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Acyl-CoA Binding Domain Containing 3 (ACBD3) Protein in Huntington's Disease Human Skin Fibroblasts

Acyl-CoA Binding Domain Containing 3 (ACBD3) protein v lidských kožních fibroblastech pacientů s Huntingtonovou chorobou

Abstract

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease caused by the expansion of polyglutamine repeats (> 35 repeats) in the nuclear gene for the huntingtin protein. HD is characterized by slow progressive changes in motor behaviour and personality that are sometimes accompanied by weight loss. To date, the exact mechanisms of HD pathophysiology have not been defined. Impaired motor behaviour reflecting massive and selective destruction of the striatum has been observed in patients with HD. Sbodio et al. [1] reported in 2013 that Acyl-CoA binding domain containing 3 (ACBD3) protein levels were elevated in the striatum of HD patients and connected with higher neurotoxicity in HD. The ACBD3 protein plays essential roles in many different cellular functions via interactions with a multitude of partners. ACBD3 is involved in neuronal stem cell self-renewal, neurodegeneration, lipid homeostasis, stress resistance, intracellular vesicle trafficking, organelle maintenance, viral replication and the apoptotic response. Herein, we found that ACBD3 in not present in the mitochondria in skin fibroblasts. Moreover, our findings also revealed that the total cellular level of ACBD3 is not consistent among the fibroblasts of HD patients.

Souhrn

Huntingtonova choroba (HD) je autozomálně dominantní neurodegenerativní onemocnění způsobené zvýšením počtu polyglutaminových repetic (> 35 repetic) v genu pro protein huntingtin. HD je charakteristická pomalými progresivními změnami pohybového aparátu a osobnosti, kdy tyto změny jsou často doprovázeny ztrátou tělesné hmotnosti. Do dnešního dne není znám přesný mechanizmus patofyziologie choroby. Poruchy pohybových funkcí reflektují masivní poškození specifických částí mozku (striatum), které bylo popsáno u pacientů s HD. V roce 2013 Sbodio et al [1] popsali zvýšené množství proteinu Acyl-CoA binding domain containing 3 (ACBD3) ve striatu HD pacientů. Protein ACBD3 hraje nezastupitelnou roli v mnoha buněčných procesech, a to především díky interakci s různými vazebnými partnery. ACBD3 je esenciální při neuronálním dělení, neurodegeneraci, udržení lipidové homeostáze, stresové odpovědi, virové replikaci, apoptóze, udržení struktury golgiho komplexu. V této práci jsme prokázali nepřítomnost proteinu ACBD3 v mitochondriích v lidských kožních fibroblastech a navíc jsme potvrdili, že změny celkové hladiny proteinu ACBD3 ve fibroblastech HD pacientů nejsou konzistentní.

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H. Kratochvilova[1], M. Rodinova[1], J. Sladkova[1], J. Klempir[2], I. Liskova[2,3], J. Motlik[3], J. Zeman[1], H. Hansikova[1], M. Tesarova[1]

[1] Department of Pediatrics and Adolescent Medicine, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
[2] Department of Neurology and Centre of Clinical Neuroscience, 1st Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic
[3] Laboratory of Cell Regeneration and Cell Plasticity, Institute of Animal Physiology and Genetics AS CR, v.v.i., Libechov, Czech Republic

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Ing. Marketa Tesarova, Ph.D.
Department of Pediatrics and Adolescent Medicine
1st Faculty of Medicine
Charles University and General University Hospital in Prague
Ke Karlovu 2
128 08 Prague, Czech Republic
e-mail: marketa.tesarova@lf1.cuni.cz

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Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease caused by the expansion of polyglutamine repeats (> 35 repeats) in the nuclear gene for the huntingtin protein (Htt) [2,3]. The onset of the disease is associated with an increased length of the polyglutamine repeats. The clinical symptoms include progressive impairment of voluntary movements, dyskinesia, dementia, behavioral changes and weight loss [3,4]. Impaired motor phenotype reflecting massive and selective destruction of the corpus striatum occur despite uniform expression of normal/mutant protein throughout the brain and body. Nevertheless, degeneration outside the central nervous system in patients and in HD animal models has been detected in the testes and blood [5,6].

The exact functions of the normal Htt protein is not fully clarified, but it seems to be necessary for proper embryonal development in mice [7] and protective and anti-apoptotic pathways [8]. The expansion of the polyglutamine repeats leads to expression of a mutant Htt (mHtt) protein that has an impaired structure and results in a loss of normal functions [9]. HD pathogenesis is not defined yet, but it may be caused by translocation of mHtt protein fragments into the nucleus or/and by damage to mitochondrial functions [10]. Impaired Ca^{2+} homeostasis in the HD brain leads to a reduction in the mitochondrial membrane potential [11]. Furthermore, the presence of the mutated protein results in increased level of mPTP (mitochondrial permeability transition pore) [12,13], elevated oxidative stress [14], reduced levels and activities of OXPHOS complexes and decreased ATP production [15,16]. Mutant Htt may affect mitochondrial fission and fussion machinery via direct association with the organelle, thus damaging the entire mitochondrial network [17]. Recent work identified disrupted protein transport into the mitochondria due to presence of mHtt protein, which also probably contributes to pathology of the disease [18].

In recent work, markedly increased Acyl-CoA binding domain containing 3 protein (ACBD3) levels in the striatum of HD patients, in a striatal cell line harbouring polyglutamine repeats and in the brains of HD mice were identified. Enhanced levels of ACBD3 induced by a variety of stresses may be connected with higher neurotoxicity in HD [1].

ACBD3 protein, previously known as PAP7 or GCP60, is a 528-amino acid protein (60 kDa) that is ubiquitously expressed [19,20]. However, it is mostly present in steroidogenic tissues and neurons following the expression patterns of partners in agreement with its proposed functions [21,22].

The members of Acyl-CoA protein family (ACBD) play important roles in diverse cellular mechanisms. ACBD3 is essential for a variety of cellular functions, probably via their interactions with a multitude of proteins involved in neuronal stem cell self-renewal, neurodegeneration, stress resistance, intracellular vesicle trafficking, organelle maintenance, viral replication, lipid homeostasis and the apoptotic response [23,24]. ACBD3 is a Golgi apparatus protein that is also found in the cytosol during cell mitosis or upon cell stimuli. ACBD3 is also associated with mitochondria, wherein it is essential for steroidogenesis [25–27].

Free cholesterol transfer into the mitochondria, which is accomplished through a series of steps, is the limiting step for steroid biosynthesis. The transduceosome complex mediates cholesterol import and comprises ACBD3; the peripheral-type benzodiazepine receptor (PBR), which is also known as a translocator protein (TSPO); the voltage-dependent anion channel (VDAC); and protein kinase A regulatory subunit 1α (PKAR1α) [25]. Furthermore, ACBD3 is a positive regulator of steroidogenesis, as it appears to negatively control *de novo* cholesterol synthesis by inhibiting SREBP1 (Sterol Regulatory Element Binding Protein) [28].

Golgi apparatus maintenance is mediated through an ACBD3 terminal domain association with the cytoplasmic domain of the Golgi membrane protein giantin. Imbalances in ACBD3 protein levels cause disruption of the Golgi structure, which can block protein transport from the endoplasmic reticulum to the Golgi apparatus [29]. Another partner of ACBD3, PPM1L (Protein Phosphatase 1L), was originally identified as a negative regulator of stress-activated protein kinase signalling and has recently been shown to be involved in the regulation of ceramide trafficking at ER-Golgi membrane contact sites [30]. ACBD3 associates with the Golgi apparatus in neurons and interphase progenitor cells but becomes cytosolic after Golgi fragmentation during mitosis when Numb activity is needed to distinguish the two daughter cells [31].

ACBD3 has prominent impacts on cellular NAD+ metabolism by regulating PARP1 (PolyADP-Ribose Polymerase 1) activation. In a recent work, authors identified that extracellular signal-regulated kinase (ERK1/2) as well as *de novo* fatty acid biosynthesis pathways are involved in the ACBD3-mediated activation of PARP1 [21]. The consequences of PARP1 activation leads to cellular and tissue damage [32].

Through interactions with divalent metal transporter (DMT1) and Ras homologue enriched in striatum (Rhes) proteins, ABCB3 physiologically induces iron uptake through a signalling cascade in neurons whereby stimulation of NMDA (N-methyl-D-aspartate) receptors activates nnOS (neuronal nitric oxide synthases), leading to S-nitrosylation and activation of the protein dexras1 [20,33].

ACBD3 is also physiologically associated with Rhes and Htt/mHtt in a ternary complex. ACBD3 levels are markedly elevated in the striatum of HD patients, in HD mice brains and in a striatal cell line harbouring polyglutamine repeats. Enhanced ACBD3 levels elicited by endoplasmic reticulum, mitochondrial and Golgi stresses may account for the higher neurotoxicity in HD [1].

The aim of this study was to determine the localization of the ACBD3 protein in control human skin fibroblasts and to characterize the steady-state levels of ACBD3 protein in four HD patient fibroblast cell lines.

Materials and Methods

Ethics, patients and materials

The present study was carried out in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the Committee of Medical Ethics of the 1st Faculty of Medicine, Charles University and General University Hospital. Informed consent was obtained for all of the patients' cell lines. Primary skin fibroblasts were established from forearm skin biopsies.

The analyses were performed in four fibroblast cell lines from patients with confirmed HD and a healthy control of the related age. All of the patients (P1–P4) were heterozygotes with CAG repeat numbers at the mutated allele varying between 44 and 53. Clinical symptoms manifested as generalized/mild chorea, irritability, depression, apathy and cognitive dysfunction. The skin biopsy was provided 4–6 years after disease onset.

Immunocytochemistry

Primary culture skin fibroblasts were grown in DMEM medium at 37°C in a 5% CO_2 atmo-

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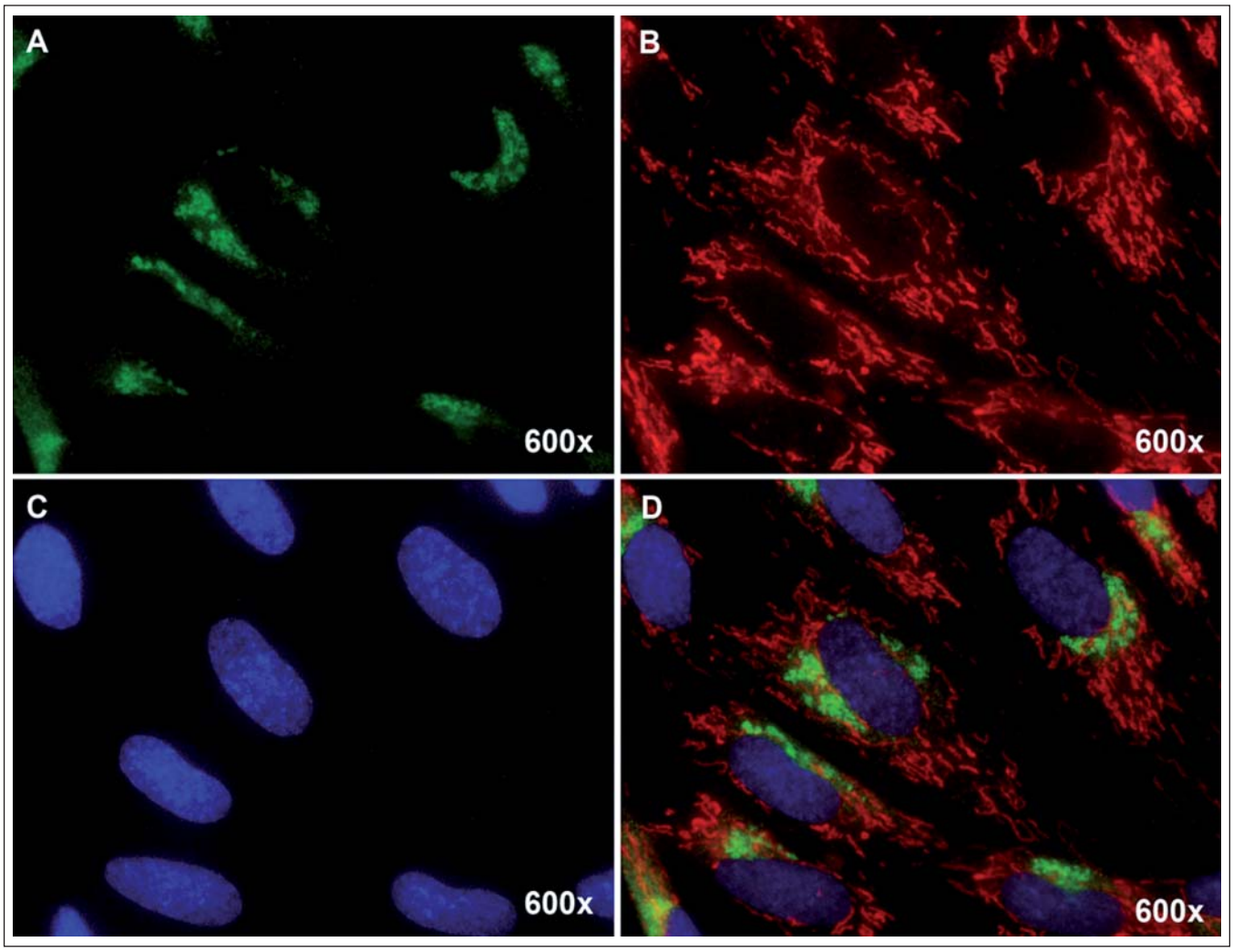


Fig. 1. Localization of the ACBD3 protein in control human skin fibroblasts.

Cultivated skin fibroblasts were visualized with specific antibodies against ACBD3 (A), mitochondrial marker mitofilin (B) and DAPI-stained nuclei (C). Mitofilin and ACBD3 do not colocalize (D). Original magnification: 600×.

sphere. The cells were grown on cover glass. After 48 hours, the cells were washed with PBS, fixed and permeabilized for 10 min with 4% paraformaldehyde for 10 min at 4°C. After blocking unspecific sites with 5% FBS, cells were incubated overnight at 4°C with specific primary antibodies (anti-mitofilin (Abcam) and anti-ACBD3 (Sigma-Aldrich)) in 5% FBS followed by a 60 min incubation at 37°C with fluorophore-conjugated secondary antibodies (1 : 500, goat anti-mouse IgG1 secondary antibody, alexa fluor® 568 conjugate; donkey anti-rabbit IgG (H + L) secondary antibody, alexa fluor® 488 conjugate). Nuclei were stained with 4',6-diamidino-2-phenylindole (DAPI). Prepared slides were analyzed by epifluorescent microscopy. Stained cells were detected with a Nikon Diaphot 200 inverted microscope (Nikon) and pictures were taken with an Olympus DP50 CCD camera and Viewfinder Lite 1.0 software (Pixera).

Cells fractionation

Fibroblasts were harvested by trypsinization, washed three times with phosphate-buffered saline, re-suspended in an isotonic STE buffer (250 mm sucrose, 10 mm Tris-HCl (pH 7,4), 1 mm EDTA, 1% (v/v) Protease Inhibitor Cocktail (Sigma-Aldrich) and disrupted on ice using a Dounce homogenizer. To remove unbroken cells and nuclei, the homogenate was centrifuged at 600 g and 4°C for 15 min. The post-nuclear supernatant was centrifuged at 10,000 g and 4°C for 25 min. The resulting supernatant represented the cytosolic fraction, and the mitochondrial pellet was washed twice with STE buffer. The protein concentration was determined with the Bio-Rad Protein Assay Kit (Bio-Rad). The isolated mitochondria and cytosol were stored at –80°C.

SDS-PAGE/WB/immunodetection

Tricine SDS-PAGE was carried out under standard conditions with 12% polyacrylamide 0.1% (w/v) SDS (Sodium Dodecyl Sulfate) gels. Cell pellets (fibroblast)/mitochondria/cytosol were incubated for 20 min on ice with RIPA buffer (50 mm Tris/HCl (pH 7.4), 150 mm NaCl, 1 mm PMSF, 1 mm EDTA, 1% Triton X-100, 0.1% SDS (v/v) and 1% (v/v) Protease Inhibitor Cocktail (Sigma-Aldrich)) and centrifuged at 51,000 g for 25 min at 4°C. Samples were dissociated in a solution containing 50 mm Tris/HCl (pH 6.8), 12% (v/v) glycerol, 4% SDS, 2% (v/v) 2-mercaptoetha-

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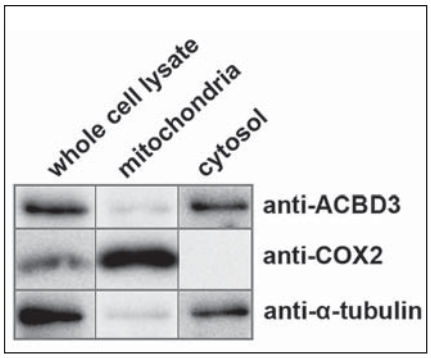


Fig. 2. ACBD3 protein does not localize to the mitochondria in control human skin fibroblasts.

Whole cell lysates and mitochondrial and cytosolic fractions were separated by 12% SDS-PAGE/WB. The resulting immunoblots were probed with specific antibodies. The majority of the anti-ACBD3 protein and anti--α-tubulin signal was observed in the cytosol. The anti-COX2 signal was only found in the mitochondria. All of the proteins were identified in the whole cell lysates.

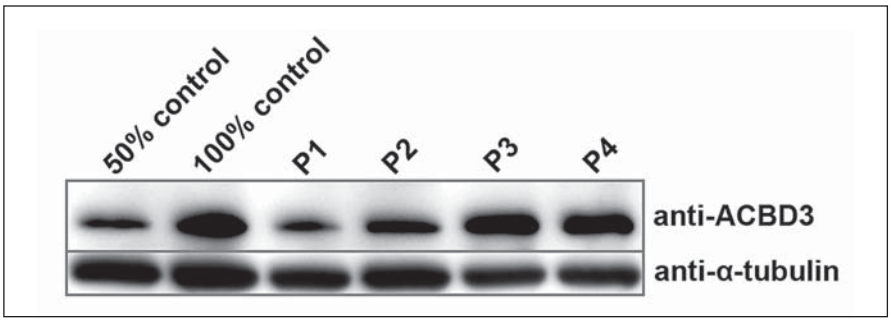


Fig. 3. Steady-state levels of ACBD3 protein in four HD human skin fibroblasts.

Whole fibroblast cell lysates (10 µg) were separated by 12% SDS-PAGE. Serial dilutions of the control sample (50–100%) were loaded onto the gel. The resulting western blots were immunodetected with specific antibodies. α-tubulin was used as the loading control. Reduced amounts of ACBD3 protein were observed in P1 and P2 compared with normal levels in P3, P4 and the control sample.

nol and 0.01% (w/v) Bromophenol Blue for 30 min at 37°C. In each lane 5–10 µg of protein was loaded.

Proteins were electroblotted from the gels onto PVDF membranes (Merck) using semi-dry transfer. Membranes were air-dried overnight, rinsed with 100% methanol (v/v) and blocked in TBS (Tris-Buffered Saline) with 5% non-fat dried milk for 2 hours. Primary detection was performed with mouse monoclonal antibodies against the following proteins: 1 : 1,000 ACBD3 (Sigma-Aldrich), 1 : 5,000 COX2 (Abcam) and 1 : 1,000 α-tubulin (Cell Signalling). Membranes were incubated with primary antibodies in TBS containing 0.1% (v/v) Tween 20 and 1% non-fat dried milk for 2 hours. Secondary detection was carried out with anti-mouse or anti-rabbit IgG peroxidase-conjugated antibodies (Sigma-Aldrich) in TBS containing 0.1% Tween 20 and 1% non-fat dried milk for 1 hour. The membranes were visualized with the SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Scientific) and using a Syngene Imaging System. The signal intensity of the antibodies was quantified with the Quantity one 1-D Analysis Software program (Bio-Rad).

Results

Localization of ACBD3 protein in control human skin fibroblasts

The cellular localization of ACBD3 protein was analysed in control human skin fibroblasts using two independent methods. The results from immunocytochemistry experiments are shown in Fig. 1. Cells were stained with specific antibodies against ACBD3 (Fig. 1A) and the mitochondrial marker mitofilin (Fig. 1B), and the nuclei were stained with DAPI (Fig. 1C). The resulting merged image (Fig. 1D) shows that the signals do not colocalize, indicating the absence of the ACBD3 protein in the mitochondria. However, anti-ACBD3 signal was found in the Golgi apparatus adjacent to the nuclei.

Mitochondrial cell fractionation was used to further characterize the absence of ACBD3 in mitochondria (Fig. 2). Whole cell lysates, mitochondrial and cytosol fractions were separated by 12% SDS-PAGE, and the resulting immunoblots were incubated with specific antibodies (Fig. 2). The signal of the mitochondrial compartment marker COX2 (subunit of cytochrome c oxidase) was only present in the mitochondria. In contrast, the majority of the anti-ACBD3 signal was found in the cytosol as well as anti-α-tubulin signal (cytoskeletal protein). All of the proteins were identified in the whole cell lysates.

Steady-state levels of ACBD3 protein in four HD human skin fibroblasts

Steady-state levels of ACBD3 protein were characterized in four available HD fibroblast cell lines and a fibroblast cell line from a healthy control. Whole fibroblast cell lysates (10 µg) were separated by 12% SDS-PAGE (Fig. 3); α-tubulin was used as a loading control. Serial dilutions of the control sample (50–100%) were loaded into the gel. The amounts of ACBD3 protein were not consistent among the samples. P1 and P2 displayed significantly decreased ACBD3 protein levels in comparison with P3, P4 and the control sample.

Discussion

In this study, we identified the localization of the ACBD3 protein in control human skin fibroblasts by two independent methods. Immunocytochemistry and cell fractionation followed by SDS-PAGE/WB and immunodetection revealed a non-mitochondrial localization of ACBD3 (Fig. 1, 2). This analysis was prompted by our previous experiments in HEK293 cells, which revealed the presence of the ACBD3 protein in the mitochondria and its association with the outer mitochondrial membrane [34]. Nevertheless, our results in human skin fibroblasts indicated that ACBD3 is a Golgi resident protein.

The mitochondrial association of ACBD3 protein has been shown in steroidogenic cells, where it is part of the complex that mediates the import of free cholesterol into the mitochondria [23]. Due to the ubiquitous expression of its components, a similar complex may form in non-steroidogenic cells; however, the mechanism of cholesterol import has not been fully characterized yet. Several proteins in the family are defined by the presence of a STAR-related lipid transfer (START) domain that plays key roles in the delivery of cholesterol to mitochondrial membranes [28]. Moreover, mitochondria-associated ER membranes (MAM) form membrane contact sites with mitochondria and may contribute to the transport of ER cholesterol to the mitochondria, either independently or in conjunction with lipid-transfer proteins. Our data indicate that ACBD3 is not associated with the mitochondria but is mainly found

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in the Golgi apparatus in human skin fibroblasts. This indicates that ACBD3 probably does not participate in mitochondria cholesterol import in human skin fibroblasts.

The function of ACBD3 is perhaps connected to Golgi apparatus maintenance [29] in human skin fibroblasts. The functional connection between ACBD3 and PARP1 has been detected in HEK293, HeLa and NIH3T3 (mouse embryonal fibroblast) cells [21]. ACBD3 is a crucial regulator of PARP1 activity, protein PARylation and cellular NAD+ metabolism through ERK1/2- and SREBP1-dependent pathways. PARP1 plays a major role in the pathogenesis of neurodegenerative diseases as well as in some metabolic diseases such as obesity and diabetes. ACBD3 as a regulator of PARP1 activity may be involved in ageing, inflammation and mitochondrial dysfunction [21,32].

Markedly elevated levels of ACBD3 in the striatum of HD patients, in a striatal cell line harbouring elevated polyglutamine tract in huntingtin, and in the brains of HD mice has been reported [1]. ACBD3 depletion abolishes HD neurotoxicity, in contrast to the increase in ACBD3 due to protein overexpression. Nevertheless, according to our results, ACBD3 protein levels in HD patients' cultured skin fibroblasts were individual (Fig. 3).

All of our patients were heterozygotes with a classical age of onset between 27 and 35. Their mutant alleles contained between 44 and 53 CAG repeats. Our results revealed reduced ACBD3 protein levels in two of the HD patients compared with normal to mildly increased amounts in the other two. Our data indicate that the changes in ACBD3 protein levels are not consistent in HD patients' cultured skin fibroblast compared to HD patients' brain tissues [1]. It further confirms that sub-cellular localization of ACBD3 protein is cell specific. Therefore more studies are required to determine the exact role of the ACBD3 protein in various tissues and cell lines and in the pathogenesis of HD.

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