




## BRIEF REPORT

# Phosphatidylethanolamines are the Main Lipid Class Altered in Red Blood Cells from Patients with VPS13A Disease/Chorea-Acanthocytosis

Kevin Peikert, MD,<sup>1,2,3</sup>  Adrian Spranger,<sup>1</sup> Gabriel Miltenberger-Miltenyi, MD,<sup>4</sup>  Hannes Glaß, PhD,<sup>1</sup> Björn Falkenburger, MD,<sup>5,6</sup> Christian Klose, PhD,<sup>7</sup> Donatienne Tyteca, PhD,<sup>8</sup> and Andreas Hermann, MD, PhD<sup>1,2,3,9\*</sup> 

<sup>1</sup>Translational Neurodegeneration Section “Albrecht Kossel”, Department of Neurology, University Medical Center Rostock, University of Rostock, Rostock, Germany <sup>2</sup>Center for Transdisciplinary Neurosciences Rostock (CTNR), University Medical Center Rostock, Rostock, Germany <sup>3</sup>United Neuroscience Campus Lund-Rostock (UNC), Rostock, Germany <sup>4</sup>Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal <sup>5</sup>Department of Neurology, Technische Universität Dresden, Dresden, Germany <sup>6</sup>Deutsches Zentrum für Neurodegenerative Erkrankungen, Dresden, Germany <sup>7</sup>Lipotype GmbH, Dresden, Germany <sup>8</sup>CELL Unit, de Duve Institute, UCLouvain, Brussels, Belgium <sup>9</sup>Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) Rostock/Greifswald, Rostock, Germany

**ABSTRACT: Background:** VPS13A disease is an ultra-rare disorder caused by loss of function mutations in *VPS13A* characterized by striatal degeneration and by red blood cell (RBC) acanthocytosis.

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**\*Correspondence to:** Prof. Andreas Hermann, Translational Neurodegeneration Section “Albrecht Kossel”, Department of Neurology; University Medical Center Rostock, Gehlsheimer Straße 20, 18147 Rostock, Germany; E-mail: [andreas.hermann@med.uni-rostock.de](mailto:andreas.hermann@med.uni-rostock.de)

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VPS13A is a bridge-like protein mediating lipid transfer at membrane contact sites.

**Objectives:** To assess the lipid composition of patient-derived RBCs.

**Methods:** RBCs collected from 5 VPS13A disease patients and 12 control subjects were analyzed by mass spectrometry (lipidomics).

**Results:** While we found no significant differences in the overall lipid class level, alterations in certain species were detected: phosphatidylethanolamine species with both longer chain length and higher unsaturation were increased in VPS13A disease samples. Specific ceramide, phosphatidylcholine, and sphingomyelin species were also altered.

**Conclusions:** The presented alterations of particular lipid species in RBCs in VPS13A disease may contribute to (1) the understanding of acanthocyte formation, and (2) future biomarker identification. Lipid distribution seems to play a key role in the pathophysiology of VPS13A disease. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

VPS13A disease (formerly known as chorea-acanthocytosis) is a neurodegenerative disorder of young adulthood and an important differential of Huntington's disease.<sup>1</sup> Together with XK disease (McLeod syndrome) it has been classified as neuroacanthocytosis syndrome as it is characterized by striatal degeneration and the presence of deformed red blood cells (RBCs), referred to as acanthocytes.<sup>2</sup> While acanthocytosis is a core feature, the proportion of deformed RBCs varies intra-individually, and they may be even absent in individual cases.<sup>3</sup> Typical clinical manifestations include a variety of movement disorders (chorea and dystonia with orofacial predominance, in later stages parkinsonism), epilepsy, behavioral and cognitive impairment, as well as peripheral neuropathy and myopathy.<sup>1</sup>

The autosomal-recessive condition is caused by biallelic pathogenic variants in the *VPS13A* gene leading in most cases to a complete loss of the respective protein, VPS13A/chorein.<sup>4</sup> VPS13A belongs to a family of four proteins, VPS13A-D, that are all related to neurodegenerative or neurodevelopmental disorders, such as hereditary parkinsonism (VPS13C) or ataxia (VPS13D).<sup>5-7</sup> Only recently, VPS13A has been assigned to the new protein superfamily of bridge-like lipid transfer proteins (BLTPs).<sup>8,9</sup> Forming hydrophobic grooves that span between two organellar membranes at membrane contact sites, these proteins mediate direct bulk lipid transfer, most likely selective for phospholipids.<sup>10</sup> VPS13A localizes

between the endoplasmic reticulum and mitochondria, lipid droplets, or the plasma membrane.<sup>10</sup> At the plasma membrane it has been shown to form a complex with the putative scramblase XK.<sup>11,12</sup> In support of a pathomechanistic role of altered membrane lipid distribution and supply in VPS13A disease, elevated levels of several sphingolipids and phospholipids have been recently found in the striatum of VPS13 patients.<sup>13</sup> Also, in Huntington's disease, a distinct shift in the sphingolipid profile of the caudate has been reported.<sup>14</sup>

In this exploratory study, we aimed to study the lipid composition of RBCs from VPS13A patients for various reasons as follows. (1) RBCs are – besides neurons – prominently affected by the disease as a high proportion are acanthocytic. (2) RBCs are “products” of a complex rearrangement of membranes and organelles during erythropoiesis<sup>15</sup> potentially requiring membrane lipid transfer. (3) RBCs are – in contrast to brain tissue – easily obtainable. RBC lipid composition may therefore be an ideal biomarker candidate.

## Methods

Five genetically confirmed VPS13A patients (4 males, 1 female; mean age 45.6, minimum 32, maximum 52 years) and 12 healthy controls (9 males, 3 females; mean age 40.7, minimum 23, maximum 56 years) were included in this study. Demographic and clinical data are shown in Table 1. There was no statistically significant difference in age and sex distribution (Table S1). The study was approved by the ethics committee at the Technische Universität Dresden (EK45022009, EK78022015). All participants gave written informed consent in accordance with the Declaration of Helsinki.

Ethylenediaminetetraacetic acid (EDTA) blood samples were processed in accordance with the sample preparation guidelines from Lipotype GmbH (Dresden, Germany; see Supplementary Material Data S1). Mass spectrometry-based lipid analysis was performed as previously described using a QExactive Orbitrap mass spectrometer (Thermo Fisher Scientific, Darmstadt, Germany).<sup>16</sup> Table S2 shows the list of analyzed lipid classes and the structural detail level of the analysis.

Lipid data were analyzed in mole percent (mol%) for better comparability. An occupational threshold was applied to solidify findings (see Supplementary Material Data S2).

Multiple *t*-tests on all remaining (sub)species were performed (without assuming a consistent standard deviation) and the Benjamini–Hochberg procedure (false discovery rate of 5%) was applied. Analysis was performed at different levels: lipid class, lipid (sub)species, structural or functional category, as well as grouped by chain length/double bonds number/OH-groups number.

For visualization of the results on the lipid (sub)species level a volcano plot was generated.

Acanthocyte proportion was determined according to the standard procedure.<sup>17</sup>

## Results

Untargeted lipidomic analysis was achieved by mass spectrometry by screening for 23 lipid classes. In total, 575 lipid species and subspecies were measured. After application of the occupational threshold, 313 lipid species and subspecies remained for further analysis. Of the 23 classes, 13 were easily detectable including ceramide (Cer), cholesterol (Chol), hexosylceramide (HexCer), lyso-phosphatidylcholine (LPC), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylcholine-ether (PE O-), phosphatidylinositol (PI), phosphatidylserine (PS), and sphingomyelin (SM), in agreement with previous reports on RBCs.<sup>18</sup> Moreover, we were able to detect additional species such as lyso-phosphatidylethanolamine (LPE), phosphatidate (PA), and phosphatidylcholine-ether (PC O-).

At the lipid class level, no relevant differences between healthy controls and VPS13A patients could be detected (Fig. S1A). Also, after grouping the lipids into structural (glycerophospholipids, sphingolipids, and sterols) or functional categories (lyso vs. membrane lipids), analysis did not reveal striking differences (Fig. S1B,C), as was the case for the number of double bonds, hydroxyl groups, and the fatty acid chain length of the lipids (Fig. S1D–F).

At the lipid species and subspecies level, however, distinct differences with small effect size (fold change) were observed. The increase of Cer34:1;2 was the most significant finding (Fig. 1A,B). Most of the (sub)species with significant change after the Benjamini–Hochberg procedure belonged to the PE or PE O- classes. Within the PEs, a shift in the fatty chain lengths became obvious in VPS13A patients: PE subspecies with longer fatty acid chains tended to be increased, and species with shorter chains to be decreased (Fig. 1C). This is in line with the (nonsignificant) decrease of lipids with medium length fatty acid chains and increase of lipids with very long chains that has been observed in the overall chain length analysis (Fig. S1F). In addition, decrease of single PC and SM species were also detected.

Significant acanthocytosis (>6.3%) was confirmed in all VPS13A patients to varying degrees (Table 1, Fig. S2).

## Discussion

VPS13A disease has recently become paradigmatic for a new pathophysiological concept in neurodegeneration: disturbed bulk lipid transfer at membrane contact sites.<sup>2,10,19</sup> VPS13A is a bridge-like protein enabling direct bulk lipid transfer between intracellular membranes.

**TABLE 1** Cohort characteristics

ID	Sex	Age (years)	Main clinical manifestation	Acanthocytes (%) <sup>a</sup>	Disease duration (years) <sup>b</sup>	Chorein Western blot <sup>c</sup>	Medications	Nutritional lifestyle
VPS13A_1	M	32	Drug-resistant epilepsy, mild chorea, tics, cognitive impairment, peripheral neuropathy, myopathy	24	9	Chorein absent	Lacosamide 600 mg/day, zonisamide 400 mg/day; PRN: lorazepam/midazolam	Varied, well-balanced meals, vitamin D supplementation
VPS13A_2	M	42	Epilepsy, feeding dystonia, orofacial dyskinesia, chorea, peripheral neuropathy, myopathy, impulse control disorder	41	12	Chorein absent	Levetiracetam 1.5 g/day, quetiapine 500 mg/day, ramipril 2.5 mg/day, metoprolol 47.5 mg/day; PRN: metamizole, ibuprofen, pantoprazole	Varied, well-balanced meals
VPS13A_3	F	49	Epilepsy, parkinsonism, dystonia, dysarthria peripheral neuropathy, cognitive impairment	14	28	Chorein absent	Levetiracetam 4000 mg/day, valproate 2000 mg/day, clobazam 10 mg/day, zonisamide 200 mg/day	Varied, well-balanced meals, vitamin D supplementation
VPS13A_4	M	51	Parkinsonism, dystonia, dysarthria, peripheral neuropathy mild depression	65	13	Chorein absent	Scopoderm transdermal therapeutic system/ day; PRN: melperone	Varied, well-balanced meals
VPS13A_5	M	52	Epilepsy, parkinsonism, dystonia, dysarthria, dysphagia, peripheral neuropathy, cognitive impairment	20	19	Chorein absent	Lamotrigine 550 mg/day, oxcarbazepine 1.5 g/day, lacosamide 300 mg/day, levodopa 300 mg/day, esomeprazole 40 mg/day	Via PEG tube

Abbreviations: M, male; F, female; PRN, pro re nata (prescription taken as needed); PEG, percutaneous endoscopic gastrostomy.

<sup>a</sup>According to the “Storch method”, the cut-off for significant acanthocytosis is 6.3%.<sup>17</sup>

<sup>b</sup>Since onset of first symptoms.

<sup>c</sup>Additionally, all cases have been confirmed by genetic testing.

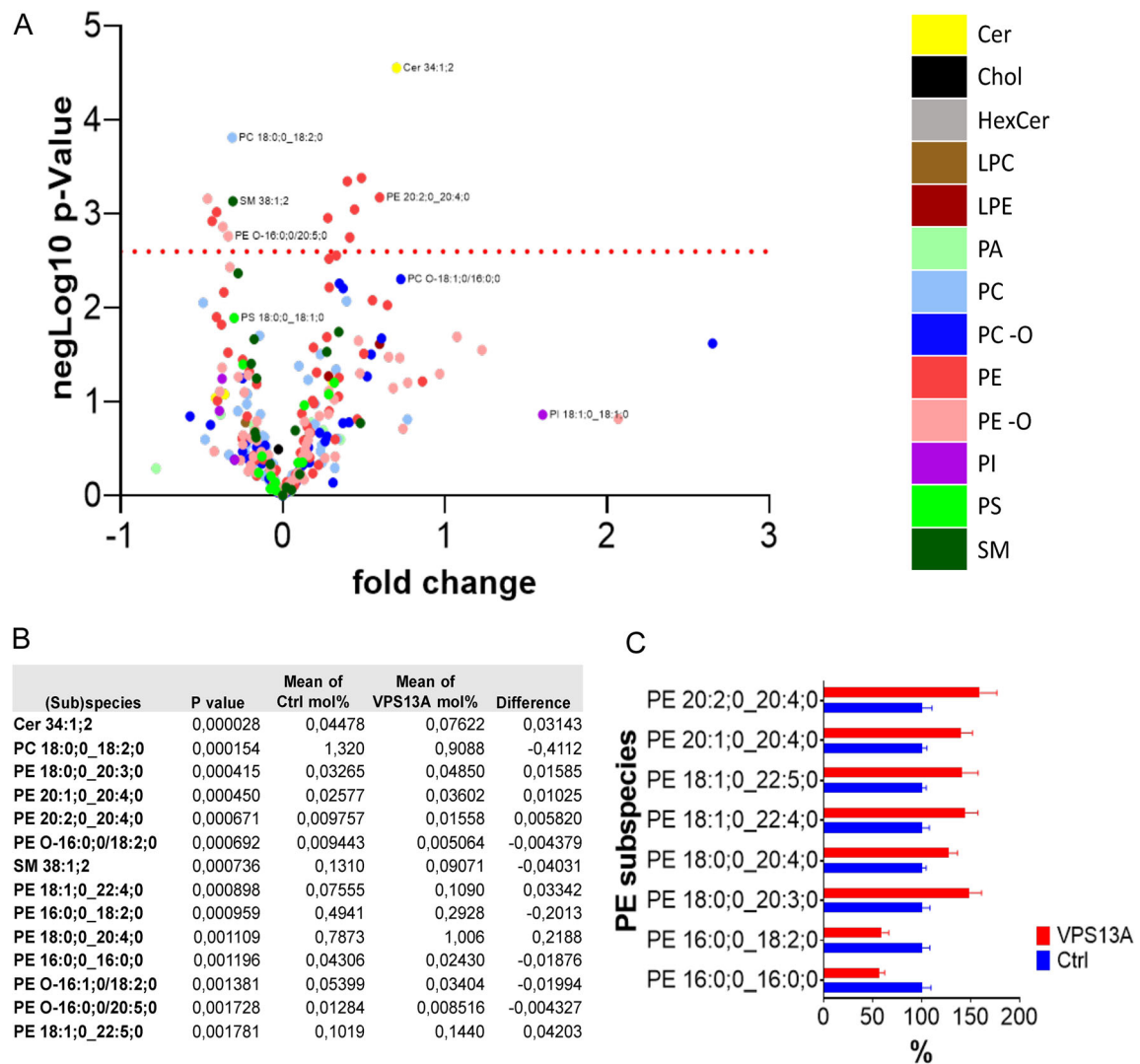
It seems that disturbances of this process are central for VPS13A and related diseases although the exact role of bulk lipid transfer in neuronal and other mainly affected cells such as RBCs is the subject of further research.

Based on these recent molecular developments in the field, we studied for the first time the lipid composition of RBCs from VPS13A patients using state-of-the-art lipidomics analysis. RBCs are clearly affected by the disease as acanthocytosis is a core feature and VPS13A-deficient RBCs reflect at least partly the pathophysiology of the disease: Both RBCs and the central nervous system show similar cellular disturbances, such as impaired autophagy, hyperphosphorylated Lyn kinase, or dysregulated actin network.<sup>1,20-24</sup> Therefore, RBCs may be an easily accessible surrogate and biomarker for pathology of the nervous system, even if the exact connection between acanthocytosis and neurodegeneration is still the subject of speculation.<sup>20</sup> Of note, there is significant evidence that lipid dysmetabolism is causal for the development of acanthocytosis. First, hypobetalipoproteinemia/abetalipoproteinemia leads to the appearance of acanthocytes.<sup>25,26</sup> Second, in

liver failure where acanthocytosis is observed, irregularities in lipid metabolism, particularly an excess of cholesterol, have been associated with the deformation of RBCs.<sup>27</sup> Conversely, lipid analysis in the “pre-lipidomics era” has not revealed conclusive differences in RBCs from neuroacanthocytosis patients.<sup>20</sup>

In line with that, our study did not show a generalized major disturbance of lipid classes, but revealed interesting specific changes at the lipid species and sub-species level, including PE (O-), but also single Cer, PC, and SM (sub)species.

PE play a central role in autophagosome formation and are a regulator of autophagy,<sup>28</sup> a process which has been shown to be impaired in VPS13A disease, as reflected by the presence of membrane remnants,<sup>21,22</sup> and which is essential during erythropoiesis. Moreover, the relative abundance of PE species highly evolves during reticulocyte maturation into RBCs: longer and more unsaturated PE species decrease whereas smaller and more saturated PE species increase<sup>29</sup> (Minetti et al., BioRxiv, <https://doi.org/10.1101/2023.06.02.543386>, preprint). Interestingly, we



**FIG. 1.** Lipidomics analysis at species and subspecies level. Volcano blot showing all analyzed (sub)species (**A**). The horizontal dotted line represents the threshold of statistical significance after the Benjamini–Hochberg procedure with a false discovery rate of 5%. (**B**) shows all significantly different (sub)species between the healthy control and VPS13A disease groups. (**C**) Relative change of phosphatidylethanolamine (PE) subspecies in VPS13A disease sorted by fatty acid chain length and double bond number; results are expressed as percentage of controls (healthy control values were set at 100%). Ctrl, controls; VPS13A, VPS13A patients; Cer, ceramide; Chol, cholesterol; HexCer, hexosylceramide; LPC, lyso-phosphatidylcholine; LPE, lyso-phosphatidylethanolamine; PA, phosphatidate; PC (O-) phosphatidylcholine (-ether); PE (O-) phosphatidylethanolamine (-ether); PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

showed here a reverse “acyl chain remodeling”: the former group increased in VPS13A patients while the latter decreased, suggesting impairment of RBC maturation. Therefore, we are tempted to speculate that these findings may be related to acanthocyte formation during erythropoiesis. Supporting this possibility, Cer, PC, and PE species were also shown to be similarly affected in hypobetalipoproteinemia, another acanthocyte-related disease.<sup>26</sup> Interestingly, Csf1, a VPS13-like BLTP, has been shown to transfer PEs to the ER for glycosylphosphatidylinositol (GPI) anchor synthesis.<sup>30</sup>

Also, as PE is a non-bilayer forming lipid, especially with longer chain length,<sup>31</sup> an increase of longer PE species might at least partially explain the

morphological alterations of acanthocytes. Moreover, non-bilayer lipids may affect integration of proteins into membranes, their lateral movement, and their function.<sup>32</sup>

Cer acts as the foundational element for complex sphingolipids and is important in cellular signaling. Accordingly, abnormal Cer levels have been associated with several neurodegenerative conditions.<sup>33</sup>

The rather specific lipid alterations may be viewed as unexpected considering the function of VPS13A as a lipid transfer protein. However, as most of the altered lipids are phospholipids, this finding is consistent with the suspected role of VPS13A as a (specifically) phospholipid transferring protein.<sup>10</sup> Also, quantitative



analyses might not have captured localized changes in membrane composition without major disturbances of overall lipid content. Furthermore, variations within the RBC population (eg, acanthocytic vs. non-acanthocytic) could have masked specific alterations in a subgroup of cells. As VPS13A plays a role in lipid transfer between organellar membranes and as mature RBCs lack such organelles, the pathogenic process occurs potentially mainly during erythropoiesis. Therefore, quantitative lipid analysis might reveal more pronounced alterations in RBC precursor cells. Another limitation of this study relates to the low number of patient samples due to the ultra-rarity of the disease, which might have resulted in insufficient statistical power to detect even more subtle changes.

The RBC lipidomics data presented are not conclusive with the data derived from post mortem brain tissue<sup>13</sup>: here, the most significantly altered lipids included bis(monoacylglycerol)phosphate, sulfatide, lysophosphatidylserine, and phosphatidylcholine ether, while PE showed no significant differences at group level. This is partially due to the differences in covered lipid classed by the measurements. However, this may also point to different effects of VPS13A deficiency in RBCs and the brain.

Further studies need to focus on lipid composition of RBC precursor cells and on potential localized changes in distinct RBC membrane domains. Our results may lead to the development of PE species as biologically relevant biomarker candidate for VPS13A disease, which is a prerequisite for future clinical studies.<sup>34</sup> ■

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## Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.