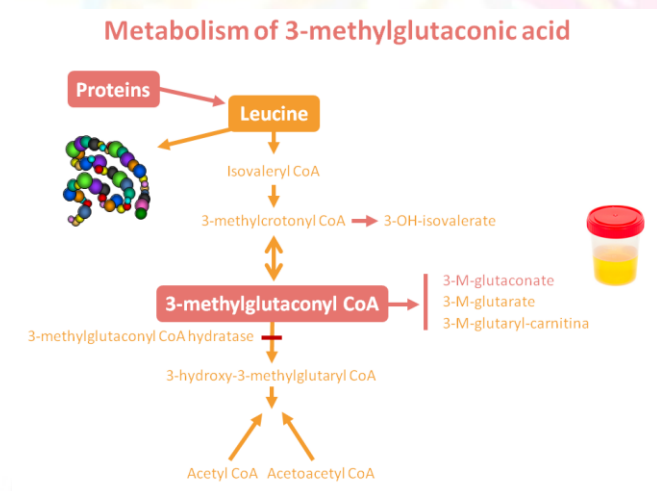


3-METHYLGLUTACONIC ACIDURIA

WHAT IS 3-METHYLGLUTACONIC ACIDURIA (3-MGA-URIA)?

3-MGA-uria comprises a heterogeneous group of inherited metabolic diseases characterized by a significant and sustained increase in the urinary excretion of **3-methylglutaconic acid (3-MGA)**. 3-MGA-uria is a hallmark of the biochemical profile and often the key to diagnosis for these diseases.

WHAT IS 3-METHYLGLUTACONIC ACID (3-MGA)?



This is a branched chain organic acid, which is an intermediary metabolite of **leucine catabolism**.

In the urine of healthy individuals only traces of 3-MGA (<10 mmol/mol creatinine) can be detected, but in many metabolic diseases (organic acidurias, mitochondrial and neuromuscular diseases) higher concentrations (20 - 40 mmol/mol creatinine) can be excreted, sometimes associated with **3-methylglutaric acid**, when patients are in metabolic decompensation.

In the so called **3-MGA-urias**, the excretion of 3-MGA can generally be detected in concentrations **higher than 40mmol/mol creatinine**, regardless of the clinical status.

The cause of this excretion is only known in **3-MG-CoA hydratase deficiency (3-MGA-uria type I)**, but the

HOW ARE THE 3-MGA-URIAS CLASSIFIED?

This group of diseases were traditionally labelled by roman numbers (I-V) in the order of discovery, without considering the mechanisms by which they occurred (pathogenesis). However, as soon as the genetic basis of these diseases has been known, the classification based in pathomechanisms and genetics has been adopted, although its metabolic origin is in some cases not yet fully understood.

Table I summarizes the **classification of 3-MGA-urias**, their **genetic and metabolic basis** and their **mechanism of pathogenesis** (modified of Wortmann et al, J Inherit Metab Dis 2013; 36:923-928).

Group	Patogenic mechanism	Disease	Old type	Gene	Protein & funtion
Primary 3-MGA-uria	Organic aciduria	3-MG-CoA hydratase deficiency	I	AUH	3-MG-CoA hydratase, Leucine catabolism
Secondary 3-MGA-uria	Defective phospholipid remodelling	TAZ defect, Barth syndrome	II	TAZ	Tafazzin, cardiolipin remodelling
		SERAC1 defect MEGDEL syndrome	IV	SERAC1	SERAC1, phosphatidyl-glycerol remodelling, cardiolipin composición
	Mitochondrial membrane associated disorder	OPA3 defect, Costeff syndrome	III	OPA3	OPA3, respiratory chain protective function
		DNAJC19 defect, DCMA syndrome	V	DNAJC19	DNAJC19, mitochondrial protein import
	Unknown	NOS 3-MGA-uria	IV	Unknown	Unknown

As indicated in Table I, we consider only **primary 3-MGA-uria the 3-methylglutaconyl-Coenzyme A hydratase deficiency**, a defect of leucine catabolism. Among the **secondary 3-MGA-urias** we must include:

- **Defects remodeling of phospholipids:**
 - TAZ defect or Barth syndrome.
 - SERAC1 defect or MEGDEL syndrome.
- **Disorders associated with the mitochondrial membrane:**
 - OPA3 deficiency or Costeff syndrome
 - DNAJC19 deficiency or DCMA syndrome
 - TMEM70 deficiency

The other 3-MGA-urias are considered of **unknown origin** (NOS: Not Otherwise specified origin) and are

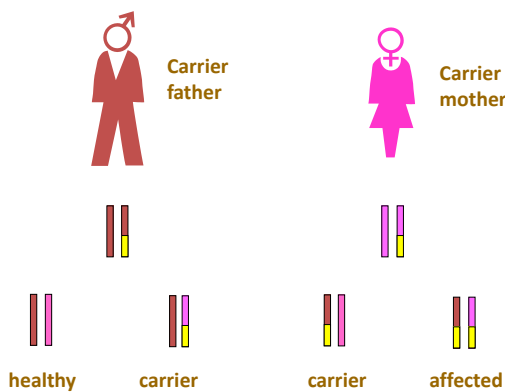
depending on further studies to their proper classification.

WHY DO 3-MGA-URIAS OCCUR?

They occur due to mutations (stable and heritable changes) in the *AUH*, *TAZ*, *SERAC1*, *OPA3*, *DNAJC19*, *TMEM70* genes and also other yet unknown genes, which are coding for the corresponding protein listed in Table I.

Disease	Clinical picture
3-MG-CoA hidratasa deficiency	Leucoencefalopathy adult onset, dementia and progressive spasticity
TAZ defect, Barth syndrome	(Cardio)myopathy, short stature, neutropenia, OXPHOS dysfunction, hypocholesterolemia, cognitive phenotype, mild dysmorphic features
SERAC1 defect, MEGDEL syndrome	Progressive spasticity, dystonia, deafness, Leigh-like neuroimaging, severe psychomotor retardation, hypocholesterolemia, OXPHOS dysfunction
OPA3 defect, Costeff syndrome	Ataxia /extrapyramidal dysfunction, optic atrophy
DNAJC19 defect, DCMA syndrome	Dilated cardiomyopathy, ECG abnormalities, non progressive cerebellar ataxia, testicular dysgenesis, failure to thrive, anemia, hepatic steatosis
TMEM70 defect	Variable phenotype, hypertrophic cardiomyopathy, ATPase deficiency, myopathy, dysmorphia, cataracts, psychomotor retardation, lactic acidosis, hyperammonemia
NOS 3-MGA-uria	Variable, mostly progressive neurological disease

Autosomal recessive inheritance



All these diseases are transmitted with an **autosomal recessive inheritance** except for Barth syndrome, which is transmitted with an X-linked inheritance (see XXXX).

In autosomal recessive inheritance both parents are carriers of a mutation in the respective genes, but they do not suffer any clinical sign of the disease. If both parents transmit to the child a mutant allele of this gene, the child will suffer a 3-MGA-uria (corresponding to the mutant gene).

WHAT ARE THE CLINICAL MANIFESTATIONS OF THE 3-MGA-URIAS?

The **clinical features** are summarized in the Table II (modified of Wortmann et al, J Inherit Metab Dis 2013, 36:923-928).

The **deficiency of 3-MG-CoA hydratase or 3-MGA-uria type I** presented in childhood with nonspecific symptoms (intellectual disability and seizures). Recently some adult patients were described who developed a slowly progressive leukoencefalopathy (involvement of the white matter of the brain). An adult patient has developed progressive dementia and spasticity, while others expressed dysarthria (disorder in articulating words) and ataxia (decreased ability to coordinate voluntary muscle movements). Symptoms seen in early childhood are considered a progressive degenerative disorder, which is influenced by anomalous accumulation of neurotoxic metabolites (3-MGA and 3-hydroxyisovalerate) which cause cellular dysfunction and ultimately cell death. This suggests the importance of treatment with restricted leucine diet (the precursor amino acid) in this disease.

Barth syndrome or 3-MGA-uria type II presents with cardiac and skeletal myopathy, short stature, neutropenia, cognitive dysfunction and dysmorphic features. There is a dysfunction of the mitochondrial respiratory chain and hypocholesterolemia (low blood cholesterol).

Costeff syndrome or 3-MGA-uria type III occurs in childhood with bilateral optic atrophy, extrapyramidal signs, spasticity, ataxia, dysarthria, and mental retardation, in a decreasing order of frequency. Although most patients show an autosomal recessive inheritance some patients have been described with dominant mutations in the *OPA3* gene, presenting optic atrophy, cataracts and extrapyramidal signs, without 3-MGA-uria.

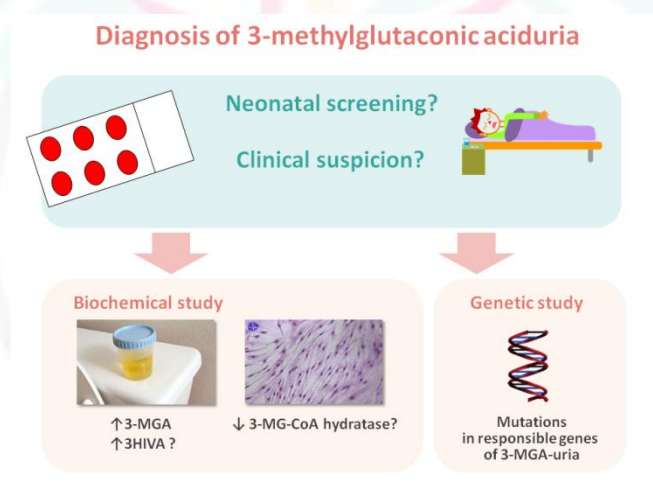
Patients with **MEGDEL syndrome or 3-MGA-uria type IV** presents with cardiomyopathy, which in some early onset cases may be hypertrophic and severe. Some patients also show cataracts, hypotonia, developmental delay, and lactic acidosis. A group of patients were described with brain MR images similar to Leigh syndrome, sensorineural deafness, recurrent lactic acidemia, neonatal infections and severe hypoglycemia (low blood glucose). The clinical spectrum of this syndrome is expanding as more patients are described, and is frequently associated with progressive neurological deterioration variable organ dysfunction, mitochondrial energy metabolism (OXPHOS) dysfunction and increased excretion of 3-MGA.

DCMA syndrome or 3-MGA-uria type V is characterized by dilated cardiomyopathy, non progressive ataxia, testicular dysgenesis (defective development of a body part during intrauterine life), failure to thrive, anemia and hepatic steatosis (abnormal fat accumulation).

The **TMEM70 defect** occurs generally in the neonatal period with hypotonia, hypertrophic cardiomyopathy, psychomotor retardation, 3-MGA-uria, lactic acidosis and hyperammonemia. The patients show a complex V (ATPase) deficiency of the mitochondrial respiratory chain.

HOW ARE THEY DIAGNOSED 3-MGA-URIAS?

The diagnosis can be based on the patient's clinical findings or elevated excretion of 3-MGA, which occurs especially in children selected through the neonatal screening expanded to the organic acidurias.



The finding of a slightly elevated excretion of 3-MGA may be accompanied by other metabolites such as organic acids (metabolites of fatty acids β -oxidation, methylmalonic acid, propionic acid), may be secondary to glycogen storage disease or a defect in the urea cycle. In these cases the metabolic study leads to the definitive diagnosis.

In other cases, the **3-MGA can be found isolated**, but only slightly or occasionally increased; it may be suggestive of a mitochondrial, hematologic, neuromuscular disease or another genetic syndrome. When **3-MGA is significantly and permanently high** (> 40mmol/mol creatinine) and considering the clinical picture of the patient, there are several possibilities:

- **3-MGA is excreted together with 3-hydroxy-isovaleric acid:** this is a primary 3-MGA-uria, caused by a **defect of 3-MG-CoA hydratase**. We can determine the enzyme AUH deficiency or the AUH gene mutations.
- Absence of 3-OH-isovaleric acid, and on the basis on clinical picture, we can **perform the mutational study of the other genes** known to date.
- Failure to find mutations in any of them, the disease is classified as **NOS-3-MGA-uria** (from English: Not Otherwise Specified), pending final classification when the disease-causing gene is known.

DO 3-MGA-URIAS HAVE A SPECIFIC TREATMENT?

In **primary 3-MGA-uria due to 3-MG-CoA hydratase deficiency**, 3-MGA accumulates, and, as happens in other organic acidurias, it may have a neurotoxic effect and cause cell death. In this case, **leucine-restricted diet**, the precursor amino acid of the interfered metabolic pathway, may have a therapeutic effect, although the number of cases diagnosed and treated is too small to draw definitive conclusions.

In other types of 3-MGA-uria, the excretion of 3-MGA is secondary and does not appear to be related to their metabolic. Therefore, the treatment of these diseases cannot be based on decreasing the formation of 3-MGA, but consists of a **symptomatic and supportive treatment**.

Translation

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