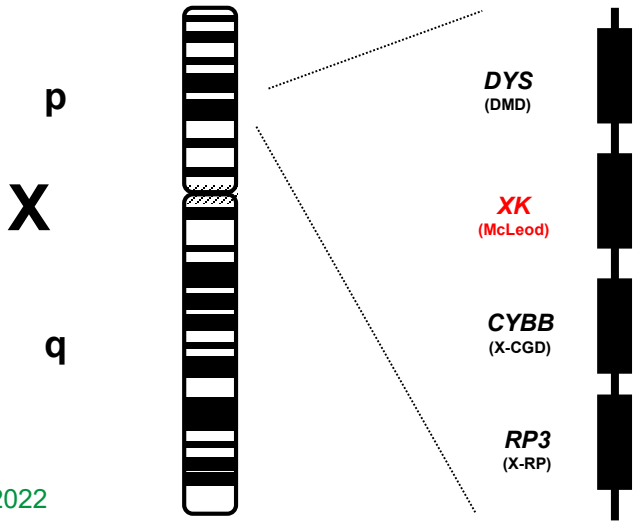
It is interesting to note that the tissue distribution and mRNA expression pattern of XK is almost identical to that of a recently isolated brain Na^+-dependent neutral amino acid transporter that has structural similarity to glutamate

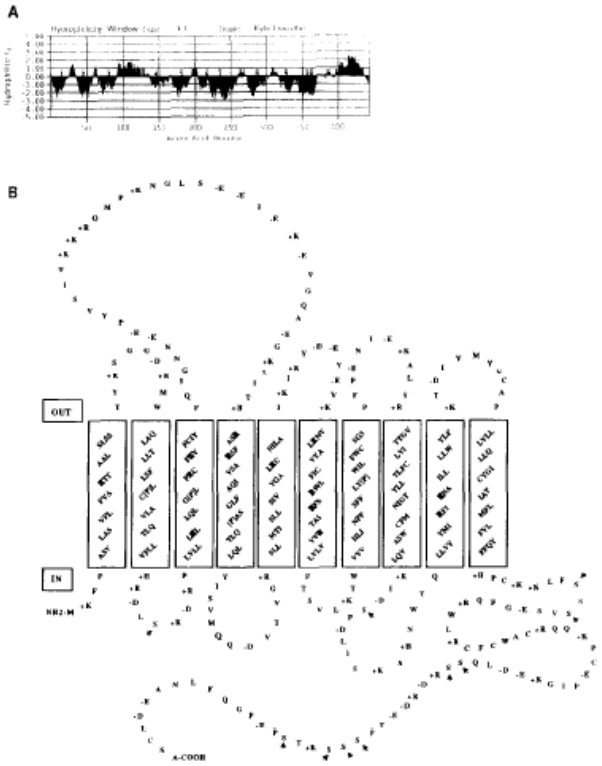
McLeod XK gene and protein (1994)

Cell, Vol. 77, 869–880, June 17, 1994, Copyright © 1994 by Cell Press

Isolation of the Gene for McLeod Syndrome That Encodes a Novel Membrane Transport Protein

Mengfatt Ho,* Jamel Chelly,* Nick Carter,†
Adrian Danek,‡ Paul Crocker,*
and Anthony P. Monaco*





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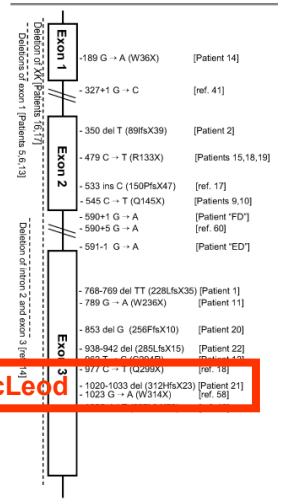

H. McLeod

Fig 2. Schematic representation of the XK gene with known mutations. The approximate position of all presently reported mutations in XK is indicated and, in parentheses, the resulting changes in the sequence of the XK protein (see also Table 2). Square brackets refer to patients in the present series or to reports from the literature.

In 9 patients the identified mutation is expected to cause the synthesis of a shortened, truncated form of XK. While the location of the in-frame stop codon in this situation can be predicted (see Table 2), the exact fate of the protein cannot be easily foreseen. However, it is likely that a truncated protein will lack critical posttranslational modifications and this will subsequently result in its degradation. Western blot analysis of tissues expressing the *XK* gene with the help of N-terminal directed antibodies would provide insight into the stability of these truncated proteins and immunohistochemical analyses using these molecular probes could be used to identify intracellular processing problems caused by the mutations. In addition to our own findings, five recently reported mutations share this mechanism of a frameshift in transcription with subsequent synthesis of a shorter than normal protein[13,14,18,58] (see Fig 2).

The only missense mutation found is a nonconservative cysteine to arginine change (Patient 12). Cysteine residues can be critical for forming intra- and intermolecular covalent linkages via disulfide bonds. The absence of this critical cysteine residue in XK could seriously disrupt the secondary structure of the nascent protein in the lumen of the endoplasmic reticulum, which in turn could lead to aberrant trafficking of the protein to the plasma membrane.[59] At present, only one other missense mutation is known, yet details have not been published.[20,38]

In Patients 3 and 4, we found mutations likely to affect the splicing of the *XK* mRNA. In each case, the spliceosome complex is likely to find another sequence in a different location that can act as a splice acceptor (Patient "ED") or splice donor (Patient "FD") in order to splice the message, albeit incorrectly. Aberrant splicing events could lead to deletions of coding sequence or inclusion of intron sequence in the mRNA. Both of these scenarios are likely to affect the function of the *XK* gene product. Because "ED" and "FD" were little affected,[9] a small amount of functional XK protein might still be synthesized and prevent full development of the disease. One further subject with this type of mutation, however, was associated with definite chorea,[41] whereas another was neurologically unaffected and did not even show CK elevation.[60] Detailed analyses of XK expression are needed to better understand these cases.

An intriguing question derives from the late development of most McLeod symptoms. Could XK, huntingtin, and chorein at least temporarily substitute for each other? In any case, the investigation of XK and its function can be expected to shed light on general mechanisms of basal ganglia disease. One clear aim, however, should be the development of causal therapy for the slow but relentlessly progressing neurodegeneration of McLeod syndrome.

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McLeod Neuroacanthocytosis: Genotype and Phenotype

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McLeod syndrome is caused by mutations of *XK*, an X-chromosomal gene of unknown function. Originally defined as a peculiar Kell blood group variant, the disease affects multiple organs, including the nervous system, but is certainly underdiagnosed. We analyzed the mutations and clinical findings of 22 affected men, aged 27 to 72 years. Fifteen different *XK* mutations were found, nine of which were novel, including the one of the eponymous case McLeod. Their common result is predicted absence or truncation of the XK protein. All patients showed elevated levels of muscle creatine phosphokinase, but clinical myopathy was less common. A peripheral neuropathy with areflexia was found in all but 2 patients. The central nervous system was affected in 15 patients, as obvious from the occurrence of seizures, cognitive impairment, psychopathology, and choreatic movements. Neuroimaging emphasized the particular involvement of the basal ganglia, which was also detected in 1 asymptomatic young patient. Most features develop with age, mainly after the fourth decade. The resemblance of McLeod syndrome with Huntington's disease and with autosomal recessive chorea-acanthocytosis suggests that the corresponding proteins—XK, huntingtin, and chorein—might belong to a common pathway, the dysfunction of which causes degeneration of the basal ganglia.

Ann Neurol 2001;50:755–764

Finding	Frequency (%)
Weak Kell erythrocyte antigens	100 (91–100)
Acanthocytosis	100 (91–100)
Elevation of serum creatine phosphokinase	100 (100)
Elevation of lactate dehydrogenase	91 (45–95)
Elevation of aspartate aminotransferase	33 (23–55)
Elevation of alanine aminotransferase	33 (23–55)
Elevation of γ-glutamyltransferase	33 (18–64)
Reduced haptoglobin	80 (18–95)
Splenomegaly	38 (23–64)
Hepatomegaly	42 (23–68)
Cardiac disease	65 (50–73)
Areflexia: ankles	90 (86–91)
Areflexia: arms	62 (59–64)
Muscle weakness	65 (59–68)
Muscle biopsy: myopathic	80 (36–91)
Muscle biopsy: neuropathic	64 (32–82)
Electromyography: myopathic	14 (9–45)
Electromyography: neuropathic	79 (50–86)
Reduced vibration sense in feet	40 (27–59)
Seizures	50 (27–73)
Psychopathology	83 (45–91)
Cognitive impairment	54 (32–73)
Limb chorea	94 (68–95)
Dystonia	38 (23–64)
Facial hyperkinesia	86 (55–91)
Involuntary vocalizations	58 (32–77)
Habitual tongue/lip biting	8 (5–45)
Dysarthria	77 (45–86)
Parkinsonian features	19 (14–41)

Neuroacanthocytosis: Hardie et al. 1991

Brain (1991), **114**, 13–49

NEUROACANTHOCYTOSIS

A CLINICAL, HAEMATOLOGICAL AND PATHOLOGICAL STUDY OF 19 CASES

by R. J. HARDIE,[1] H. W. H. PULLON,[3]* A. E. HARDING,[1] J. S. OWEN,[5] M. PIRES,[2] G. L. DANIELS,[4] Y. IMAI,[5] V. P. MISRA,[6] R. H. M. KING,[6] J. M. JACOBS,[2] P. TIPPETT,[4] L. W. DUCHEN,[2] P. K. THOMAS[1,6] *and* C. D. MARSDEN[1]

(From the [1]University Department of Clinical Neurology and [2]Department of Neuropathology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, the [3]Department of Haematological Medicine, King's College Hospital School of Medicine and Dentistry, the [4]Medical Research Council Blood Group Unit, University College London, and the [5]Departments of Academic Medicine and [6]Neurological Science, Royal Free Hospital School of Medicine, London, UK)

SUMMARY

Nineteen cases are described, including 12 cases from three different families and 7 nonfamilial cases, in which multisystem neurological disease was associated with acanthocytosis in peripheral blood and normal plasma lipoproteins. Mild acanthocytosis can easily be overlooked, and scanning electron microscopy may be helpful. Some neurologically asymptomatic relatives with significant acanthocytosis were identified during family screening, including some who were clinically affected.

The mean age of onset was 32 (range 8–62) yrs and the clinical course was usually progressive but there was marked phenotypic variation. Cognitive impairment, psychiatric features and organic personality change occurred in over half the cases, and more than one-third had seizures. Orofaciolingual involuntary movements and pseudobulbar disturbance commonly caused dysphagia and dysarthria that was sometimes severe, but biting of the lips or tongue was rarely seen. Chorea was seen in almost all symptomatic cases but dystonia, tics, involuntary vocalizations and akinetic-rigid features also occurred. Two cases had no movement disorder at all. Computerized tomography often demonstrated cerebral atrophy. Caudate atrophy was seen less commonly, and nonspecific focal and symmetric signal abnormalities from the caudate or lentiform nuclei were seen by magnetic resonance imaging in 3 out of 4 cases.

Depression or absence of tendon reflexes was noted in 13 cases and neurophysiological abnormalities often indicated an axonal neuropathy. Sural nerve biopsies from 3 cases showed evidence of a chronic axonal neuropathy with prominent regenerative activity, predominantly affecting the large diameter myelinated fibres. Serum creatine kinase activity was increased in 11 cases but without clinical evidence of a myopathy.

Postmortem neuropathological examination in 1 case revealed extensive neuronal loss and gliosis affecting the corpus striatum, pallidum, and the substantia nigra, especially the pars reticulata. The cerebral cortex appeared spared and the spinal cord showed no evidence of anterior horn cell loss.

Two examples of the McLeod phenotype, an X-linked abnormality of expression of Kell blood group antigens, were identified in a single family and included 1 female. The genetics of neuroacanthocytosis are unclear and probably heterogeneous, but the available pedigree data and the association with the McLeod phenotype suggest that there may be a locus for this disorder on the short arm of the X chromosome.

Correspondence to: Dr R. J. Hardie, Department of Neurology, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
* Present address: Haematology Department, Palmerston North Hospital, Private Bag, Palmerston North, New Zealand.

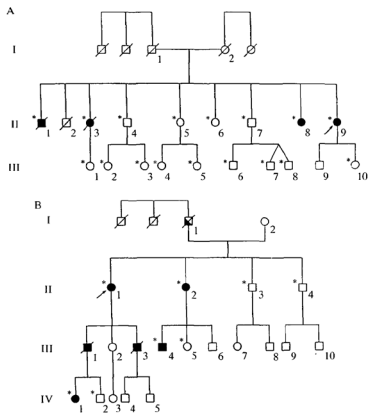


FIG. 1. Pedigree of families H (A) and L (B). Arrow = index case, circle = female, square = male, filled symbols indicate neurological disease, * = examined by us, open symbols unaffected, half-filled = probably affected by history, open with * indicates neurologically normal on examination by us and no acanthocytes on blood film.

Methods

Haematology

Blood was collected into tubes containing ethylene-diamine-tetracetic acid (EDTA) and in addition, where possible, a blood film was made from fresh blood without EDTA contact. When this was not possible, blood films were made from EDTA-containing samples within 1 h of collection. Each sample was processed by a Coulter S-Plus JR or STKR and the blood count parameters obtained. The dried blood films were stained with May-Grunwald Giemsa stain at pH 6.8 and subsequently examined by light microscopy at ×1000 magnification under oil immersion. Care was taken to examine them at a point where the film was only one cell thick and with minimal space between the cells. In each case 500 cells were counted and the proportions of acanthocytes and echinocytes estimated.

For the purposes of this study an acanthocyte was defined as a dense, slightly contracted red cell which had a number of irregularly spaced thorny surface projections, often with terminal bulbs (Brecher and Bessis, 1972). Echinocytes also have an abnormal cell surface, but with more abundant and evenly distributed surface projections that have a much broader base in relation to their length. We regarded an acanthocyte count of >3% as significant.

TABLE 1. CLINICAL FEATURES OF AFFECTED CASES

Case	Sex	Age (yrs) of onset	Age (yrs) at last examination (or death*)	Dementia	Seizures	Psychiatric features	Orofacial dyskinesia	Dysphagia	Dysarthria	Movement disorder	Tendon reflexes
Family H											
1	M	37	61*	+	+	+	O	+	+	P	O
2	F	[illegible]	[illegible]	+	[illegible]	[illegible]	[illegible]	[illegible]	+V	CP	R
3	F	[illegible]	[illegible]	+	O	[illegible]	[illegible]	[illegible]	+V	CDPT	R
4	F	44	47	+	O	+	O	O	+V	CPT	O
Family L											
5	F	51	57	+	+	+	+	O	+	CT	O
6	F	–	56	O	O	O	O	O	O	C	+
7	M	24	31*	O	+	+	O	O	O	C	O
8	M	22	31*	O	+	O	O	O	O	O	O
9	M	–	27	O	O	O	O	O	O	CT	O
10	F	–	14	O	O	O	O	O	O	O	R
Family B											
11	F	12	24	+	O	+	+B	O	+	DPT	+
12	M	8	23	+	O	+	O	O	+	D	+
Sporadic cases											
13	M	44	51	+	+	+	+	+	+V	CP	O
14	M	62	67	+	O	+	+	O	+V	CDPT	+
15	F	22	25	+	+	+	+B	+	+V	CDT	+
16	F	28	36	+	+	+	+B	+	+V	CDT	R
17	M	8	18	+	O	O	+	+	+	D	+
18	M	33	36	O	O	O	+	+	+V	D	R
19	M	39	44	O	+	O	+	+	+V	D	R

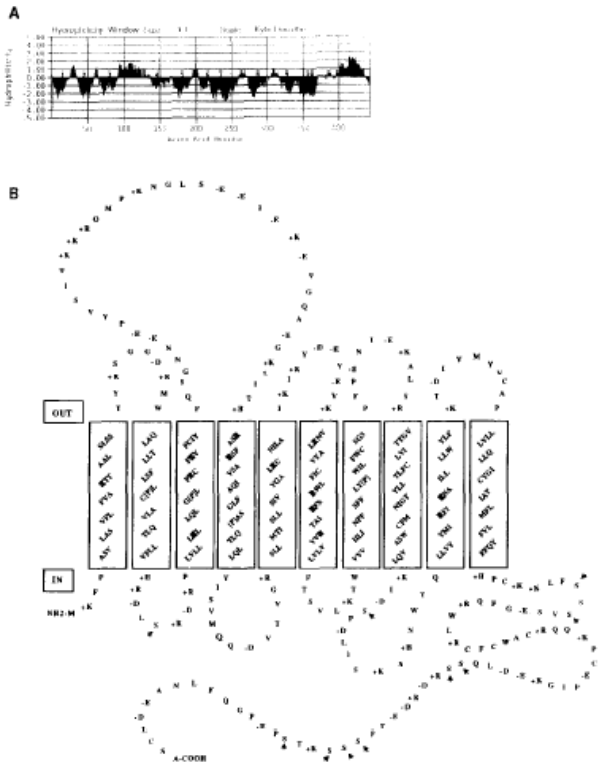
B = tongue/lip biting; V = vocalizations; C = chorea; D = dystonia; P = parkinsonism; T = tics; O = absent; R = reduced; + = present.

McLeod syndrome (XK)

VPS13A and XK bulk lipid transfer diseases

Adrian Danek - danek@lmu.de

XK protein 1984ff.



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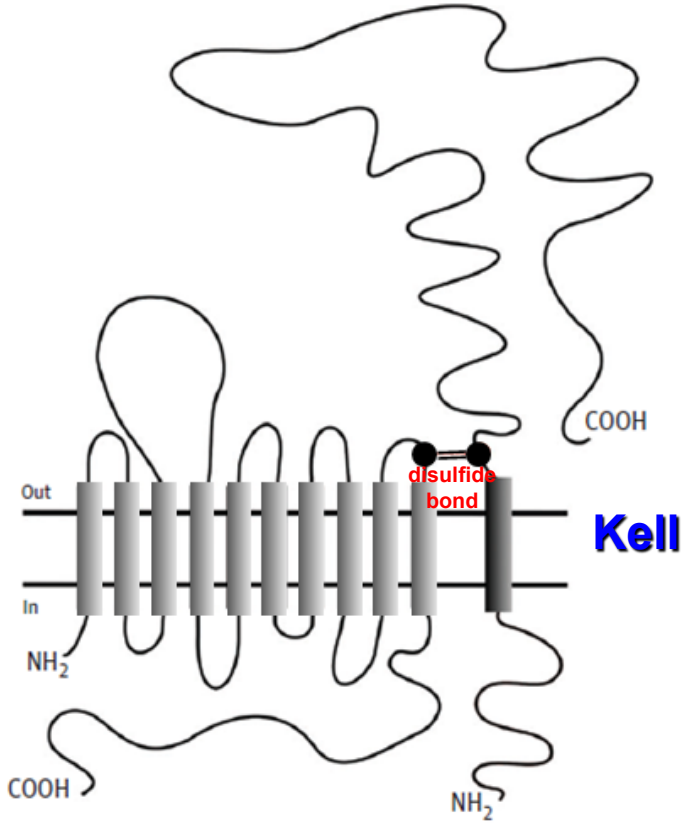


XK protein and AlphaFold (2021)

FOCUS | EDITORIAL

Check for updates

Method of the Year 2021: Protein structure prediction

Deep Learning based approaches for protein structure prediction have sent shock waves through the structural biology community. We anticipate far-reaching and long-lasting impact.

The potential to predict protein three-dimensional (3D) structures given a linear sequence of amino acids has captivated computational biologists for

A year ago, at the CASP14 meeting, AlphaFold2 from DeepMind outperformed all other approaches, and by a wide margin. On average, the fraction of a

on structural biology, and the caveats of predicted structures.

The burning question, however, is, now that it is possible to predict accurate

FOCUS | COMMENT

Check for updates

Protein structure predictions to atomic accuracy with AlphaFold

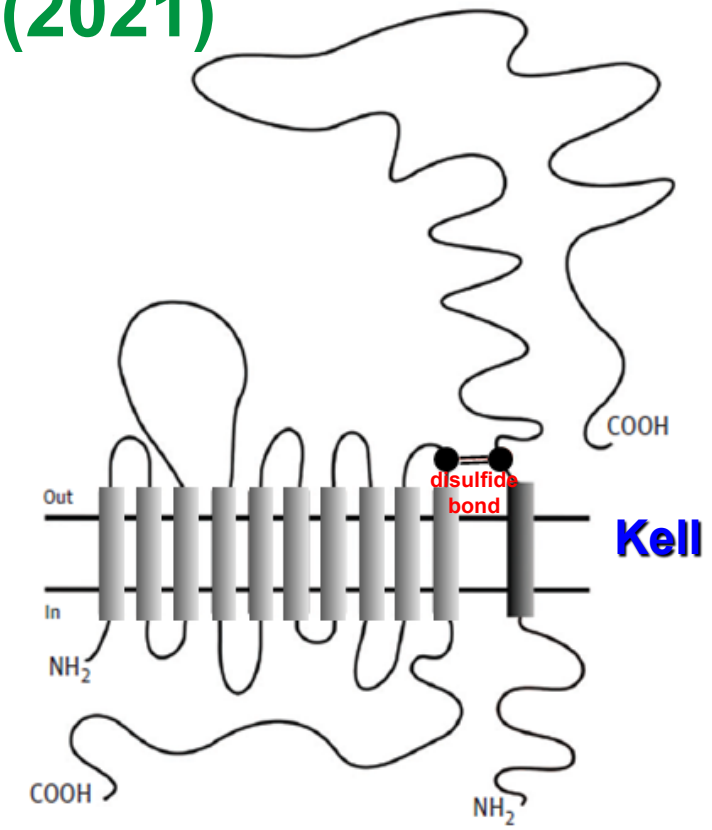
AlphaFold is a neural-network-based approach to predicting protein structures with high accuracy. We describe how it works in general terms and discuss some anticipated impacts on the field of structural biology.

John Jumper and Demis Hassabis

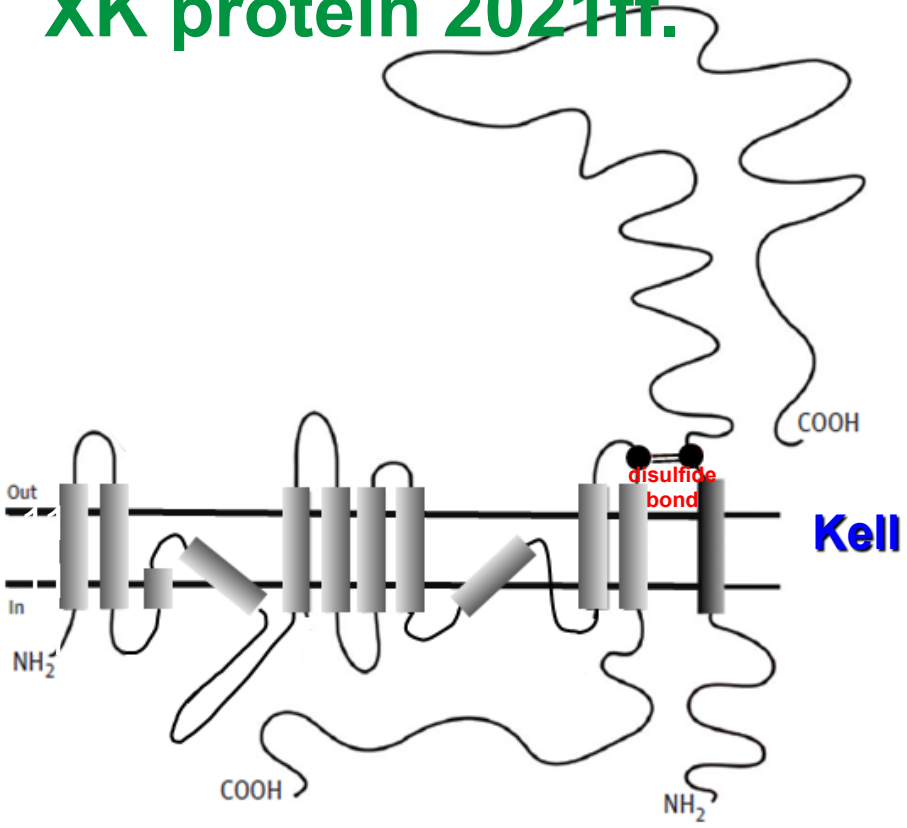
In the 2020 Critical Assessment of protein Structure Prediction (CASP14), the AlphaFold system[1] predicted almost two-thirds of the target protein structures at an accuracy that the assessors considered

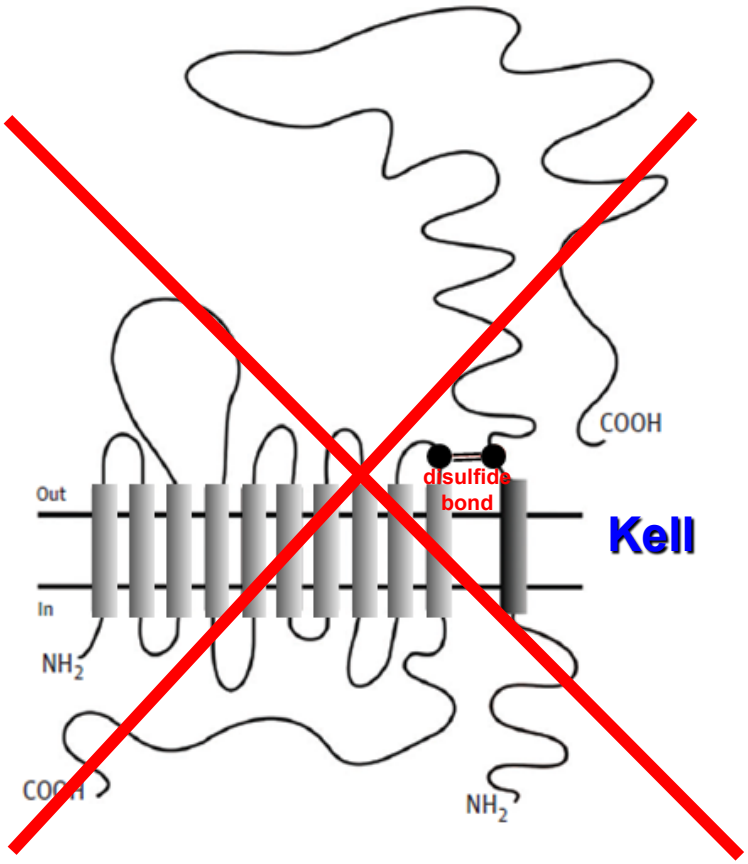
machine-learning algorithms, consisting of pipelines of alternating linear and nonlinear components, called layers, that are typically 'trained' (the process of optimizing parameters) using gradient descent on the

interpreted as a communication between different sequence positions, we add a special connection to our 'pair representation' that enables the network to modulate these interactions on the basis of its understanding

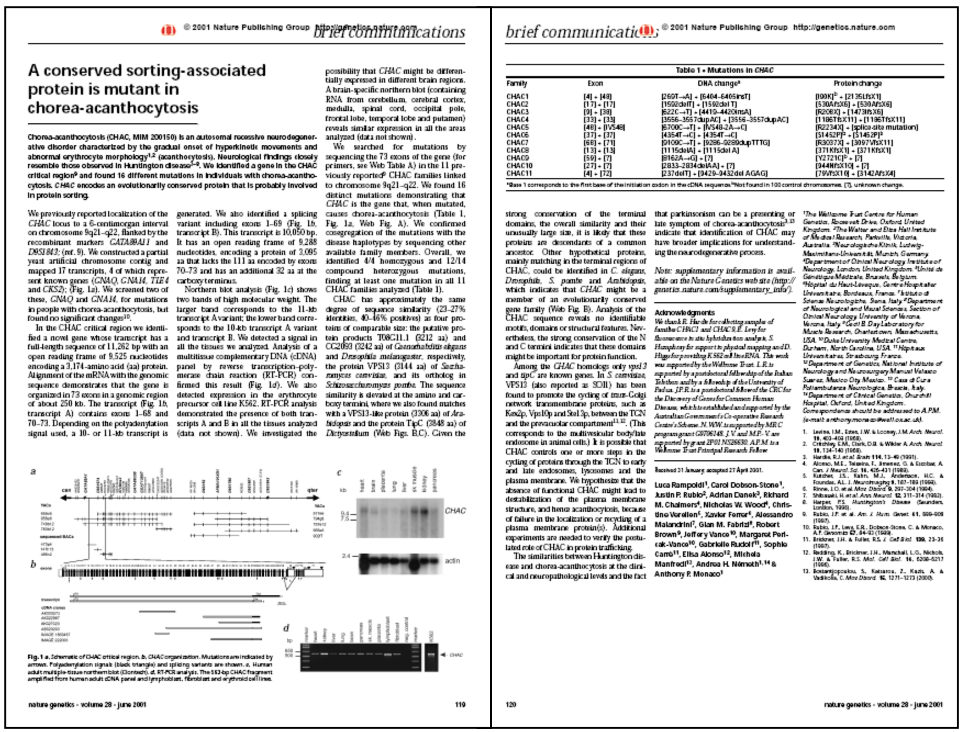


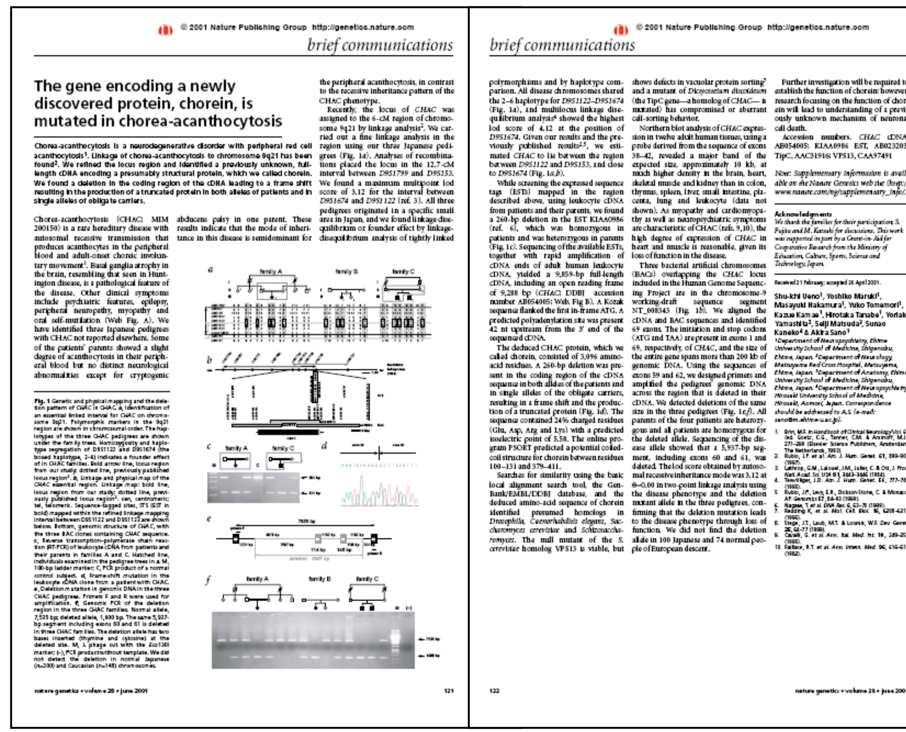
XK protein 2021ff.



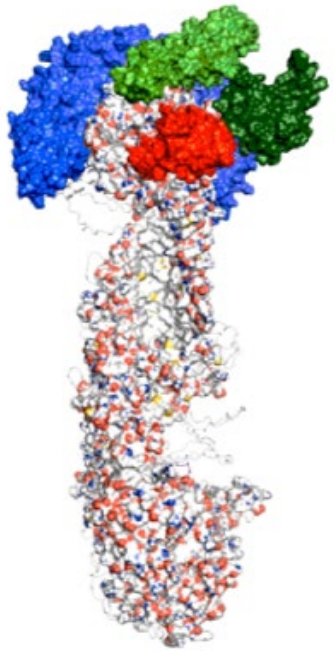


2001: *VPS13A* gene („nonMcLeod neuroacanthocytosis“ tested)

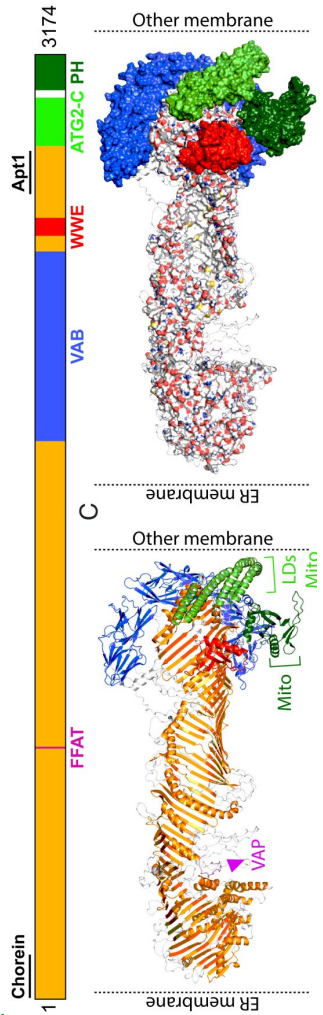




VPS13A protein (aka chorein)



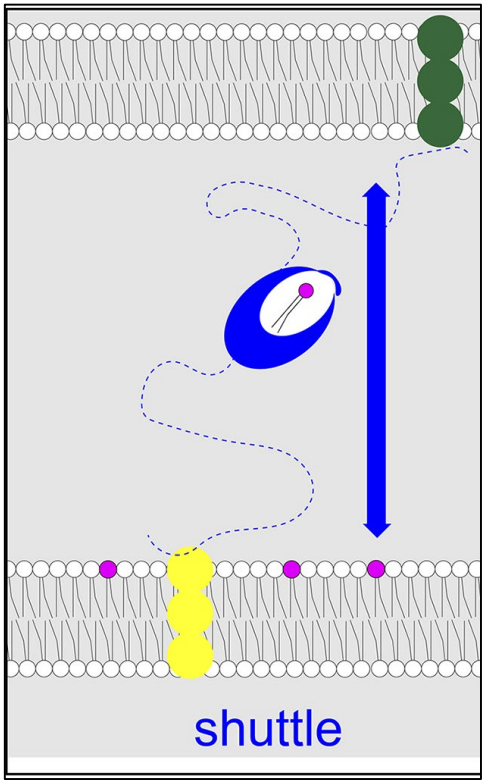
Guillén-Samander et al. 2022



Webinar outline

- Mutual introduction
- Problems of „neuroacanthocytosis“/„Levine-Critchley syndrome“
- XK and VPS13A diseases (novel nomenclature)
  - clinical features - genetic background - diagnosis
- **Bulk lipid transfer as recently discovered mechanism**
- Reference material
- Questions and answers

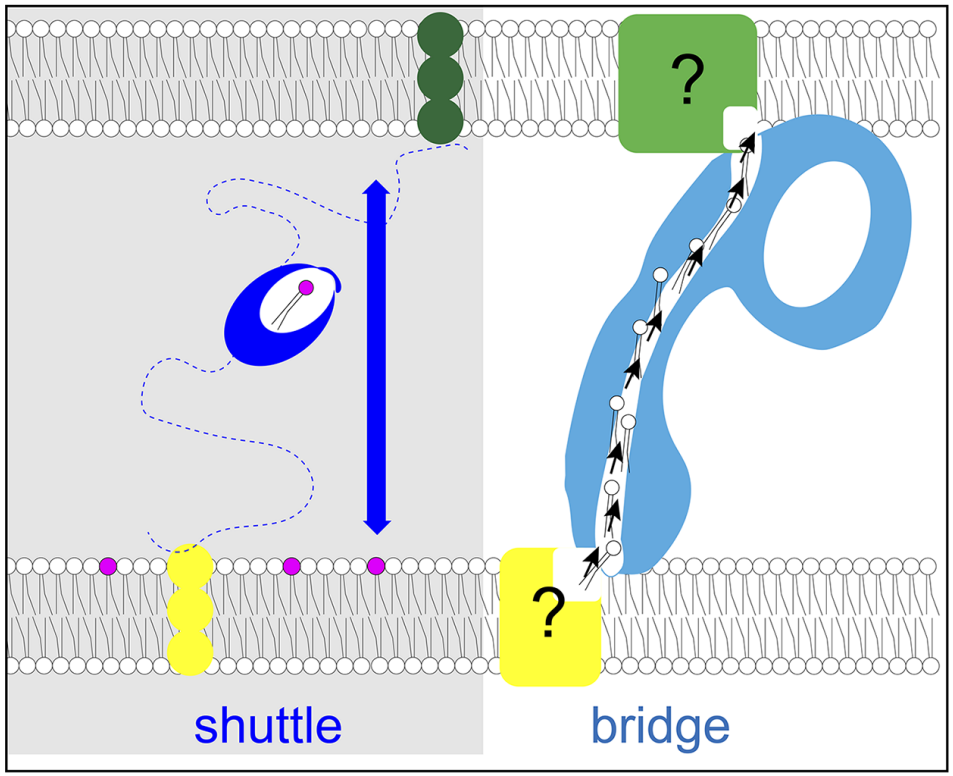
Lipid exchange between membranes



Important mechanism of interaction between cellular organelles

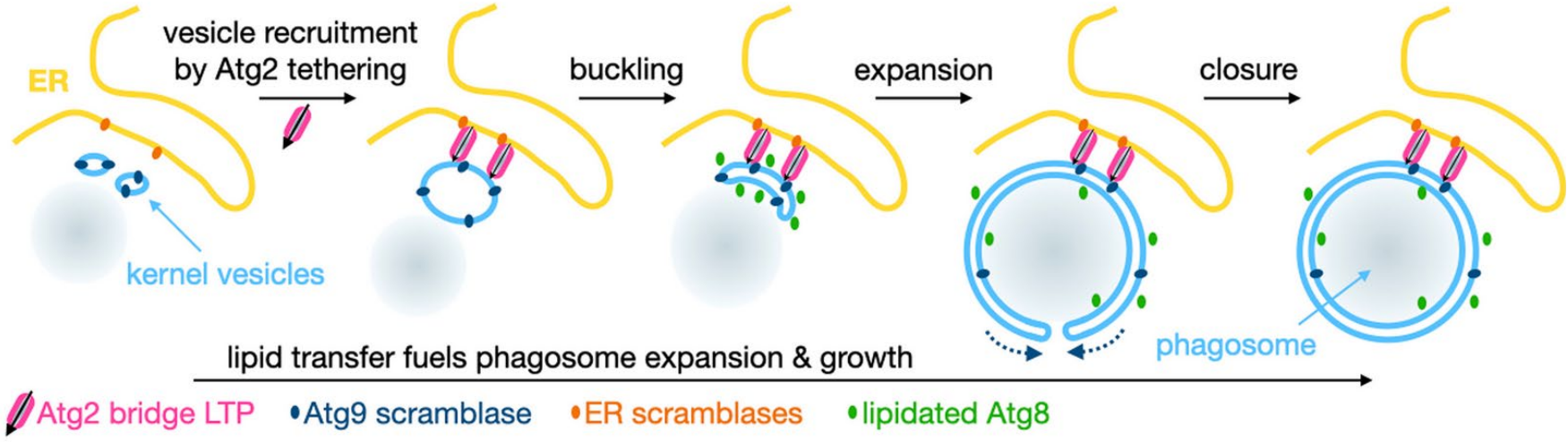
Reinisch & Prinz *J Cell Biol* (2021) 220 (3): e202012058

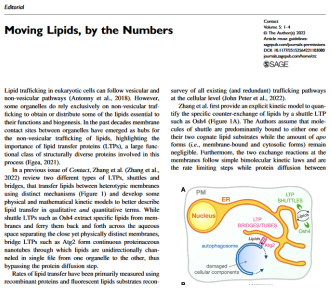
Lipid exchange between membranes



Reinisch & Prinz *J Cell Biol* (2021) 220 (3): e202012058

Bulk lipid transfer, e.g. into phagosome





Editorial

Moving Lipids, by the Numbers

Lipid trafficking in eukaryotic cells can follow vesicular and non-vesicular pathways (Antonny et al., 2018). However, some organelles do rely exclusively on non-vesicular trafficking to obtain or distribute some of the lipids essential to their functions and biogenesis. In the past decades membrane contact sites between organelles have emerged as hubs for the non-vesicular trafficking of lipids, highlighting the importance of lipid transfer proteins (LTPs), a large functional class of structurally diverse proteins involved in this process (Egea, 2021).

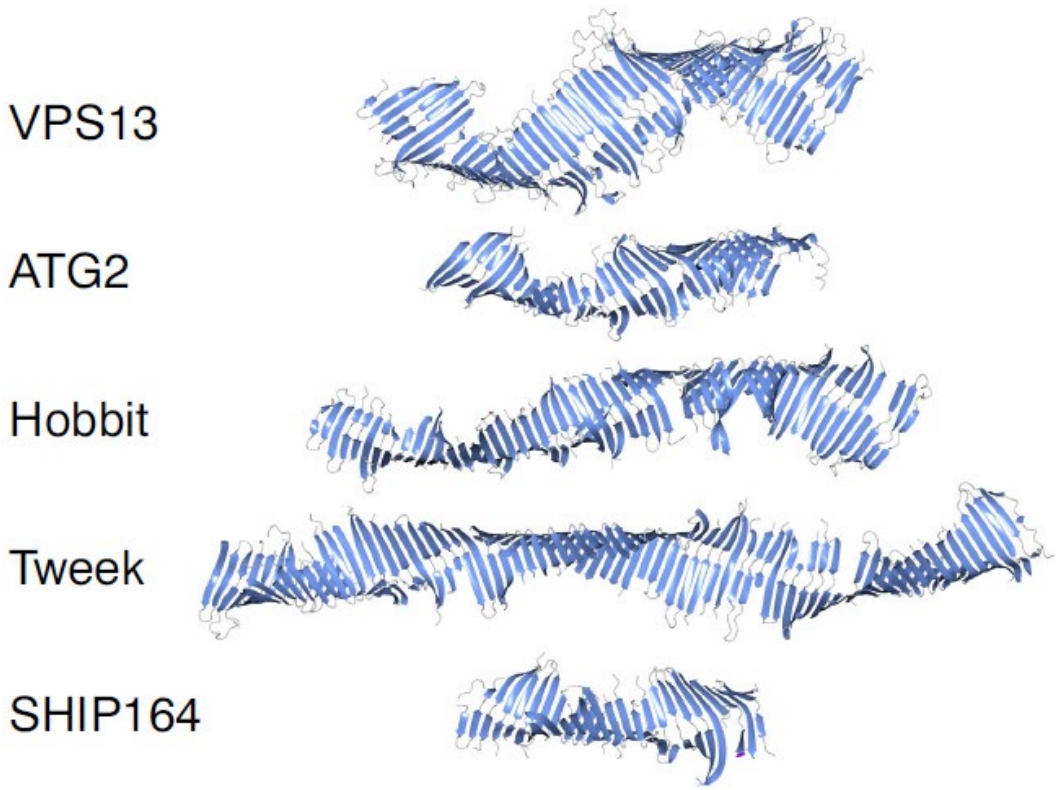
In a previous issue of *Contact*, Zhang et al. (Zhang et al., 2022) review two different types of LTPs, shuttles and bridges, that transfer lipids between heterotypic membranes using distinct mechanisms (Figure 1) and develop some physical and mathematical kinetic models to better describe lipid transfer in qualitative *and* quantitative terms. While shuttle LTPs such as Osh6 extract specific lipids from membranes and ferry them back and forth across the aqueous space separating the close yet physically distinct membranes, bridge LTPs such as Atg2 form continuous protein/aqueous nanotubes through which lipids are unidirectionally channeled in single file from one organelle to the other, thus bypassing the protein diffusion step.

Rates of lipid transfer have been primarily measured using recombinant proteins and fluorescent lipids substrates recon-

survey of all existing (and redundant) trafficking pathways at the cellular level (John Peter et al., 2022).

Zhang et al. first provide an explicit kinetic model to quantify the specific counter-exchange of lipids by a shuttle LTP such as Osh4 (Figure 1A). The Authors assume that molecules of shuttle are predominantly bound to either one of their two cognate lipid substrates while the amount of *apo* forms (*i.e.*, membrane-bound and cytosolic forms) remain negligible. Furthermore, the two exchange reactions at the membranes follow simple bimolecular kinetic laws and are the rate limiting steps while protein diffusion between

Bulk lipid transfer proteins



CellPress
Trends in Cell Biology

Review

A novel superfamily of bridge-like lipid transfer proteins

Sarah D. Neuman,[1] Tim P. Levine,[2,*] and Arash Bashirullah[1,*]

Lipid transfer proteins mediate nonvesicular transport of lipids at membrane contact sites to regulate the lipid composition of organelle membranes. Recently, a new type of bridge-like lipid transfer protein has emerged; these proteins contain a long hydrophobic groove and can mediate bulk transport of lipids between organelles. Here, we review recent insights into the structure of these proteins and identify a repeating modular unit that we propose to name the repeating β-groove (RBG) domain. This new structural understanding conceptually unifies all the RBG domain-containing lipid transfer proteins as members of an RBG protein superfamily. We also examine the biological functions of these lipid transporters in normal physiology and disease and speculate on the evolutionary origins of RBG proteins in bacteria.

Highlights

VPS13, ATG2, SHIP164, Csf1, and the Hob proteins comprise a novel superfamily of conserved lipid transfer proteins with long hydrophobic grooves.

All these long hydrophobic grooves are built from multiple repeating modules that consist of five β-sheets followed by a loop, for which we propose the name the 'repeating β-groove' (RBG) domain.

RBG proteins carry out lipid transport at membrane contact sites, with functions in lipid homeostasis and membrane biogenesis. Some of these processes require bulk lipid transfer, which appears to be one of the primary molecular functions of RBG proteins.

Eukaryotic RBG proteins likely evolved from structurally related prokaryotic proteins that transfer lipids between the inner and outer membranes in Gram-negative bacteria.

Nonvesicular lipid transfer occurs at membrane contact sites

The lipid composition of each organelle membrane is unique and plays an essential role in maintaining organelle identity and function. Lipids can be moved between organelles via vesicular or nonvesicular trafficking. Seminal work in the 1980s suggested that phospholipids and sterols are primarily transported via nonvesicular routes [1,2]; since then, evidence supporting the primacy and importance of nonvesicular lipid transport has continued to grow. Nonvesicular lipid trafficking is carried out by lipid transfer proteins (LTPs), cytoplasmic proteins that lower the energy barrier for lipids to move between membranes across aqueous spaces [3].

Most known LTPs fold to form a box-like shape with a hydrophobic lining capable of holding a single lipid [4,5]. These box-like LTPs transfer lipids via a shuttling mechanism, selecting one lipid molecule at a time based on headgroup and transferring it from donor to acceptor membranes [4]. Often this occurs at membrane contact sites, locations where two organelles are in close enough proximity that a single protein can bridge the gap [6].

In the past 4 years, a new class of LTP has emerged. These LTPs are large proteins that fold to form long bridge-like structures that span the entire distance between membranes at membrane contact sites [7–13]. The hydrophobic lining of these LTPs enables them to function like lipid superhighways connecting organelle membranes [7,9,12,13]. Five members of this LTP family have been identified: VPS13, ATG2, the Hob proteins, Tweek/Csf1/KIAA1109, and SHIP164 [7–9,12–18]. In this review, we examine recent advances in understanding the structure of this novel superfamily of bridge-like LTPs, highlighting a shared structural feature composed of a repeating series of β-sheets that we call the RBG domain. We also review recent developments in characterizing the molecular, cellular, and physiological functions of these proteins and speculate on their evolutionary origins.

A new family of eukaryotic LTPs with long hydrophobic grooves

VPS13 and ATG2 are large (3000–4000 and ~2000 amino acids, respectively) proteins that are highly conserved among eukaryotes. Structural studies in the past 4 years showed that both

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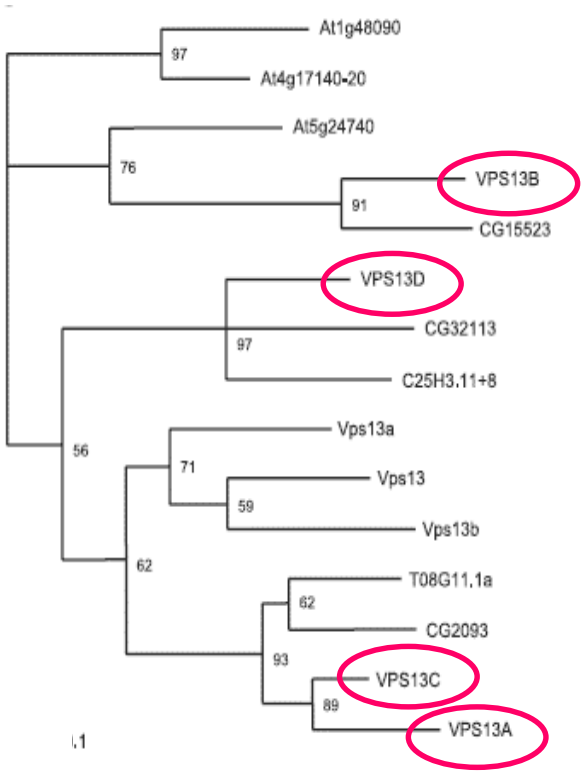
October 25, 2022

VPS13A and XK bulk lipid transfer diseases
Adrian Danek - danek@lmu.de

VPS13 gene family

- ***VPS13A*** → **ChAc**
- ***VPS13B*** → **Cohen syndrome**
- ***VPS13C*** → **Lewy body pathology**
- ***VPS13D*** → **ataxia syndromes**



Velayos-Baeza A et al. Genomics 2004;84:536

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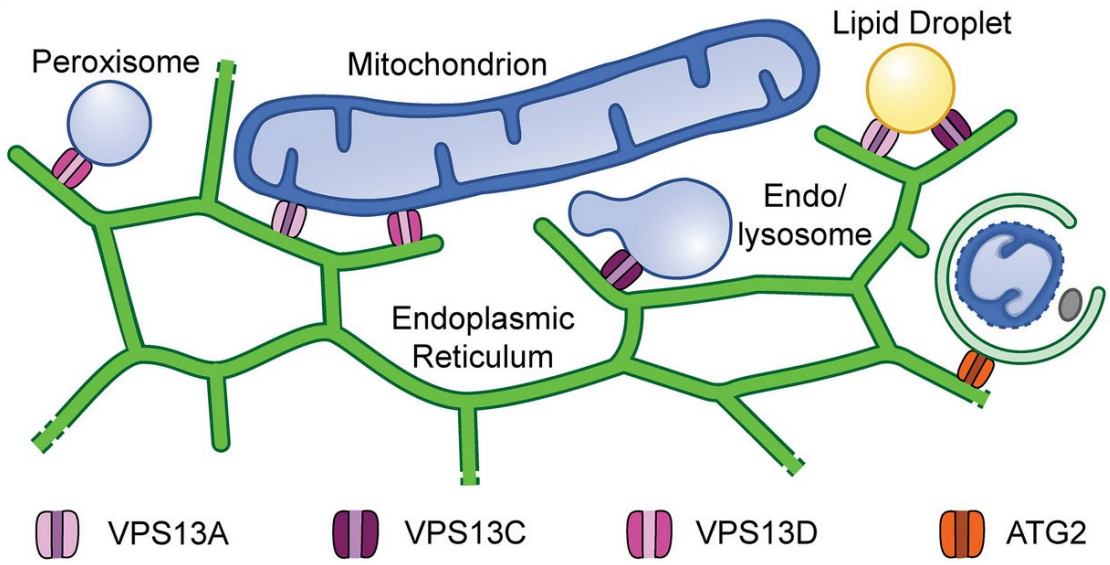
Review

Insights into VPS13 properties and function reveal a new mechanism of eukaryotic lipid transport☆

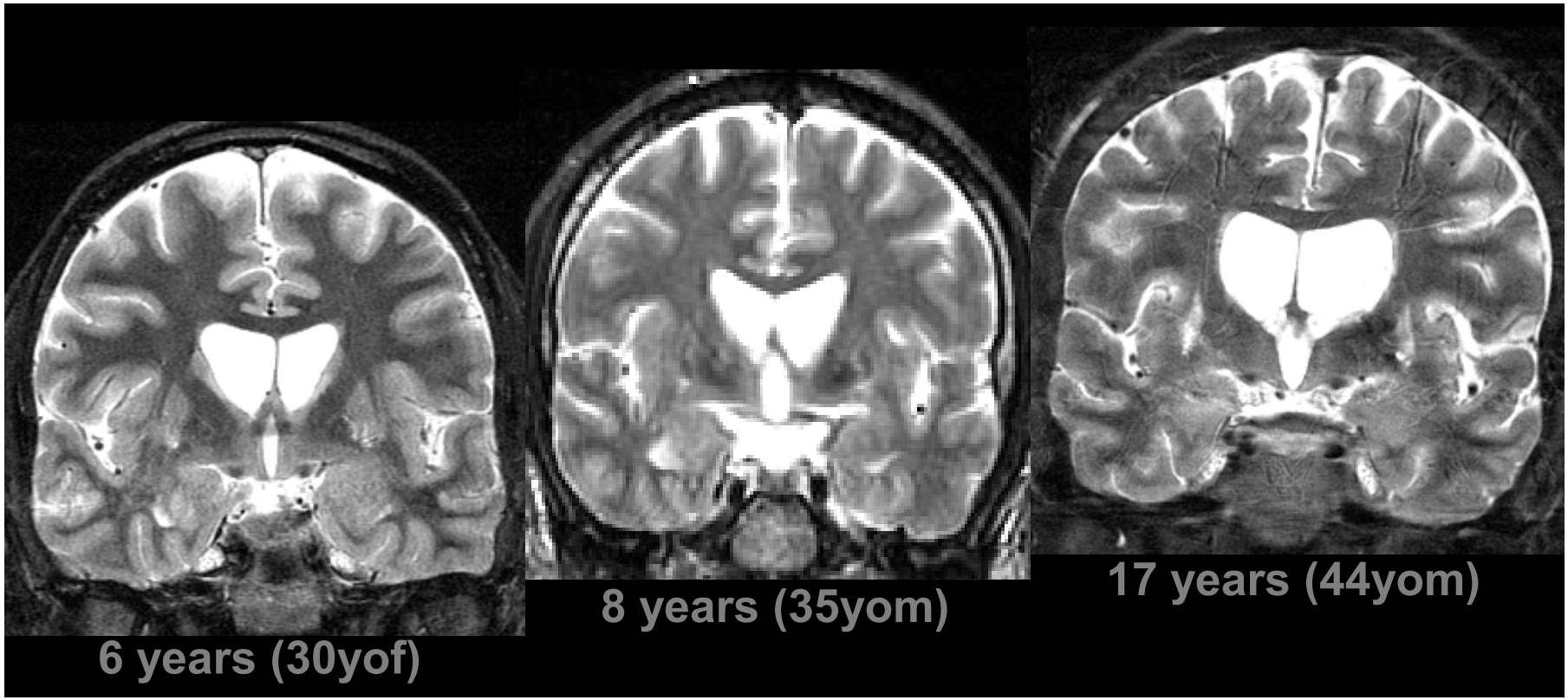
Marianna Leonzino [a,b,c,d,*], Karin M. Reinisch [b,c,*], Pietro De Camilli [a,b,c,*]



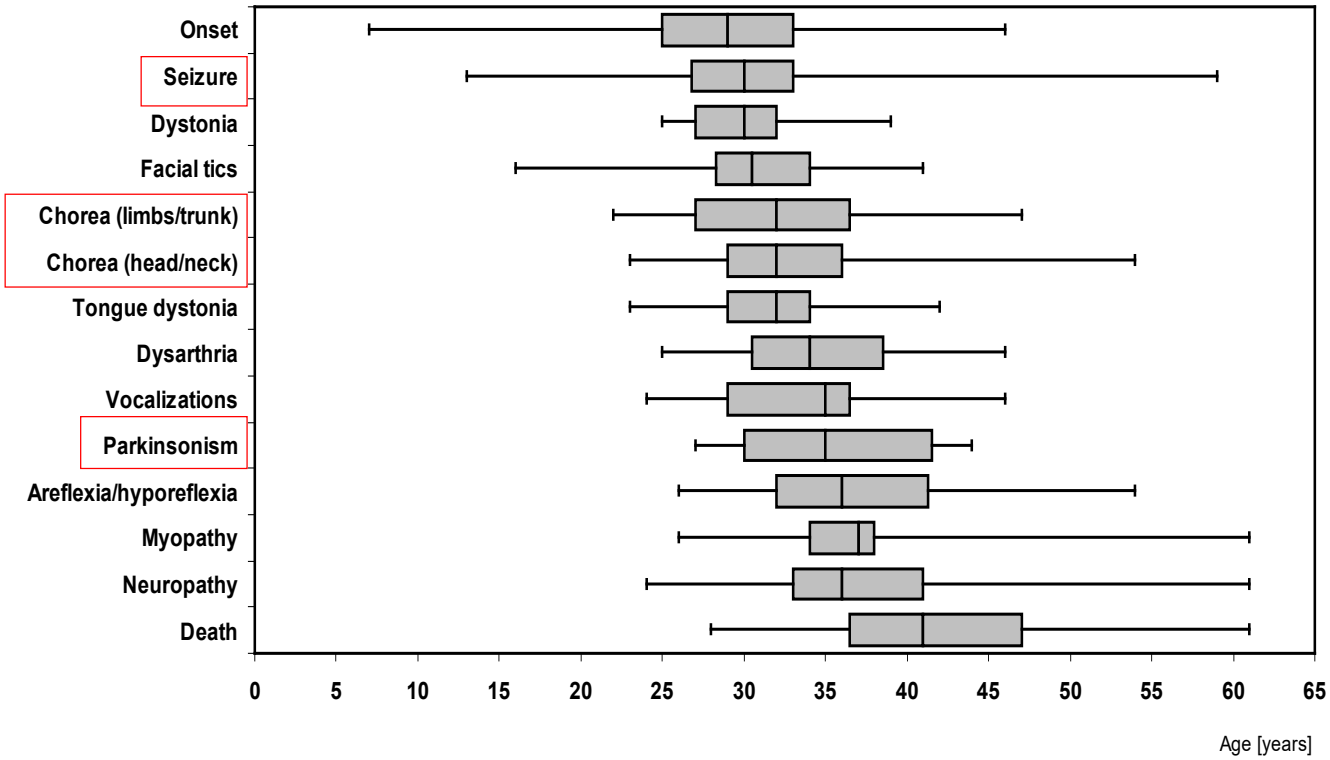
Webinar outline

- Mutual introduction
- Problems of „neuroacanthocytosis“/„Levine-Critchley syndrome“
- **XK and VPS13A diseases (novel nomenclature)**
  - **clinical features - genetic background - diagnosis**
- Bulk lipid transfer as recently discovered mechanism
- Reference material
- Questions and answers

Progressive brain atrophy/neurodegeneration



Course of VPS13A disease



Orofacial dyskinesia

Tongue Protrusion and Feeding Dystonia: A Hallmark of Chorea-Acanthocytosis

Bader et al. *Mov Disord* 25 (2010) 127-129

Critchley family: VPS13A disease

OBSERVATION

Chorea-Acanthocytosis Genotype in the Original Critchley Kentucky Neuroacanthocytosis Kindred

Antonio Velayos-Baeza, PhD; Elke Holinski-Feder, MD, PhD; Birgit Neitzel; Benedikt Bader, MD; Edmund M. R. Critchley, DM(Oxon), FRCP; Anthony P. Monaco, MD, PhD; Adrian Danek, MD; Ruth H. Walker, MB, ChB, PhD

Objective: To determine the molecular nature of the neurological disease in the seminal family reported by Critchley et al in the 1960s, characterized by a hyperkinetic movement disorder and the appearance of acanthocytosis on peripheral blood smear. The eponym *Levine-Critchley syndrome*, subsequently termed *neuroacanthocytosis*, has been applied to symptomatically similar, but genetically distinct, disorders, resulting in clinical and diagnostic confusion.

Design: DNA analysis.

Setting: Molecular biology research laboratories.

Participants: First- and second-degree relatives of the original Critchley et al proband from Kentucky.

Main Outcome Measures: Mutations in the *VPS13A* gene.

Results: A mutation was identified in the *VPS13A* gene, responsible for autosomal recessive chorea-acanthocytosis. Haplotype reconstruction suggested that this mutation was homozygous in the proband.

Conclusion: These findings strongly support the diagnosis of chorea-acanthocytosis as the disorder described in the original report.

Arch Neurol. 2011;68(10):1330-1333

NEUROACANTHOCYTOSIS (NA) is an umbrella term for a genetically and phenotypically heterogeneous group of neurological conditions that occur together with spiny red blood cells known as acanthocytes. Some of the earliest cases of NA reported in the Western literature were given the eponym *Levine-Critchley syndrome* in recognition of the work of Irvine Levine, MD, and Edmund Critchley, DM(Oxon), FRCP. In the 1960s, these authors independently reported a neurological condition characterized by acanthocytes and normolipoproteinemia in patients from 3 different families from New England,[1] Kentucky,[2] and the United Kingdom.[3]

Advances in molecular medicine have led to the recognition of several different disorders covered by the term *neuroacanthocytosis*[4,5] and have made contemporary use of this ambiguous term obsolete, apart from as a descriptor for a group of hyperkinetic disorders in which acanthocytosis may be seen. The main NA syndromes are defined by at least 4 genetically distinct conditions: autosomal recessive chorea-acanthocytosis (ChAc),[6,7] X-linked McLeod syndrome,[8] autosomal recessive pantothenate kinase–associated neurodegeneration,[9] and autosomal dominant Huntington disease–like 2.[10] Chorea-acanthocytosis and McLeod syndrome are considered the "core" NA syndromes, as acanthocytosis is a frequent finding in both disorders, while it is only occasionally seen in Huntington disease–like 2[10] and pantothenate kinase–associated neurodegeneration.[9]

From the literature, all of the Critchley et al cases[2,3] appear to have a phenotype identical to that seen in patients in whom a molecular diagnosis of ChAc has been confirmed,[4,5,11] but the same does not apply to the New England family described by Levine,[1] and no assumption can be made in this regard without genetic testing.

A nephew of the proband from the original Critchley et al Kentucky pedigree contacted one of us (R.H.W.) via the Internet, expressing an interest on behalf of the family in participating in any further research on the disorder affecting his uncle. Samples were obtained from several surviving family members allowing us to determine the molecular nature of the neurological disease in this seminal NA family.

Author Affiliations: The Wellcome Trust Centre for Human Genetics, Oxford (Drs Velayos-Baeza and Monaco), and University of Central Lancashire, Preston (Dr Critchley), England; Medizinisch Genetisches Zentrum (Dr Holinski-Feder and Ms Neitzel) and Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität (Drs Bader and Danek), Munich, Germany; and Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, and Mount Sinai School of Medicine, New York, New York (Dr Walker).

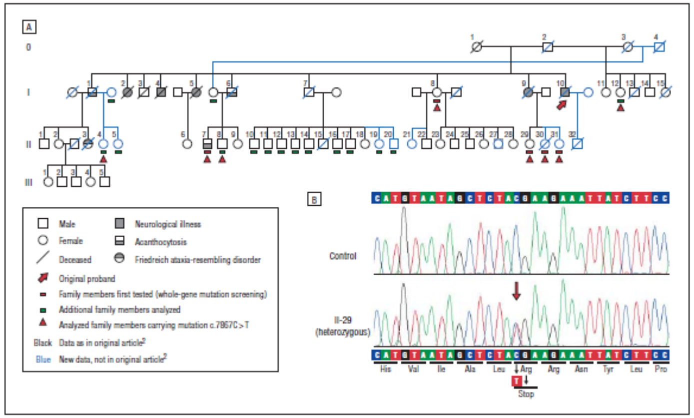


Figure. Updated pedigree for the Kentucky family and their mutation. A, Information about all family members examined by Critchley et al (original Figures 4 and 6 from Critchley et al[2]), with new data shown in blue. The proband and family members tested in the present work are indicated. B, Chromatograms obtained after sequencing exon 56 of the *VPS13A* gene in an unaffected individual (control) and in the Kentucky family member II-29 showing the C>T transition at position c.7867 (p.R2623X) detected in this family. Identical chromatograms showing this mutation in heterozygosis were obtained for family members carrying haplotype 1 (eTable 3 and eFigure, http://www.archneurol.com) as well as for "proband 23"[11] and her father.

METHODS

To determine whether the original condition reported for this family was indeed ChAc, we screened the causative gene, V[illegible] for mutation[illegible][11] The stu[illegible] was a[illegible]roved by the rel-e[illegible]nt institu[illegible] [illegible] D[illegible] [illegible] Sciences, Manchester, England) or saliva (Oragene OG[illegible]00; DNA Genotek, Kanata, Ontario, Canada) samples from [illegible] appropriate family members. For the initial mutation screening, all translated exons plus flanking region[illegible] were [illegible] merase chain reaction and sequenced [illegible] cols. For genotyping, 10 polymorphic [illegible] markers on chromosome 9 flanking the VPS1[illegible] gene and single nucleotide polymorphism rs10869920 (c.9077-133, intron 67) were analyzed (eTable 1, http://www.archneurol.com). Haplotypes were constructed manually by minimization of recombination events between markers and confirmed using Merlin.[12] Original medical records from the initial evaluation of the proband at the University of Kentucky, Lexington, were reviewed for additional information.

RESULTS

Part A of the **Figure** shows the updated pedigree of the Kentucky family reported by Critchley et al.[2] The proband's only surviving sibling (I-8 in the Figure), now aged 78 years, has features consistent with Parkinson disease. No family members were affected outside the proband's generation. If the underlying disease in this family is autosomal recessive ChAc, any direct descendant (II-6, II-29, II-30, II-31, and II-32) of an affected individual would be a heterozygous carrier of a *VPS13A* mutant allele. Blood samples were collected from family members II-29, II-30, II-31 (presumably heterozygous), II-7 (probably heterozygous), and I-8 (50% probability of being hetero[illegible] [illegible] amplification and sequencin[illegible] [illegible] 56 of the *VPS13A* gene (c.7867C>T; p.R2623X) was found in family member II-7. We then checked for this mutation in the other 4 available samples and found this mutation in all indi[illegible] [illegible]. This [illegible] previously been [illegible] [illegible] p[illegible] hete[illegible].[11]

A second change was also detected in all 5 analyzed samples in the amplified flanking region of exon 68 (c.9077-262C>T, in intron 67). This change does not appear as a single-nucleotide polymorphism in any database and we could not detect it in 180 control chromosomes. However, its location in an intronic position far away from the splicing consensus sequences suggests that it probably does not have any pathogenic effect.

To have a clearer genetic picture for this family, additional (saliva) samples from other available potentially informative members were collected (Figure, A) to perform genotyping. These samples were examined for the 2 changes mentioned earlier. Blood samples were obtained from both parents of proband 23. This family trio was analyzed as described earlier and additionally for the 2 mutations previously reported (c.7867C>T and c.1208_1211del),[11] which we found were from paternal

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Neuroacanthocytosis: Hardie et al. 1991

Brain (1991), **114**, 13–49

NEUROACANTHOCYTOSIS

A CLINICAL, HAEMATOLOGICAL AND PATHOLOGICAL STUDY OF 19 CASES

by R. J. HARDIE,[1] H. W. H. PULLON,[3]* A. E. HARDING,[1] J. S. OWEN,[5] M. PIRES,[2] G. L. DANIELS,[4] Y. IMAI,[5] V. P. MISRA,[6] R. H. M. KING,[6] J. M. JACOBS,[2] P. TIPPETT,[4] L. W. DUCHEN,[2] P. K. THOMAS[1,6] *and* C. D. MARSDEN[1]

(From the [1]University Department of Clinical Neurology and [2]Department of Neuropathology, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, the [3]Department of Haematological Medicine, King's College Hospital School of Medicine and Dentistry, the [4]Medical Research Council Blood Group Unit, University College London, and the [5]Departments of Academic Medicine and [6]Neurological Science, Royal Free Hospital School of Medicine, London, UK)

SUMMARY

Nineteen cases are described, including 12 cases from three different families and 7 nonfamilial cases, in which multisystem neurological disease was associated with acanthocytosis in peripheral blood and normal plasma lipoproteins. Mild acanthocytosis can easily be overlooked, and scanning electron microscopy may be helpful. Some neurologically asymptomatic relatives with significant acanthocytosis were identified during family screening, including some who were clinically affected.

The mean age of onset was 32 (range 8–62) yrs and the clinical course was usually progressive but there was marked phenotypic variation. Cognitive impairment, psychiatric features and organic personality change occurred in over half the cases, and more than one-third had seizures. Orofaciolingual involuntary movements and pseudobulbar disturbance commonly caused dysphagia and dysarthria that was sometimes severe, but biting of the lips or tongue was rarely seen. Chorea was seen in almost all symptomatic cases but dystonia, tics, involuntary vocalizations and akinetic-rigid features also occurred. Two cases had no movement disorder at all. Computerized tomography often demonstrated cerebral atrophy. Caudate atrophy was seen less commonly, and nonspecific focal and symmetric signal abnormalities from the caudate or lentiform nuclei were seen by magnetic resonance imaging in 3 out of 4 cases.

Depression or absence of tendon reflexes was noted in 13 cases and neurophysiological abnormalities often indicated an axonal neuropathy. Sural nerve biopsies from 3 cases showed evidence of a chronic axonal neuropathy with prominent regenerative activity, predominantly affecting the large diameter myelinated fibres. Serum creatine kinase activity was increased in 11 cases but without clinical evidence of a myopathy.

Postmortem neuropathological examination in 1 case revealed extensive neuronal loss and gliosis affecting the corpus striatum, pallidum, and the substantia nigra, especially the pars reticulata. The cerebral cortex appeared spared and the spinal cord showed no evidence of anterior horn cell loss.

Two examples of the McLeod phenotype, an X-linked abnormality of expression of Kell blood group antigens, were identified in a single family and included 1 female. The genetics of neuroacanthocytosis are unclear and probably heterogeneous, but the available pedigree data and the association with the McLeod phenotype suggest that there may be a locus for this disorder on the short arm of the X chromosome.

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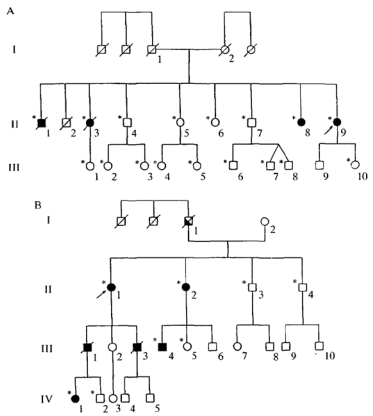


FIG. 1. Pedigree of families H (A) and L (B). Arrow = index case, circle = female, square = male, filled symbols indicate neurological disease, * = examined by us, open symbols unaffected, half-filled = probably affected by history, open with * indicates neurologically normal on examination by us and no acanthocytes on blood film.

Methods

Haematology

Blood was collected into tubes containing ethylene-diamine-tetracetic acid (EDTA) and in addition, where possible, a blood film was made from fresh blood without EDTA contact. When this was not possible, blood films were made from EDTA-containing samples within 1 h of collection. Each sample was processed by a Coulter S-Plus JR or STKR and the blood count parameters obtained. The dried blood films were stained with May-Grunwald Giemsa stain at pH 6.8 and subsequently examined by light microscopy at ×1000 magnification under oil immersion. Care was taken to examine them at a point where the film was only one cell thick and with minimal space between the cells. In each case 500 cells were counted and the proportions of acanthocytes and echinocytes estimated.

For the purposes of this study an acanthocyte was defined as a dense, slightly contracted red cell which had a number of irregularly spaced thorny surface projections, often with terminal bulbs (Brecher and Bessis, 1972). Echinocytes also have an abnormal cell surface, but with more abundant and evenly distributed surface projections that have a much broader base in relation to their length. We regarded an acanthocyte count of >3% as significant.

TABLE I. CLINICAL FEATURES OF AFFECTED CASES

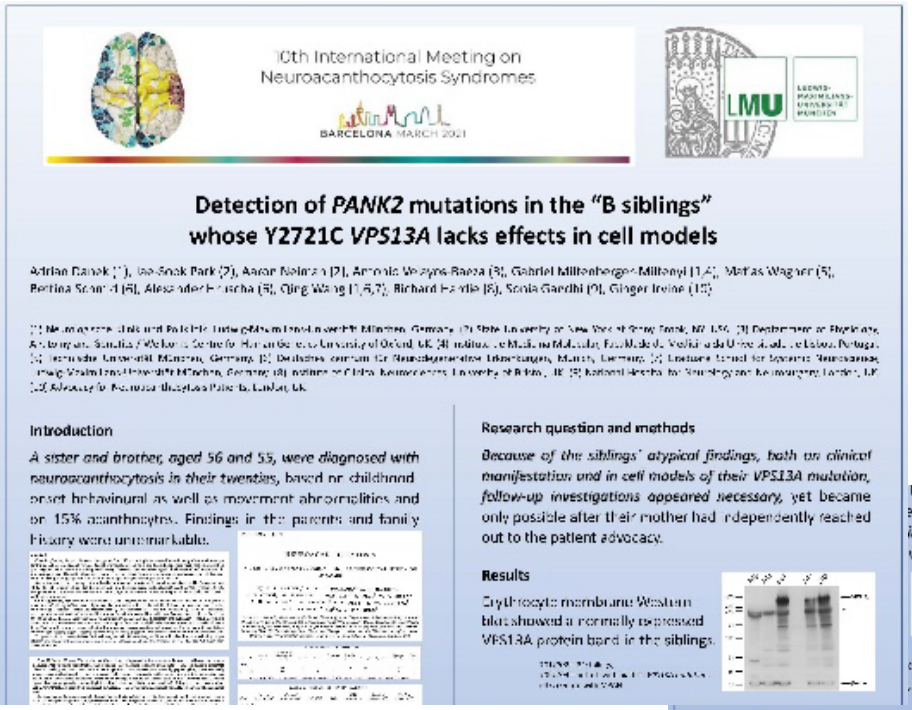
Case	Sex	Age (yrs) of onset	Age (yrs) at last examination (or death*)	Dementia	Seizures	Psychiatric features	Orofacial dyskinesia	Dysphagia	Dysarthria	Movement disorder	Tendon reflexes
Family H											
1	M	37	61*	+	+	+	O	+	+	P	O
2	F	39	61*	+	O	+	+	+	+V	CP	R
3	F	40	49	+	O	O	O	+	+V	CDPT	R
4	F	44	47	+	O	+	O	O	+V	CPT	O
Family L											
5	F	51	57	+	+	+	+	O	+	CT	O
6	F	–	56	O	O	O	O	O	O	C	+
7	M	–	31	O	O	O	O	O	O	C	O
8	M	–	31	O	O	O	O	O	O	O	O
9	M	–	27	O	O	O	O	O	O	CT	O
10	F	–	14	O	O	O	O	O	O	O	R
Family B											
11	F	12	24	+	O	+	+B	O	+	DPT	+
12	M	8	23	+	O	+	O	O	+	D	+
Sporadic cases											
13	M	44	51	+	+	+	+	+	+V	CP	O
14	M	62	67	+	O	+	+	O	+V	CDPT	+
15	F	22	25	+	+	+	+B	+	+V	CDT	+
16	F	28	34	+	+	+	+B	+	+V	CDT	R
17	M	18	18	+	O	O	+	+	+	D	+
18	M	33	36	O	O	O	+	+	+V	D	R
19	M	39	44	O	+	O	+	+	+V	D	R

B = tongue/lip biting; V = vocalizations; C = chorea; D = dystonia; P = parkinsonism; T = tics; O = absent; R = reduced; + = present.

VPS13A disease

VPS13A

VPS13A and XK bulk lipid transfer diseases
Adrian Danek - danek@lmu.de



10th International Meeting on Neuroacanthocytosis Syndromes

BARCELONA MARCH 2021

Detection of *PANK2* mutations in the "B siblings" whose Y2721C *VPS13A* lacks effects in cell models

Adrian Danek [1*], Jee-Sook Park [2], Aaron Nelson [2], Antonio Vazquez-Barrio [3], Gabriel Miltenberger-Miltenyi [1,4], Matias Wagner [5], Bettina Schmid [6], Alexander Fischa [6], Qing Wang [1,6,7], Richard Beattie [8], Sonia Gandhi [9], Ginger Irvine [10]

Introduction

A sister and brother, aged 56 and 55, were diagnosed with neuroacanthocytosis in their twenties, based on childhood onset behavioural as well as movement abnormalities and on 15% acanthocytes. Findings in the parents and family history were unremarkable.

Research question and methods

Because of the siblings' atypical findings, both on clinical manifestation and in cell models of their VPS13A mutation, follow-up investigations appeared necessary, yet became only possible after their mother had independently reached out to the patient advocacy.

Results

Erythrocyte membrane Western blot showed a normally expressed VPS13A protein band in the siblings.

linkage also in this "CHAC9" gene (CHAC, later renamed *single heterozygous missense* was found in this family.

even, exceptional because of and normal CK levels.

Studies of cognate yeast mutations, Y2720C included

Their mutation, along with missense mutations VPS13A L67P, I90K, A1053P, and I2771R was modelled in yeast (Park et al. 2015; Dziurkowska et al. 2017). Among the cognate mutations (Vps13 L56P, C89K, L11D?, Y27D2C, and I2749R) only *Y2702C, corresponding to the CHAC9 mutation, failed to show a phenotype in yeast.* In human-derived cells (HEK293T) we found the *Y2721C mutant protein localizes like wild-type VPS13A protein.*

Conclusions

We conclude that Y2721C is a benign *VPS13A* polymorphism and that *the siblings' diagnosis is not ChAc but pantothenate kinase associated neurodegeneration*

These observations show that

a clinical diagnosis of ChAc must be confirmed by

- *reduced chorein expression and/or*
- *proof of pathogenic mutations in both VPS13A alleles.*

Mere presence of a single VPS13A mutation with unclear functional effects (e.g. missense mutations) is clearly insufficient to support the diagnosis.

Acknowledgement: Supported by the Advocacy for Neuroacanthocytosis Patients.

~~Neuroacanthocytosis~~

Brain (1991), **114**, 13–49

NEUROACANTHOCYTOSIS

A CLINICAL, HAEMATOLOGICAL AND PATHOLOGICAL STUDY OF 19 CASES

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SUMMARY

Nineteen cases are described, including 12 cases from three different families and 7 nonfamilial cases, in which multisystem neurological disease was associated with acanthocytosis in peripheral blood and normal plasma lipoproteins. Mild acanthocytosis can easily be overlooked, and scanning electron microscopy may be helpful. Some neurologically asymptomatic relatives with significant acanthocytosis were identified during family screening, including some who were clinically affected.

The mean age of onset was 32 (range 8–62) yrs and the clinical course was usually progressive but there was marked phenotypic variation. Cognitive impairment, psychiatric features and organic personality change occurred in over half the cases, and more than one-third had seizures. Orofaciolingual involuntary movements and pseudobulbar disturbance commonly caused dysphagia and dysarthria that was sometimes severe, but biting of the lips or tongue was rarely seen. Chorea was seen in almost all symptomatic cases but dystonia, tics, involuntary vocalizations and akinetic-rigid features also occurred. Two cases had no movement disorder at all. Computerized tomography often demonstrated cerebral atrophy. Caudate atrophy was seen less commonly, and nonspecific focal and symmetric signal abnormalities from the caudate or lentiform nuclei were seen by magnetic resonance imaging in 3 out of 4 cases.

Depression or absence of tendon reflexes was noted in 13 cases and neurophysiological abnormalities often indicated an axonal neuropathy. Sural nerve biopsies from 3 cases showed evidence of a chronic axonal neuropathy with prominent regenerative activity, predominantly affecting the large diameter myelinated fibres. Serum creatine kinase activity was increased in 11 cases but without clinical evidence of a myopathy.

Postmortem neuropathological examination in 1 case revealed extensive neuronal loss and gliosis affecting the corpus striatum, pallidum, and the substantia nigra, especially the pars reticulata. The cerebral cortex appeared spared and the spinal cord showed no evidence of anterior horn cell loss.

Two examples of the McLeod phenotype, an X-linked abnormality of expression of Kell blood group antigens, were identified in a single family and included 1 female. The genetics of neuroacanthocytosis are unclear and probably heterogeneous, but the available pedigree data and the association with the McLeod phenotype suggest that there may be a locus for this disorder on the short arm of the X chromosome.

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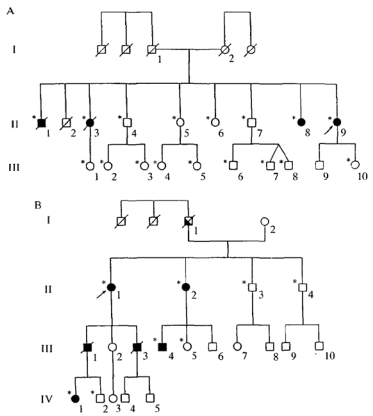


FIG. 1. Pedigree of families H (A) and L (B). Arrow = index case, circle = female, square = male, filled symbols indicate neurological disease, * = examined by us, open symbols unaffected, half-filled = probably affected by history, open with * indicates neurologically normal on examination by us and no acanthocytes on blood film.

Methods

Haematology

Blood was collected into tubes containing ethylene-diamine-tetracetic acid (EDTA) and in addition, where possible, a blood film was made from fresh blood without EDTA contact. When this was not possible, blood films were made from EDTA-containing samples within 1 h of collection. Each sample was processed by a Coulter S-Plus JR or STKR and the blood count parameters obtained. The dried blood films were stained with May-Grunwald Giemsa stain at pH 6.8 and subsequently examined by light microscopy at ×1000 magnification under oil immersion. Care was taken to examine them at a point where the film was only one cell thick and with minimal space between the cells. In each case 500 cells were counted and the proportions of acanthocytes and echinocytes estimated.

For the purposes of this study an acanthocyte was defined as a dense, slightly contracted red cell which had a number of irregularly spaced thorny surface projections, often with terminal bulbs (Brecher and Bessis, 1972). Echinocytes also have an abnormal cell surface, but with more abundant and evenly distributed surface projections that have a much broader base in relation to their length. We regarded an acanthocyte count of >3% as significant.

TABLE I. CLINICAL FEATURES OF AFFECTED CASES

Case	Sex	Age (yrs) of onset	Age (yrs) at last examination (or death*)	Dementia	Seizures	Psychiatric features	Orofacial dyskinesia	Dysphagia	Dysarthria	Movement disorder	Tendon reflexes
Family H											
1	M	37	61*	+	+	+	O	+	+	P	O
2	F	[illegible]	[illegible]	O	+	+	+	+	+V	CP	R
3	F	[illegible]	[illegible]	O	O	O	+	+	+V	CDPT	R
4	F	44	47	+	O	+	O	O	+V	CPT	O
Family L											
5	F	51	57	+	+	+	+	O	+	CT	O
6	F	–	56	O	O	O	O	O	O	C	+
7	M	[illegible]	31	O	O	O	O	O	O	C	O
8	M	[illegible]	31	O	O	O	O	O	O	O	O
9	M	–	27	O	O	O	O	O	O	CT	O
10	F	–	14	O	O	O	O	O	O	O	R
Family B											
11	F	[illegible]	[illegible]	O	O	+	+	+	+	DPT	+
12	M	8	23	O	+	+	O	O	+	D	+
Sporadic cases											
13	M	44	51	+	+	+	+	+	+V	CP	O
14	M	62	67	+	O	+	+	O	+V	CDPT	+
15	F	22	25	+	+	+	+B	+	+V	CDT	+
16	F	28	31	+	+	+	+B	+	+V	CDT	R
17	M	[illegible]	18	+	O	[illegible]	+	+	+	D	+
18	M	33	36	O	O	O	+	+	+V	D	R
19	M	39	44	O	+	O	+	+	+V	D	R

B = tongue/lip biting; V = vocalizations; C = chorea; D = dystonia; P = parkinsonism; T = tics; O = absent; R = reduced; + = present.

XK disease

VPS13A disease

PKAN („PANK2 disease“)

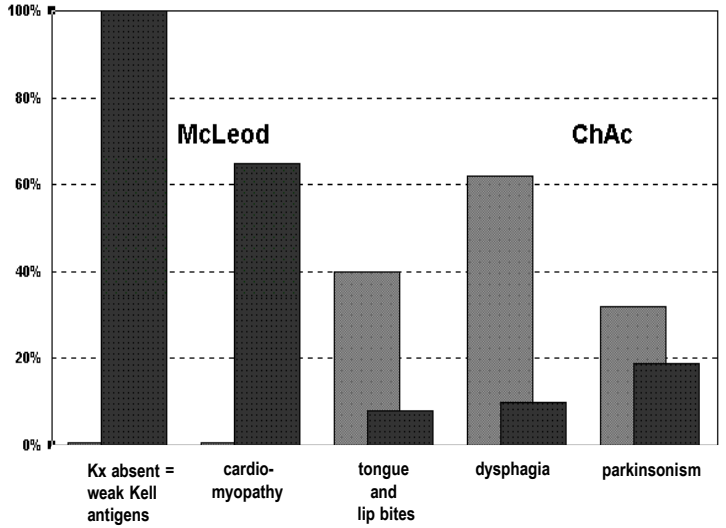
VPS13A & PKAN

Webinar outline

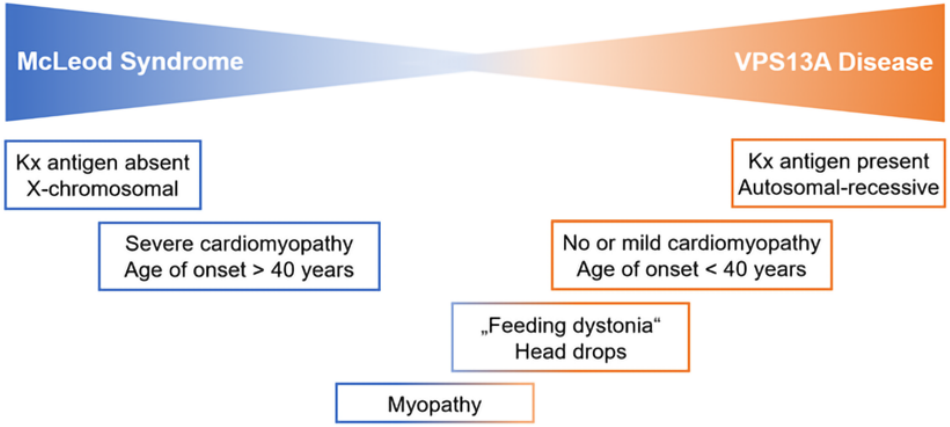
- Mutual introduction
- Problems of „neuroacanthocytosis“/„Levine-Critchley syndrome“
- XK and VPS13A diseases (novel nomenclature)
  - **clinical features** - genetic background - **diagnosis**
- Bulk lipid transfer as recently discovered mechanism
- Reference material
- Questions and answers

Similarity of XK and VPS13A diseases

Findings	Frequency (%) in McLeod[a]	Frequency (%) in ChAc[b]
Weak Kell antigens	100	0
Acanthocytosis	100	88
Elevation in CK	100	85
Elevation in LDH	91	75
Elevation in AST	33	57
Elevation in ALT	33	50
Elevation in γGT	33	17
Reduction in haptoglobin	80	100
Splenomegaly	38	22
Hepatomegaly	42	11
Cardiomyopathy	65	0
Areflexia: ankles	90	90
Areflexia: arms	62	85
Muscle weakness	65	54
Muscle biopsy: myopathic	80	0
Muscle biopsy: neuropathic	64	100
Electromyography: myopathic	14	0
Electromyography: neuropathic	79	67
Pallhypaesthesia feet	40	13
Seizures	50	42
Psychopathology	83	60
Cognitive changes	54	73
Chorea	94	85
Dystonia	38	50
Hyperkinesia face	86	90
Involuntary vocalisations	58	62
Tongue and lip biting	8	40
Dysarthria	77	88
Dysphagia	10	62
Parkinsonian features	19	32



Rampoldi et al. J Mol Med 80(2002)475



Very wide differential diagnostic spectrum

- Obsessive compulsive
- Psychosis
- Tourette‘s

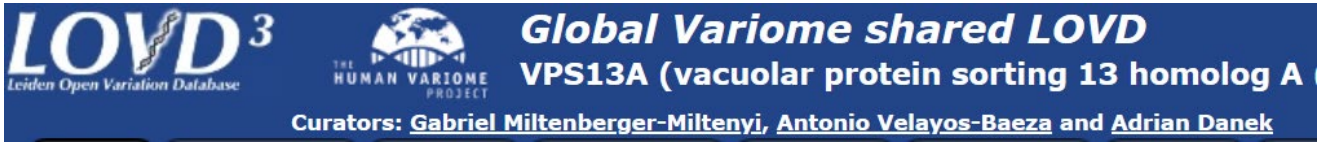
- Motor neuron disease
- Neuropathy
- Myopathy

- Huntington‘s
- Parkinson‘s
- Ataxia

- Epilepsy
- Dementia
- Neurodegeneration with brain iron accumulation group

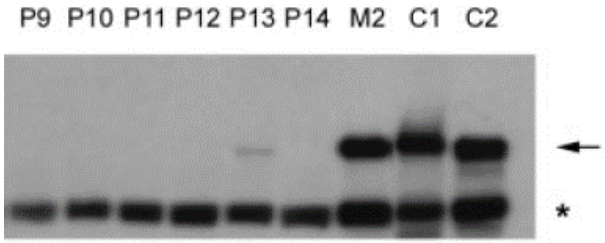
Diagnostic tools VPS13A

- Mutation registry → DNA change of relevance?



https://databases.lovd.nl/shared/genes/VPS13A

- Chorein Western Blot



Chorein Detection for the Diagnosis of Chorea-Acanthocytosis

Carol Dobson-Stone, PhD,[1] Antonio Velayos-Baeza, PhD,[1] Lea A. Filippone,[2] Sarah Westbury,[3] Alexander Storch, MD,[4] Torsten Erdmann, MD,[5] Stephen J. Wroe, MD, FRCP,[6] Klaus L. Leenders, MD,[7] Anthony E. Lang, MD, FRCP,[8] Maria Teresa Dotti, MD,[9] Antonio Federico, MD,[9] Saidi A. Mohiddin, MD, MRCP,[10] Lameh Fananapazir, MD, FRCP,[10] Geoff Daniels, PhD,[11] Adrian Danek, MD,[12] and Anthony P. Monaco, MD[1]

Chorea-acanthocytosis (ChAc) is a severe, neurodegenerative disorder that shares clinical features with Huntington's disease and McLeod syndrome. It is caused by mutations in *VPS13A*, which encodes a large protein called chorein. Using antichorein antisera, we found expression of chorein in all human cells analyzed. However, chorein expression was absent or noticeably reduced in ChAc patient cells, but not McLeod syndrome and Huntington's disease cells. This suggests that loss of chorein expression is a diagnostic feature of ChAc.

Ann Neurol 2004;56:299–302

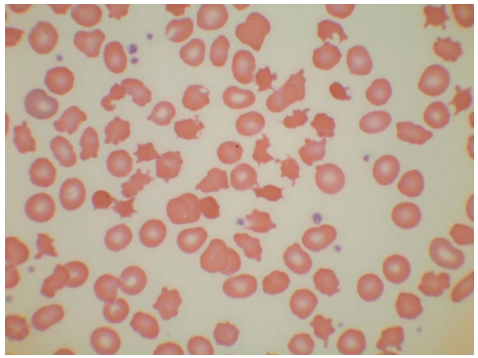
Diagnostic tools XK

- Mutation registry → only partly existent

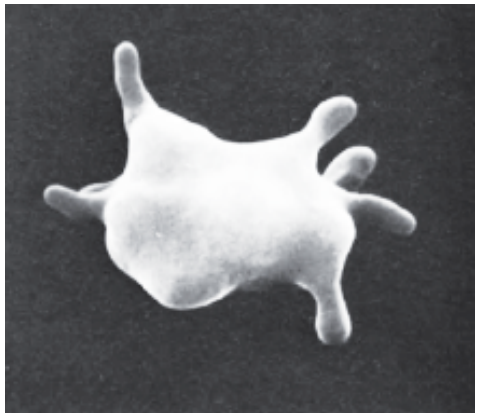
- Kell phenotyping in blood bank

  ask for exclusion/confirmation of McLeod phenotype
  „Kell positive“ or „Kell negative“ <u>is irrelevant</u>

Role of acanthocytosis



- Is there „NA without acanthocytes“?
- Cut-off value?
- Fluctuations over disease course?
- Repeat how often for „exclusion“ of diagnosis?
- Dry or wet smear?
- Routine lab or microscopy (POC)?
- Lumping with echinocyte numbers?
- Electron microscopy?



Testing for acanthocytosis (Storch et al.)

J Neurol (2005) 252 : 84–90
DOI 10.1007/s00415-005-0616-3

ORIGINAL COMMUNICATION

Alexander Storch
Markus Kornhass
Johannes Schwarz

Testing for acanthocytosis

A prospective reader-blinded study in movement disorder patients

Abstract The presence of acanthocytosis in peripheral blood smears remains the hallmark of the clinical diagnosis of most neuroacanthocytosis syndromes, such as chorea-acanthocytosis (ChAc) and McLeod syndrome. Genetic analyses and/or specific laboratory tests are available only for a minority of these disorders. Testing for acanthocytosis is hampered by the lack of data on normal amounts of acanthocytes assessed by a standardized method. We report a prospective reader-blinded study designed to establish control values for abnormally shaped erythrocytes in healthy volunteers and pa-

Wet Blood Smear Preparation

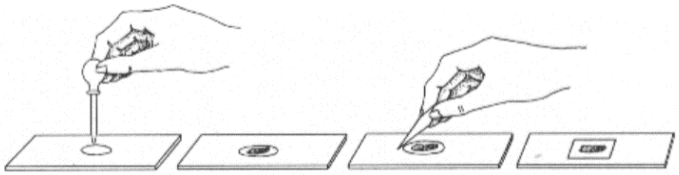
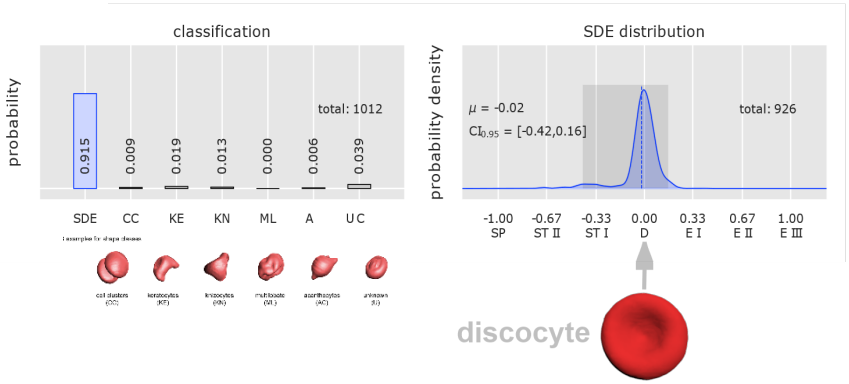


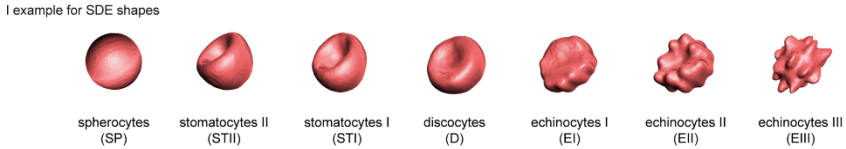
Table 1. Parameters of the standardized acanthocyte screening test (adapted from *Storch et al, 2003*).

Blood/Smear Type	Normal value[a]	Specificity	Sensitivity[b]
EDTA/dry smear	< 1.2 %	0.99	Low (1/3)
EDTA/wet preparation	< 3.7 %	0.98	Low (1/3)
Diluted/dry smear	< 3.0 %	0.99	Middle (2/3)
Diluted/wet preparation	< 6.3 %	0.98	High (3/3)

[a] 99th percentile of healthy controls and defined movement disorder patients
[b] Number of detected patients per genetically confirmed ChAc patients

Representative healthy donor





Representative VPS13A disease case

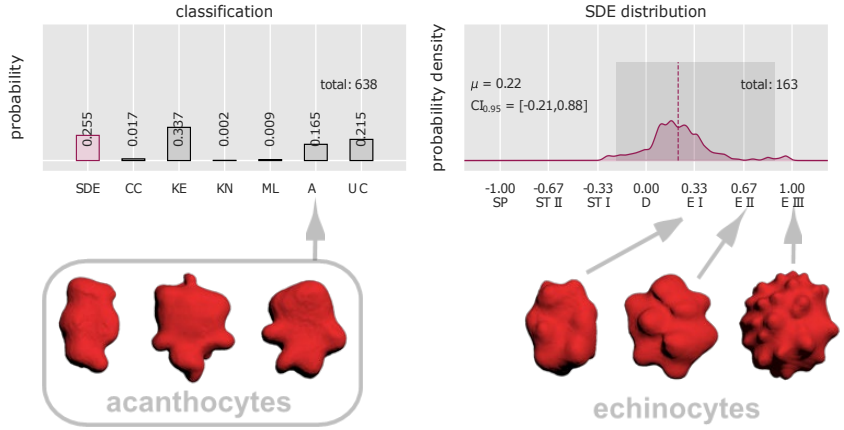


Figure. Distinction of acanthocytes from echinocytes based on 3D confocal images and classification with artificial neural networks (figure modified from (Rabe et al, 2021). To arrive at these classifications, a drop of blood was dropped directly (i.e. without anticoagulant exposure) from the blood-drawing needle tip into glutaraldehyde for fixation (Abay et al, 2019), followed by staining with Cell Mask deep red and confocal microscopic imaging (Quint et al, 2017). Artificial intelligence-based classification allows unbiased automated analysis, including a 'stomatocyte-discocyte-echinocyte' (SDE) classification on a continuous scale (instead of in discrete classes). For design and validation of the artificial neural network see (Simionato et al, 2021

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Similarity of XK and VPS13A diseases

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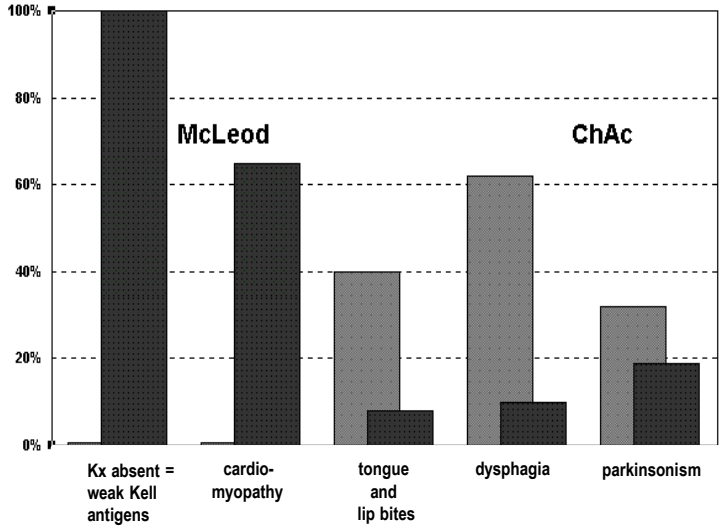
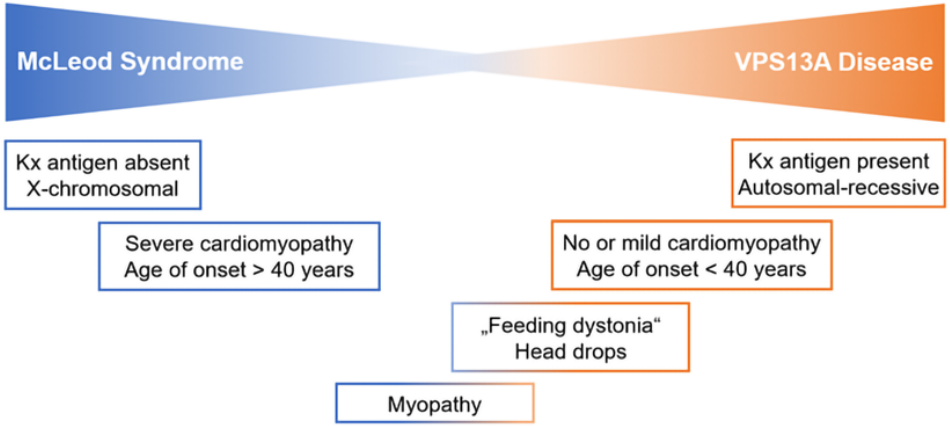


Rampoldi et al. J Mol Med 80(2002)475



Is XK disease „delayed“ VPS13A disease?

Feeding Dystonia in McLeod Syndrome

Andreas R. Gantenbein, MD,[1] Nathalie Damon-Perrière, MD,[2] Jörg E. Bohlender, MD,[3] Marie Chauveau, MD,[2] Chrystelle Latxague, PhD,[2] Marcelo Miranda, MD,[4] Hans H. Jung, MD,[1]* and François Tison, MD, PhD[2]

[1]*Department of Neurology, University Hospital Zürich, Zürich, Switzerland;* [2]*Department of Neurology, University Hospital Bordeaux, Bordeaux, France;* [3]*Department of Oto-Rhino-Laryngology, Division of Phoniatry, University Hospital Zürich, Zürich, Switzerland;* [4]*Department of Neurology, Clinica Las Condes, Santiago, Chile*

online video

ABSTRACT

Background: The X-linked McLeod syndrome belongs to the group of neuroacanthocytosis syndromes and has a Huntington-disease–like phenotype with a choreatic movement disorder, cognitive alterations, and psychiatric symptoms. Another neuroacanthocytosis syndrome, the autosomal recessive chorea-acanthocytosis, has a similar presentation, but distinct clinical features, believed to be characteristic, such as tongue protrusion dystonia, feeding dystonia, and rubber-man–like appearance.
Methods: This work comprised a case series of 3 patients with McLeod syndrome.
Results: The 3 patients with McLeod syndrome developed severe feeding dystonia and tongue protrusion as well as rubber-man–like appearance in 1 patient during the course of the disease.
Conclusion: These observations indicate that there is an extended phenotypic overlap between McLeod syndrome and chorea-acanthocytosis. © 2011 *Movement* Disorder Society
Key Words: McLeod syndrome; neuroacanthocytosis; feeding dystonia

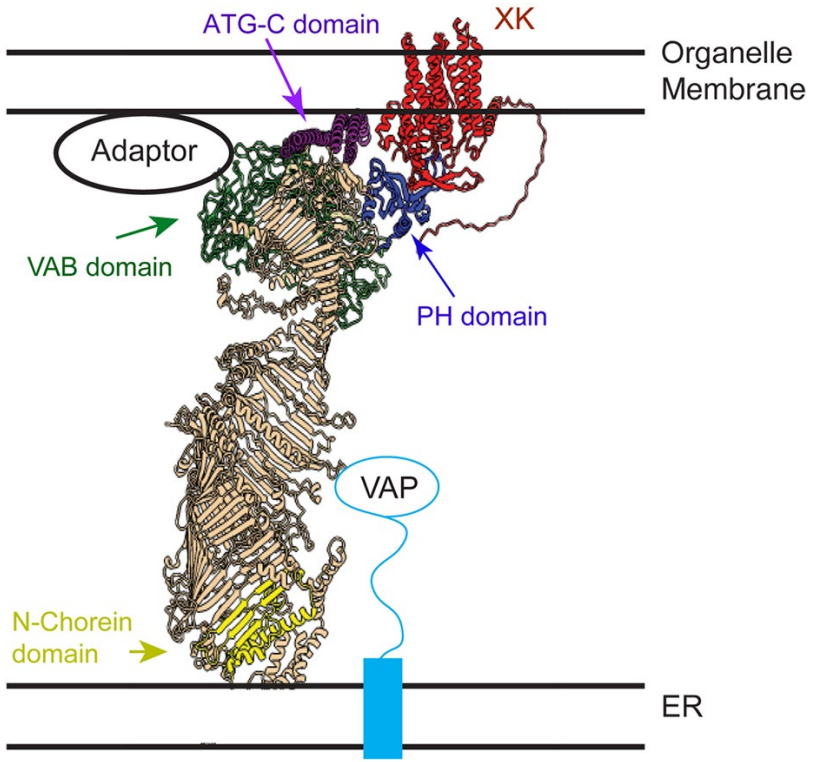
Molecular interaction of VPS13A & XK

© 2022. Published by The Company of Biologists Ltd | Journal of Cell Science (2022) 135, jcs260227. doi:10.1242/jcs.260227

RESEARCH ARTICLE

Interaction between VPS13A and the XK scramblase is important for VPS13A function in humans

Jae-Sook Park[1], Yiying Hu[2,3], Nancy M. Hollingsworth[1], Gabriel Miltenberger-Miltenyi[4] and Aaron M. Neiman[1,*]

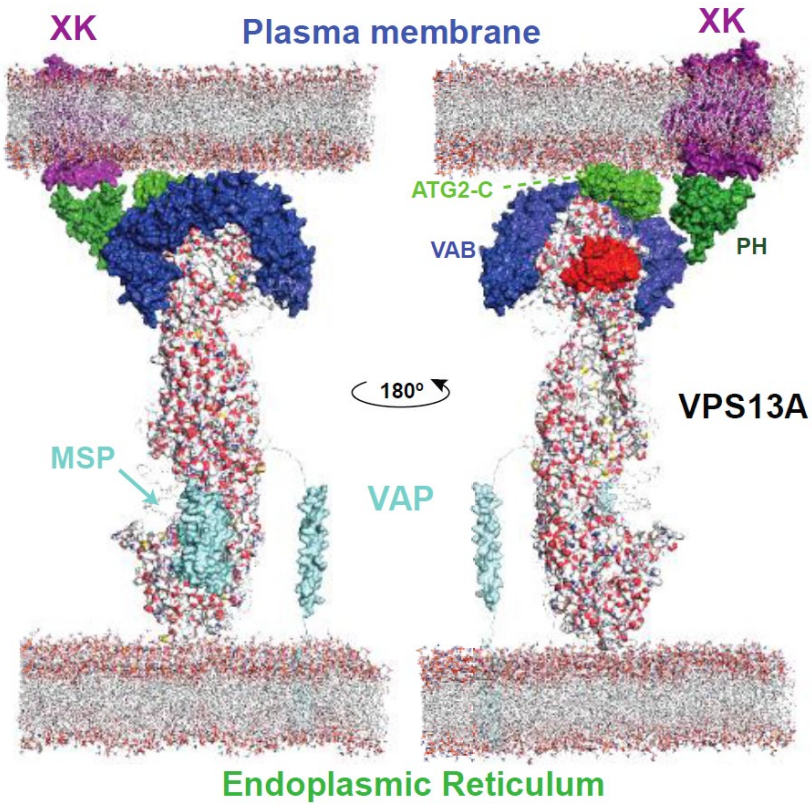


PNAS RESEARCH ARTICLE | CELL BIOLOGY OPEN ACCESS

A partnership between the lipid scramblase XK and the lipid transfer protein VPS13A at the plasma membrane

Andrés Guillén-Samander[a,b,c,d], Yumei Wu[a,b,c,d], S. Sebastian Pineda[e,f,g], Francisco J. García[h,i], Julia N. Eisen[a,b,c,d], Marianna Leonzino[a,b,c,d,j,k], Berrak Ugur[a,b,c,d], Manolis Kellis[e,f,g], Myriam Heiman[h,i], and Pietro De Camilli[a,b,c,d,l,1]

Contributed by Pietro De Camilli; received March 30, 2022; accepted July 1, 2022; reviewed by Tim Levine and Antonella De Matteis



„Levine-Critchley syndrome“: obsolete

Adrian Danek [1], Nevena Krstić [2], Michael T. Hayes [3], Robert C. Green [4], Connie M. Westhoff [5], Sunitha Vege [5], Ruth H. Walker [6]

[1]Neurologische Klinik und Poliklinik, Ludwig-Maximilians-Universität, Munich, Germany; [2]Department of Obstetrics and Gynecology, University of South Florida, Tampa, FL, USA; [3]Department of Neurology, and [4]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [5]New York Blood Center, New York, NY, USA; [6]Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA

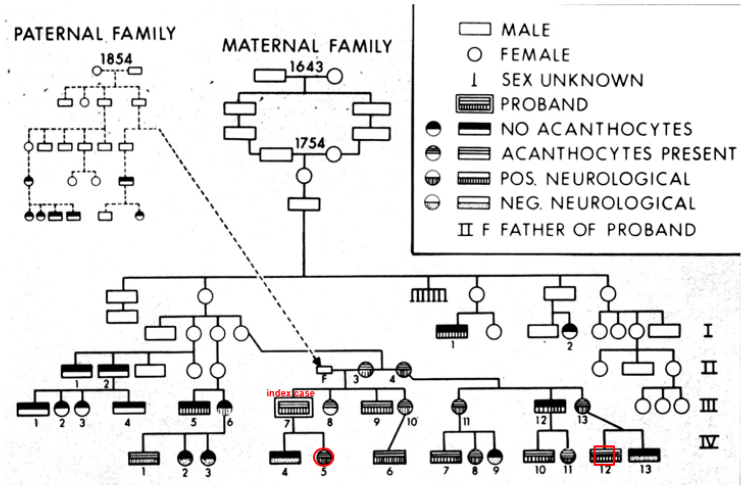
Abstract

In the 1960s, two families of patients with neurological features and red blood cell acanthocytosis in the absence of lipoprotein abnormalities were described independently by Irving Levine and Edmund Critchley (Levine et al., 1968; Critchley et al., 1968). The condition was later designated „Levine-Critchley syndrome“, or alternatively as “neuroacanthocytosis".

In 2011, we demonstrated that Critchley's family was affected by mutations in the autosomal *VPS13A* gene (Velayos-Baeza et al., 2011). We now make a diagnosis of XK disease (McLeod syndrome) in Levine´s family.

We confirm the c.906delT (p.Ile302Metfs*21) mutation in the X-chromosomal gene *XK* In the daughter of his index case.

Method
The daughter of Levine´s index case was contacted with the help of her family and a buccal mucosa sample was analysed for the presence of the *XK* mutation found in her cousin once removed.



XK mutation: c.906delT (p.Ile302Metfs*21)

Levine family: XK Critchley family: VPS13A

Reference material: general

McLeod Neuroacanthocytosis Syndrome

Hans H Jung [1], Adrian Danek [2], Ruth H Walker [3], Beat M Frey [4], Kevin Peikert [5]
Margaret P Adam, David B Everman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace,
Lora JH Bean, Karen W Gripp, Anne Amemiya, editors.

In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
2004 Dec 3 [updated 2021 Sep 16].

Affiliations + expand

PMID: 20301528 Bookshelf ID: NBK1354

Chorea-Acanthocytosis

Antonio Velayos Baeza [1], Carol Dobson-Stone [2], Luca Rampoldi [3], Benedikt Bader [4],
Ruth H Walker [5], Adrian Danek [4], Anthony P Monaco [1 6]
Margaret P Adam, David B Everman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace,
Lora JH Bean, Karen W Gripp, Anne Amemiya, editors.

In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
2002 Jun 14 [updated 2019 Apr 18].

Affiliations + expand

PMID: 20301561 Bookshelf ID: NBK1387

→ **VPS13A disease (update 2022/23)**

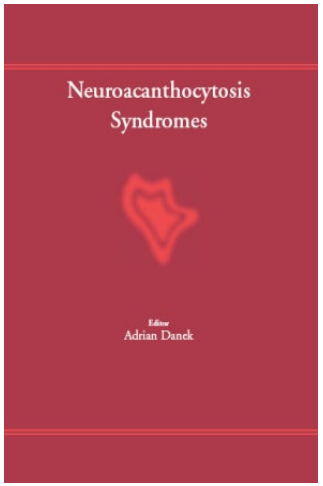
Kevin Peikert et al.

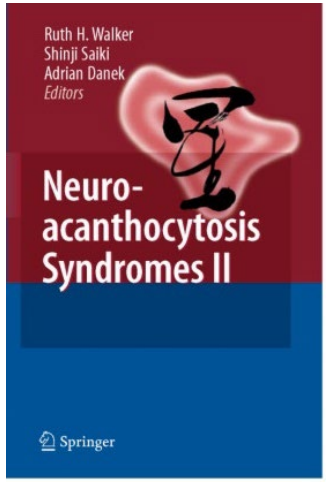
Reference: historic

Neuroacanthocytosis symposia

- Seeon, Germany 2002
- Montreal, Canada 2005
- Kyoto, Japan 2006

- London/Oxford, UK 2008
- Bethesda, USA 2010
- Ede, Netherlands 2012
- Stresa, Italy 2014
- Ann Arbor, USA 2016
- Dresden, Germany 2018





Tremor and Other Hyperkinetic Movements

Reading: Proceedings of the Tenth International Meeting on Neuroacanthocytosis Syndromes Share:

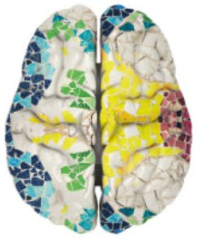
Conference Proceedings

Proceedings of the Tenth International Meeting on Neuroacanthocytosis Syndromes

Authors: Merce Masana, Manuel J. Rodriguez, Jordi Alberch

Abstract

The 10th International Meeting on Neuroacanthocytosis Syndromes was held online on March 10th–12th, 2021. The COVID19 pandemic situation made our planned meeting in Barcelona on March 2020 to be suspended by one year, and finally took place online. The meeting followed the previous nine international symposia, the last of which was held in Dresden, Germany in March, 2018. The setting of the meeting encouraged interactions, exchange of ideas and networking opportunities among the high number of participants from around the globe, including scientists, neurologists and specially patients and caregivers. A total of 27 oral communications were distributed in 8 sessions with topics ranging from molecular and cellular functions of VPS13 genes and proteins, their involvement in Neuroacanthocytosis Syndromes and finally clinical aspects and patients care. In addition, 5 posters were presented. Altogether, scientists and neurologists discussed recent advances and set the bases for next steps, action points, and future studies in close collaboration with the patient's associations, which are always actively involved in the whole process.



10th International Meeting on Neuroacanthocytosis Syndromes

BARCELONA MARCH 2020

NA News

Neuroacanthocytosis information and research

NA News 39 23 June 2022

NA News 38 28 February 2022

NANews 37 28 November 2021
NANews 37 Polish 28 November 2021

NANews 36 14 July 2021
NANews 36 Polish 14 July 2021
NANews 36 Deutsch 14 July 2021

NANews 35 - 20 November 2020
NANews 35 Polish 20November 2020
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NA News 34 3 July 2020
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NA News 33 December 2019
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NANews 32 20 May 2019
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VPS13A and XK bulk lipid transfer diseases
Adrian Danek - danek@lmu.de

VPS13 Forum meetings (Zoom)

Bulk lipid transfer as novel disease mechanism and the WIPI4/ATG2a molecular complex	Tassula Proikas-Cezanne, University of Tübingen, Germany; Vassilena Iankova; LMU Munich, Germany
Clinical aspects of McLeod syndrome (XK disease) with focus on unmet needs in blood banking	Hans Jung, University of Zurich, Switzerland; Beat M. Frey, Swiss Red Cross, Switzerland; Kevin Peikert, University of Rostock, Germany
Neuropathology of Neuroacanthocytosis Syndromes project	Ruth H. Walker, John F. Crary and Amber Tetlow, Mount Sinai Brain Bank New York, USA; Gabriel Miltenberger-Miltenyi, LMU Munich, Germany
Patient registries and natural history studies	Bernhard Landwehrmeyer, University of Ulm, Germany; Megan O'Boyle, RARE-X, USA
VPS13 proteins and XK in membrane lipid dynamics	Pietro De Camilli, Yale University, New Haven, CT, USA; Aaron M Neiman, Stony Brook University, NY, USA; Shikegazu Nagata, Osaka University, Japan
Disease insight from animal models	Eric H. Baehrecke University of Massachusetts, USA; Ody Sibon University of Groningen, The Netherlands; Lucia de Franceschi University of Verona, Italy
Blood cell physiology and acanthocyte genesis	Lars Kaestner, Saarland University, Germany; Donatienne Tyteca, UCLouvain, Belgium; Felix Reichel, MPI Erlangen, Germany
Update on neuropathology and recent clinical research	Ruth H. Walker, Mount Sinai Brain Bank New York, USA; Gabriel Miltenberger-Miltenyi and Adrian Danek, LMU Munich, Germany
Membrane contact site proteins in neuronal and red cell function	Tim P. Levine, University College London Institute of Ophthalmology, London, UK; Lesley J. Bruce, Bristol Institute for Transfusion Sciences, NHS Blood and Transplant, UK

Upcoming 10th VPS13 Forum: Medical Q & A

Monday, November 28, 2022 - 2:00-4:00 pm (Central European Time)

Medical Questions and Answers with Panel of Experts and Patient Advocates

Adrian Danek, Andreas Hermann, Ginger Irvine, Hans Jung, Gabriel Miltenberger-Miltenyi, Alzbeta Mühlbäck, Kevin Peikert, Ruth H Walker, Cornelius Werner, Joy Willard-Williford

Dysphagia in rare movement disorders such as Huntington's disease

Why we should get rid of the term neuroacanthocytosis – or shouldn´t we?

We encourage patients, family members, and caregivers to submit medical questions prior to the meeting and to indicate if a translation from English into their mother language will be needed. Please submit your questions to: kevin.peikert@med.uni-rostock.de

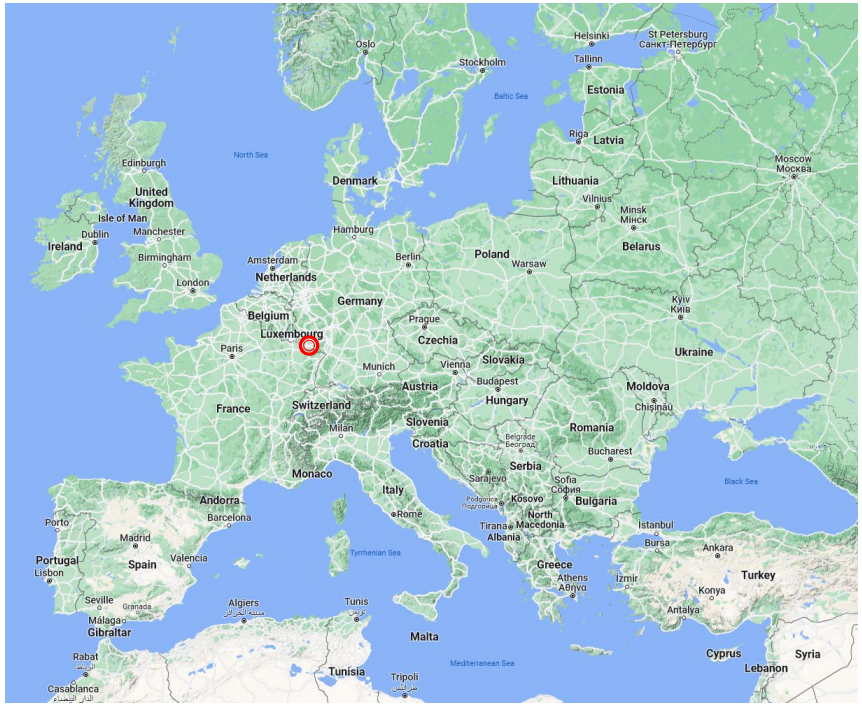
Zoom-link: https://uni-rostock-de.zoom.us/j/62806527413?pwd=ZXk0TG5vQ1M5dDA4WEFYVk5xV2RVQT09

11th International Meeting

September 15-17, 2023

Homburg/Saar

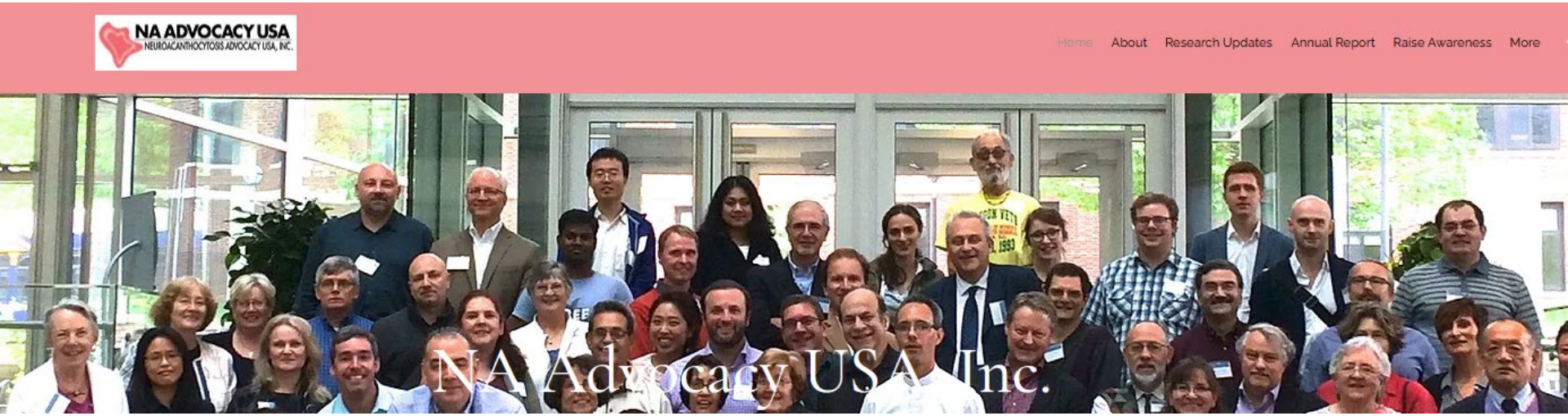
Universitätsklinikum



Adrian Danek - danek@lmu.de

Patient advocacies

Advocacy for Neuroacanthocytosis Patients
An ultra rare disease
www.naadvocacy.org



Q&A 3: Acanthocytes are (single answer)

1 skin lesions in diabetes.

2 an obligatory finding in XK disease.

3 deformed red blood cells.

4 easily picked up in routine investigations.

5 required for diagnosing VPS13A disease.

Q&A 4: bulk lipid transport (several correct)

1 is a long established and understood mechanism.

2 requires tube-like molecules.

3 is unrelated to phagosome formation.

4 requires scramblases.

5 relates to membrane contact sites.

Q&A 5: XK disease (several correct)

1 is diagnosed in blood banks (Duffy serology).

2 carries risks for blood transfusions.

3 is transmitted as an autosomal recessive trait.

4 is often accompanied by cardiomyopathy.

5 is typically characterized by hyperCKemia.

Q&A 6: VPS13A disease (several correct)

1 does not present with parkinsonism.

2 seems to relate to defective bulk lipid transport.

3 is transmitted as an autosomal dominant trait.

4 is often accompanied by cardiomyopathy.

5 is typically characterized by hyperCKemia.

Joint webinar series

THANK YOU

Next Webinar: ‘When is it appropriate to suspect a metabolic disorder in a child with chorea?‘

08 November 2022, 15-16h CET