The Basics: What Are Mitochondria and Mitochondrial Disease?

What Does It Mean For Dysautonomia?

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Dysautonomia International; 18-July, 2015
Herndon, Virginia
Dr. Boles is a consultant for Courtagen, which provides diagnostic testing.

- Medical Director of Courtagen Life Sciences Inc.
  - Test development
  - Test interpretation
  - Marketing
- Researcher with prior NIH and foundation funding
  - Studying sequence variation that predispose towards functional disease
  - Treatment protocols
- Clinician treating patients
  - Interest in functional disease (CVS, autism)
  - Geneticist/pediatrician 20 years at CHLA/USC
  - In private practice since 2014
There are no approved treatments for mitochondrial disease.

Everything is “off label”
• Presented to my clinic at age 11 years.
• Cyclic vomiting syndrome from ages 1-10 years, with 2-day episodes twice a month of nausea, vomiting and lethargy.
• Episodes had morphed into daily migraine.
• Chronic pain throughout her body.
• Chronic fatigue syndrome = chief complaint.
• Substantial bowel dysmotility/IBS
  Multiple admissions for bowel clean-outs.
• Excellent student
• Pedigree: probable maternal inheritance
NextGen sequencing at age 14 years revealed the p.Ile253Val variant in the TRAP1 gene.

TRAP1 encodes a mitochondrial chaperone involved in antioxidant defense.

This patient is one of 26 unrelated cases identified by Courtagen to date who have previously unidentified disease associated with mutations in the ATPase domain.

The common feature recognized at present is chronic pain, fatigue and GI dysmotility.

Tachycardia/palpitations and dizziness may also be common.

That variant comes from Payton’s father, who himself has frequent pain, fatigue and diarrhea.

In these patients, chronic pain and fatigue improved greatly on aggressive antioxidant therapy.

On aggressive antioxidant therapy, all manifestations of disease in Payton were substantially improved. Issues remaining included chronic abdominal pain and moderate fatigue. She became functional in life, but still on a shortened school schedule.
1. An ATPase domain hydrolyze the energy-rich triphosphate bond of ATP to convert into mechanical work of folding proteins.

2. The two homodimers of TRAP1 are shown in grey and pink.

2. ATP bound in its pocket is shown in green, in each dimer.

3. The “common mutation” p.Ile253Val is labeled in each dimer.

4. The “salt bridge” mutations, R128H (p.Arg128His) and E192K (p.Glu192Lys), are labeled in one dimer.

Can we design a therapy that blocks ATP entrance into mutant TRAP1, but not normal TRAP1?
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Can we design a therapy that blocks ATP entrance into mutant TRAP1, but not normal TRAP1?

Computer modeling was performed based on the human TRAP1 crystal structure by Jeffrey Skolnick at the Georgia Institute of Technology.
What Are Mitochondria?
What Are Mitochondria?

Ask the Wookieepedia!
Midi-chlorians were intelligent microscopic life forms that lived symbiotically inside the cells of all living things.

"Without the midi-chlorians, life could not exist, and we would have no knowledge of the Force. They continually speak to us, telling us the will of the Force. ” - Qui-Gon Jinn
What Are Mitochondria?

Don’t they look similar?
Mitochondrial Genetics
The Basics

Mitochondrial DNA

- 37 genes
- 16,000 base pairs
- Maternal inheritance

Nuclear DNA

- ~22,000 genes
- 3,000,000,000 base pairs
- 1,013 genes encode mitochondrial proteins
- Autosomal recessive
- Autosomal dominant
- X-linked
Maternal Inheritance

mtDNA is inherited exclusively from the mother. There is no recombination.

Thus, all relatives with red symbols have exactly the same mtDNA sequence, in the absence of a new mutation.
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The Basics

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Metabolic Pathways
Fats
- Glycerol
- Fatty acids
  - β-oxidation
  - NAD$^+$ → NADH
  - FAD$^{++}$ → FADH$_2$

Carbohydrates
- Sugars
  - Gluconeogenesis
  - NAD$^+$ → NADH
  - ADP + P → ATP

Proteins
- Amino acids (20+)

Glycogen

Lactate
- Pyruvate
- Glucogenic amino acids
- Ketogenic amino acids

Acetate
- Krebs Cycle
  - 3NAD$^+$ → 3NADH
  - FAD$^{++}$ → FADH$_2$
  - complex 1, complex 2

Ketones

Simplified Map of Energy Metabolism
Electron Transport Chain
Genetic defects affecting the body’s ability to make ATP (energy) are termed “mitochondrial disorders”

Mutations can be in the nuclear DNA (chromosomes) or the mitochondrial DNA (mtDNA)
These conditions are genetic, although many families have only one affected person. Even when familial, with every relative affected in a very different manner, the connections are difficult to see.

Signs and symptoms come and go to different parts of the body depending on the energy flux of each tissue in each minute. Patients are often not believed, or thought to be “psychiatric”.

In addition to the 37 genes on the mtDNA, there are at least another 1,088 genes in the nucleus that encode proteins which are imported into the mitochondria.

Many patients do NOT have a real diagnosis!
What Is Mitochondrial Dysfunction?
"Mitochondrial Dysfunction" = mitochondria are not working properly

Can be “primary” due to an underlying defect within the mitochondria = “mitochondrial disease”

Can be “secondary” due to an underlying defect outside the mitochondria = “???????????”
Mitochondria are derived from ancient bacterial symbiotes that live within our cells.

They have maintained some of the original bacterial DNA.
- This mtDNA is inherited only from the mother.
- Mutations in the mtDNA can cause mitochondrial disease and dysfunction.

Most of the DNA that codes for mitochondrial proteins is in the nucleus.
- Most of that DNA comes equally from both parents.
- Mutations in those genes can cause mitochondrial disease and dysfunction.

Many diseases that derive from defects outside of the mitochondria can result in secondary mitochondrial dysfunction.

Mitochondria make the vast majority of the energy that the cell uses.
- All cells need energy – for nearly everything they do.
- Thus, mitochondrial disease can affect almost any part of the body, and contribute towards almost every condition/disease.
What is Mitochondrial Disease?

How can you stand here and tell us that mitochondrial disease can underlie just about any disease!
How can you stand here and tell us that mitochondrial disease can underlie just about any disease!

Are you a quack?
Energy!
Mitochondrial Medicine
The Spectrum of Mito

**Brain**
- Developmental delays
- Dementia
- Neuro-psychiatric disturbances
- Migraines
- Autistic Features
- Mental retardation
- Seizures
- Atypical cerebral palsy
- Strokes

**Nerves**
- Weakness (may be intermittent)
- Absent reflexes
- Fainting
- Neuropathic pain
- Dysautonomia - temperature instability

**Muscles**
- Weakness
- Cramping

**Kidneys**
- Gastrointestinal problems
- Dysmotility
- Irritable bowel syndrome
- Hypotonia
- Muscle pain
- Gastroesophageal reflux
- Diarrhea or constipation
- Pseudo-obstruction

**Ears & Eyes**
- Visual loss and blindness
- Ptosis
- Ophthalmoplegia
- Optic atrophy
- Hearing loss and deafness
- Acquired strabismus
- Retinitis pigmentosa

**Heart**
- Cardiac conduction defects (heart blocks)
- Cardiomyopathy

**Liver**
- Hypoglycemia (low blood sugar)
- Liver failure

**Pancreas & other glands**
- Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
- Parathyroid failure (low calcium)

**Systemic**
- Failure to gain weight
- Fatigue
- Unexplained vomiting
- Short stature
- Respiratory problems
Helen:

- **Cyclic vomiting syndrome**
- Ocular myopathy (ptosis and ophthalmoplegia)
- Pigmentary retinopathy
- Mild developmental delay
- Ataxia
- Hypotonia
- Muscle weakness
- Exercise intolerance
- Severe GI dysmotility
- Episodic leg pain
- Photophobia
- Growth retardation
Large mtDNA Deletion Case Growth Curves

Weight is paralleling the curves.

Weight is appropriate for height.

G-tube placed at age 5.5 years
A case of Kearns-Sayre syndrome:

The 3K base-pairs between the blue lines is deleted in a proportion of the mtDNA.

The deleted molecules are smaller, and replicate faster, causing disease progression.

Prognosis: progressive multi-system failure leading to death.
What Is Functional Disease?

A poem by a 14-year-old patient
I never know when its going to come back
This fatigue is an internal attack
It so easily cripples me
Only no one can see

It's so hard when you easily tire
And everyone around you thinks your lazy and a liar
They can't see so they don't know
I know in my heart it's real though

It's a relief to get the answer and know you're not crazy
You can finally prove you're not just lazy
It's still not easy and never will be
But maybe some day the world will see
20 “Functional” Disorders:

- Attention deficit hyperactivity disorder
- Anxiety disorder
- Autistic spectrum disorders
- Chronic fatigue syndrome
- Complex regional pain syndrome
- Cyclic vomiting syndrome
- Depression (MDD)
- Fibromyalgia
- Functional abdominal pain
- Interstitial cystitis
- Insomnia (chronic, severe)
- Irritable bowel syndrome
- Migraine
- Panic disorder
- Post-traumatic stress disorder
- Postural orthostatic tachycardia syndrome
- Restless legs syndrome
- Temporomandibular disorder
- Tinnitus
- Vulvovaginitis syndrome
Comorbidity:
Functional Conditions Are Often Found Together

• 44% of patients with interstitial cystitis also have symptoms suggestive of irritable bowel syndrome (IBS) (v. 12% of controls).
• 59% of patients with cyclic vomiting syndrome met the standardized questionnaire criteria for a generalized anxiety disorder.
• 67% of migraineurs fulfilled criteria for chronic fatigue syndrome.
• 75% of patients with cyclic vomiting syndrome are projected to develop migraine by age 18.
• 20% to 80% of patients with temporomandibular disorders suffer from additional chronic pain disorders such as headache, low back pain, fibromyalgia, and irritable bowel syndrome.
Maternal Inheritance of Functional Disorders - 1
Maternal Inheritance of Functional Disorders - 2

- Asthma
- SIDS
- Dysmotility
- Near SIDS
- Frequent fevers
- CRPS
- CVS
- Decreased tearing
- Muscle cramps
- Dysmotility
- Vital sign changes
- Lethargy
- Developmental delay
- Abdominal pain
- Migraine
- ADHD
Maternal Inheritance of Functional Disorders - 4
The elephant is lying down due to chronic fatigue.
Quantitative Pedigree Analysis
In Cyclic Vomiting Syndrome
Figure 2: Labeling of pedigrees as “probable maternal inheritance,” “probable non-maternal inheritance,” or “indeterminate.”
Functional Disorder-Associated mtDNA Polymorphisms

16519 C>T
mtDNA control region

3010 G>A
16S-ribosomal RNA gene
Cyclic Vomiting and Migraine Prevalence of Two mtDNA Common Variants in Haplogroup H Individuals With Functional Disorders

<table>
<thead>
<tr>
<th></th>
<th>Cyclic Vomit Syndr.</th>
<th>Odds Ratio (95% C.I.)</th>
<th>Migraine w/o Aura</th>
<th>Odds Ratio (95% C.I.)</th>
<th>Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td>16519T</td>
<td>21/30 70%</td>
<td>6.2 (2.7-14)</td>
<td>58/112 52%</td>
<td>3.6 (2.2-5.9)</td>
<td>63/231 27%</td>
</tr>
<tr>
<td>3010A</td>
<td>9/30 30%</td>
<td>N/A</td>
<td>37/112 33%</td>
<td>N/A</td>
<td>143/444 32%</td>
</tr>
<tr>
<td>3010A among pts with 16519T</td>
<td>6/24 29%</td>
<td>17 (2-156)</td>
<td>15/58 26%</td>
<td>15 (1.9-117)</td>
<td>1/63 1.6%</td>
</tr>
</tbody>
</table>
Chronic Fatigue Syndrome
The 3010A mtDNA Variant
Predicts a Several-fold Increase in Functional Symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Headache</th>
<th>Fainting or Dizziness</th>
<th>Muscle Pain</th>
<th>Muscle Weakness</th>
<th>Sleep Problems</th>
<th>Numbness or Tingling</th>
</tr>
</thead>
<tbody>
<tr>
<td>3010A</td>
<td>14/21</td>
<td>11/21</td>
<td>19/21</td>
<td>17/21</td>
<td>19/22</td>
<td>12/21</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>52%</td>
<td>90%</td>
<td>81%</td>
<td>86%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>18%</td>
<td>57%</td>
<td>61%</td>
<td>48%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Chi Square</strong></td>
<td><strong>P = 0.04</strong></td>
<td><strong>P = 0.02</strong></td>
<td><strong>P = 0.03</strong></td>
<td><strong>P = 0.22</strong></td>
<td><strong>P = 0.01</strong></td>
<td><strong>P = 0.06</strong></td>
</tr>
<tr>
<td><strong>Odds Ratio</strong></td>
<td><strong>4.0</strong></td>
<td><strong>4.7</strong></td>
<td><strong>5.9</strong></td>
<td><strong>NA</strong></td>
<td><strong>6.0</strong></td>
<td><strong>3.7</strong></td>
</tr>
<tr>
<td><strong>(95% C.I.)</strong></td>
<td>(1.1-18)</td>
<td>(1.2-23)</td>
<td>(1.2-54)</td>
<td><strong>NA</strong></td>
<td>(1.4-38)</td>
<td>(0.95-18)</td>
</tr>
<tr>
<td><strong>T-test</strong></td>
<td><strong>P = 0.001</strong></td>
<td><strong>P = 0.06</strong></td>
<td><strong>P = 0.025</strong></td>
<td><strong>P = 0.03</strong></td>
<td><strong>P = 0.046</strong></td>
<td><strong>P = 0.03</strong></td>
</tr>
</tbody>
</table>
• Functional disease:
  – is very common.
  – can affect nearly any part of the body.
  – can be mild to disabling.
  – is often clustered: with many functional conditions in the same patient.
  – is often present in a maternal inheritance pattern.
  – can be associated by specific mtDNA variants
What Have You Learned?

• Functional disease:
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  – can be mild to disabling.
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  – can be associated by specific mtDNA variants

• In addition, functional disease:
  – responds to the same therapies (e.g. amitriptyline, SSRIs, coenzyme Q10).
  – is related to dysautonomia.
  – may actually be different manifestations of a single disease.
Karl, age 27 years
Abdominal migraine

- Presented with cyclic episodes of abdominal pain, nausea, vomiting and pallor.
- Episodes became very frequent and coalesced to near-continuous.
- Status-post cholecystectomy and appendectomy
- On narcotics, fully disabled, and labeled as a drug addict
- Other issues: migraine headaches, fatigue, GERD, anxiety
- Seen in my clinic at age 23 and placed on amitriptyline, coenzyme Q10 and L-carnitine. Initial success with only rare episodes.
- Stopped treatment, and at age 26 was refractory to above therapy, including episodes every 4 to 7 days for several hours; again disabled. Had 10-15 ER visits in 5 months.
- Family history is negative.
Karl, age 27 years
Abdominal migraine

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- Seen in my clinic at age 23 and placed on amitriptyline, coenzyme Q10 and L-carnitine. Initial success with only rare episodes.
- Stopped treatment, and at age 26 was refractory to above therapy, including episodes every 4 to 7 days for several hours; again disabled. Had 10-15 ER visits in 5 months.
- nucSEEK sequencing revealed 3 known mutations in the RYR2 gene.
- The patient was placed on propranolol.
- Dramatic improvement with the resolution of episodes.
• **Ryanodine receptor 2**
• Encodes a stress-induced calcium channel across the endoplasmic reticulum
• Links with VDAC on the outer mitochondrial membrane to link ER directly with mitochondria
• Dominant mutations are associated with adrenergic-triggered arrhythmia (often fatal) and right-sided cardiomyopathy
• Channel also present in neurons
• Highly-conserved variants are associated with cyclic vomiting
• Have “functional triad” as well – common in CVS
• All are VERY nervous people, with stress-triggered disease
• Disease responds favorably to beta blockade (propranolol)
**RYR2 variants predispose towards many of the same functional conditions**

*Neurogastroenterology and Motility, 2015*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Variant</th>
<th>Selected Functional Co-morbidities*</th>
<th>Control</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p.Ser1400Gly</td>
<td>Fatigue</td>
<td></td>
<td>p.Arg1119His</td>
</tr>
<tr>
<td></td>
<td>p.Ser1400Gly,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p.Cys2559Tyr</td>
<td>Chronic pain, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>p.Ser1400Gly</td>
<td>GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>p.Ser1400Gly</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>p.Ser1400Gly</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>p.Ser1400Gly</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>p.Gly1885Glu</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>p.Gly1885Glu</td>
<td>Chronic pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>p.Gly1885Glu</td>
<td>Chronic pain, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>p.Arg3506Ter</td>
<td>Chronic pain, fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>p.Asn4736Asp</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p.Ile1925Thr,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>p.Ile2721Thr</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>p.Met1564Ile</td>
<td>Chronic pain, fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>p.Arg1051Cys</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>p.Ile217Val</td>
<td>Fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>p.Phe4022Tyr</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>p.Ala1136Val</td>
<td>Chronic pain, fatigue, GI dysmotility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>p.Ala1136Val</td>
<td>Fatigue</td>
<td></td>
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</tr>
</tbody>
</table>

**Cyclic vomiting syndrome:**

18/75 (24%) subjects vs 3/60 (5%)

Of controls have well conserved

**RYR2 variants.**

Odds ratio 6.0 (95% C.I 1.7-22)

P = 0.0018
MELAS: Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes

3243 A>G
Transfer RNA gene for leucine (UUR)

Brain disease
Muscle disease

Malignant migraine > Stroke-like episodes > Stroke > Disability and death
Thomas, age 22 years
POTS

- Presented as the lesser-affected brother of a girl with multi-system presumed “mitochondrial disease”.
- Had mild “functional” symptoms only in first decade, such as occasional pain, fatigue and dyautonomia.
- Episode of complex regional pain syndrome following removal of benign tumor on back.
- In early adolescence, developed episodes of POTS/pre-syncope that were dramatic, occurred with little warning, often in school.
- Episodes appeared like grand-mal seizures, paramedics called to school often.
- Episodes became frequent, sometimes followed by severe dysautonomia failure that required ICU admissions for up to a few weeks.
- Effectively disabled by his condition.
Maternal Inheritance of Functional Disorders - 1

Cancer

Colitis
Colitis

Seizures, CVS, Migraine, Bipolar, Anxiety

GERD, Migraine, Depression, Seizures, Hearing loss

Seizures, CVS, Migraine, Bipolar, Anxiety

Migraine
Muscle weakness
Hypoglycemia

Ptosis
Reyes syndrome
Failure to thrive
Thomas’ mtDNA

Three different length heteroplasmic variants mtDNA control region – area involved in replication and transcription of mtDNA
Maternal Inheritance of Functional Disorders

Cancer

Colitis

Migraine, Seizures, CVS, Muscle Weakness, Depression, ASD/VSD

GERD, Migraine, Depression, Seizures, Hearing loss

Seizures, CVS, Migraine, Bipolar, Anxiety

CRPS, CVS, Migraine, Seizures, Migraine, Depression

Migraine

Muscle weakness

Hypoglycemia

Abdominal migraine

Ptosis

Reyes syndrome

Failure to thrive

Bipolar, Migraine

Dyslexia

Preemie

CVS

Blind

CRPS

Migraine

GERD

SIDS

CP

ASD/VSD
• Presented as the lesser-affected brother of a girl with multi-system presumed “mitochondrial disease”.
• Had mild “functional” symptoms only in first decade, such as occasional pain, fatigue and dyautonomia.
• Episode of complex regional pain syndrome following removal of benign tumor on back.
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• Episodes appeared like grand-mal seizures, paramedics called to school often.
• Episodes became frequent, sometimes followed by severe dysautonomia failure that required ICU admissions for up to a few weeks.
• Effectively disabled by his condition.
• Asked me for medical clearance to go SCUBA diving with his high-school class from a remote base on Catalina Island.
• Placed on L-arginine supplementation, which dramatically improved his POTS to about one episode a year.
• L-arginine is an amino acid, part of natural protein. It is involved with nitric oxide synthesis, which dilates blood vessels. It is very effective in preventing stroke in MELAS.
• He DID go SCUBA diving with his class!
• On sequencing of nuclear-encoded mitochondrial proteins he was found to have a mutation in the TRAP1 gene, p.Tyr229*
• His affected sisters and affected mother have the same mutation.
• Doing very well at present, essentially normal other than chronic fatigue (sleeps 10-11 hours at night) and some pain.
Suspect mitochondrial/metabolic disease if there are two or more of the following “Red Flags”:

- Autistic spectrum disorder/pervasive developmental disorder
- Loss of milestones/regression
- Movement disorder (including ataxia, dystonia, chorea, tics)
- Stroke or stroke-like episodes
- Myopathy, especially ocular or cardiac
- Chronic bowel dysmotility (especially if severe or at more than one level)
- Cyclic vomiting
- Dysautonomia (including POTS, frequent tachycardia, unexplained fevers)
- Chronic pain condition (including migraine, myalgia)
- Chronic fatigue
- Mood disorders
- Waxing and waning clinical course (including altered mental status or psychosis)
- Hypoglycemia
- Metabolic acidosis (either renal tubular loss and/or anion gap)
- Elevated liver transaminases (including only trace elevated, if frequent)