


CASE REPORT

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Novel pathogenic *VPS13A* mutation in Moroccan family with Choreoacanthocytosis: a case report

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Abstract

Background: Choreoacanthocytosis (ChAc), is a rare neurodegenerative disease, characterized by movement disorders and acanthocytosis in the peripheral blood smears, and various neurological, neuropsychiatric and neuromuscular signs. It is caused by mutations in *VPS13A* gene with autosomal recessive pattern of inheritance.

Case presentation: Here we report two patients belonging to a consanguineous Moroccan family who present with movement disorder pathology. They were suspected to have choreoacanthocytosis according to biological, clinical and radiological finding. Thus, whole-exome sequencing was performed for precise diagnosis and identified a homozygous novel nonsense mutation c.337C > T (p.Gln113*) in exon 5 of *VPS13A* in the two affected siblings.

Conclusion: Here, we report a novel nonsense p.Gln113* mutation in *VPS13A* identified by whole-exome sequencing, which caused ChAc in a Moroccan family. This is the first description of ChAc in Morocco with genetic confirmation, that expands the mutation diversity of *VPS13A* and provide clinical, neuroimaging and deep brain stimulation findings.

Keywords: Choreoacanthocytosis, *VPS13A* gene, Nonsense mutation

Background

Choreoacanthocytosis (ChAc) is a neurodegenerative disease that clinically resembles other pathologies such as Huntington's disease-like 2, McLeod's syndrome, pantothenate kinase-associated neurodegeneration, all grouped into the Neuroacanthocytosis syndrome [1, 2]. ChAc is characterized by onset at adult age, often between 30 and 40 years and by the combination of movement disorders due to degeneration of basal ganglia and acanthocytosis in the peripheral blood non often reported as a beginning symptom but may appear late during the disease course. Clinically, ChAc is heterogeneous

and presents mainly with chorea, parkinsonism, dystonia, tics and involuntary movements. Self-mutilation such as tongue and lip biting are common and can be considered pathognomonic of the disease [3, 4]. Other symptoms as epilepsy, neuropsychiatric and neuromuscular symptoms may be added [5], and sometimes it can be in an atypical form presenting as epilepsy [6] or obsessive-compulsive behaviour [7].

ChAc was mapped to chromosome 9q21 in a 6 cM interval [3], in which the causative gene was identified, the vacuolar protein sorting 13A gene (*VPS13A*) comprising 73 exons and encoding a 360-kDa protein named chorein [8]. ChAc follows an autosomal recessive inheritance pattern and fifty-five mutations were reported up to date as pathogenic or likely pathogenic in the *VPS13A* gene on the Clinvar web site (ncbi.nlm.nih.gov/clinvar)

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from which 29 were duplications, 17 INDEL mutations and 9 were single nucleotide variations (SNV). These mutations have been reported in approximately 1000 patients worldwide [9], but never in the African continent.

Here, we report a Moroccan family with two patients displaying clinical heterogeneity of ChAc and in whom we identified a novel nonsense mutation (p.Gln113*) in *VPS13A* by whole exome sequencing (WES).

Case presentation

Clinical information

All the studies were carried out after approval of the local ethical committee of biomedical research (CERB). A written informed consent was obtained from all of the participants in the study.

A consanguineous family of Moroccan Origin, with two affected siblings with suspicion of a movement disorder pathology, was recruited in the Department of Neurology and Neurogenetics, Specialities Hospital of Rabat (Morocco). The pedigree of the family is shown in Fig. 1.

The index patient IV.2 is a 32-year-old woman who presented during the last 2 years gradual onset of involuntary upper limb choreiform movements spreading to the whole body with trunk spasms and gait disturbance. Symptoms have worsened few months later by the appearance of oromandibular dystonia as jaw-opening dystonia, tongue protrusion hindering her from eating and talking. Patient developed later self-mutilation by biting of the tongue, lips and forearms, vocalizations and psychiatric disorders such as depression and compulsive behaviours. Neurological examination showed otherwise areflexia, generalized hypotonia and scars of lip and forearm biting. The score of mini-mental status examination was 22/30 and Montreal cognitive assessment was 19/30 showing cognitive impairment especially frontal lobe

dysfunction. Sixty percent of acanthocytes were detected in peripheral blood smear test (Fig. 2a), and serum CK, LDH, AST and ALT levels were normal. Magnetic resonance imaging (MRI) showed bilateral and symmetrical striatal atrophy (Fig. 2b-c) and electroneuromyography (ENMG) was normal. The proband received Haloperidol 1,5 mg three times daily, trihexyphenidyl 5 mg three times daily and baclofen 10 mg four times daily for 1 year but without improvement. Therefore, a bilateral GPI DBS has been performed because of the dramatic worsening of the symptoms and the ineffectiveness of drugs. A permanent quadripolar leads were implanted (model 3389; Medtronic, Minneapolis, Minn., USA), with the following stimulation parameters: right case (+), contact 0 (-); amplitude 2 V; pulse-width 60 µs; frequency 130 Hz; left case (+), contact 8 (-); amplitude 2 V; pulse-width 60 µs; frequency 130 Hz. At the 2 months follow up review, a response rate of 60% was expressed by the patient and her family. The tongue protrusion disappeared allowing the patient to eat on a sitting position, and to speak more clearly. The self-injuring has lessened to only the lip biting. We also notice a gain in posture, gait and in the sitting ability. However, the foot dystonia persisted. She is more autonomous, able to perform domestic chores alone.

The older sister IV.1, 41-year-old, suffered since the age of 36, from generalized epileptic seizures stabilized with with a daily 1500 mg of valproic acid. She presented since 3 years gait disturbance and psychiatric features, depression and apathy. Neurological examination revealed a mild resting tremor of the right arm, akinesia, generalized hypotonia, areflexia and bilateral foot dystonia. The electroencephalogram was normal but MRI and ENMG were not possible because the patient subsequently died from soft-tissue tumor complications.

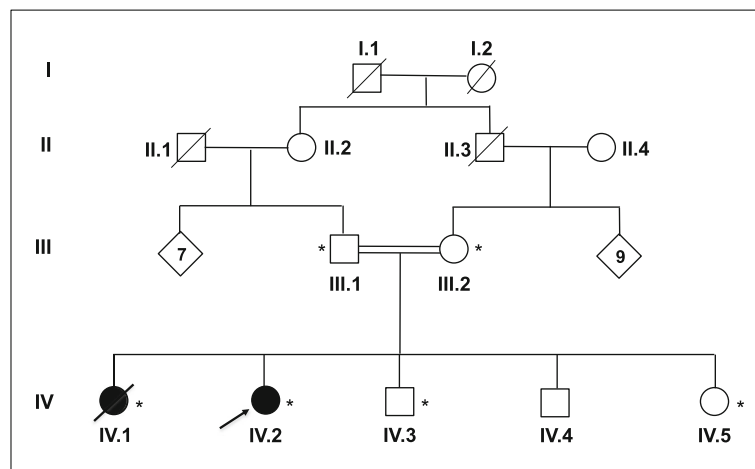


Fig. 1 Pedigree of a consanguineous Moroccan family with ChAc. Arrow: index patient. Asterisk: genetic testing performed

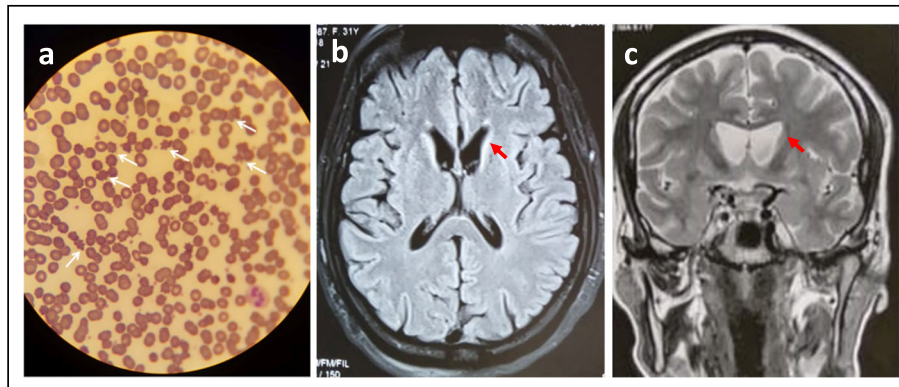


Fig. 2 Biological and neuroimaging features of patient IV.2 presenting with choreoacanthocytosis. **a** Acanthocytes on peripheral blood smear (white arrows); **b, c** Atrophy of the caudate nucleus head on axial and coronal view respectively (red arrows)

Whole exome sequencing and data analysis

Blood samples were taken from patients IV.1 and IV.2 and family members III.1, III.2, IV.3 and IV.5, and high quality genomic DNA was purified from peripheral blood leukocytes using Wizard® Genomic DNA Purification Kit from Promega.

Quality and concentrations of DNA samples were examined by Qubit dsDNA HS Assay Kit (Invitrogen, Q32851) on Qubit fluorometer (Invitrogen, Q33216). WES was performed in the patient IV.2 and his father III.2 at the Supporting Units for Technical and Scientific Research Belonging to CNRST (UATRS/CNRST, Rabat, Morocco). The target regions in the exome were amplified using Ion Proton platform (Thermo Fisher, Scientific). Library preparation, bead templating and PI Chips v2 loading were performed on Ion Chef System, and the sequencing was done on the Ion Proton machine. Sequence alignment to Hg19 and variant identification were performed with the Torrent Suite v.4.2.1 software. The generated VCF files were then imported into the online Server of Ion Reporter Software v5.6 for variant analysis and annotations. Sanger sequencing was used to validate the significant variant identified by WES using a SeqStudio automated sequencer (Thermo Fisher Scientific). Co-segregation analyses among patients' family were also performed.

Analysis of WES data showed that 94 % exons were covered by at least 40X. The primary filtering by Ion Reporter software led to the identification of 39,880 variants in 13,566 genes consisting of SNVs, MNVs and INDELS. These mutations were subsequently filtered using the zygosity in homozygous filter that yielded 3540 homozygous variants in 2836 genes. A novel homozygous c.337C>T mutation was found in exon 5 of *VPS13A* gene leading to a p.Gln113* nonsense mutation. The WES data showed that the mother III.2 was heterozygous for this variant. The p.Gln113* variant was absent from the gnomAD database of control individuals. This

nonsense mutation was validated by Sanger sequencing in all the family members (Fig. 3a) showing a co-segregation of the mutation with the disease (the two patients were homozygous and the parents and the brother IV.3 were heterozygous, the sister IV.5 was homozygous for the normal allele), absent from 192 ethnically matched controls, affect a residue highly conserved among species (Fig. 3b) and was therefore considered as pathogenic.

Discussion and conclusion

In this study, we present two ChAc patients belonging to a Moroccan consanguineous family by describing the clinical symptoms, neuroimaging characteristics and genetic findings.

The clinical phenotype of the two studied patients strongly evoked ChAc disease due to mutations in *VPS13A* gene. Since this gene is a large and contains 73 exons, it is difficult to explore by traditional Sanger sequencing. WES has become a powerful tool for identification of disease-causing variants in genetic disease when the clinical phenotype does not evoke a known disease or when the suspected causal gene is large, thus allowing to save a lot of time and money. WES using the Ion Proton technology found a novel homozygous nonsense mutation c.337C>T (p.Gln113*) in exon 5 of *VPS13A* in the proband. The mutation we validated by Sanger sequencing and segregated in all the family members according to a recessive mode of inheritance confirming the diagnosis of the ChAc in the two patients.

VPS13A encodes the protein chorein is expressed ubiquitously in the brain and in many other tissues [10]. It is composed of multiple domains, a long N-terminal region (*VPS13α*), a putative WD40 modules, a domain reminiscent of a DH domain and a C-terminal pleckstrin homology (PH) domain [11]. The underlying pathophysiology of ChAc is not yet well known, but recently it was shown that chorein may have a role in lipid

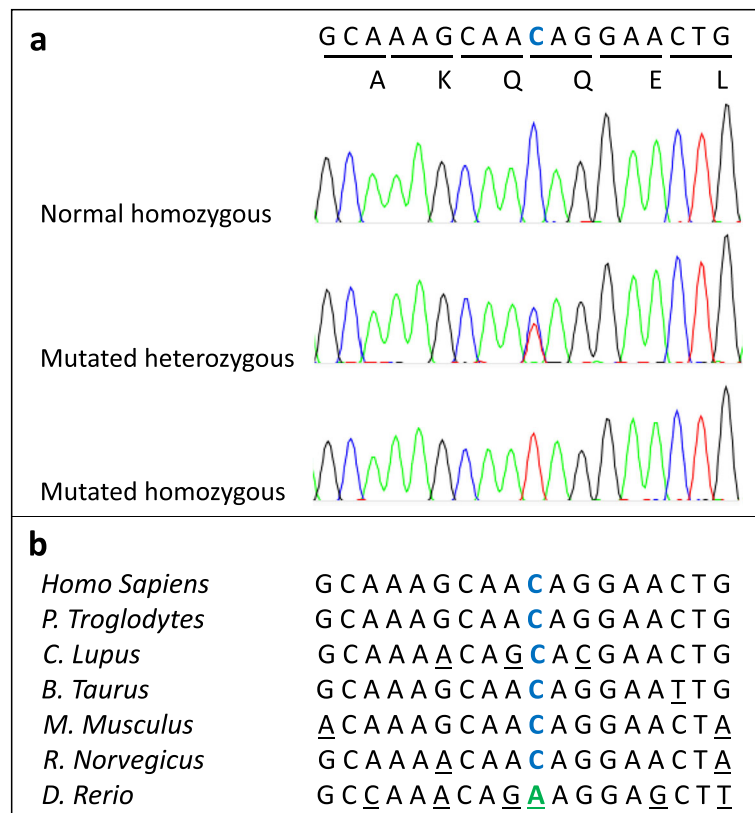


Fig. 3 Sanger validation and conservation of the novel discovered *VPS13A* nonsense mutation. **a** Sanger sequencing confirms the presence of the Gln113* mutation in *VPS13A* at heterozygous and homozygous state; **b** Partial amino acid sequence alignment of human *VPS13A* with orthologs shows evolutionary conservation between species of the Glutamine residue

exchange between organelles and thus for membrane lipid homeostasis in the nervous system. In deed, it has shown that N-terminal region of Vps13A, called Chorein_N domain, is a lipid transport module that bind to the endoplasmic reticulum and connects it to mitochondria [12]. The p.Gln113* identified in this study is located in the chorein_N domain causing loss of function due to truncated protein.

Clinically, the index patients presented hyperkinetic movements with self-injuring which are the main symptoms in choreoacanthocytosis and can be considered as pathognomonic to the diagnosis [4]. On the other hand, the proband’s sister presented generalized epilepsy as initial symptom and later parkinsonism which was previously described in patients with a long follow up when the degenerative process reaches the nigrostriatal pathways [4, 13]. This phenotypic variability has been already documented in many cases of ChAc even in twins [5] and suggests the implication of other modifier genes, epigenetic and environmental factors on the pathogenesis of neuroacanthocytosis as discussed elsewhere [14].

The clinical phenotype of both patients is enriched by depression and emotional liability. Indeed, psychiatric

features account for 60% of ChAc cases including depression, schizophrenia, paranoia, obsessive–compulsive disorder and emotional liability [15]. Beside the psychiatric symptoms, the neuropsychological tests revealed impaired executive and visuospatial functions in the index patient. Ichiba M et al. [16] described a radiological correlation to the cognitive deficit due to the mild atrophy of the frontal lobe and the decrease of brain perfusion on SPECT brain imaging, in addition to the atrophy of the head of caudate nucleus.

Nowadays, there is no curative treatment that can stop the progression of the disease, it remains symptomatic using drugs such as new generation antipsychotics and antiepileptic drugs. Botulinum toxin is indicated in perioral dystonia with a proven effect [17] but there are no evident recommendations concerning protocol, site of injection and doses.

There are a few reported cases describing the effectiveness of deep brain stimulation (DBS) in managing movement disorders in choreoacanthocytosis. The globus pallidus pars interna (GPi) remains the most used target requiring low frequency stimulation on patient with prominent chorea and high frequency

stimulation on notable dystonia. The combination of GPi and the ventralis oralis complex of the thalamus gave better results especially improvement of hyperkinetic movements with less side effects [18]. In the studied family, a GPi DBS was done recently in the proband because of the dramatic worsening of her symptoms and the ineffectiveness of drugs. After 2 months follow up, the patient showed the improvement of hyperkinetic movement and trunk spasm and a mild amelioration of dysarthria, her speech being more intelligible, whereas foot dystonia persisted. Further follow up are necessary to assess the real effect of DBS on this last symptom. These results are in accordance with a multicenter retrospective study that scrutinized the short and long term outcome of DBS in 15 patients [19]. Indeed, chorea, orofacial dyskinesia and trunk spasm were the first improved symptoms, immediately after switching on stimulation. The effect was delayed in dystonia and disappointing for dysarthria which is less sensitive to GPi-DBS or even worsened by high frequency stimulation [20].

In summary, we highlight the ChAc clinical heterogeneity in two patients belonging to a Moroccan consanguineous family, in which we identified a novel nonsense mutation c.337C > T in *VPS13A* gene. This mutation results in the production of a truncated protein with 113 amino acids (p.Gln113*).

Abbreviations

CERB: Ethical committee of biomedical research;
ChAc: Chorea-acanthocytosis; CNRST: Centre national de recherche scientifique et technique; DBS: Deep brain stimulation;
ENMG: Electroneuromyography; GPi: Globus pallidus interna; MRI: Magnetic resonance imaging; SNV: Single nucleotide variations; VPS13A: Vacuolar protein sorting 13 homolog A; WES: Whole exome sequencing

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Authors' contributions

AB conceptualized and designed the study, performed WES, analysed data and wrote the paper. IS and NB performed the DNA extraction and Sanger Validation. EEF contributed to WES. WR, HND and FO contributed to evaluating the clinical features and wrote the paper. WR and MR performed DBS pre-operative recording and side effect monitoring. AM and YA contributed to surgery intervention and lead implantation. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon request. The novel *VPS13A* mutation was submitted to ClinVar under accession number: SCV001147072.1.

Ethics approval and consent to participate

All research was approved by the ethics committee of biomedical research of Medical School and Pharmacy of Rabat (CERB). Written informed consent was obtained from all of the participants in the study.

Consent for publication

Written informed consent for publication of clinical details and clinical images was obtained from all of the participants.

Competing interests

The authors declare that they have no competing interests.

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References

- Walker RH, Schulz VP, Tikhonova IR, Mahajan MC, Mane S, Arroyo Muniz M, Gallagher PG. Genetic diagnosis of neuroacanthocytosis disorders using exome sequencing. *Mov Disord*. 2012;27(4):539–43.
- Peikert K, Danek A, Hermann A. Current state of knowledge in chorea-acanthocytosis as core neuroacanthocytosis syndrome. *Eur J Med Genet*. 2018;61(11):699–705.
- Rubio JP, Danek A, Stone C, Chalmers R, Wood N, Verellen C, et al. Chorea-Acanthocytosis: genetic linkage to chromosome 9q21. *Am J Hum Genet*. 1997;61(4):899–908.
- Shen Y, Liu X, Long X, Han C, Wan F, Fan W, et al. Novel VPS13A gene mutations identified in patients diagnosed with chorea-acanthocytosis (ChAc): case presentation and literature review. *Front Aging Neurosci*. 2017;9:95.
- Velayos Baeza A, Dobson-Stone C, Rampoldi L, Bader B, Walker RH, Danek A, et al. Chorea-Acanthocytosis. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJM B, Stephens K, Amemiya A, editors. *Gene Reviews*. Seattle: Seattle (WA): University of Washington; 2002. p. 1993–2019. [updated 2019 Apr 18].
- Weber J, Frings L, Rijntjes M, Urbach H, Fischer J, Weiller C, et al. Chorea-Acanthocytosis presenting as autosomal recessive epilepsy in a family with a novel VPS13A mutation. *Front Neurol*. 2019;9:1168.
- Elmgreen SB. Criminal behaviour associated with a novel mutation in the VPS13A-gene causing chorea-acanthocytosis. *Case Rep Psychiatry*. 2019. <https://doi.org/10.1155/2019/5947416>.
- Rampoldi L, Dobson-Stone C, Rubio JP, Danek A, Chalmers RM, Wood NW, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. *Nat Genet*. 2001;28(2):119–20.
- Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. *Orphanet J Rare Dis*. 2011;6:68.
- Kurano Y, Nakamura M, Ichiba M, Matsuda M, Mizuno E, Kato M, et al. In vivo distribution and localization of chorein. *Biochem Biophys Res Commun*. 2007;353(2):431–5.
- Fidler DR, Murphy SE, Courtis K, Antonoudiou P, El-Tohamy R, Ient J, and Levine TP. Using HHsearch to tackle proteins of unknown function: a pilot study with PH domains. *Traffic*. 2016;17:1214–26.
- Kumar N, Leonzino M, Hancock-Cerutti W, Horenkamp FA, Li P, Lees JA, et al. VPS13A and VPS13C are lipid transport proteins differentially localized at ER contact sites. *J Cell Biol*. 2018;217(10):3625–39.
- Estévez-Fraga C, López-Sendón Moreno JL, Martínez-Castrillo JC; Spanish collaborative Neuroacanthocytosis group. Phenomenology and disease progression of chorea-acanthocytosis patients in Spain. *Parkinsonism Relat Disord* 2018;49:17–21.
- Yi F, Li W, Xie N, Zhou Y, Xu H, Sun Q, Zhou L. Chorea-Acanthocytosis in a Chinese family with a pseudo-dominant inheritance mode. *Front Neurol*. 2018;9:594.
- Danek A, Jung HH, Melone MA, Rampoldi L, Broccoli V, Walker RH. Neuroacanthocytosis: new developments in a neglected group of dementing disorders. *J Neurol Sci*. 2005;229–230:171–86.
- Ichiba M, Nakamura M, Kusumoto A, Mizuno E, Kurano Y, Matsuda M, et al. Clinical and molecular genetic assessment of a chorea-acanthocytosis pedigree. *J Neurol Sci*. 2007;263(1–2):124–32.

17. Ortega MC, Skármeta NP, Diaz YJ. Management of oromandibular dystonia on a chorea acanthocytosis: a brief review of the literature and a clinical case. *Cranio*. 2016;34(5):332–7.
18. Nakano N, Miyauchi M, Nakanishi K, Saigoh K, Mitsui Y, Kato A. Successful combination of pallidal and thalamic stimulation for intractable involuntary movements in patients with neuroacanthocytosis. *World Neurosurg*. 2015; 84(4):1177.e1–7.
19. Miquel M, Spampinato U, Latxague C, Aviles-Olmos I, Bader B, Bertram K, et al. Short and long term outcome of bilateral pallidal stimulation in chorea-acanthocytosis. *PLoS One*. 2013;8(11):e79241.
20. Ziyuan L, Yang L, Xinhua W, Yingmai Y, Lin W, Wanchen D, et al. Pallidal deep brain stimulation in patients with chorea-acanthocytosis. *Neuromodulation*. 2018;21(8):741–7.

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