Joint webinar series

Mitochondrial disorder with chorea

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Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

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What is your professional background?

2

Overview

- Case presentation of a patient with a hyperkinetic syndrome
- Phenomenology and differential diagnosis
- Etiology

3

Learning objectives

By the end of this webinar you will be able:

- To discuss the differential diagnosis of chorea

- To evaluate patients with a mitochondrial disease

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Case presentation

71-year-old woman, born to non-consanguineous parents from the Assyrian minority in Turkey
- Emigrated to Sweden in early 1980s
- Illiterate widow, has 2 healthy sons

PMH
- Type 2 diabetes
- Hysterectomy at age 47
- Bilateral hearing loss, onset at age 58, uses a hearing device
- Hemithyroidectomy due to a benign follicular tumor
- α-thalassemia trait: 3.7 deletion in the α-globin gene (-α/αα) with mild anemia

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History of present illness

- Perioral movements and waddling gait, age of motor onset was not possible to determine
- Insidious short memory impairment and ADL difficulties noticed at age 52
- Onset of olfactory hallucinations at age 56, became obsessed with cleaning and doing laundry
  - This leads to conflicts with neighbors
- At age 58 her olfactory hallucinations were unbearable, and the patient attempted suicide by setting her apartment at fire

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Case presentation

- She was admitted to a psychiatric ward, cognitive difficulties noticed but no formal evaluation was made
- Initially treated with Haloperidol, later with aripiprazole (Abilify), she spend 1 year in a psychiatric ward

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Summary of phenomenology video

- Chorea (mainly perioral area and feet, intermittent in the trunk), dystonic posturing in the hands
- Absence of arm movements, waddling gait, and bradykinesia
- Apraxia is also evident
- Not shown in the video: reduced strength in both arms, mild distal muscle atrophy, however her reflexes, and muscle tone are normal

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A waddling gait is highly suggestive of:

1. Paraparesis
2. Myopathy
3. Chorea
4. Dystonia
5. None of the above

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Investigations

- CK and myoglobin levels were normal
- Lactate initially normal but recently found to be elevated
- Mild microcytic anemia (due to thalassemia trait)
- Routine tests on CSF yielded normal results
- Markers of neurodegeneration in CSF were normal
- Onconeuronal antibodies and GAD antibodies are not found
- Repeated EEG studies were normal
- Neurophysiological tests demonstrated both myopathy and demyelinating polyneuropathy

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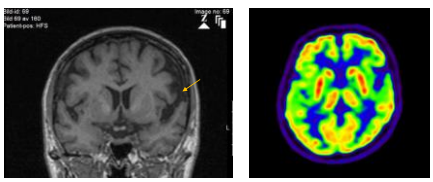
Investigations

- Neuroimaging was not contributory



Widened perisylvian sulci (arrow) at age 63 and hypometabolism in the same regions. Metabolism was normal in the basal ganglia

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Cardiac evaluation

- Repeated ECGs and measurements of NT-proBNP are normal
- Repeated echocardiographic has shown non-progressive ventricular septum hypertrophy and normal EF

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What is next step in the investigation?

1. Muscle biopsy
2. Sequencing of mitochondrial DNA from muscle
3. Whole-exome sequencing (WES)
4. All the previous

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Muscle biopsy

- Cytochrome oxidase (COX) negative fibers and red ragged fibers
- Predominance of type 1 muscle fibers
- Respiratory chain complexes (RCC)' activity was normal
- Sequencing of mitochondrial DNA from muscle biopsy was normal

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Important considerations

- Normal muscle biopsy and biochemistry does not rule out mitochondrial disease
- Lactate levels are also variable in mitochondrial disease
- Whole-genome sequencing (WGS) can be configurated to cover both nuclear and mitochondrial DNA

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This presentation is more likely caused by:

1. MELAS
2. POLG-related disorder
3. Another rarer mitochondrial disease
4. Huntington's disease (HD)
5. Huntington's disease like (SCA17, c9orf72, HDL2 and familial prion disease)
6. Neuroacanthocytosis syndromes (chorea-acanthocytosis or McLeod syndrome)

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Differential diagnosis

- Mitochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes (MELAS): absence of stroke-like episodes, migraine and neuroimaging argue against it
- Some patients with MELAS have brain calcifications
- Diabetes and cardiomyopathy are not common for POLG-related disorder
- Leigh syndrome: most often infantile onset, subacute relapsing encephalopathy , and typical neuroimaging findings

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Differential diagnosis

- HD and HDLs are autosomal dominant (Ruled out in this case)
  - Cardiomyopathy is not part of these conditions
- Hearing loss and diabetes are not features of HD, HDLs or classical neuroacanthocytosis syndromes

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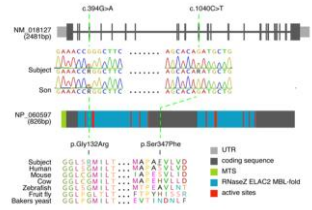
Genetic studies



- WES revealed the variants c.394G>A (p.Gly132Arg) and c.1040C>T (p.Ser347Phe) in the elacC ribonuclease Z 2 (*ELAC2)* gene
- These variants were in *trans*
- Patient's healthy son is a heterozygous mutation carrier

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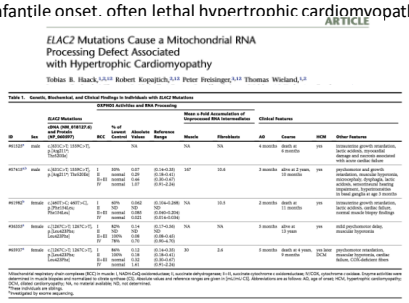
Combined oxidative phosphorylation deficiency 17 (COXPD17) OMIM # 615440

- Infantile onset, often lethal hypertrophic cardiomyopathy (HCM)



ARTICLE

ELAC2 Mutations Cause a Mitochondrial RNA Processing Defect Associated with Hypertrophic Cardiomyopathy

Tobias B. Haack,[1,2,13] Robert Kopajtich,[1,13] Peter Freisinger,[3,13] Thomas Wieland,[1,2] Ioanna Rorbach,[4] Thomas J. Nicholls,[4] Enrico Baruffini,[5] Anett Walther,[1,2] Katharina Danhauser,[1]

AJHG 2013

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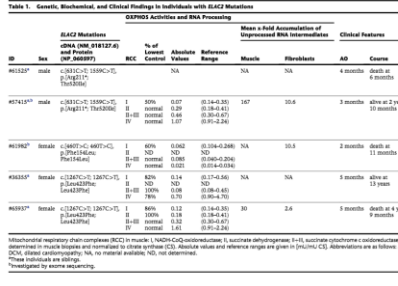

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AJHG 2013

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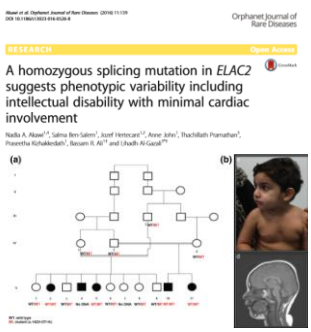
Survival beyond childhood is possible but rare in COXPD17



Orphanet Journal of Rare Diseases

RESEARCH Open Access

A homozygous splicing mutation in *ELAC2* suggests phenotypic variability including intellectual disability with minimal cardiac involvement

Nadia A. Akawi[1,4], Salma Ben-Salem[1], Jozef Hertecant[1,2], Anne John[1], Thachillath Pramathan[3], Praseetha Kizhakkedath[3], Bassam R. Ali[1,4] and Lihadh Al-Gazali[1,4]*

Global developmental delay
Mild dysmorphism in some
All but one were unable to walk
Oldest living in this family was 25 y.o.

2016

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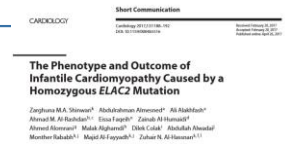
Combined oxidative phosphorylation deficiency 17 (COXPD17)



CARDIOLOGY

Short Communication

The Phenotype and Outcome of Infantile Cardiomyopathy Caused by a Homozygous *ELAC2* Mutation

- Screening among consanguineous Saudi families
- 16 cases were found, all dead of HCM or dilated cardiomyopathy (DCM), mean age of death: 4 months
- Other features: psychomotor delay and hypotonia in 3 infants; intrauterine growth retardation in 2; microcephaly, dysphagia, and sensorineural hearing impairment in 1

2017

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Combined oxidative phosphorylation deficiency 17 (COXPD17)

DOI: 10.1002/humu.23777
RESEARCH ARTICLE
Human Mutation HGVS WILEY

Mutations in *ELAC2* associated with hypertrophic cardiomyopathy impair mitochondrial tRNA 3′-end processing

- 13 patients, 10 had HCM and 3 DCM
  - Congenital-infant onset
  - 2 went through heart transplantation
  - 8 died during infancy-childhood, oldest living was 19 y.o.
- All but 1 had lactic acidosis
- All had deficits in mitochondrial respiratory chain
- Most displayed developmental delay
- 1 had cerebellar hypoplasia, 1 myopathy and 1 polyneuropathy

M Saoura et al, 2019

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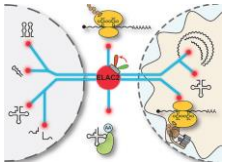
Combined oxidative phosphorylation deficiency 17 (COXPD17) OMIM # 615440

- ELAC2 encodes for RNase Z, an endonuclease responsible for the removal of the 3' extensions from tRNA precursors
- ELAC2 is essential for nuclear and mitochondrial tRNA processing
- Nuclear tRNA processing is essential for balanced production of other non-coding RNAs



Siira et al.
EMBO reports 2018

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Combined oxidative phosphorylation deficiency 17 (COXPD17) OMIM # 615440

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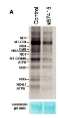
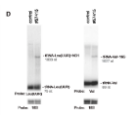
AJHG 2013



Deficits in respiratory chain's complex I



Accumulation of unprocessed mt-tRNA-mRNA intermediates

- COX negative fibers in some
- Enlarged mitochondria and abnormal cristae in myocardial biopsy

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Combined oxidative phosphorylation deficiency 17 (COXPD17) OMIM # 615440

Let's go back to our case

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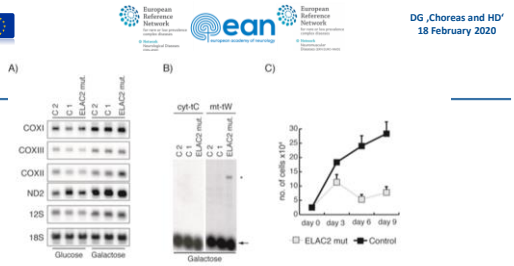

A and B: Northern blot analyses from fibroblasts
A) Steady-state levels of mitochondrial mRNAs. 18S rRNA was used as loading control. Controls: C1 and C2, patient: ELAC2mut.
B) B) Steady-state levels of mitochondrial tRNA-Tryptophane (mt-tW) and the nuclear-encoded tRNA-Cysteine (cyto-tC) from control (C1, C2) and patient fibroblasts, grown for 14 days on galactose-containing medium. *= unprocessed mitochondrial transcript, arrow = tRNA
C) Growth curves of control and patient fibroblasts grown on galactose

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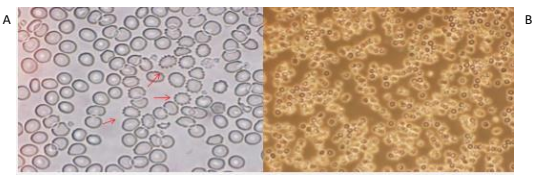
Unexpected finding



Up to 10% acanthocytes (arrows) were found in two different occasions.

A) Undiluted (100X). B) Diluted (40X) smears

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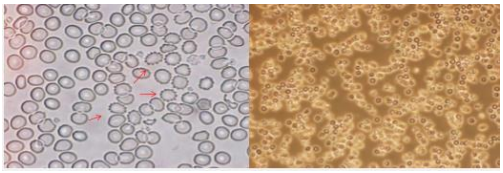
Unexpected finding

A B



Western blot for chorein was normal, re-assessment of WES data ruled out mutations in *VPS13A* and *XS*

These acanthocytes can not be explained by her thalassemia trait

Mitochondrial disease and acanthocytosis

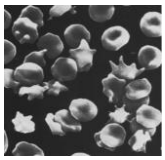
J Neurol (1986) 233 : 220–232

Journal of Neurology © Springer-Verlag 1986

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes with acanthocytosis: a clinicopathological study of a unique case

M. Mukoyama, H. Kazui, N. Sunohara, M. Yoshida, I. Nonaka, and E. Satoyoshi

National Centre for Nervous, Mental and Muscular Disorders, 4-1-1, Ogawahigashimachi, Kodaira-shi, Tokyo, Japan 187



Cognitive evaluation

Cognitive domain	Test	Result (z-score)
General intellectual ability	Raven's progressive matrices IQ	70 (-2.0)
Visuo-spatial episodic memory	ROCFT immediate recall	1.5 (<-3)
Logical memory	Immediate recall of a short story (from Luria)	Correct recall
Spatial/visual construction	ROCFT/copy	0 (<-3)

Summary of a brief cognitive assessment performed at age 67
Significant cognitive deficits correspond to the cut-off z-score ≤ -1.5 standard deviations
ROCFT = Rey Osterrieth Complex Figure Test

Follow-up of the described patient

- Oldest living patient with biallelic *ELAC2* mutations
- Her condition is clearly progressive (increasing UHDRS scores)
- Depends on a walker for mobility, has fallen several times
- Last year she fell and contracted a subdural hematoma
- The patient developed urine and fecal incontinence
- Later, sudden onset of slurred speech occurred, brain MRI demonstrated an infarction in the brain stem
- Weight loss during the follow-up

COXPD17

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CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Chorea, psychosis, acanthocytosis, and prolonged survival associated with *ELAC2* mutations

Martin Paucar, MD, PhD, Aleksandra Pajak, PhD, Christoph Freyer, PhD, Åsa Bergendal, PhD, Margit Döry, MLS, José Miguel Laffita-Mesa, PhD, Henrik Stranneheim, PhD, Kristina Lagerstedt-Robinson, PhD, Irina Savitcheva, MD, Ruth H. Walker, MB, ChB, PhD, Anna Wedell, MD, PhD, Anna Wredenberg, MD, PhD, and Per Svenningsson, MD

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Neurology® 2018;00:1-3. doi:10.1212/WNL.0000000000006320

Conclusions

- Chorea and dystonia are manifestations of some mitochondrial diseases including COXPD17
- Often a lethal disease but long survival is possible in association with *ELAC2* mutations
- The spectrum of phenotypes associated with *ELAC2* mutations is growing
- The presence of acanthocytosis has to be assessed in other patients with biallelic *ELAC2* mutations

Acknowledgments

To the patient and her son

Dr Anna Vredenberg's group at the Center For Inherited Metabolic Disorder

Professor Per Svenningsson's group at the Department of Clinical Neuroscience, Karolinska Institutet and Department of Neurology

Department of Genetics

All coworkwes at the Karolinska University Hospital

DG ‚Choreas and HD'
18 February 2020

Joint webinar series

Thank you!

Next Webinar: 'Ultrasound diagnostics for cervical dystonia'
3. March 2020, 15-16h CET