

20 Years of MH in Europe

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President European MH Group

Vice President of the Board of Directors, University Hospital Basel



Outline

- History of key elements before 2002
- 20 Years of MH in Europe
 - Clinical perspective
 - Patient's perspective
 - Anaesthesiologist's perspective
 - Organisational perspective
- Outlook



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MH – Anaesthesia related Disorder

- Various case reports already 19th century
 - High temperature during or after anaesthesia
 - Partly fatal outcome
- Anaesthetic deaths in a family
 - **Denborough MA**, Lovell RRH: Lancet 1960; 276:45
 - Denborough MA, Forster JF, Lovell RR, Maplestone PA, **Villiers JD**: Br J Anaesth 1962; 34: 395

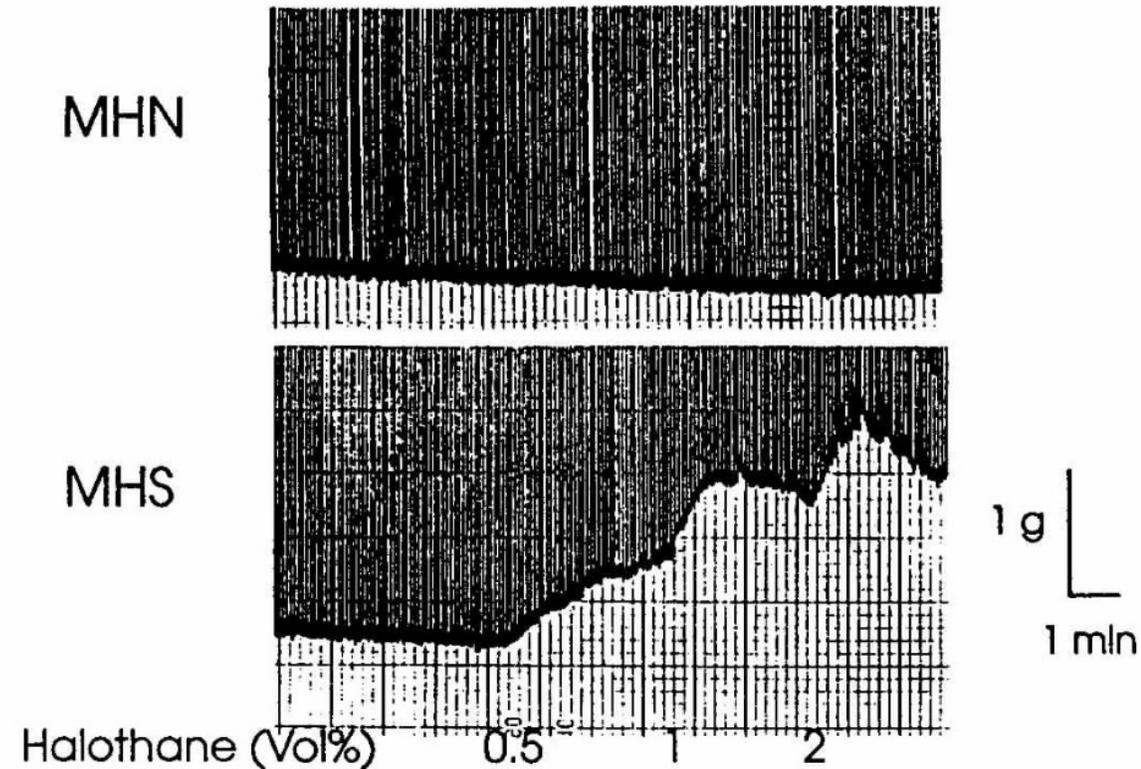


Melbourne 2009

MH – Anaesthesia induced Disease

Presymptomatic diagnosis using *in vitro*
Muscle Contracture Testing (IVCT or HCCT)

- Protocol of the European MH Group
Br J Anaesth 1984; 56: 1267
- Protocol of the North American MH Group
Anesth Analg 1989; 69: 511



THE EUROPEAN MALIGNANT

SUMMARY

A European Malignant Hyperpyrexia Group has been established to allow the following diagnoses to be made unequivocal (MHE). It is accepted that MHE classification requires the collection of further data.

In April, 1983, physicians from eight European

Correspondence to F. R. ELLIS.



Founding Members European MH Group 1983

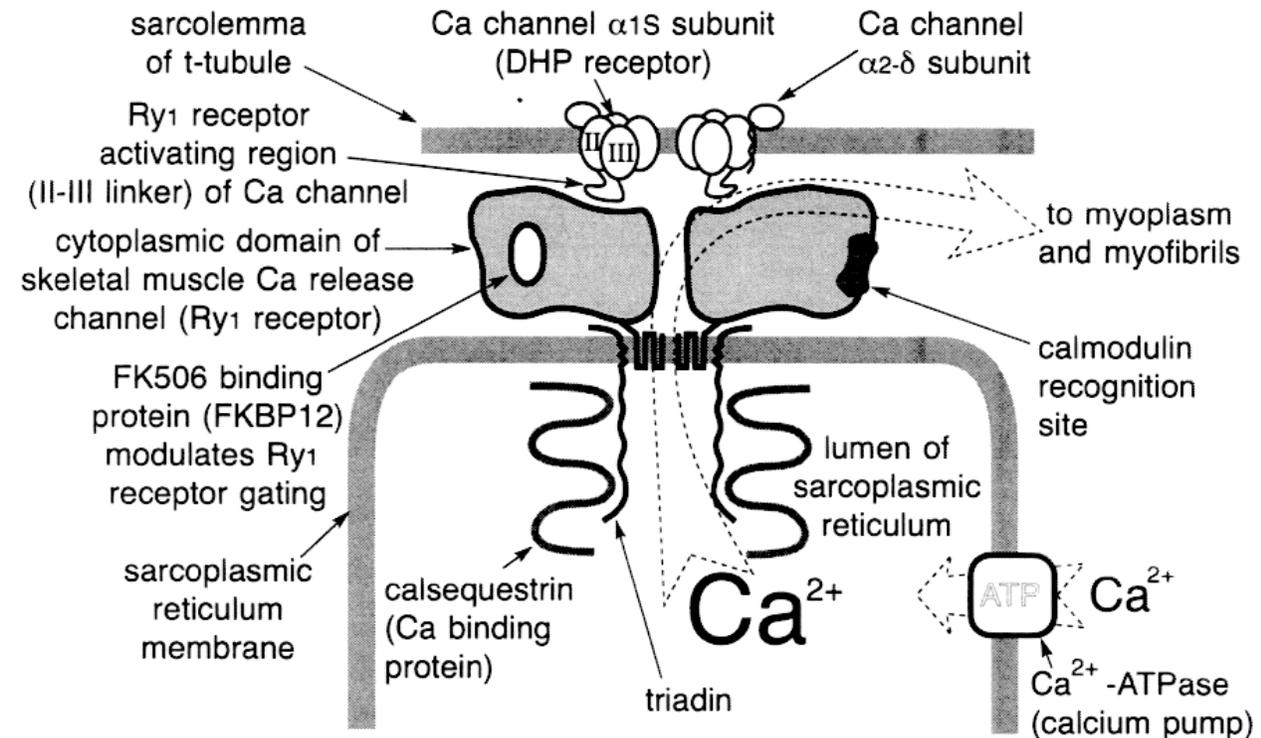


FR Ellis, UK
PJ Halsall, UK
R Fletcher, Sweden
H Ording, Denmark
JJA Heffron, Ireland
M Lehane, Ireland
K Steinbereitner, Austria
P Sporn, Austria
E Ranklev, Sweden
W Mortier, Germany
R Verburg, Netherlands

Not on Photograph:
D Theunynck, France

MH – Anaesthesia related Disorder

- Disorder of the myoplasmic Ca^{2+} regulation
- Ryanodine receptor (RYR1) as candidate gene
 - MacLennan et al. Nature 1990; 343: 559
 - McCarthy et al. Nature 1990; 343: 562



Pessah et al. Anesthesiology 1996; 84:1275

Arg 614 Cys
c.1840 C>T



Context of XXVIII. kongres ČSARIM - Brno - Basel



Karl Skarvan

Ivana Schröderova

Outline

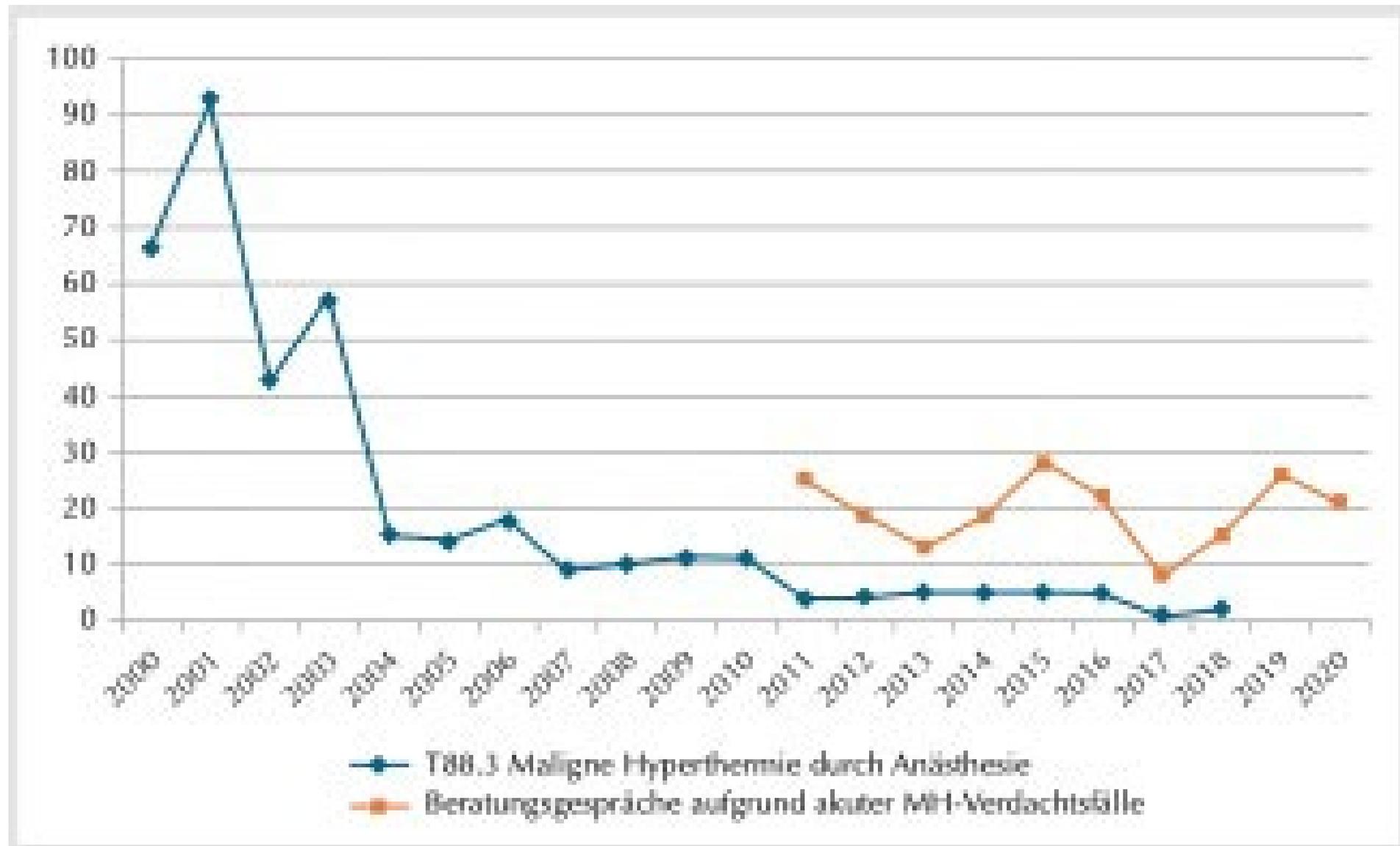
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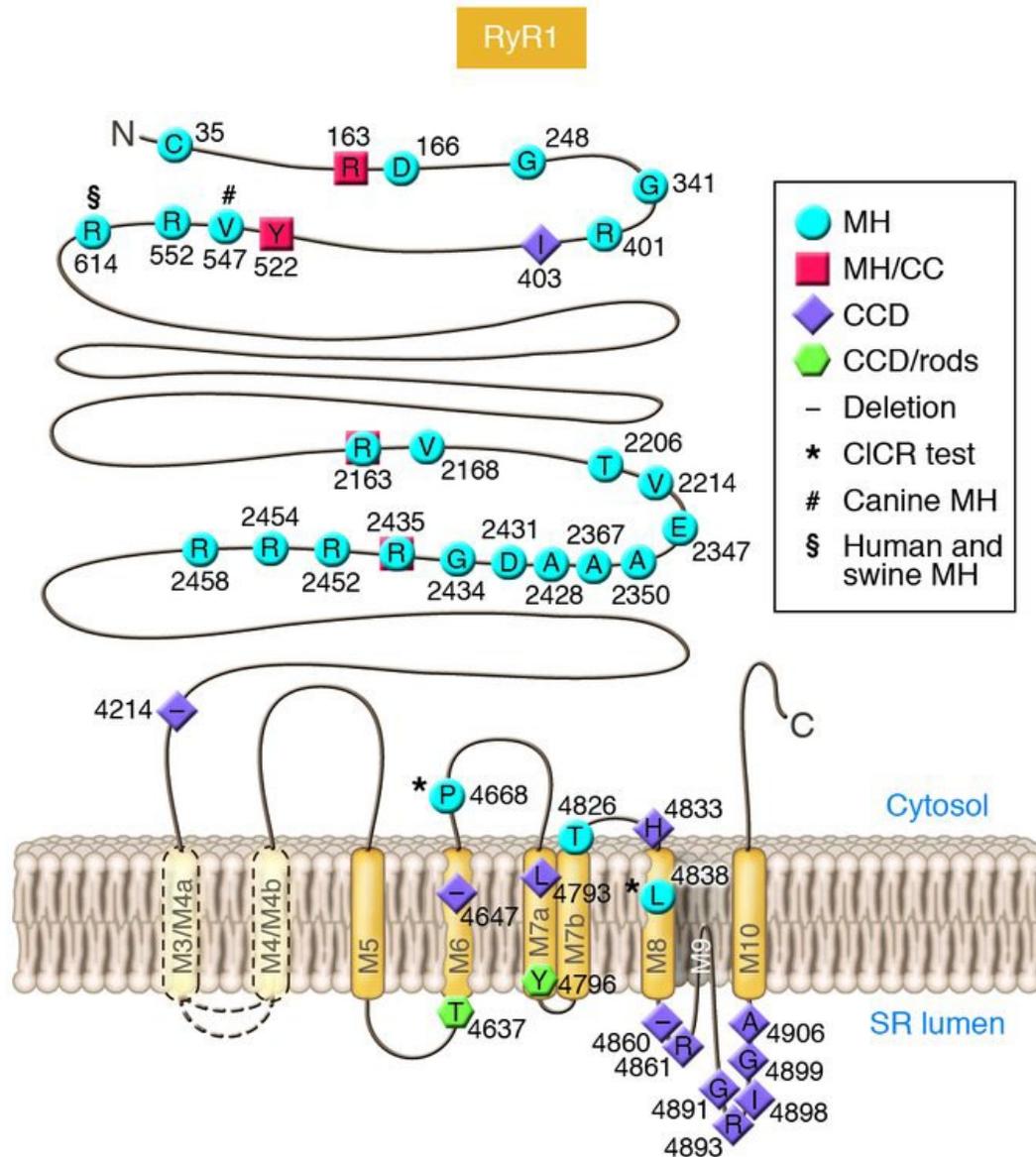
MH has always been a rare Disease....

- Estimation of clinical incidence 1 : 15'000 - 100'000 anaesthetics
- Estimated genetic predisposition 1 : 2'000 – 3'000 individuals
- Significant reduction of MH cases and MH deaths (from 80% to <5%)
- Improvement by
 - Availability of dantrolene
 - Better monitoring
 - Better knowledge
 - Better training of anaesthesiologists
 - Reduced use of volatile anaesthetics (-> Propofol) and succinylcholine
 - Identification of patients and families (presymptomatic diagnosis using IVCT and identification of causative genetic variants)

German ICD and MH-Hotline Data 2022



Development of Genetics



MH-causative gene variants

	RyR1	CACNA1S
2002	28	0
2022	48	2

Jurkat-Rott et al. JCI 2005; 115: 2000

Eltit et al. Proc Natl Acad Sci 2012; 109: 7923

www.emhg.org

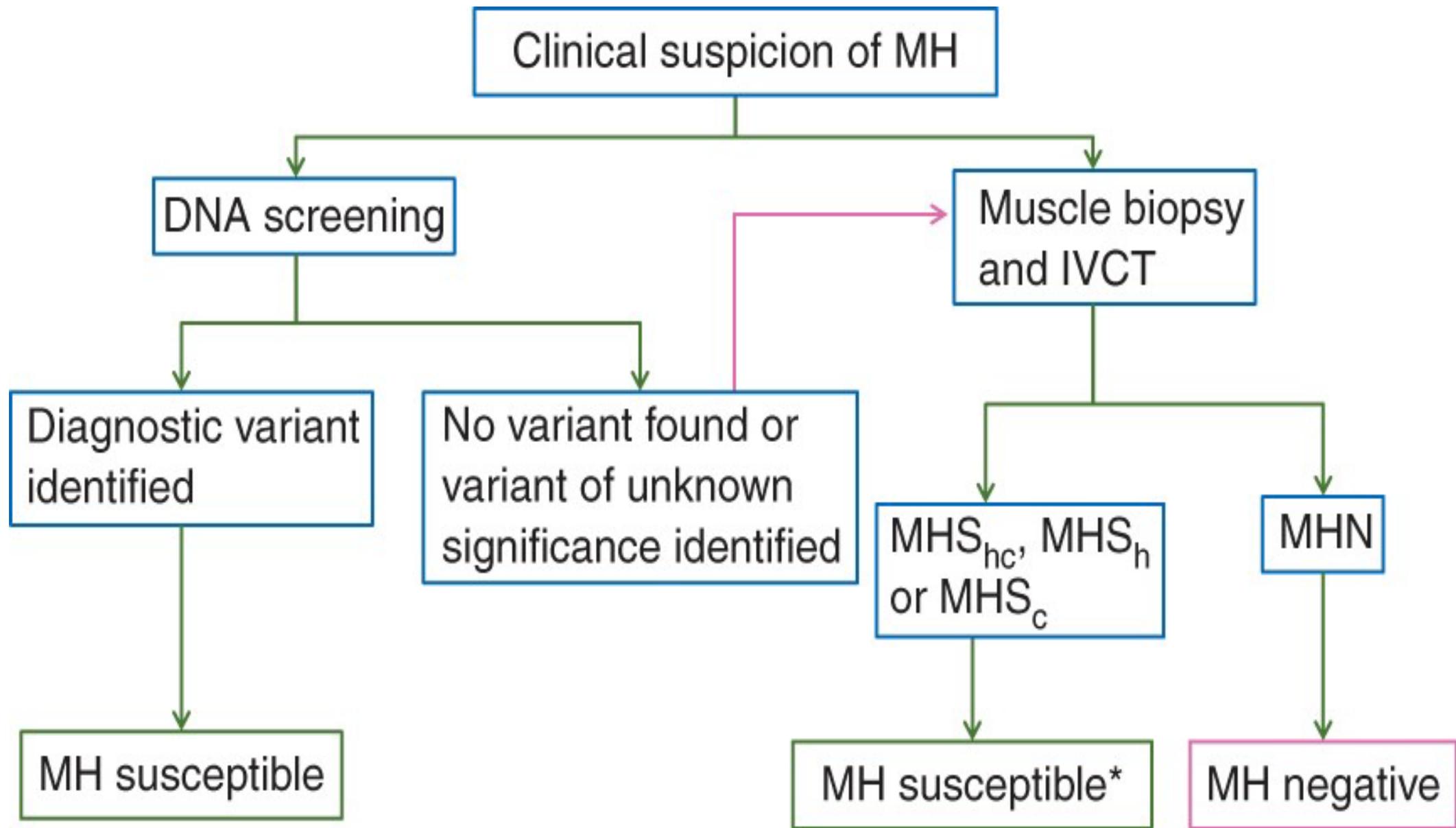
STAC3 variants causing congenital myopathy

Zaharieva et al. Hum Mutat 2018; 39: 1980

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Malignant hyperthermia in Czechia and Slovakia

Martina Klincová^{1,2,3,†}, Dagmar Štěpánková^{1,2,3,4,†}, Ivana Schröderová^{2,3,5},
Eva Klabusayová^{1,2}, Edita Ošťádalová^{2,6}, Iveta Valášková^{2,6}, Lenka Fajkusová^{2,3,6},
Jana Zídková^{2,3,6}, Renata Gaillyová⁷ and Petr Štourač^{1,2,3,4,*}

Nucleotide change	Amino acid change	Numbers <i>n</i> of CZ–SK MHS families	Numbers <i>n</i> of CZ–SK MHS individuals	Pathogenic RYR1 variant frequency
c.487C>T	p.(Arg163Cys)	1	2	0.029
c.488G>T	p.(Arg163Leu)	1 (1 SK)	5 (5 SK)	0.029
c.1589G>A	p.(Arg530His)	2	3	0.057
c.1598G>A*	p.(Arg533His)	2	4	0.057
c.1840C>T*	p.(Arg614Cys)	6 (1 SK)	35 (1 SK)	0.171
c.1841G>T	p.(Arg614Leu)	1	5	0.029
c.6488G>A	p.(Arg2163His)	1 (1 SK)	1 (1 SK)	0.029
c.6502G>A	p.(Val2168Met)	4	16	0.114
c.6617C>T	p.(Thr2206Met)	6	36	0.171
c.7048G>A	p.(Ala2350Thr)	2	3	0.057
c.7063C>T	p.(Arg2355Trp)	1	1	0.029
c.7300G>A	p.(Gly2434Arg)	1	4	0.029
c.7361G>A	p.(Arg2454His)	2	4	0.057
c.7373G>A	p.(Arg2458His)	4	19	0.114
c.7523G>A	p.(Arg2508His)	1 (1 SK)	2 (2 SK)	0.029
None	None	44 (4 SK)	69 (6 SK)	—

Rare Disease – However, if you are affected it is 100% and not meaningless

- Whilst the clinical and biochemical aspects of MH have been widely debated, little has been said of the social implications
- MH susceptible (MHS) is a label of a laboratory investigation leading sometimes to exclusion from the army, sports, and jobs in cleaning industry and anaesthesia
- The main concern expressed by MHS individuals and their families is the way their condition is disregarded by some hospital and family doctors:

«There is nothing to worry about» - when there has already been an MH death in the near family.

Ellis FR. Br J Anaesth 1988; 60: 251

Personal observation Swiss MH patient association

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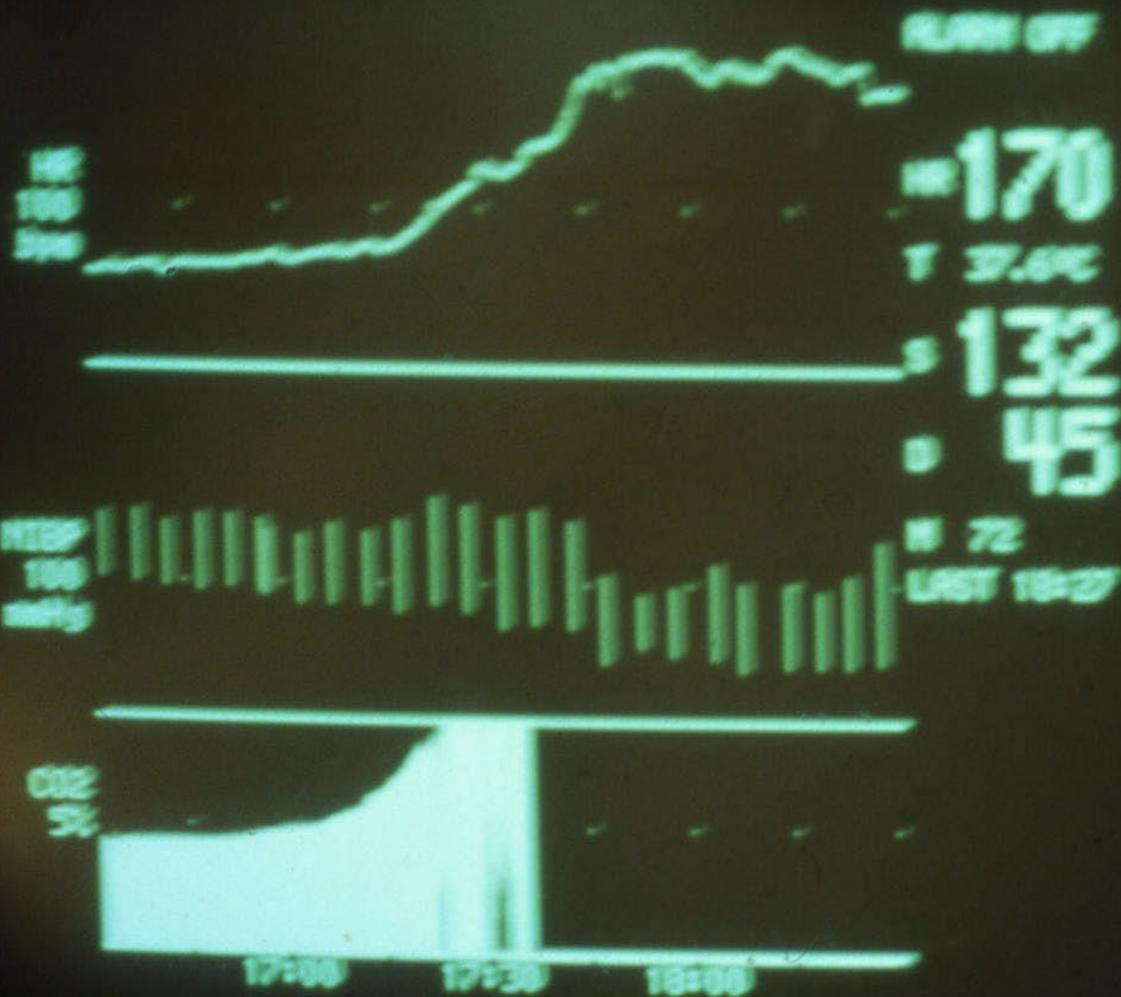
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Helsinki Declaration on Patient Safety in Anaesthesiology

2010

- Checking Equipment and drugs
- Preoperative assessment and preparation
- Syringe labelling
- Difficult/failed intubation
- **Malignant hyperpyrexia**
- Anaphylaxis
- Local anaesthetic toxicity
- Massive haemorrhage
- Infection control
- Postoperative care including pain relief



1	ECG	INFLATE DEFLATE	PR
2	PLETH PRESS	NIBP	TR
3	AUX	SETUP	MR RE
4	RETURN TO MONITOR	ALARMS ON/OFF	SLE ALA

ECG

ECG control knob with a white dial and a white cable attached.

Two small glass vials on a surface. The vial on the left has a gold cap and a white label. The vial on the right has a silver cap. A red circle highlights the silver cap.

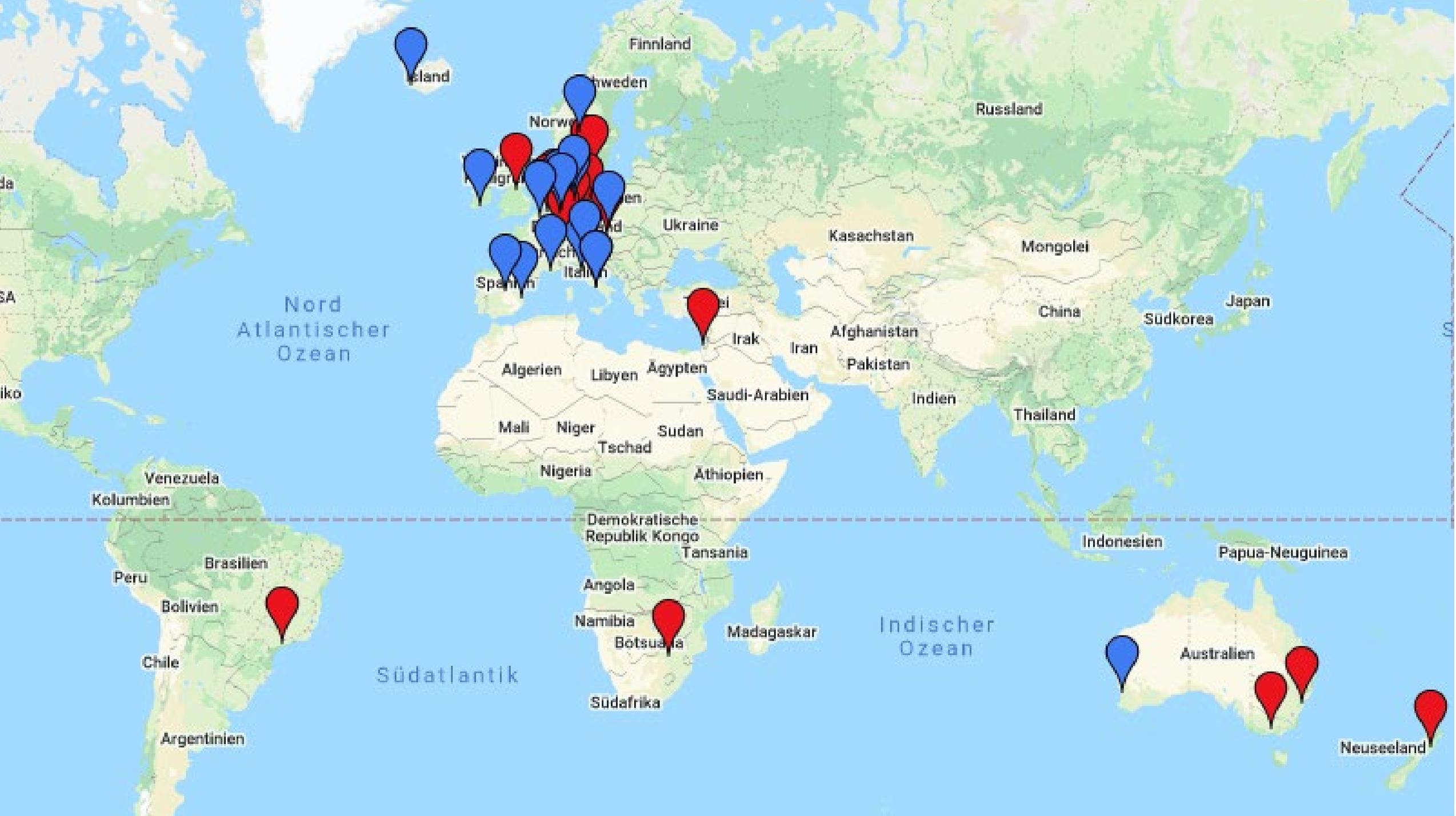
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34th EMHG Annual Meeting 2015, Lille France



Island

Finnland

Schweden

Norwegen

Dänemark

Deutschland

Polen

Tschechien

Italien

Spanien

Griechenland

Türkei

Irak

Iran

Saudi-Arabien

Ägypten

Sudan

Äthiopien

Nigeria

Tansania

Angola

Namibia

Botsuana

Südafrika

Madagaskar

Russland

Kasachstan

Mongolei

China

Südkorea

Japan

Afghanistan

Pakistan

Indien

Thailand

Indonesien

Papua-Neuguinea

Australien

Australien

Neuseeland

Nord Atlantischer Ozean

Südatlantik

Indischer Ozean

Venezuela

Brasilien

Peru

Bolivien

Chile

Argentinien

USA

USA

USA

USA

USA

USA

USA

Constitution European MH Group

Aims

- to provide a forum for discussion between the various European Malignant Hyperthermia (MH) Centres.
- to improve, **maintain and update** the quality of diagnostic standards of MH susceptibility in Europe.
- **to increase knowledge about MH for the medical community and for patients.**
- to promote inter-laboratory scientific research on MH.
- To establish a common database.
- **to promote research into the molecular aetiology and new-pharmacologically-based treatments of MH.**



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Genetics & Bioinformatics

- inclusion of pathogenic and benign variants online on website
- internationally recognised scoring matrix for MH associated variants
- list of genes with potential role in MH susceptibility



Research

- conduction of a research priority exercise for MH
- encouraging applications for research grants
- drawing up strategic options for funding of functional testing of RYR1 variants



Guideline Development & Dissemination



- standardized patient information in all European languages on website
- all national and European societies of Anaesthesia, Intensive Care and Emergency Medicine contacted and informed about treatment, MH triggers and storage of dantrolene
- implementation of formal 5 yearly review process of all EMHG guidelines

Education & Training

- pages on website containing interactive online material including simulation of clinical scenarios
- report on MH-relevant basic science clinical objectives (syllabus for anaesthesia training and specialist working in MH diagnostic centres)



Who Were the First Americans? • Veggie Vaccines • Femtosecond Flashes

SCIENTIFIC AMERICAN

SEPTEMBER 2000

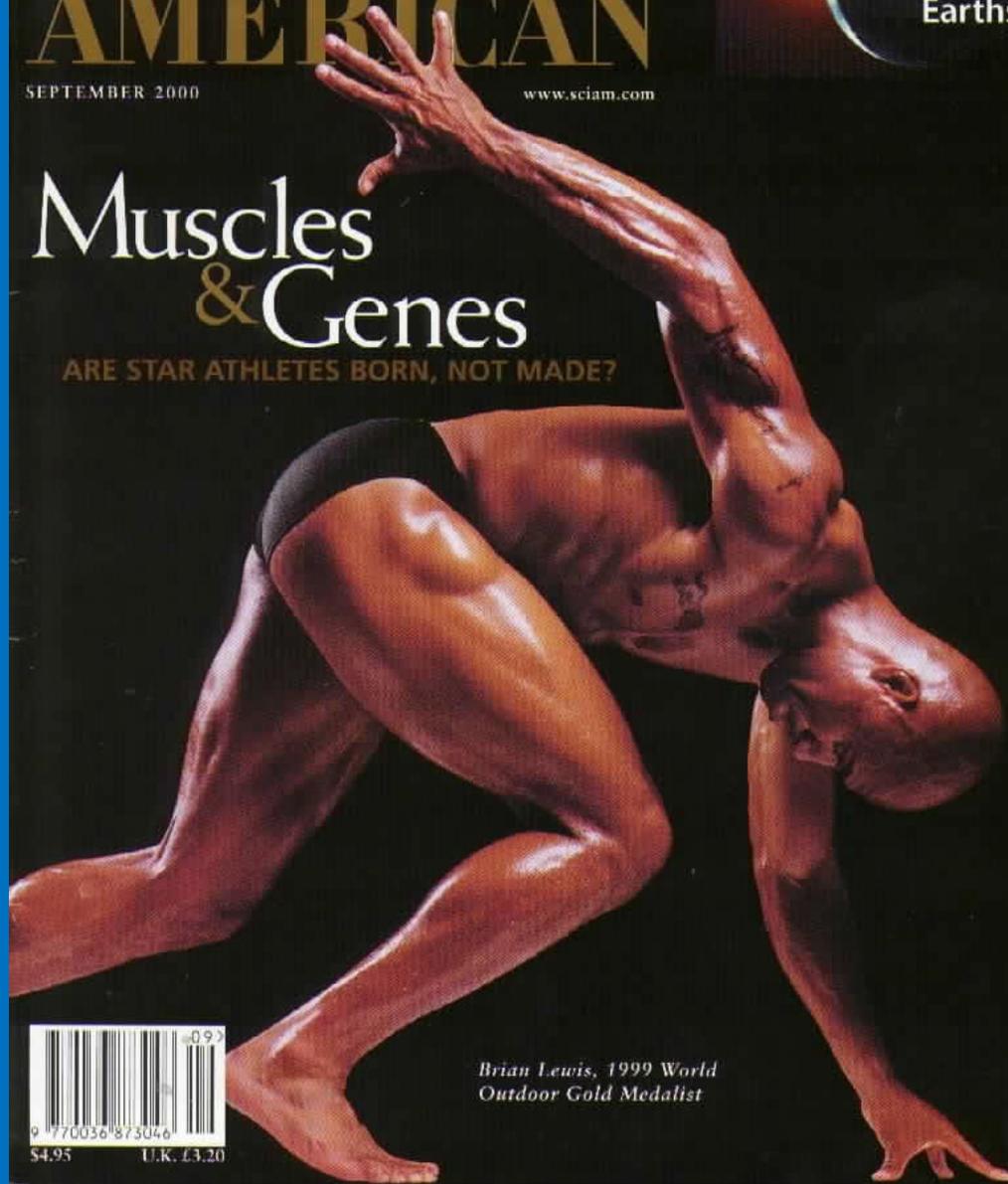
www.sciam.com



Shadows
of Other
Earths

Muscles & Genes

ARE STAR ATHLETES BORN, NOT MADE?



*Brian Lewis, 1999 World
Outdoor Gold Medalist*



\$4.95 U.K. £3.20

Gregor Johann Mendel Příběh skromného génia

Stálá expozice Mendelova muzea Masarykovy univerzity
k počtě práce Gregora Mendela a jeho následovníků

Gregor Johann Mendel The Story of a Humble Genius

A permanent exhibition of the Mendel Museum of Masaryk University
A tribute to the work of Gregor Mendel and his successors

Autor expozice / Author of the exhibition: Ondřej Dostál
Architekt / Architect: Zdeněk Fránek
Design / Design: Marek Nedělka, Ondřej Báchor
Grafický design / Graphic design Hrdina Pavlík
Překlady / Translations: Drew Berry, Adam Prentis
Střih a prezentace / Editing and presentation: Dominik Krajčůček
Realizace / Implementation: LIKO-S, a.s., MIVIS-CZ, s.r.o.

