

**Medical alert:
Genetic variant in patients
of Venezuelan ancestry and
anaesthetic complications**

Elena Méndez

October 2026

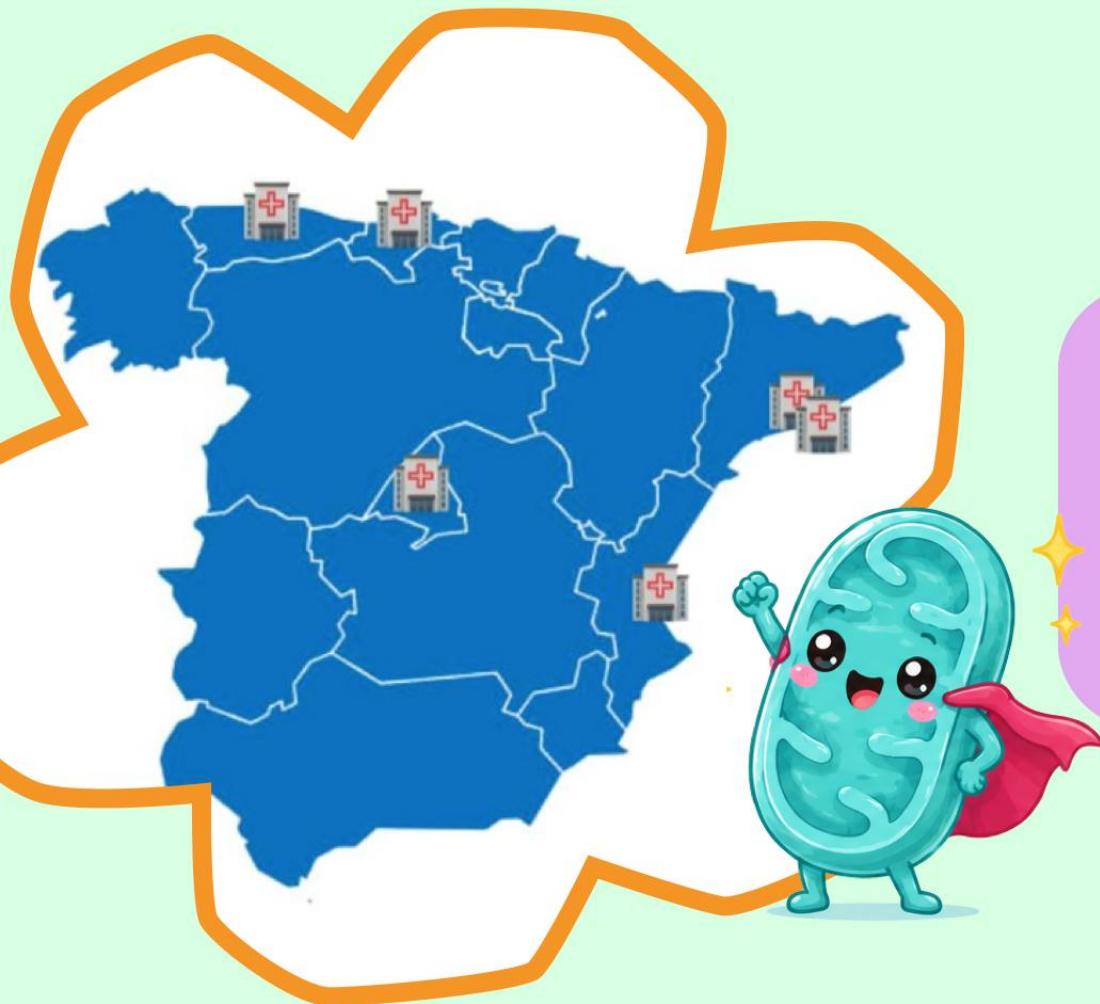
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GT mtND4 July 2025



- **Elena Méndez** - Hospital Universitario Central de Asturias
- **Consuelo G. Cebrián** - Hospital Universitari i Politècnic La Fe
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- **Pascual Sanabria** - Hospital Universitario Infantil La Paz
- **Francisca Munar** - Hospital Universitario Vall d'Hebron
- **Gabriela Alcaraz** - Hospital Universitario Sant Joan de Déu
- **Patricio González** - Hospital Universitario Infantil La Paz
- **Francisco Escribà** - Hospital Universitari i Politècnic La Fe / Vicepresidente SEDAR Pediàtrica





**DR. EDUARDO
RUIZ PESINI**

**DRA. YAREMY
HERNÁNDEZ**

AND THEN OUR LIVES BEGAN TO SOUND LIKE THIS...

- National and international meetings and webinars
- Official SEDAR statements and recommendations (September 2025 and April 2026)
- Six new members joined the working group
- SEDAR podcast
- Departmental teaching sessions ++++++
- Genetic testing becoming available in more hospitals
- Consensus statement published in REDAR

Total remuneration received: €0





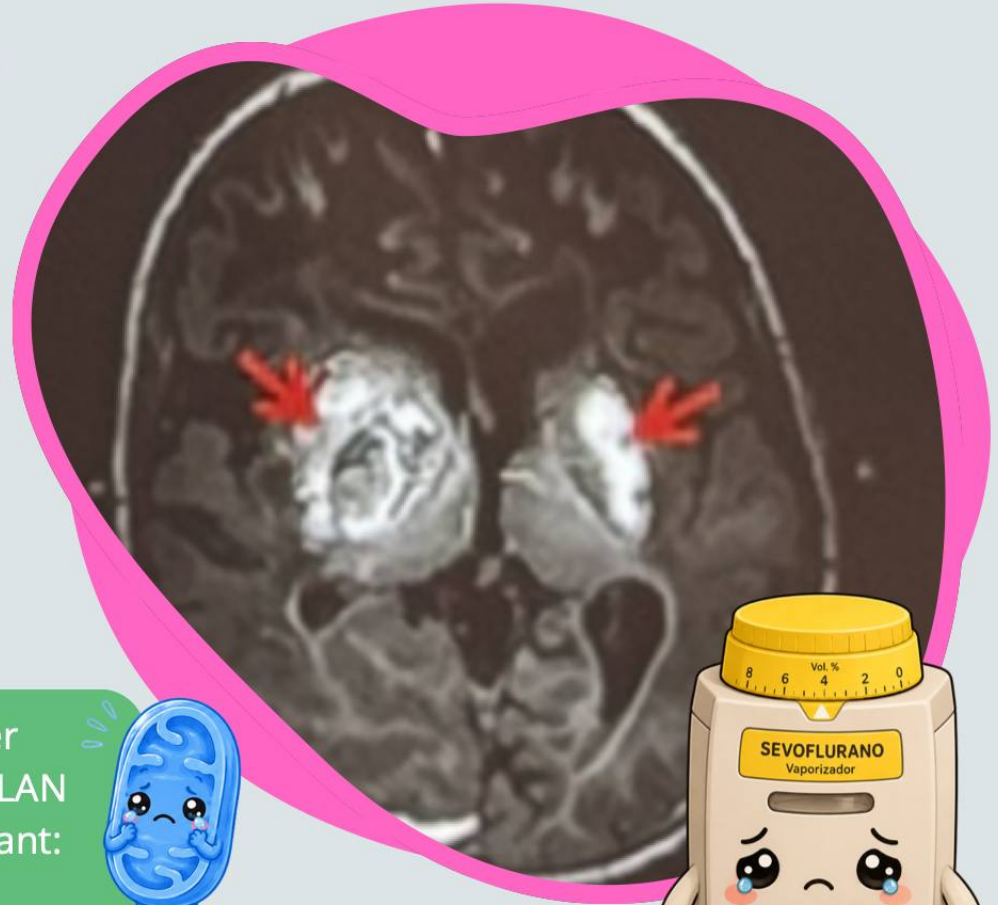
GT mtND4 Oct. 2026

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WHAT'S HAPPENING?

- Previously healthy patients
- Procedure under anaesthesia
- Induction: sevoflurane
- No intraoperative incidents; observations within normal limits
- Delayed emergence / failure to regain consciousness
- Notable findings: lactic acidosis and hyperglycaemia
- MRI: diffuse hypoxic-ischaemic abnormalities involving the basal ganglia and cerebellum

All patients shared one further feature: MATERNAL VENEZUELAN ANCESTRY + mtDNA ND4 variant: **11232 T > C**



THE MITOCHONDRIA

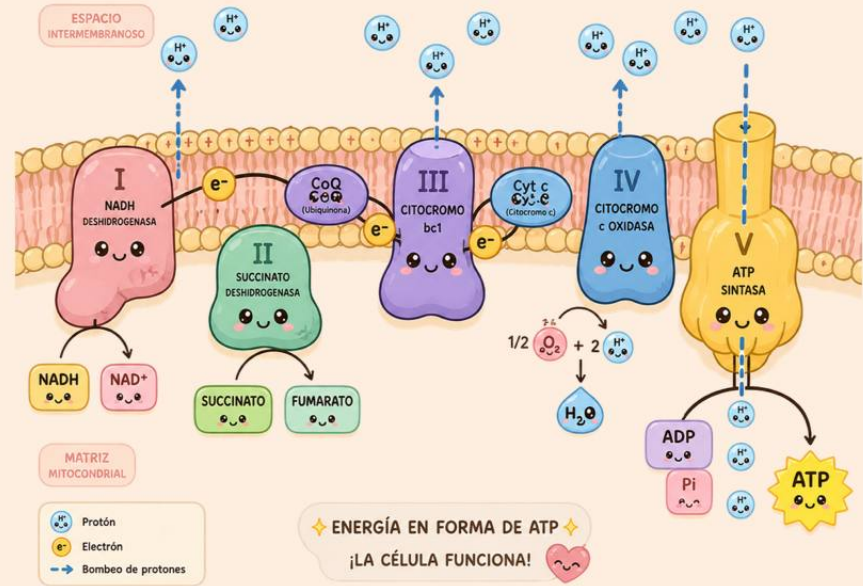
MAIN ROLE (although not the only one): ATP production through oxidative phosphorylation in the electron transport chain (ETC), comprising complexes I-V.

ETC proteins are encoded by genes of two origins: nuclear DNA (nDNA) and mitochondrial DNA (mtDNA).

mtDNA is a circular molecule present in multiple copies per cell and highly susceptible to variation.

It encodes 37 genes:

- 13 ETC proteins → OXPHOS
 - 7 subunits of complex I
 - 1 subunit of complex III
 - 3 subunits of complex IV
 - 2 subunits of complex V
- 24 RNA genes:
 - 2 rRNAs
 - 22 tRNAs



Oxidative phosphorylation:

- A series of redox reactions
- Location: inner mitochondrial membrane
- Four multienzyme complexes (I-IV) + ATP synthase (complex V) + mobile electron carriers

MITOCHONDRIA AND ANAESTHESIA

(Almost) all anaesthetic agents interfere with mitochondrial function in vitro. However, patients with complex I abnormalities appear particularly sensitive to sevoflurane.

- Processed EEG (pEEG) monitoring!

Until now, all anaesthetic agents had been used in these patients without serious consequences. Maintaining perioperative homeostasis remains the most important safety measure.



Anaesthetic agent	Mitochondrial effect in vitro
Barbiturates	Complex I inhibition
Etomidate	Complex I inhibition; weak effect on complex III
Propofol	Inhibition of complexes I, II and III (possibly IV); inhibition of carnitine palmitoyltransferase I (long-chain fatty acid transport into mitochondria)
Benzodiazepines	Inhibition of complexes I, II and III
Ketamine	Possible complex I inhibition? Increased metabolism?
Dexmedetomidine	No reports
Fentanyl, remifentanyl	Minimal effect
Morphine	Moderate complex I inhibition
Volatile anaesthetic agents	Complex I inhibition; coenzyme Q inhibition; moderate effect on complex V
Bupivacaine	Inhibition of carnitine-acylcarnitine translocase (less pronounced with lidocaine and ropivacaine)

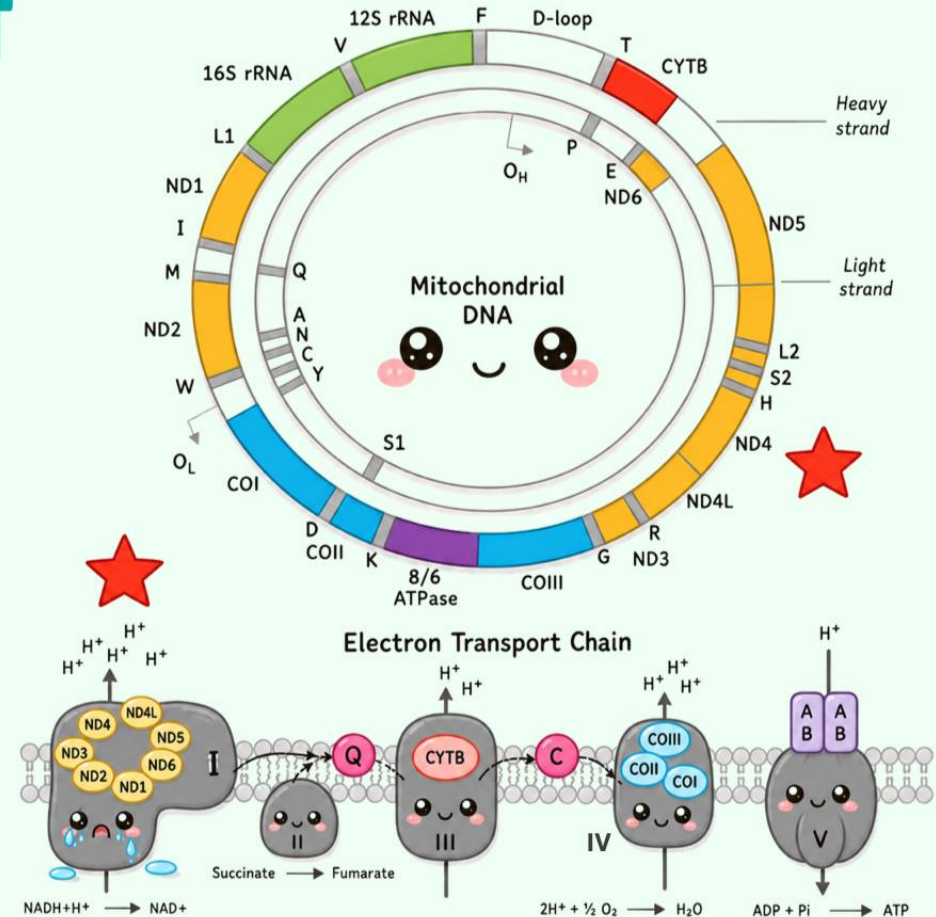
THE 11232 T > C VARIANT

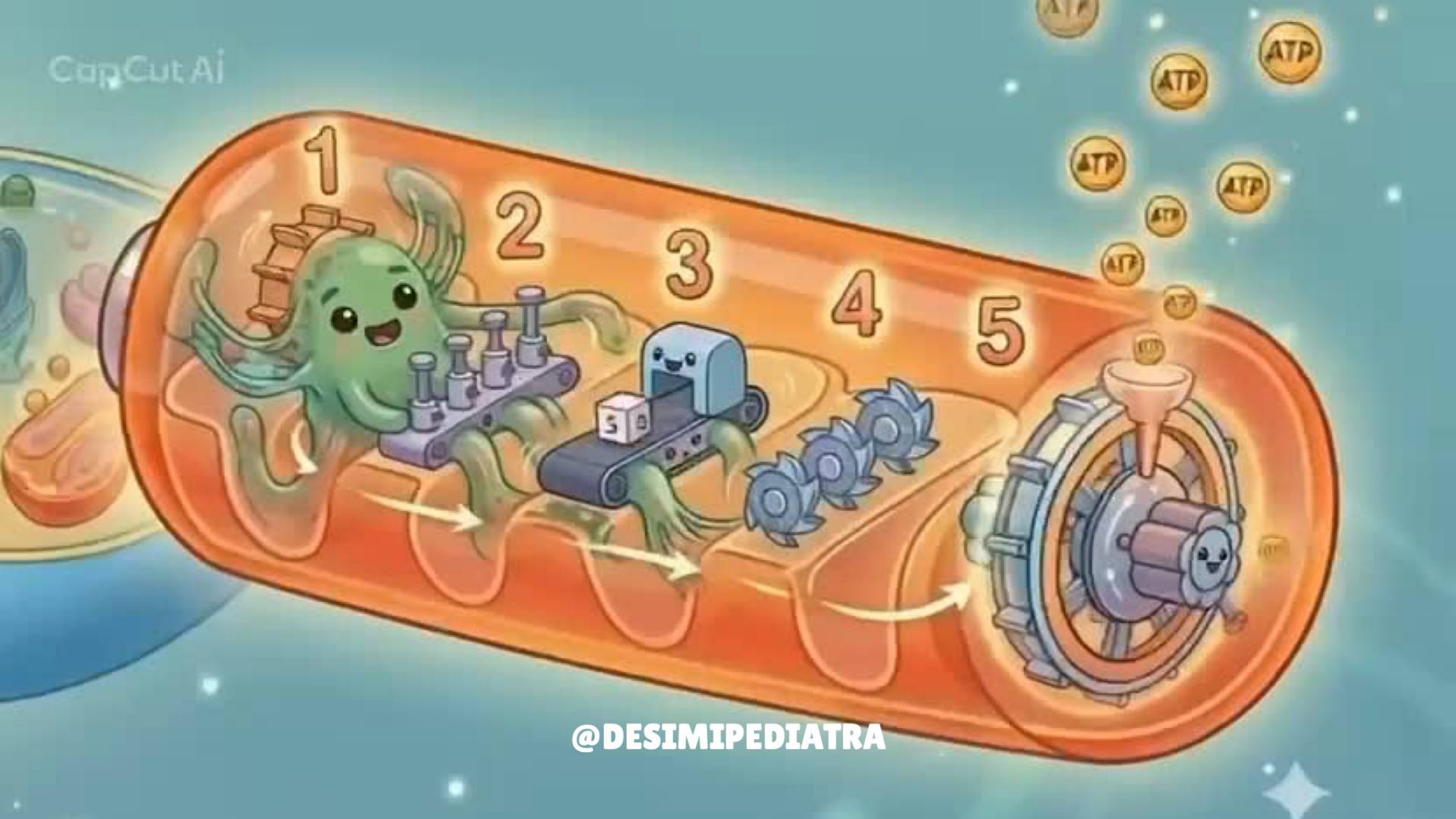
Previously identified, but until recently classified as a variant of uncertain significance (VUS).

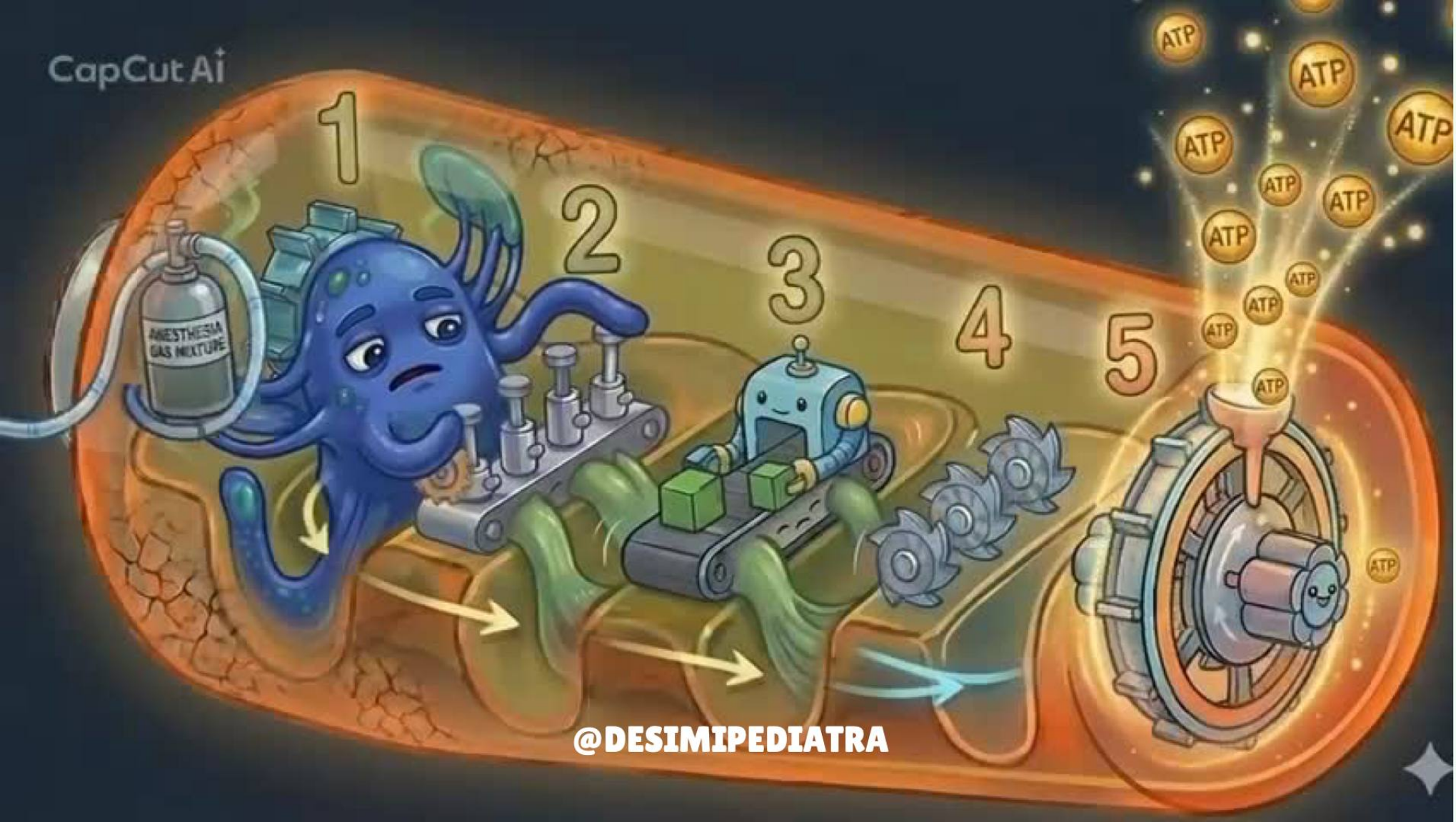
Disease or pharmacogenetic effect?

- A previously healthy patient develops clinical manifestations following exposure to an external agent.
- This is NOT a classical mitochondrial disease; only the maternal inheritance pattern is shared.

Impaired cellular energy production and increased generation of harmful reactive oxygen species (ROS).







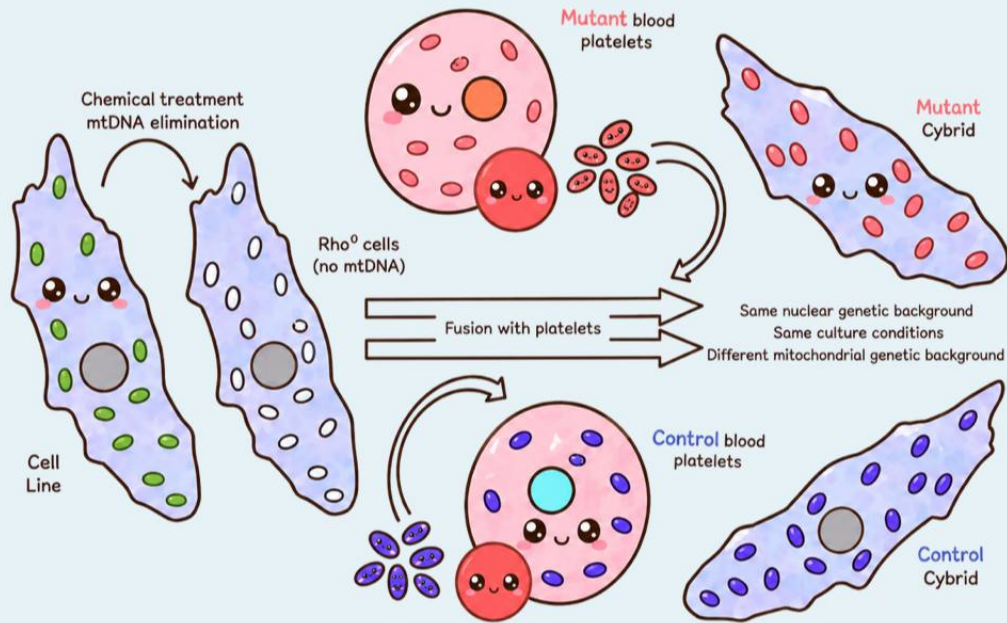


Criterion	Mitochondrial disease	mtND4 variant
Clinical presentation	Chronic, progressive, multisystem involvement	Previously healthy patients
Pathophysiology	Pleiotropy (multiple mitochondrial genes)	Specific complex I deficiency
Baseline status	Pre-existing metabolic / neurological symptoms	Asymptomatic
Affected gene	Mitochondrial and/or nuclear DNA	Mitochondrial DNA
Inheritance	Maternal (mtDNA); autosomal dominant/recessive (nDNA)	Maternal (mtDNA)
Haplotype	Homoplasmy; heteroplasmy common: variable severity	Homoplasmy
Clinical involvement	Neurological, cardiac, muscular, respiratory...	Neurological
Anaesthetic agents	Risk linked to metabolic stress	Pharmacogenetic susceptibility
Volatile agents	Generally safe (preferred?)	Triggering agents
Exposure	Dose-independent	Possibly dose-dependent
Propofol	Risk of PRIS with prolonged infusions	Safe at therapeutic doses



FUNCTIONAL STUDIES IN FIBROBLASTS

Dr. Eduardo Ruiz Pesini



ANESTHESIOLOGY

Effects of a Mitochondrial Genetic Variant on Sevoflurane Hypersensitivity

Javier Sanz-Pons, M.S., Celia Aladrén-Herrer, M.S.,
Juan Darío Ortigoza-Escobar, M.D., Ph.D.,
Ester López-Gallardo, Ph.D., Antonio Martín-Navarro, Ph.D.,
Carlos Alberto Lanz-Martínez, M.D.,
Yohanna Alexandra Camacho-Medina, M.D.,
Isabel Fernández-González, M.D.,
Javier Urbano, M.D., Ph.D., Julio Montoya, Ph.D.,
Yaremy Hernández-Castillo, M.D., Ph.D.,
Pilar Bayona-Bafaluy, Ph.D.,
Eduardo Ruiz-Pesini, Ph.D.

ANESTHESIOLOGY 2026; 144:1286–98



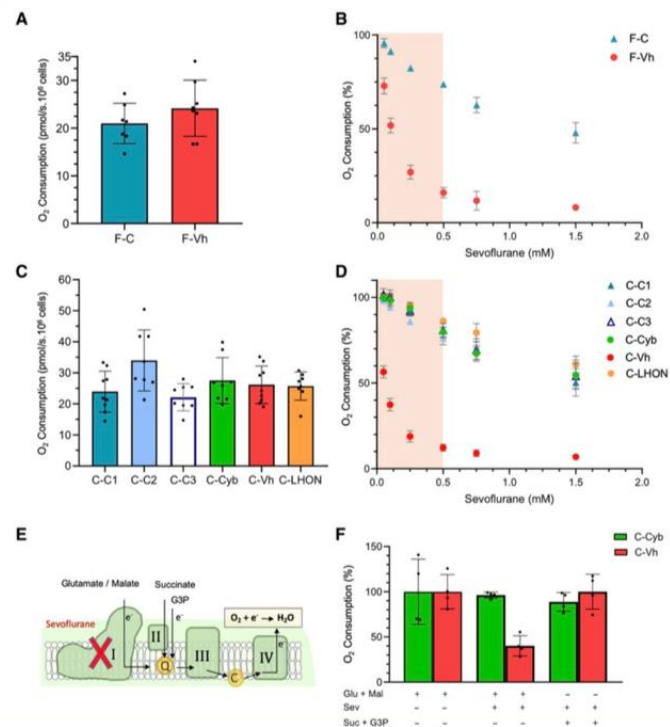


Fig. 2. Effect of sevoflurane on cellular respiration. (A) Oxygen consumption in fibroblasts (measured in intact cells suspended in high glucose medium; N = 7 to 8). (B) Percentage inhibition of oxygen consumption in fibroblasts exposed to increasing concentrations of sevoflurane (relative to the initial rate shown in A; N = 4). (C) Oxygen consumption in cybrids (measured in intact cells suspended in high glucose medium; N = 8 to 9). (D) Percentage inhibition of oxygen consumption in cybrids exposed to increasing concentrations of sevoflurane (relative to the initial rate shown in C; N = 4). (E) Schematic representation of the mitochondrial electron transport chain indicating the suspected site of sevoflurane action (red cross) and the complex-specific substrates used to determine the mitochondrial respiratory complex targeted by sevoflurane. (F) Inhibition of substrate-dependent oxygen consumption by sevoflurane (measured in permeabilized cells supplied with complex-specific substrates, as indicated in E; sevoflurane was added at 0.05 mM; N = 4). C-C1, cybrid-control 1; C-C2, cybrid-control 2; C-C3, cybrid-control 3; C-Cyb, cybrid-harboring the m.15164T>C transition in the *MT-CYB* gene; C-LHON, cybrid-harboring the m.11778G>A pathologic mutation; C-Vh, cybrid-harboring the Venezuelan haplotype; F-C, control fibroblasts; F-Vh, fibroblasts harboring the Venezuelan haplotype. The pink areas in B and D indicate blood clinical concentrations. I, II, III, IV, Q, and c code for respiratory complex I, II, III, IV, ubiquinone, and cytochrome c, respectively. The respiratory complex I substrates are glutamate (Glu) and malate (Mal). The respiratory complex II substrate is succinate (Suc). The respiratory complex III substrate via ubiquinone (Q) is glycerol-3-phosphate (G3P). The values are the means ± SD.

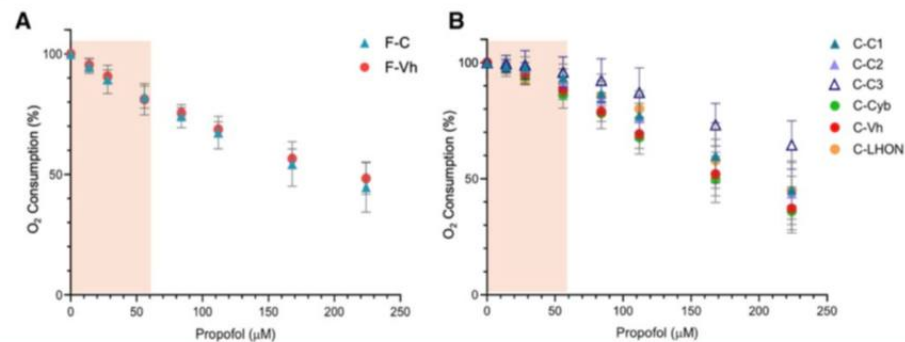
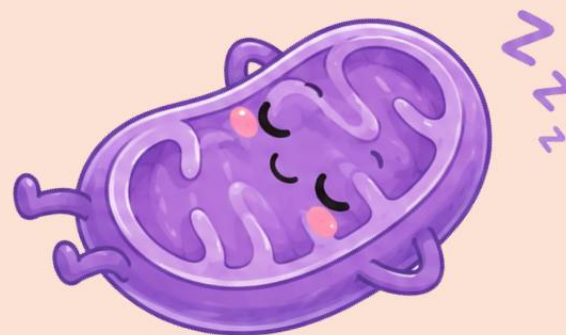


Fig. 3. Effect of propofol on cellular respiration. (A) Percentage inhibition of oxygen consumption in fibroblasts exposed to increasing concentrations of propofol (relative to the initial rate shown in fig. 2A; N = 4). (B) Percentage inhibition of oxygen consumption in cybrids exposed to increasing concentrations of propofol (relative to the initial rate shown in fig. 2C; N = 4). F-C, control fibroblasts; F-Vh, fibroblasts harboring the Venezuelan haplotype; C-C1, cybrid-control 1; C-C2, cybrid-control 2; C-C3, cybrid-control 3; C-Cyb, cybrid-harboring the m.15164T>C transition in the *MT-CYB* gene; C-LHON, cybrid-harboring the m.11778G>A pathologic mutation; C-Vh, cybrid-harboring the Venezuelan haplotype. The pink areas in A and B indicate blood clinical concentrations. The values are the means ± SD.

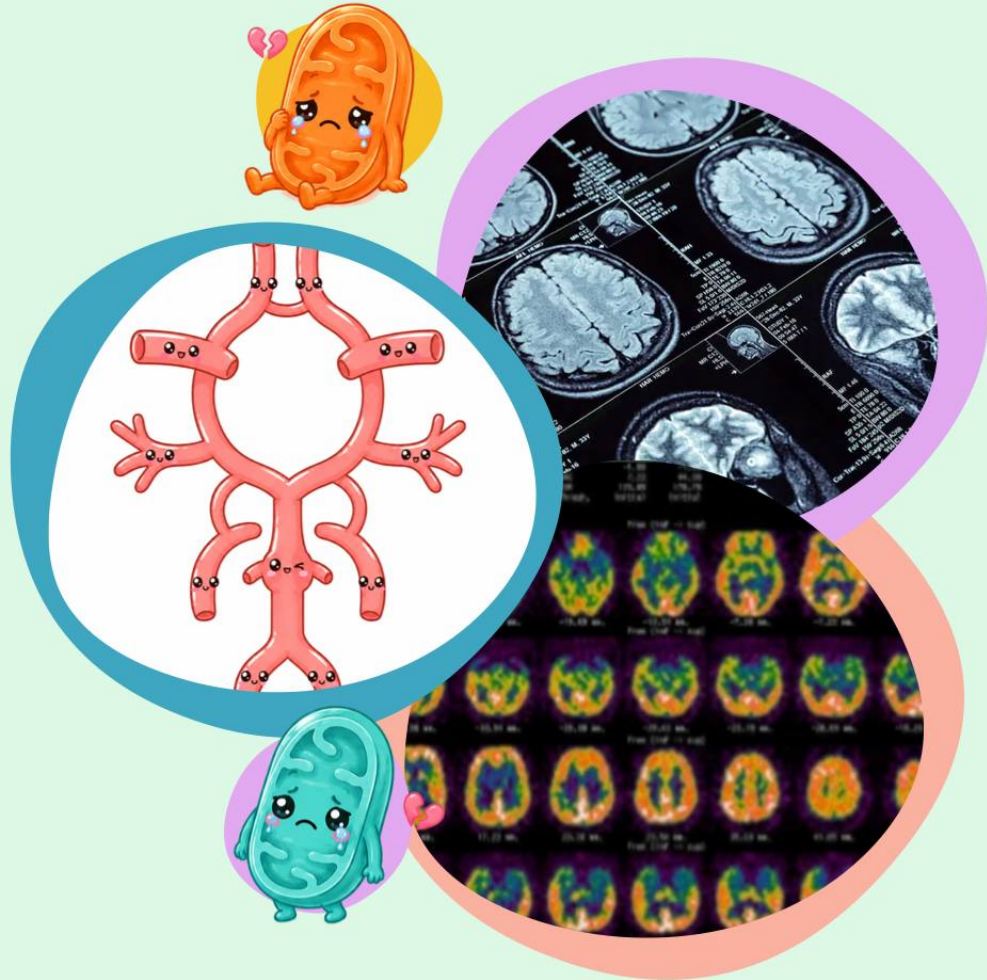


WHY THE BRAIN AND BASAL GANGLIA?

Around 200 kg of ATP are generated each day, equivalent to 1,200 W. The brain uses 70% of this energy.

Blood supply to the basal ganglia:

- Perforating lenticulostriate arteries, recurrent artery of Heubner and posterior choroidal artery
- Minimal collateral anastomoses
- Well-defined vascular territories
- Little overlap
- Vulnerability: lacunar stroke



WHAT MAKES THIS DIFFERENT FROM OTHER POTENTIALLY SEVERE ANAESTHETIC COMPLICATIONS?

- No prior phenotypic abnormalities: **Unpredictable**
- **No treatment:** By the time it is recognised, it may be too late (pEEG? lactate?)





European
Reference
Network

for rare or low prevalence
complex diseases

Network
Neuromuscular
Diseases (ERN EURO-NMD)



European Society of
Anaesthesiology and
Intensive Care



EUROPEAN SOCIETY
FOR PAEDIATRIC ANAESTHESIOLOGY



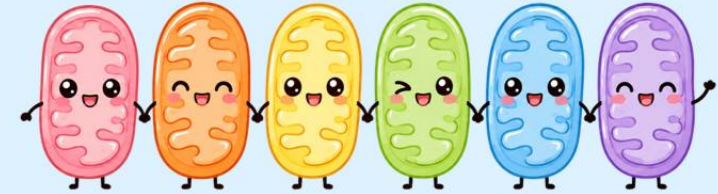
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Y TERAPÉUTICA DEL DOLOR



American Society of
Anesthesiologists



WHAT DO WE RECOMMEND IN CLINICAL PRACTICE?



Last updated: April 2026



Sociedad Española de
Anestesiología y Reanimación

journal homepage: www.elsevier.es/redar

Documento de consenso

Eventos adversos graves asociados a anestesia general con agente halogenados en pacientes de ascendencia venezolana.
Recomendaciones en práctica clínica

Severe adverse events associated with general anesthesia with halogenated agents in patients of Venezuelan ancestry. Recommendations for clinical practice

Méndez Martínez ^{a,*}, C. García Cebrián ^b, A.M. González González ^c, P. S. Bauzá ^e, G. Alcaraz García-Tejedor ^f, P. González Pizarro ^d, D. Méndez ^h, J. Encarnación Martínez ⁱ, K. Sifontes Romero ^j, M. Almendra ^k, F.J. Escrivà Alepuz ^l y J. García Fernández ^m

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**cirugía programada
(diferible)**

realizar test genético prioritario
y diferir la cirugía hasta obtener
el resultado confirmado


**cirugía urgente
(no diferible)**

evitar halogenados mediante
técnica TIVA y realizar el test
genético de forma diferida

seguridad farmacológica y monitorización



**vigilancia
estricta
de EEG**

monitorizar la
profundidad
de anestesia y el NIRS



fármacos prohibidos (evitar)
no utilizar sevoflurano, desflurano e
isoflurano (halogenados), succinilcolina,
atropina ni neostigmina

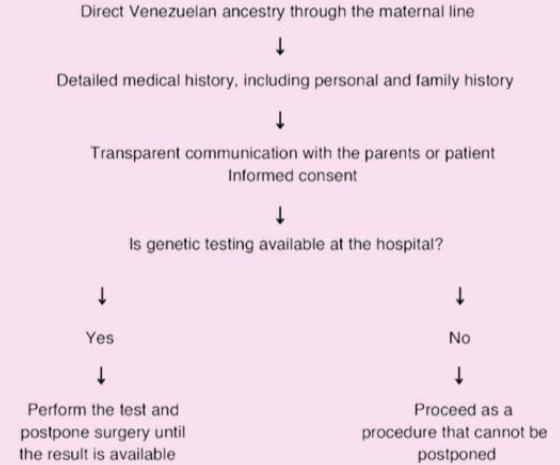
 permitidos seguros	 precaución duda	 prohibidos riesgo
midazolam, dexmedetomidina, fentanilo, remifentanilo,	propofol (evitar dosis altas o perfusiones prolongadas),	sevoflurano, desflurano, isoflurano, succinilcolina,

PREOPERATIVE ASSESSMENT RISK SCREENING

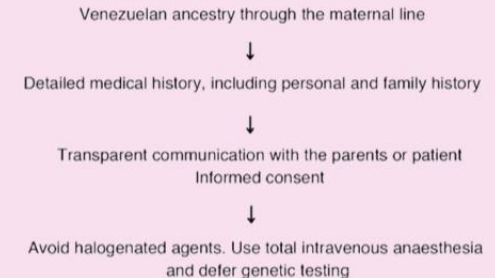


- A pre-anaesthetic assessment is mandatory
- Targeted history: ask specifically and sensitively about Venezuelan ancestry through the maternal line (consider unknown ancestry and donor eggs)
- **Any patient with direct maternal Venezuelan ancestry should be considered at risk, regardless of any family history of anaesthetic complications**
- Arrange genetic testing before or after the procedure depending on whether it can be postponed

Can the anaesthetic procedure be postponed?



Anaesthetic procedure cannot be postponed



HOW SHOULD I ANAESTHETISE THEM?



Anaesthetic considerations

- Consider **locoregional anaesthesia** with or without sedation, if possible
- Anaesthesia **machine**: purge to remove residual halogenated anaesthetic, including ventilator cycling, replacement of tubing and soda lime, and removal of the vaporiser
- **Fluid therapy**: prioritise balanced solutions, avoid Ringer lactate, minimise fasting, and avoid stressful situations
- **Premedication**: anxiolysis, EMLA, and venepuncture under nitrous oxide
- **Avoid halogenated agents**
- **Propofol**: meticulous titration. Use caution with high doses and prolonged infusions. Combine with remifentanyl and dexmedetomidine to reduce total doses
- Midazolam, dexmedetomidine, and ketamine are considered safe
- Fentanyl and remifentanyl: prioritise ultra short acting opioids

Monitoring

- Advanced haemodynamic monitoring: arterial catheter and frontal NIRS for long or complex procedures
- Monitoring of anaesthetic depth and cerebral function
- Monitoring of neuromuscular blockade: rocuronium and sugammadex
- Ventilation and EtCO₂ monitoring. Fresh gas flow equal to minute volume
- Intraoperative measurements, if available:
 - Lactate
 - pH
 - Glucose
 - Base excess
 - Anion gap
- Avoid leaving tourniquets in place
- Maintain parameters within the normal range, with particular attention to maintaining normothermia



WHAT HAPPENS NEXT?



Postoperative care

- Consider admission to a postoperative high dependency unit according to the patient's age and availability:
 - Long and complex procedures
 - Delayed awakening or signs of neurotoxicity
- For patients requiring critical care, maintain intensive monitoring during the first 12 to 24 hours:
 - Neurological status and recovery
 - Metabolic parameters
 - Optimal pain control, avoiding stress and agitation
- If the patient's progress is favourable, consider transfer to a ward according to the established pathway.
- If surgery or examination under anaesthesia is performed as a planned ambulatory procedure, this pathway may be followed, except where there are findings suggestive of neurotoxicity.
- If focal neurological signs or altered consciousness develop, consider the following according to each centre's resources:
 - Activation of the stroke code protocol
 - Neuroradiological assessment, CT or MRI
 - Treatments agreed in consultation with Neurology

HOT OFF THE PRESS



RESEARCH LETTER



Check for updates

A Rapid and Cost-effective Method to Identify the Mitochondrial Variant m.11232T>C Associated with Adverse Neurologic Effects in Patients Exposed to Sevoflurane

Lorena M. Vega-Prado¹, Carlos Lombardía-González¹,
Elena Méndez-Martínez¹, Victoria Alvarez¹,
Andrés Concha-Torre¹, Eduardo Ruiz-Pesini², Eliecer Coto^{1,*}

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Consensus Statment

Severe adverse events associated with general anesthesia with halogenated agents in patients of Venezuelan ancestry. Recommendations for clinical practice

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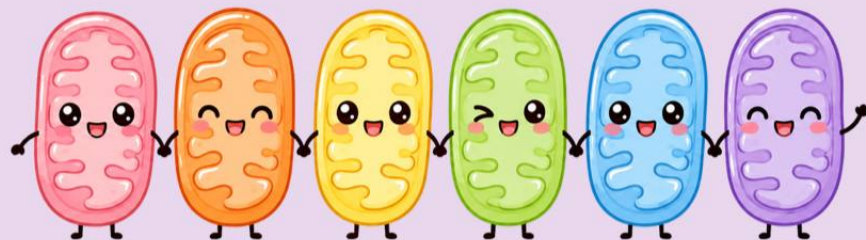
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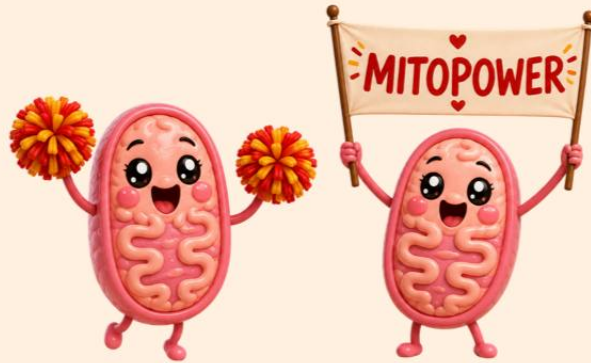
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THANK YOU!



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