European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Choreas and HD'
3 December 2019

Joint webinar series

Neuroacanthocytosis syndromes

Adrian Danek
Ludwig-Maximilians-Universität Munich, Germany

Speaker: Prof. Dr. med. Adrian Danek

Since 2002 Professor of Cognitive Neurology at LMU, contributed to > 200 PubMed listed papers, H-Index 39.

Expertise and research focus: cognitive neurology, functional neuroanatomy, dementia, neuroacanthocytosis

- Student of medicine at the Ludwig-Maximilians-Universität (LMU) in Munich, Germany
- 1992-1999 assistant professor, Department of Neurology, LMU Munich (Prof. Brandt)
- 1999-2001 visiting scientist, associate investigator: Cognitive Neuroscience Section, NINDS, National Institutes of Health, Bethesda, Md, USA (Dr. J. Grafman)

- 2010-2013 coordinator of ERA-net network "European multidisciplinary initiative on neuroacanthocytosis"; www.med.uni-muenchen.de/forschung/verbuende/euprojekte/abgeschlossen/emina/index.html)
- Financed by the Advocacy for Neuroacanthocytosis Patients (www.naadvocacy.org) he offers a Western blot for chorein determination in blood samples →free diagnostic tool used by physicians worldwide for >700 patients so far - confirming a diagnosis of chorea-acanthocytosis (ChAc) in ~ 30% of the cases.
- Curator of web-based NA patient database within the European Huntington´s Disease network (www.euro-hd.net/html/na/registry) for trial readiness in spite of world-wide dispersal
- Curator (with A. Velayos-Baeza and G. Miltenberger-Miltenyi) of the VPS13A gene homepage of the Leiden Open Variation Database (https://databases.lovd.nl/shared/genes/VPS13A)

General information about the webinars

- RARE neurological, neuromuscular and movement disorders
- 30-35min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Target audience: neurologists, residents, paediatric neurologists, geneticists from RND members, RND affiliated partners, and non-RND HCPs across Europe and worldwide
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- Post-webinar survey (2-3min): satisfaction, topic ideas for next webinars

Neuroacanthocytosis (NA) syndromes

Learning objectives

- Appreciate the heterogeneity of NA syndromes
  - Chorea-acanthocytosis (ChAc), McLeod syndrome (MLS) etc.
- Become able to distinguish the two core syndromes
  - Know about genes and patterns of inheritance
- Learn about helpful clinical and laboratory hints
  - Estimate the contribution of blood films
- Hear about current basic science insights
  - *VPS13* gene family, membrane contact sites, lipid transfer
- Know where to find additional information
  - Reviews, books, symposia, Advocacy for NA Patients

Adrian Danek, Ludwig-Maximilians-Universität München, Neurologische Klinik (Direktorin: Prof. Dr. M. Dieterich)

Webinar outline

- Mutual introduction
- Concept of „neuroacanthocytosis“ (NA)
- MLS & ChAc, the two core NA syndromes
  - clinical features - genetic background - epidemiology
  - suggestive hints - differential diagnosis - diagnostic procedures
- Basic science news
- Mutation and patient registries for trial readiness
- Reference material
- Questions and answers

Q&A 1: participants' background

Expertise:

- Adult neurology?
- Child neurology?
- Psychiatry?
- Cardiology?
- Blood banking?
- Hematology?
- Genetics?

Type of clinic:

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

Q&A 2: participants' previous experience

- Patients with McLeod syndrome?
- Patients with chorea-acanthocytosis?

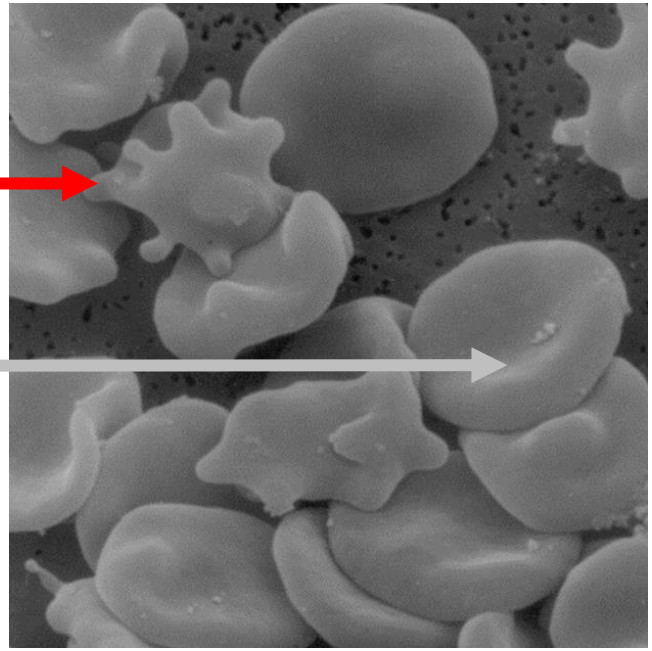
- Experience with acanthocyte determination?
- With method of Storch et al. (J.Neurol. 2005)?

- Availability of Kell blood group phenotyping?
- Information on chorein Western blot?

What is acanthocytosis?

Acanthocyte

Discocyte



ἄκανθα : thorn

ἀκή (*akē* “point”) + *ἄνθος* (*anthos* “flower”)

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

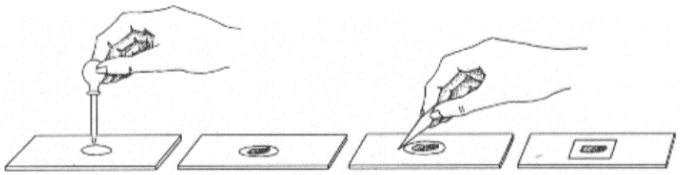


Table 1. Parameters of the standardized acanthocyte screening test (adapted from *Storch et al, 2003*).

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

Neuroacanthocytosis:

neurological findings

plus

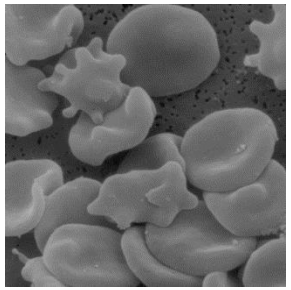
acanthocytosis

(an umbrella term for a variety of diseases)

Neuroacanthocytosis: a variety of diseases

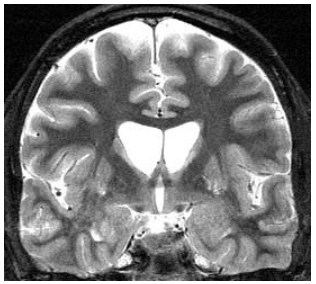
Neuroacanthocytosis with lipoprotein disorders

- Abetalipoproteinemia
- Familial hypobetalipoproteinemia
- Anderson disease
- Atypical Wolman disease



Neuroacanthocytosis with basal ganglia involvement

- McLeod syndrome
- Chorea-acanthocytosis
- Pantothenate kinase associated neurodegeneration (PKAN)
- Aceruloplasminemia? (single case)
- *ELAC2* mutations? (single case)
- Huntington‘s Disease-like 2? (acanthocytes not a general feature)



Two core neuroacanthocytosis syndromes

McLeod syndrome (MLS)	**X-linked**	***XK***
Chorea-acanthocytosis (ChAc)	**autosomal recessive**	***VPS13A***

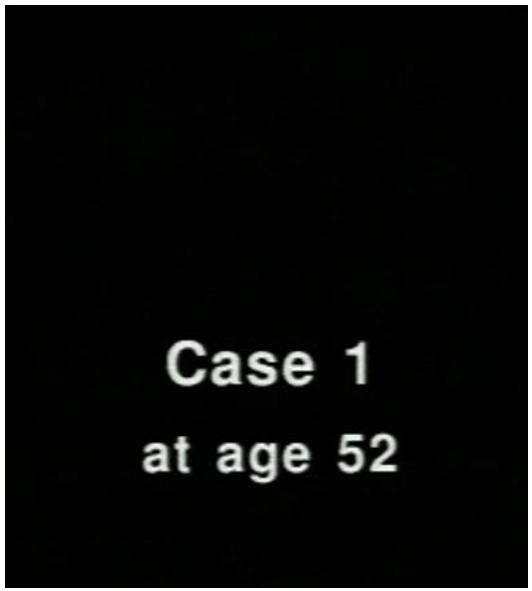
A new phenotype (McLeod) in the Kell blood-group system

Allen FH et al. Vox Sanguinis. 1961;6:555–60

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.

The serological findings can be briefly summarized by stating that McLeod is negative with anti-K1 (Kell), anti-K3 (Penney), and anti-K5 (Peltz), and reacts weakly with anti-K2 (Cellano), and anti-K4 (Rautenberg).

Brothers with heart disease & ↑ muscle CK



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]

Movement Disorders
Vol. 16, No. 5, 2001, pp. 882–889

Published by Wiley-Liss, Inc.

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]

MLS: Multi-system disease with CNS involvement

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

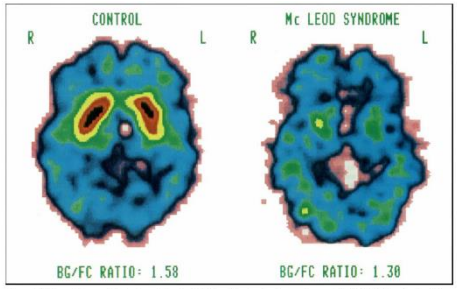


Figure 2. Pattern of accumulation of a radioactively labeled D_2-selective dopamine agonist (^{123}I-IBZM) in horizontal SPECT brain images of a normal control (left) and a patient with McLeod syndrome (right). Reduced striatal dopamine

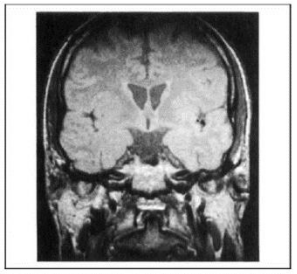


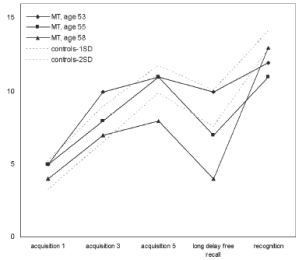
Figure 1. Proton-density-weighted MRI in a 52-year-old patient with chorea and the McLeod erythrocyte phenotype discloses slight atrophy of the caudate nucleus

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

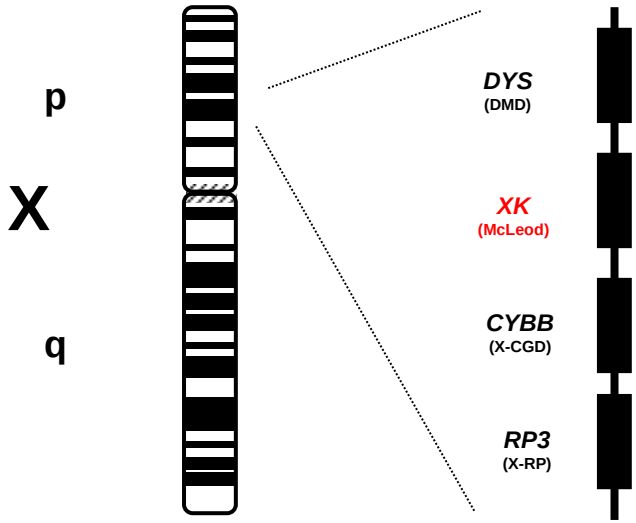


estimate: <300 cases world-wide

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*

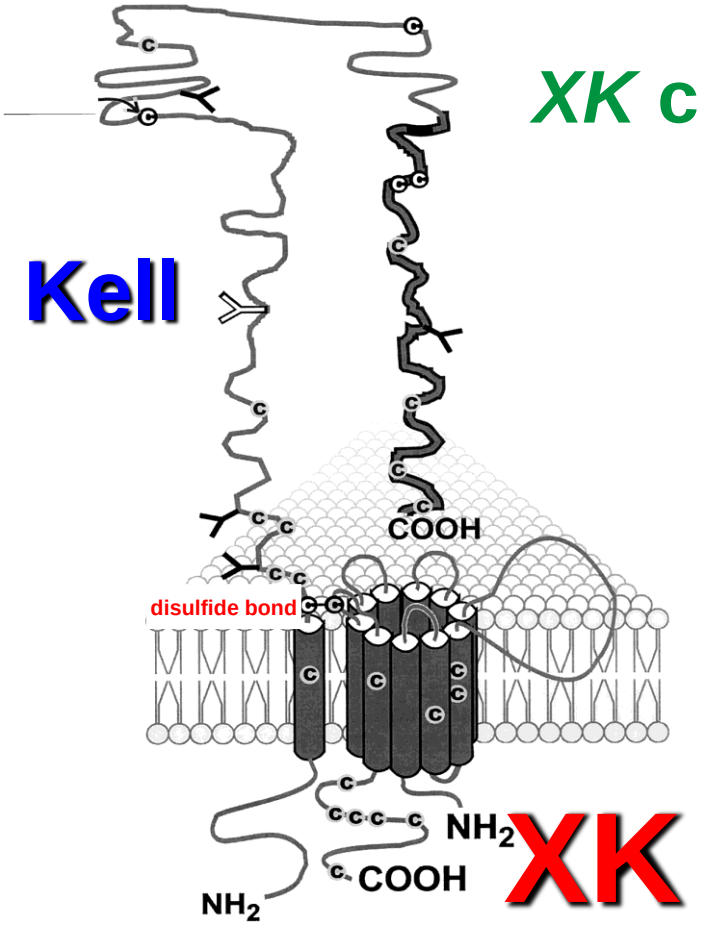


Finding	Frequency (%)
Weak Kell erythrocyte antigens	100 (91–100)
Acanthocytosis	100 (91–100)
Elevation of serum creatine phosphokinase	100 (100)
Elevation of lactate dehydrogenase	91 (45–95)
Elevation of aspartate aminotransferase	33 (23–55)
Elevation of alanine aminotransferase	33 (23–55)
Elevation 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)

McLeod Neuroacanthocytosis: Genotype and Phenotype

Adrian Danek, MD, PhD,[1] Justin P. Rubio, PhD,[2] Luca Rampoldi, PhD,[3] Mengfatt Ho, D Phil (Oxon),[2] Carol Dobson-Stone, MBiochem,[2] François Tison, MD, PhD,[3] William A. Symmans, MD,[4,5] Matthias Oechsner, MD,[5] Wolfgang Kalchreuth, MD,[6] Julie M. Watt, BSc,[7] Alastair J. Corbett, MD, FRACP,[8] Hisham H. M. Hamdalla, MD, MRCP (UK),[9] Andrew G. Marshall, MD, MRCP (UK),[10] Ian Sutton, MD, MRCP (UK),[11] Maria Teresa Dotti, MD,[12] Alessandro Malandrini, MD,[12] Ruth H. Walker, MD, PhD,[13] Geoff Daniels, PhD,[14] and Anthony P. Monaco, MD, PhD[2]

Ann. Neurol. 2001;50:755



XK codes for the Kx/XK protein

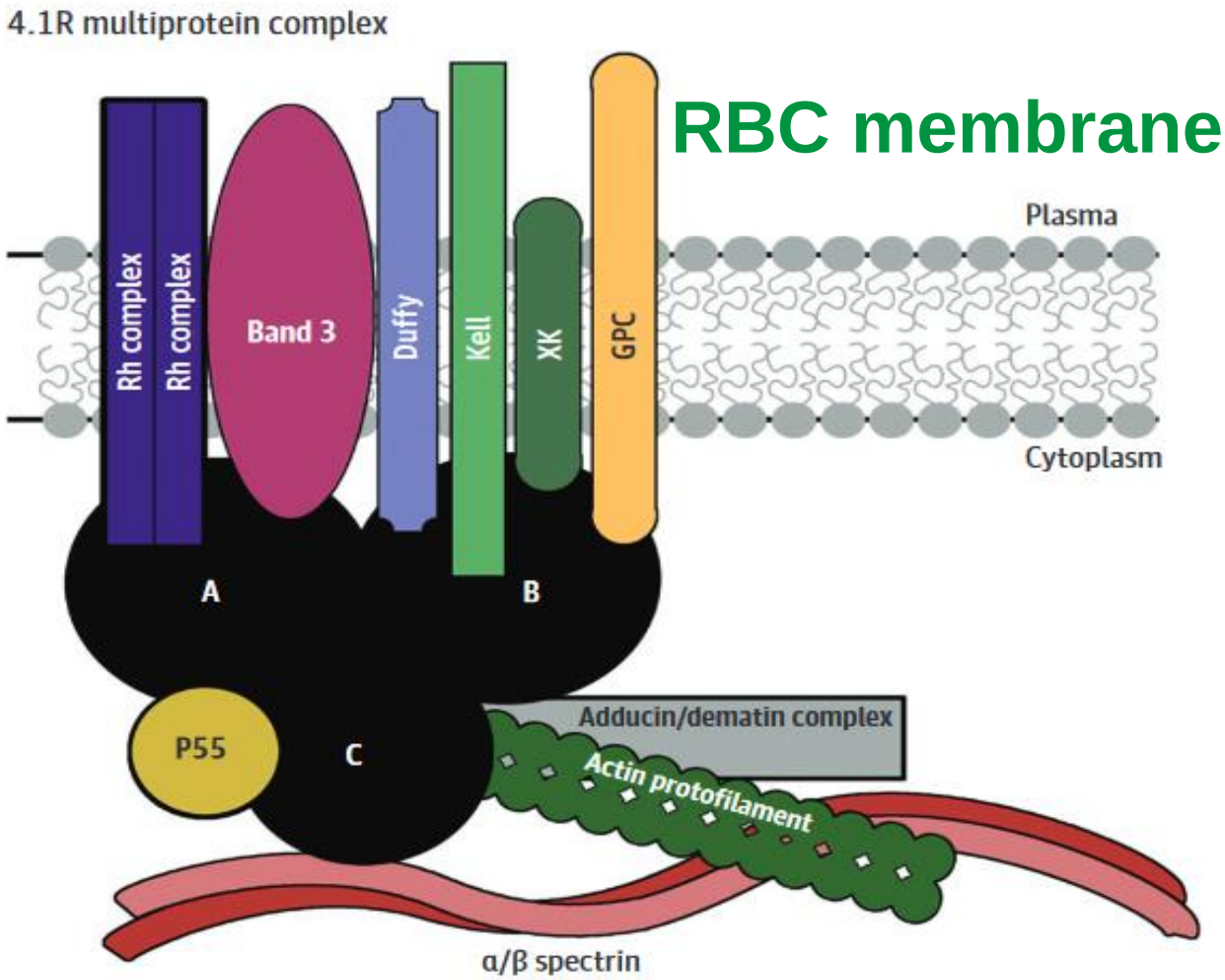
Membrane protein bound to

Kell blood group protein

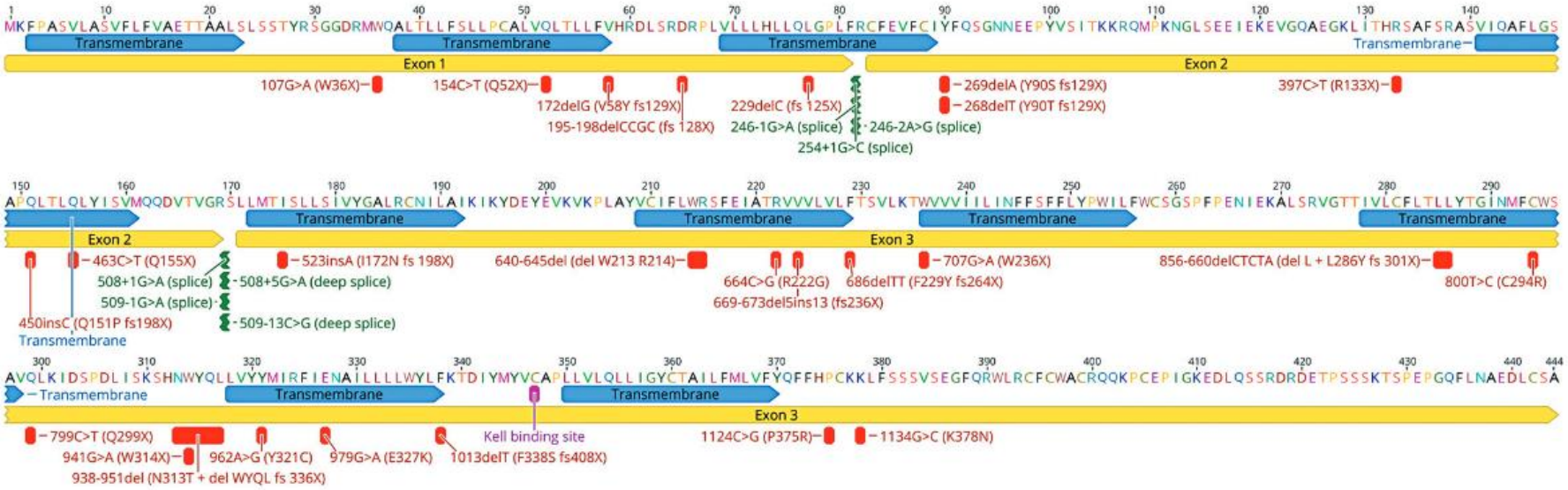
Member of family of

“XK related proteins”

RBC membrane model



Roulis et al. JAMA Neurol. 2018;75:1554



Hugh McLeod deletion

Kx protein:

444 amino acids

10 transmembrane domains

Kell binding site

Roulis et al. JAMA Neurol. 2018;75:1554

Chorea-acanthocytosis (ChAc)

Initially described by
I. Levine (1960/1968) and E. Critchley (1967/1968)

New England & Kentucky families
with females and males affected; recessive?


„I can´t sit still and it´s very unsettling. I guess I would call them uncontrollable body movements.“
https://global.oup.com/us/companion.websites/9780195393514

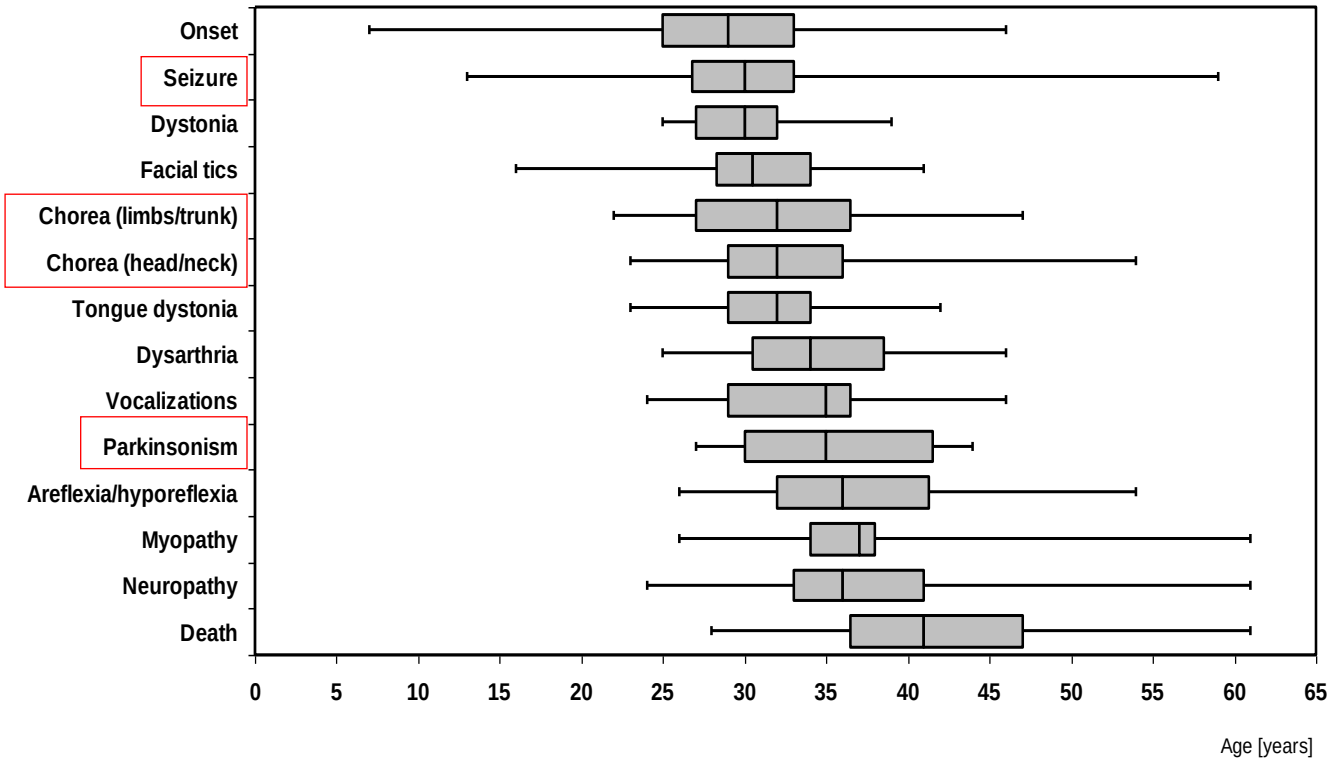
Impaired stance and gait („rubber man“)

Orofacial dyskinesia

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

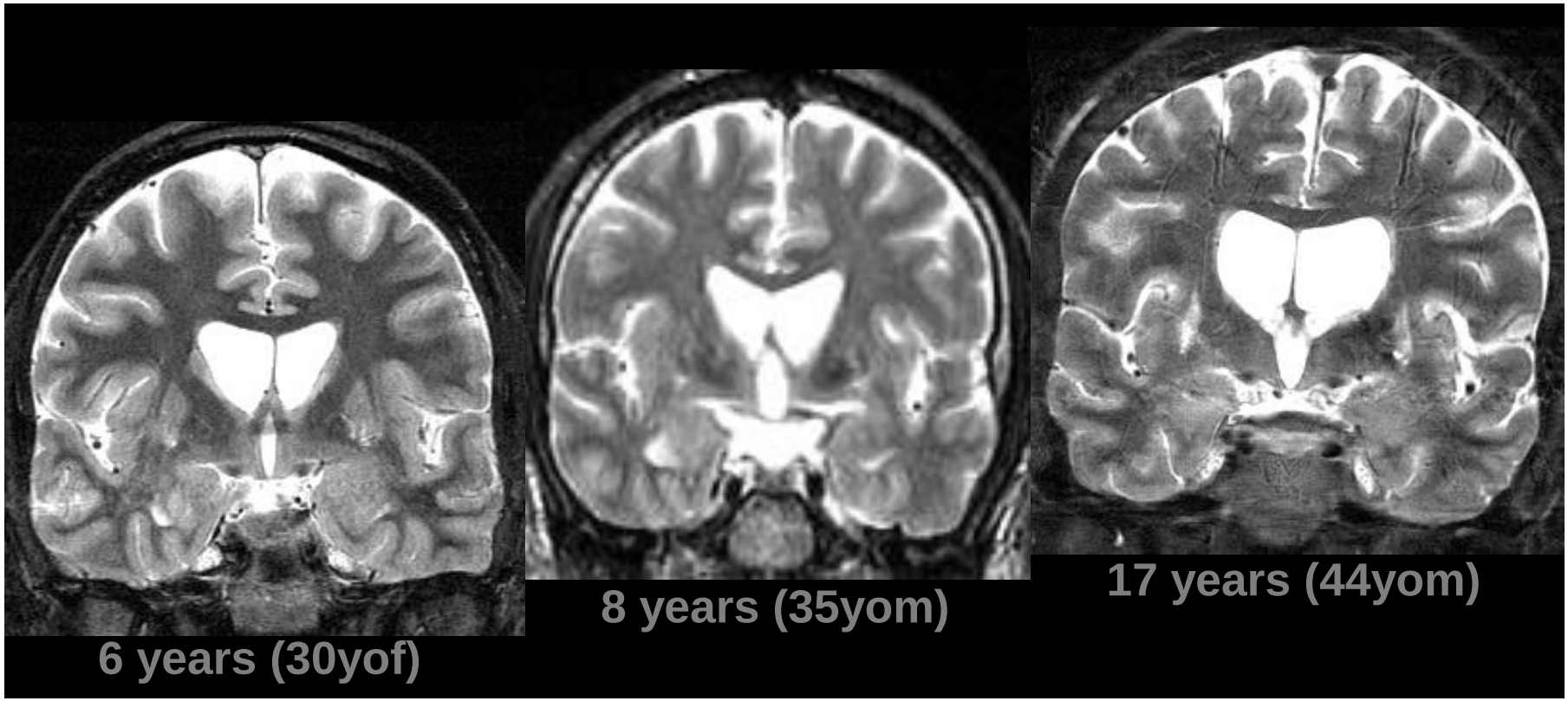
Bader et al. *Mov Disord* 25 (2010) 127-129

Course of ChAc



Progression to hypokinesia

Progressive brain atrophy/neurodegeneration



VPS13A (3174aa, 73 exons): mutation spectrum

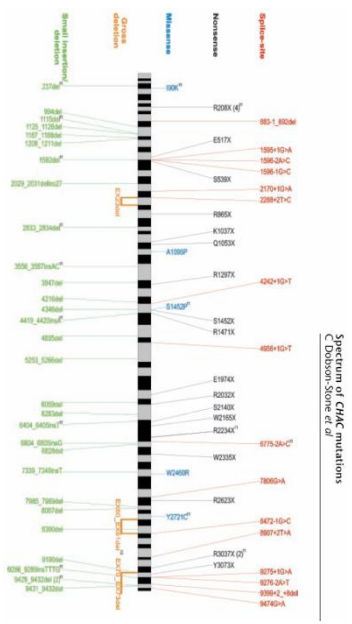


Table 2 *VPS13A* disease mutations described in ChAc patients

#	Location	DNA change[a]	Protein change[a]	Genotype[b]	Refs.
		Missense			
1	Exon 4	c.269T>A	p.I90K	ht	[26]
2	Exon 31	c.3283G>C	p.A1095P	ht	[12]
3	Exon 37	c.4354T>C	p.S1452P	hm	[26]
4	Exon 53	c.7378T>C	p.W2460R	hm	[12]
5	Exon 57	c.8016G>C	p.K2672N	ht	[43]
6	Exon 59	c.8162A>G	p.Y2721C	ht	[26]
		Nonsense			
7	Exon 9	c.622C>T	p.R208X	ht, hm	[12, 26]
8	Exon 13	c.1078C>T	p.Q360X	ht	[11]
9	Exon 17	c.1549G>T	p.E517X	ht	[12]
10	Exon 18	c.1616C>G	p.S539X	ht	[12]
11	Exon 22	c.2191C>T	p.R731X	ht	[11]
12	Exon 23	c.2347C>T	p.Q783X	hm	[11]
13	Exon 25	c.2593C>T	p.R865X	hm	[12]
14	Exon 29	c.3109A>T	p.K1037X	ht	[12]
15	Exon 30	c.3157C>T	p.Q1053X	hm	[12]
16	Exon 34	c.3889C>T	p.R1297X	ht	[12]
17	Exon 37	c.4355C>G	p.S1452X	ht	[12, 14]
18	Exon 37	c.4411C>T	p.R1471X	hm, ht	[11, 12]
19	Exon 41	c.5084T>A	p.L1695X	ht	[11]
20	Exon 45	c.5920C>T	p.E1974X	hm	[12]
21	Exon 46	c.6094C>T	p.R2032X	ht	[12]
22	Exon 48	c.6419C>G	p.S2140X	ht	[12]
23	Exon 48	c.6494G>A	p.W2165X	hm	[12]
24	Exon 48	c.6700C>T	p.R2234X	ht	[26]
25	Exon 50	c.7015G>A	p.W2339X	ht	[12]
26	Exon 56	c.7867C>T	p.R2623X	ht	[12]
27	Exon 68	c.9109C>T	p.R3037X	ht	[12, 26]
28	Exon 70	c.9219C>G	p.Y3073X	ht	[12]
		Small insertion/deletion			
29	Exon 4	c.237del	p.E80KfsX11	ht	[26]
30	Exon 5	c.365_372dupAACAAAAA	p.V125NfsX4	ht	[11]
31	Exon 13	c.994del	p.A332LfsX10	ht	[12]
32	Exon 13	c.1115del	p.K372SfsX2	hm	[26]
33	Exon 13	c.1125_1128del	p.S375RfsX23	ht	[12]
34	Exon 14	c.1187_1188del	p.F396X	hm	[12]
35	Exon 14	c.1208_1211del	p.Q403RfsX6	ht	[12]
36	Exon 17	c.1592del	p.I531KfsX7	hm	[26]
37	Exon 20	c.2029_2031delinsTT	p.H677delinsTYX	ht	[12]
38	Exon 27	c.2833_2834del	p.K945EfsX11	ht	[26]
39	Exon 33	c.3556_3557dupAC	p.V1187LfsX12	hm	[11, 26]
40	Exon 34	c.3847del	p.L1283WfsX7	hm	[12]
41	Exon 35	c.3995_3996delinsA	p.F1332X	ht	[11]
42	Exon 36	c.4216del	p.V1406CfsX20	ht	[12]
43	Exon 37	c.4346del	p.S1449FfsX5	ht	[12]

(continued)

Table 2 (continued)

#	Location	DNA change[a]	Protein change[a]	Genotype[b]	Refs.
		Small insertion/deletion			
44	Exon 38	c.4419dupA	p.G1474RfsX7	ht	[26]
45	Exon 38	c.4428_4431del	p.G1478LfsX6	ht	[11]
46	Exon 39	c.4724del	p.P1575LfsX3	hm	[11]
47	Exon 39	c.4835del	p.P1612QfsX30	ht	[12]
48	Exon 40	c.4903_4906del	p.K1635VfsX6	ht	[11]
49	Exon 41	c.5253_5266del	p.F1751LfsX14	ht	[12]
50	Exon 45	c.5909_5910del	p.E1970VfsX4	ht	[14]
51	Exon 46	c.6059del	p.P2020LfsX9	hm	[11, 12]
52	Exon 47	c.6283del	p.S2095QfsX10	ht	[12]
53	Exon 48	c.6404dupT	p.S2136KfsX2	ht	[26]
54	Exon 49	c.6804dupG	p.S2269VfsX7	ht	[12]
55	Exon 49	c.6828del	p.V2277LfsX12	ht	[11, 12]
56	Exon 53	c.7339dupT	p.Y2447LfsX5	ht	[12]
57	Exon 57	c.7985_7989del	p.P2662RfsX6	ht	[12]
58	Exon 57	c.8007del	p.K2669NfsX22	ht	[12]
59	Exon 61	c.8390del	p.G2797DfsX2	ht	[12]
60	Exon 67	c.9065_9066del	p.Q3022RfsX10	ht	[11]
61	Exon 70	c.9190del	p.V3064SfsX17	ht	[12]
62	Exon 71	c.9286_9289dupTTTG	p.T3098CfsX12	ht	[26]
63	Exon 71	c.9367del	p.V3123FfsX14	ht	[43]
64	Exon 72	c.9429_9432del	p.R3143SfsX5	ht	[12, 26]
65	Exon 72	c.9431_9432del	p.E3144VfsX6	hm, ht	[11, 12]
		Gross deletion[c]			
66	Exons 2–3	c.101-?_187+?del	p.A35_G63del	hm	[11]
67	Exons 8–9	c.556-?_696+?del	p.T186_L232del	hm	[11]
68	Exon 23	c.2289-?_3427+?del	p.I766HfsX14	hm	[12]
69	Exons 46–50	c.5992-?_7026+?del	p.I1998_Q2342del	hm	[14]
70	Exon 54	c.7420-?_7652+?del	p.D2474FfsX2	hm	[11]
71	Exon 60–61	c.8211+1232_8472-245delinsTC	p.V2738AfsX5	hm	[40]
72	Exon 70–73[e]	c.9189+8647_*GNA14*-c.723+897del	(p.V2064_L3174del)?	hm, ht	[12, 15]
		Splice site[a]			
73	Intron 3	c.188–5T>G	[SA:77 (no)][f]	ht	[14]
74	Intron 6	c.405+1G>A	[SD:no (83)]	ht	[14]
75	Intron 6	c.405+5G>A	[SD:no (83)]	ht	[11]
76	Intron 11	c.883–1_892del	[SA:no (82)]	ht	[12]
77	Intron 17	c.1595+1G>A	[SD:no (86)]	ht	[12]
78	Intron 17	c.1596–2A>C	[SA:no (89)]	ht	[12, 14]
79	Intron 17	c.1596–1G>C	[SA:no (89)]	ht	[12, 14]
80	Intron 21	c.2170+1G>A	[SD:no (85)]	ht	[12]
81	Intron 22	c.2288+2T>C	[SD:no (83)] A1378GfsX7; Exon 36 skipped	ht	[12]
82	Intron 36	c.4242+1G>T	skipped; [SD:no (93)]	hm, ht	[12, 15]

(continued)

Table 2 (continued)

#	Location	DNA change[a]	Protein change[a]	Genotype[b]	Refs.
83	Intron 40	c.4956+1G>T	[SD:no (83)]	ht	[12]
84	Intron 48	c.6775–2A>C	[SA:no (82)]	ht	[26]
85	Exon 55	c.7806G>A	[SD:no (76)] I2652H6X12; Exon 57 skipped; [SD:no (0.34)][f]	ht	[12]
86	Exon 57	c.8055G>A	[SA:no (88)]	ht	[30]
87	Intron 61	c.8472–1G>C	[SA:no (88)]	ht	[12]
88	Intron 65	c.8907+2T>A	[SD:no (75)]	ht	[12, 14]
89	Intron 70	c.9275+1G>A	[SD:no (80)]	ht	[12]
90	Intron 70	c.9276–2A>T	[SA:no (92)]	ht	[12]
91	Intron 71	c.9399+2_+8del	[SD:no (92)]	ht	[12]
92	Exon 72	c.9474G>A	[SD:no (81)]	ht	[12]

#mutation number

Currently > 140 distinct mutations known, all over *VPS13A*

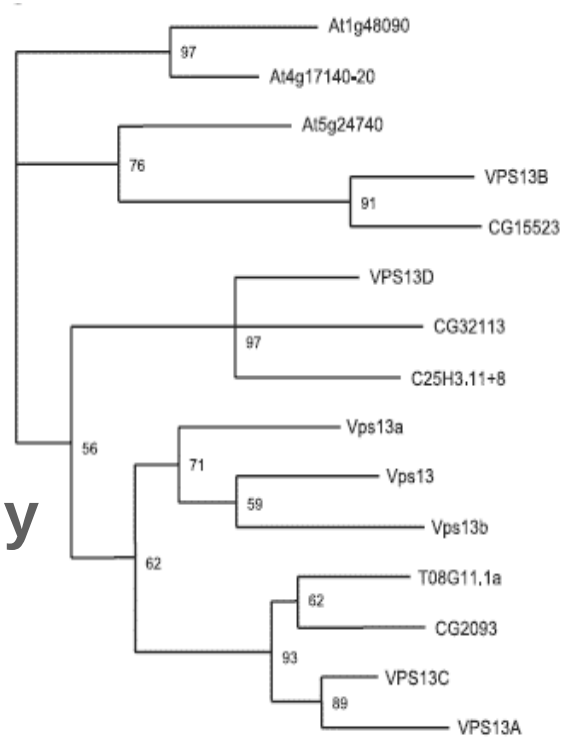
Most lead to gene product deficiency

<10 missense mutations

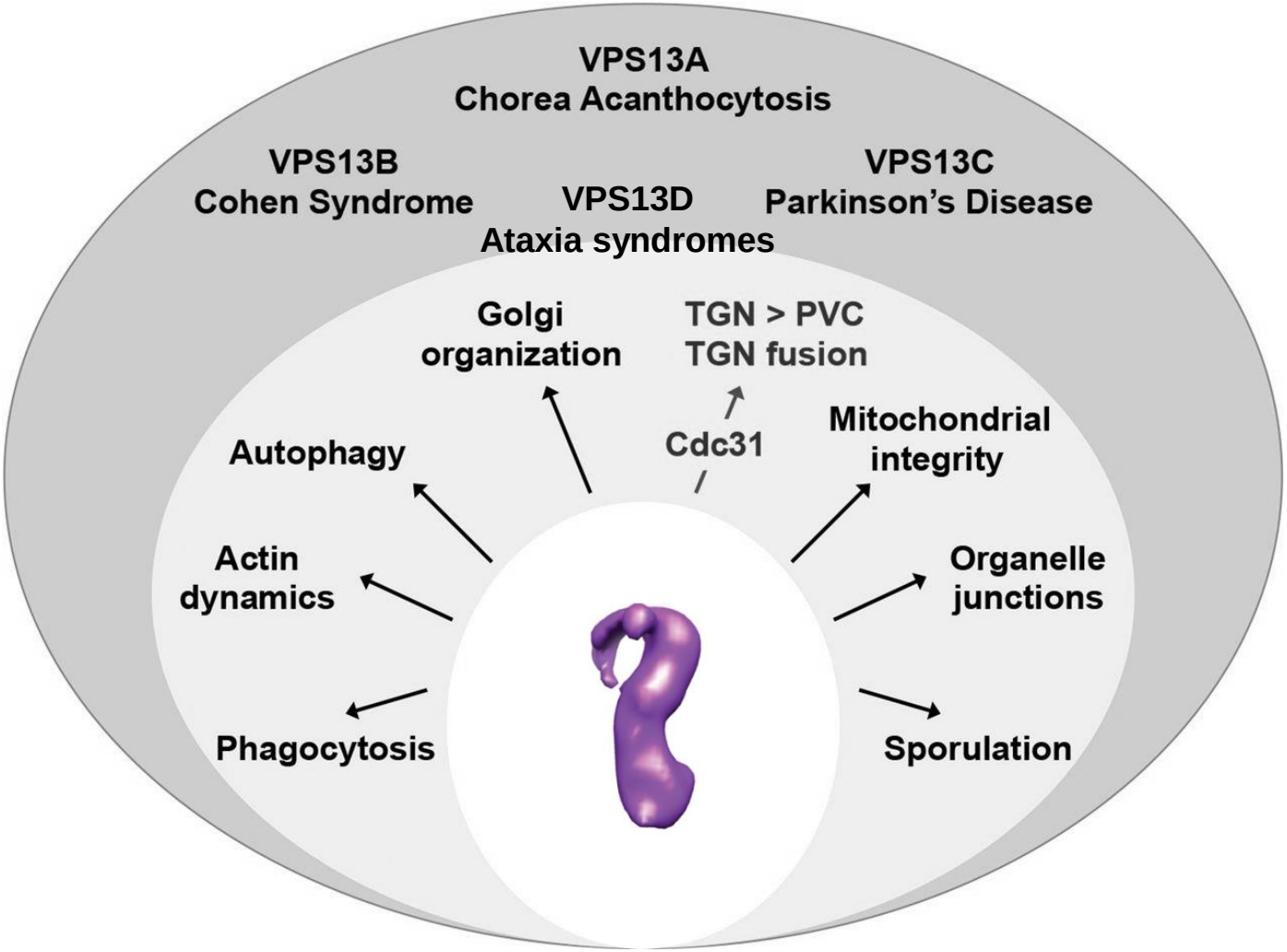
Dobson-Stone C, et al. Eur.J Hum.Genet. 2002;10:773
Velayos-Baeza A et al. The function of chorein. In: Neuroacanthocytosis II; 2008;87

VPS13 gene family

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

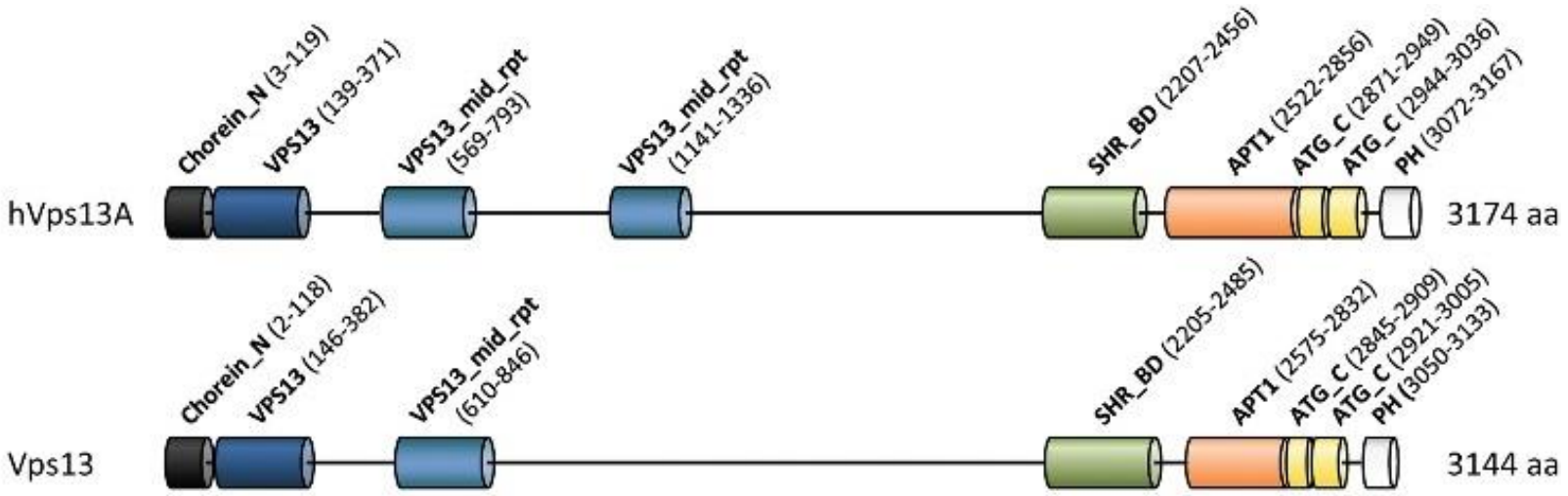


Velayos-Baeza A et al. Genomics 2004;84:536



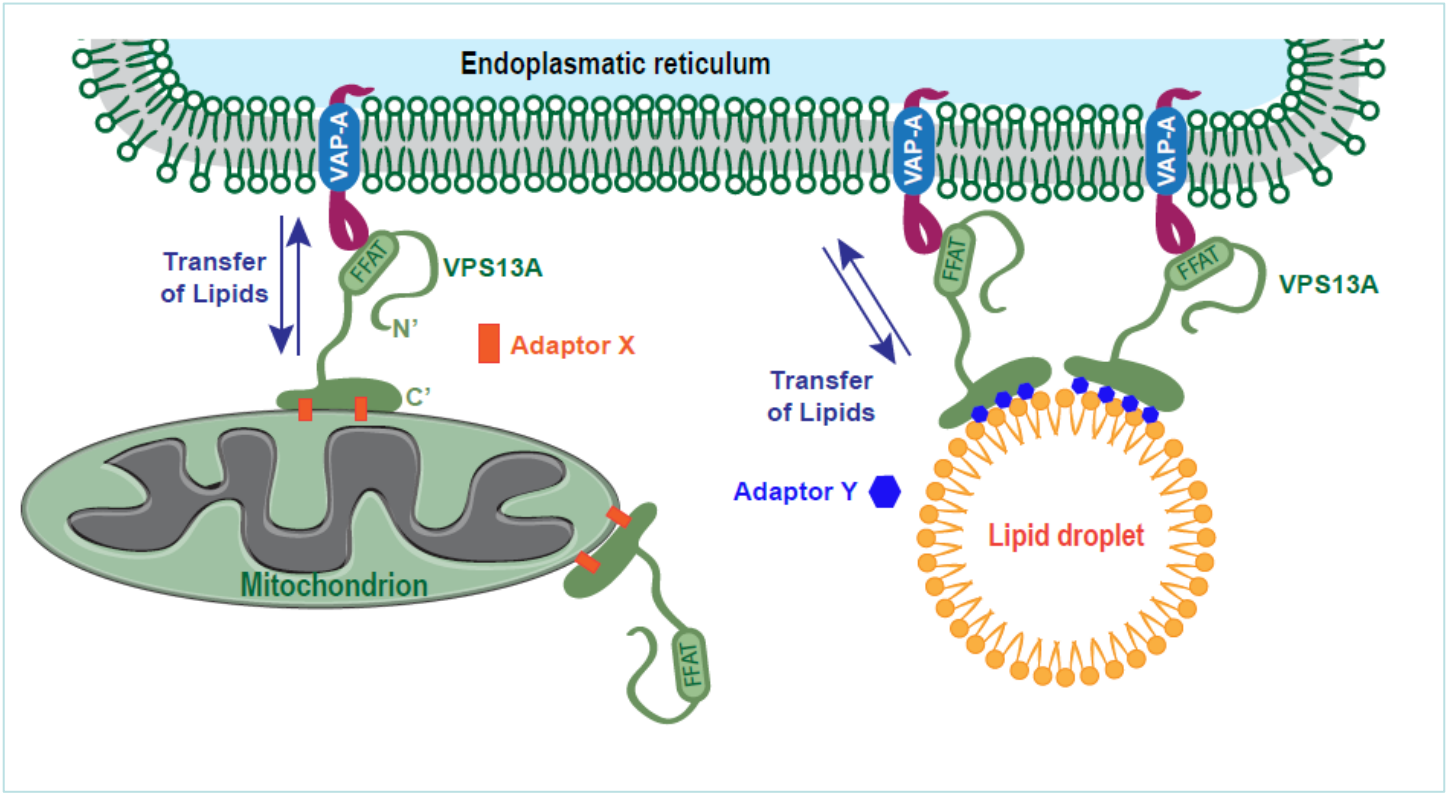
modified from Myers & Payne, J Cell Biol. 2017;216:299

Basic science: VPS13 functional domains



Rzepnikowska et al. Traffic 2017;18:711

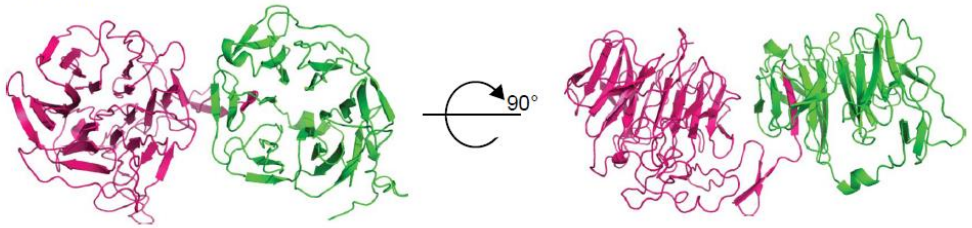
VPS13 family: inter-organellar lipid transfer



Yeshaw et al. Elife. 2019 Feb 11;8:e43561

(Yeast) Vps13 Adaptor Binding domain

H. sapiens VPS13A
Residues 1857-2490

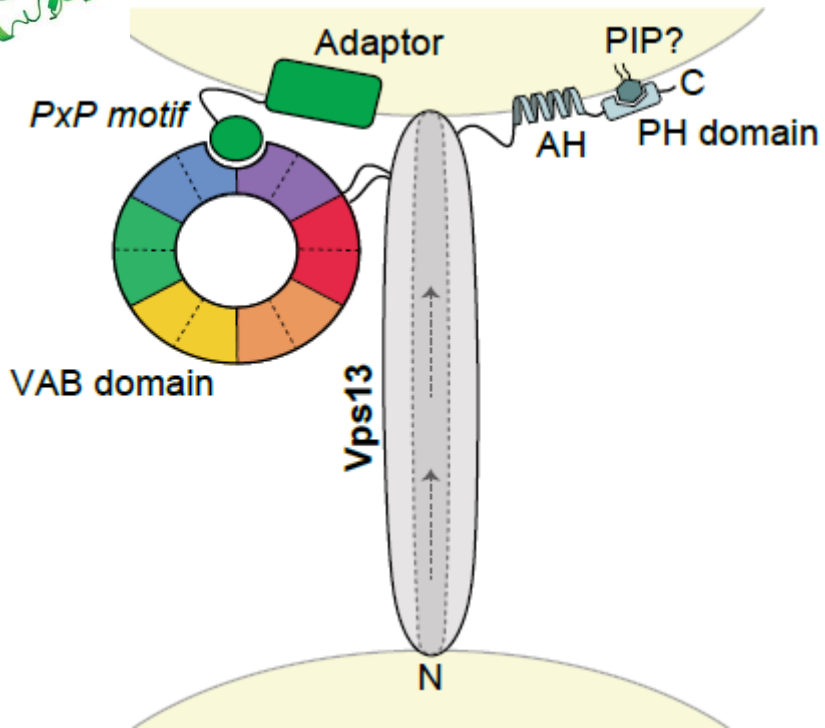


A VPS13D spastic ataxia mutation disrupts the conserved adaptor binding site in yeast Vps13

Samantha K. Dziurdzik[1,2], Björn D. M. Bean[3], Michael Davey[1], Elizabeth Conibear[1,2]

[1]Centre for Molecular Medicine and Therapeutics, British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, Canada V5Z 4H4

[2]Department of Medical Genetics, University of British Columbia, Vancouver, Canada V6H 3N1



DG ‚Choreas and HD'
December 3, 2019

Very wide differential diagnostic spectrum

- Obsessive compulsive
- Psychosis
- Tourette‘s

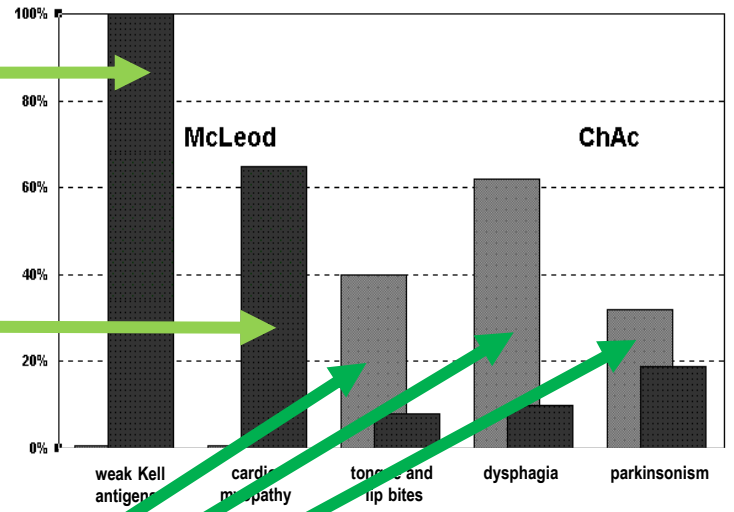
- Motor neuron disease
- Neuropathy
- Myopathy

- Huntington‘s
- Parkinson‘s
- Ataxia

- Epilepsy
- Dementia
- Neurodegeneration with brain iron group

Distinction MLS vs ChAc

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

Is MLS „delayed chorea-acanthocytosis“?

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

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Funding agencies: C.L. and F.T. have been supported by the EC-funded (E-Rare JTC 2009) EMINA project (European Multidisciplinary Initiative on Neuroacanthocytosis).
Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 10 January 2011; **Revised:** 13 May 2011; **Accepted:** 23 May 2011
Published online 28 June 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23843

Chorea-acanthocytosis (ChAc)

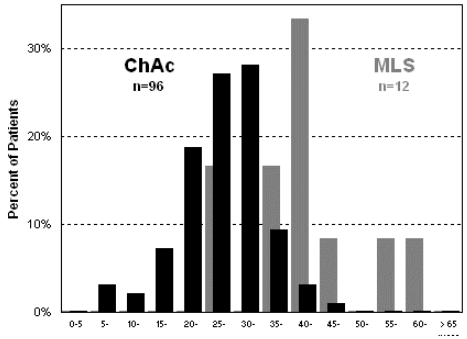
Tongue Protrusion and Feeding Dystonia: A Hallmark of Chorea-Acanthocytosis

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

Younger males and females

- **Degeneration of CNS structures (movement disorders, seizures, cognitive impairment, psychopathology, endocrine, MND)**
- **Peripheral nerve**
- **Muscle (CK elevation, atrophy, weakness)**

Ubiquitous, global prevalence ~ 5000?

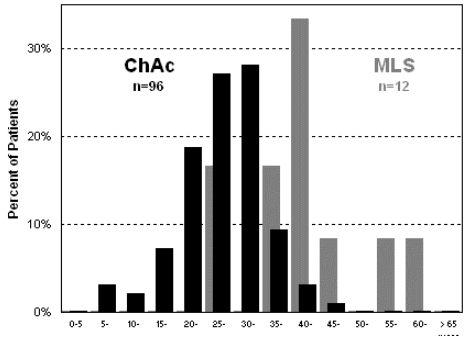


McLeod syndrome (MLS)

X-linked, older men (brothers, uncles/nephews)

- **Mutation affects an element of Kell erythrocyte antigen system**
- **Apart from cardiomyopathy (very common), sex-linkage & age, almost identical with ChAc**
- **Heart monitoring**
- **Banking of blood for later use**

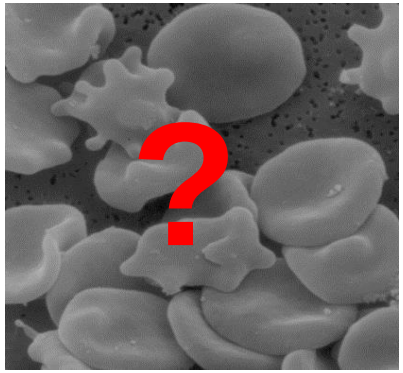
Ubiquitous, global prevalence ~ 500?



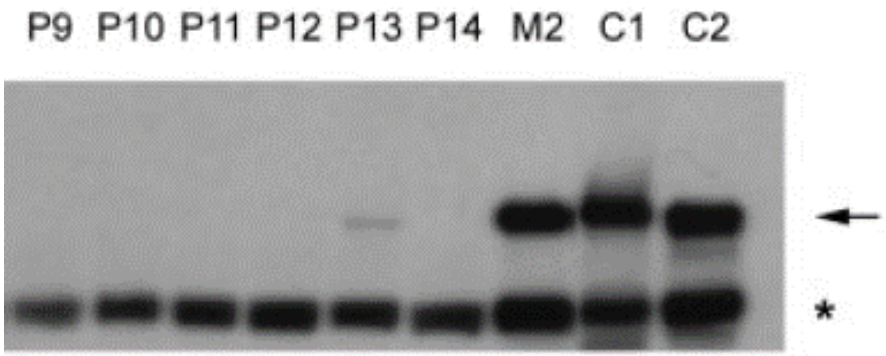
Diagnosis of ChAc & MLS

- Clinical and paraclinical findings
- Family history
- Exclusion of HD
- CK elevation
- Dedicated Kell serology and genetic testing of *XK*
- Genetic testing of *VPS13A* (sensitivity <100%!)
- Chorein Western blot (sensitivity <100%!)

- {Acanthocytosis}



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]

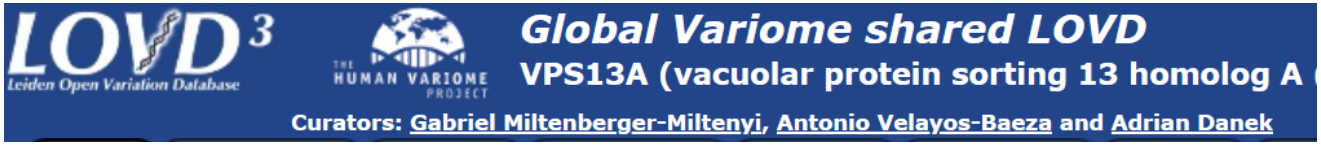
Chorea-acanthocytosis (ChAc) is a severe, neurodegenerative disorder that shares clinical features with Huntington's disease and McLeod syndrome. It is caused by mutations in *VPS13A*, which encodes a large protein called chorein. Using antichorein antisera, we found expression of chorein in all human 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

Origin of 164 patient samples diagnosed with ChAc according to Western Blot (2006 - Jan 2016)

Tools to improve diagnosis and treatment

- Mutation registry → DNA change of relevance?



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

- Patient registry → natural history, trial readiness

Reference material: general

McLeod syndrome and *XK* gene

Ho et al. Cell 1994;77:869
Roulis et al. JAMA Neurol. 2018;75:1554
Jung et al. GeneReviews 2019 www.ncbi.nlm.nih.gov/books/NBK1354

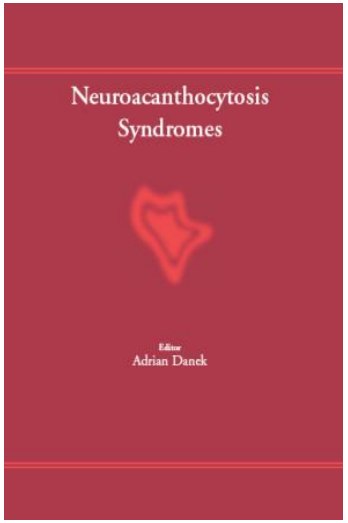
Chorea-acanthocytosis and *VPS13A* gene

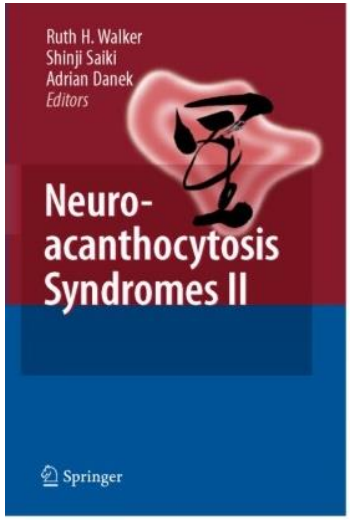
Rampoldi et al. Nature Genetics 2001;28:119
Ueno et al. Nature Genetics 2001;28:121
Peikert et al. Eur J Med Genet. 2018;61:699
Velayos-Baeza et al. GeneReviews 2019 www.ncbi.nlm.nih.gov/books/NBK1387

Acanthocyte determination

Storch et al. J Neurol. 2005;252:84

Reference: history





NA symposia 2002, 2005, 2006

Danek Springer 2004

Walker et al. Springer 2008

Outdated

Gandhi et al. (Neuroacanthocytosis Syndromes II; 2008;43-) followed up on the often quoted paper by Hardie et al. „Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases" Brain 1991;114:13, a heterogenous series now known to have comprised 6 cases of from an MLS family and 1 case of HARP syndrome, and with only 6 definite ChAc cases where mutations had been found in both alleles of *VPS13A.* In 3 cases only one allele was found mutated and on the remaining 3 cases no genetic information is as yet available.

Reference: basic science & recent symposia

VPS13 family

Velayos-Baeza A et al. Genomics 2004;84:536
Wang et al. GeneReviews 2016 www.ncbi.nlm.nih.gov/books/NBK1482
Schormair et al. Clin Genet. 2018;93:603
Lesage et al. Am J Hum Genet. 2016;98:500
Meijer GeneReviews 2019 www.ncbi.nlm.nih.gov/books/NBK537720

VPS13 function

Rzepnikowska et al. Traffic 2017;18:711
Yeshaw et al. Elife 2019;8:e43561
Dziurdzik et al. bioRxiv. 2019;768366

NA symposia 2016 & 2018

Pappas et al. Tremor Other Hyperkinet Mov. 2017;7:428
Peikert & Hermann. Tremor Other Hyperkinet Mov. 2018 8:579

Reference: NA newsletter & NA symposia

NANews 32 20 May 2019
NANews 32 Polish 20 May 2019
NANews 32 Deutsch 20 May 2019

NANews 31 26 November 2018
NANews 31 Polish 26 November 2018
NANews 31 26 November 2018 Deutsch

NANews 30 July 6 2018
NANews 30 Polish July 6 2018
NANews 30 Deutsch July 6 2018

NA News 29 December 4 2017
NANews 29 Polish December 4 2017
NANews 29 Deutsch 04 Dec 2017

NANews 28 March 30 2017
NANews 28 Deutsch March 30 2017

NANews 27 October 6 2016
NANews 27 Deutsch October 6 2016

NANews 26 April 8 2016
NANews 26 Deutsch April 8 2016

NANews 25 October 2015
NANews 25 Deutsch October 2015

NANews Extra November 29 2014

NA News

Neuroacanthocytosis information and research

NA News Issue 17 :: 11 Apr 2012
Published by The Advocacy for Neuroacanthocytosis Patients, Ginger and Glenn Irvine

:: How to recognise Neuroacanthocytosis

The first signs of the diseases in the neuroacanthocytosis (NA) group are subtle and easily overlooked. Initial symptoms, which often occur in the person's mid 20s, may include grunts or tic noises made unconsciously in the throat, progressing to drooling and problems in controlling the tongue from ejecting food. Involuntary biting of the tongue, lips and/or cheeks may follow.

At the beginning there can be a general, slight physical awkwardness. Things on a shelf are knocked off for no apparent reason. Difficulty with walking and balance can also be early symptoms. Problems controlling trunk, leg and arm movements are often barely noticeable at the beginning, but become increasingly difficult as the disease progresses. Several patients find it difficult to sleep at night and others report fatigue and weakness.

Personality change may also be an early indication. The carefree young adult becomes obsessive-compulsive and uncharacteristically forgetful or just loses confidence or drive. Fainting or epileptic seizures may also occur. Mood changes may happen and a person often becomes isolated, in part out of embarrassment.

There are several reports of the problems beginning after a traumatic event including physical attack, unexpected failure of an exam and birth of a child.

CLINICAL SIGNS

A defining symptom that is not apparent is the spiky red blood cells, or acanthocytes, from which the NA disease group

Welcome to NA News Issue 17

In this issue we're pleased to announce the Second Joint International Symposium on Neuroacanthocytosis and Neurodegeneration with Brain Iron Accumulation, this October. We also reveal the two research projects selected following the Advocacy's call for proposals in 2011, and we review progress on funded research to date including the 120 confirmed diagnoses that have resulted from the Advocacy sponsored diagnostic test. Please consider supporting NA fundraisers coming up this spring, including the London Marathon and Rare Plants for Rare Disease research. Let us know what you think of any article: just click below each story to comment.

0 Comments | Post a Comment

Details revealed of October Symposium on Neuroacanthocytosis and NBIA

Details have been published of the agenda for the The Second Joint International Symposium on Neuroacanthocytosis and Neurodegeneration with Brain Iron Accumulation. Delegates will gather in The Netherlands from 26-27 October 2012 for "New breakthroughs in NAnBIA - towards unravelling underlying mechanisms."

Read more»
0 Comments | Post a Comment

Winning grant applications announced by the Advocacy

A tremendous response was received to the Advocacy's call for research applications at the end of 2011. After review by our independent scientific panel, two of the seven research grant applications were approved for Aaron Neiman, Stony Brook University, New York and Florian Wegner, Alexander Storch and Andreas Hermann at Dresden Technical University. Additionally a third award was made directly by the family of NA patient Mark Williford to Alicia Rivera PhD at Children's Hospital, Harvard Medical School, Boston.

Read more»
0 Comments | Post a Comment

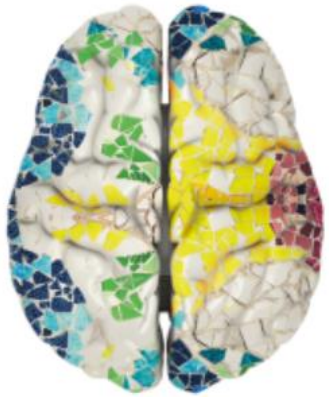
New trustees join the Advocacy to augment business development capabilities

New trustees have joined the Advocacy: Eva Stock, originally from Boston and now living and working in London as Director of Sponsor Relations for FOCUS, brings marketing and business development expertise to the Board. Amin Somji, originally from Zanzibar and now in Kenya, is a Chartered Accountant whose experience will be invaluable to the Advocacy in planning for further growth.

Read more»

- Dresden, Germany 2018
- Ann Arbor, USA 2016
- Stresa, Italy 2014
- Ede, Netherlands 2012
- Bethesda, USA 2010
- London/Oxford, UK 2008
- Kyoto, Japan 2006
- Montreal, Canada 2005
- Seeon, Germany 2002

www.neuroacanthocytosis2020.com



10th International Meeting on
Neuroacanthocytosis Syndromes

BARCELONA MARCH 2020

Patient Advocacy

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

Founded by
Glenn Irvine† and
Ginger Irvine

Mail: gingerirvine@gmail.com

ePAG (European Patient Advocacy Groups) Voice

Astri Arnesen - Patient Representative for: **Choreas & Huntington's Disease** and president of the European Huntington Association
astri@eurohuntington.org

ePAGs Mission:

- Our overall aim is to work together with clinicians to have an active, sustainable network that contributes to equal access to expertise and treatment for patients all over Europe.
- Partnering in the network activities and development and advocate for patient centric services.
- We have very high ambitions for the networks and we want to contribute in any way we can to make them successful.

ePAG (European Patient Advocacy Groups) Voice

ePAGs role in ERN-RND:

- Participate in ongoing activites within the network and give input from our perspective as affected by the disease
- Disseminate information about the network, spread awareness in our disease community
- Lobby for implementation of the network partners into their respective national health plans
- Lobby for extension of the network to include all countries in Europe

Next milestone/need in this Disease Group:

To have better distribution of clinics into the network and have more clinicians connected and working together to give patients treatment in accordance with best evidence based knowlegde.

Q & A 3: Acanthocytes are

1 skin lesions in diabetes.

2 an obligatory finding in McLeod syndrome.

3 deformed red blood cells.

4 easily picked up in routine investigations.

5 required to diagnose an NA syndrome.

Q & A 4: Neuroacanthocytosis syndromes

1 are heterogeneous.

2 comprise cases with *ELAC2* mutations.

3 can be differentiated with dedicated Kell serology.

4 may be taken for Huntington´s disease.

5 are dyslipidemias.

Q & A 5: McLeod syndrome

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: Chorea-acanthocytosis

1 does not present with parkinsonism.

2 is caused by *VPS13C* mutations.

3 is transmitted as an autosomal dominant trait.

4 is often accompanied by cardiomyopathy.

5 is typically characterized by hyperCKemia.

European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Choreas and HD‘
3 December 2019

Joint webinar series

THANK YOU

Next Webinar: ‘Non-progressive congenital ataxia‘
17 December 2019, 15-16h CET