

Diagnosis

- Exposure to trigger agents: Ether, Halothane, Methoxyflurane, Enflurane, Isoflurane, Sevoflurane, Desflurane, Succinylcholine

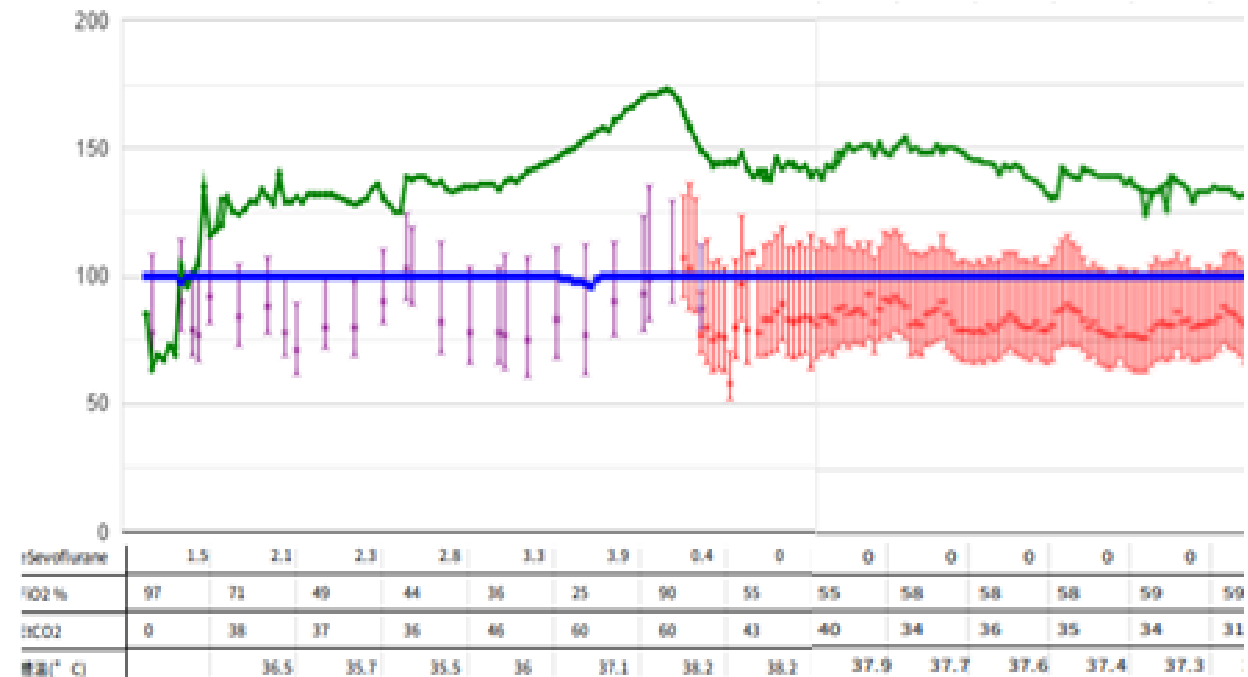
BOX 35.1 Clinical Signs of Malignant Hyperthermia

Early Signs

- Elevated end-tidal CO₂
- Tachypnea and/or tachycardia
- Masseter spasm if succinylcholine has been used
- Generalized muscle rigidity
- Mixed metabolic and respiratory acidosis
- Profuse sweating
- Mottling of skin
- Cardiac arrhythmias
- Unstable blood pressure

Late Signs

- Hyperkalemia
- Rapid increase of core body temperature
- Elevated creatine phosphokinase levels
- Gross myoglobinemia and myoglobinuria
- Cardiac arrest
- Disseminated intravascular coagulation



Treatments

- Stop trigger agents
- Active cooling
- Dantrolene
- Intensive care

1. Discontinue all triggering anesthetics, maintain intravenous agents, such as sedatives, opioids, and nondepolarizing muscular blockers as needed, and hyperventilate with 100% oxygen with a fresh flow to at least 10 L/min. With increased aerobic metabolism, normal ventilation must increase. However, CO₂ production is also increased because of neutralization of fixed acid by bicarbonate; hyperventilation removes this additional CO₂.
2. Administer dantrolene rapidly (2.5 mg/kg intravenously [IV] to a total dose of 10 mg/kg IV) every 5 to 10 minutes until the initial symptoms subside.
3. Administer bicarbonate (1-4 mEq/kg IV) to correct the metabolic acidosis with frequent monitoring of blood gases and pH.
4. Control fever by administering iced fluids, cooling the body surface, cooling body cavities with sterile iced fluids, and if necessary, using a heat exchanger with a pump oxygenator. Cooling should be halted at 38°C to prevent inadvertent hypothermia.
5. Monitor and treat arrhythmia. Advanced cardiac life support protocol may be applied.
6. Monitor and maintain urinary output to greater than 1 to 2 mL/kg/h and establish diuresis if urine output is inadequate. Administer bicarbonate to alkalinize urine to protect the kidney from myoglobinuria-induced renal failure.
7. Further therapy is guided by blood gases, electrolytes, CK, temperature, muscle tone, and urinary output. Hyperkalemia should be treated with bicarbonate, glucose, and insulin, typically 10 units of regular insulin and 50 mL of 50% dextrose for adult patients. The most effective way to lower serum potassium is reversal of MH by effective doses (ED) of dantrolene. In severe cases, calcium chloride or calcium gluconate may be used.
8. Recent data demonstrated that magnesium level could be a prerequisite for dantrolene efficacy in managing MH crisis.
9. Analyze coagulation studies (e.g., international normalized ratio [INR], platelet count, prothrombin time, fibrinogen, fibrin split, or degradation products).
10. Once the initial reaction is controlled, continued monitoring in the intensive care unit for 24 to 48 hours is usually recommended.

Prevention and early detection

- MH: Autosomal dominant with variable penetrance.
 - Family history and pedigree.
 - DNA sequencing .
- IVCT/CHCT/CICR
 - Low availability for fresh muscle biopsy and specific lab.
- Use nontriggering anesthetics for known susceptible individuals.

Genetic study

- DNA sequencing
 - Genomic DNA 10mcg (50-100 mcg/microliter)
 - Blood Collection Tubes with K2 EDTA: 5-10 mL patient peripheral blood
 - Next generation sequencing (NGS; illumine system) ± Sanger sequencing
- Pathogenicity references and interpretation
 - ClinVar, gnomAD, EMHG...
 - ACMG Practice Guideline (Richards et al., 2015)
- Alliance collaboration
 - Integration MH data in Asian
 - International transport: Genomic DNA with 4 degree Celsius storage.

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Clinical Trial / Research Approval

Date of approval: **Feb 27, 2024**

NTUH-REC No.:202301150RINB

Title of protocol: Malignant hyperthermia (MH): genetic profiling for Taiwan and other Asian patients, and functional investigation of RYR1 variants

Trial/Research Institution: National Taiwan University Hospital

Department/ Principal Investigator: Department of Anesthesiology / Dr. Yeh Huei-Ming

The continuing review of the protocol has been approved by the Research Ethics Committee B of the National Taiwan University Hospital, and will be fully ratified in the 180th meeting of Research Ethics Committee. The committee is organized under, and operates in accordance with, the Good Clinical Practice guidelines and governmental laws and regulations.

The duration of this approval is from **Mar 10, 2024** to **Mar 9, 2025**. The investigator is required to report serious adverse events and unanticipated problems in accordance with the governmental laws and regulations and NTUH requirements and apply for a continuing review not less than six weeks prior to the approval expiration date.

Daniel Fu-Chang Tsai, M.D. Ph.D.
Chairman
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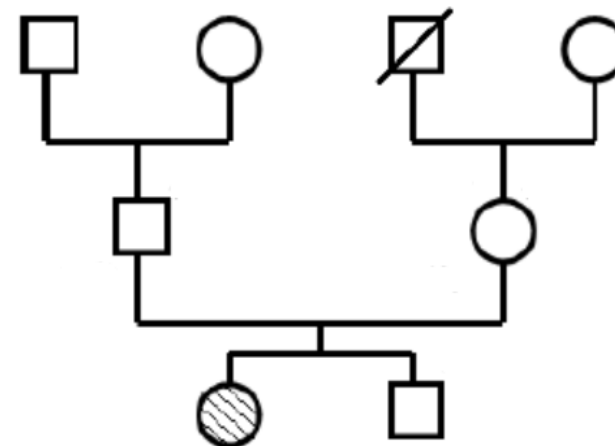
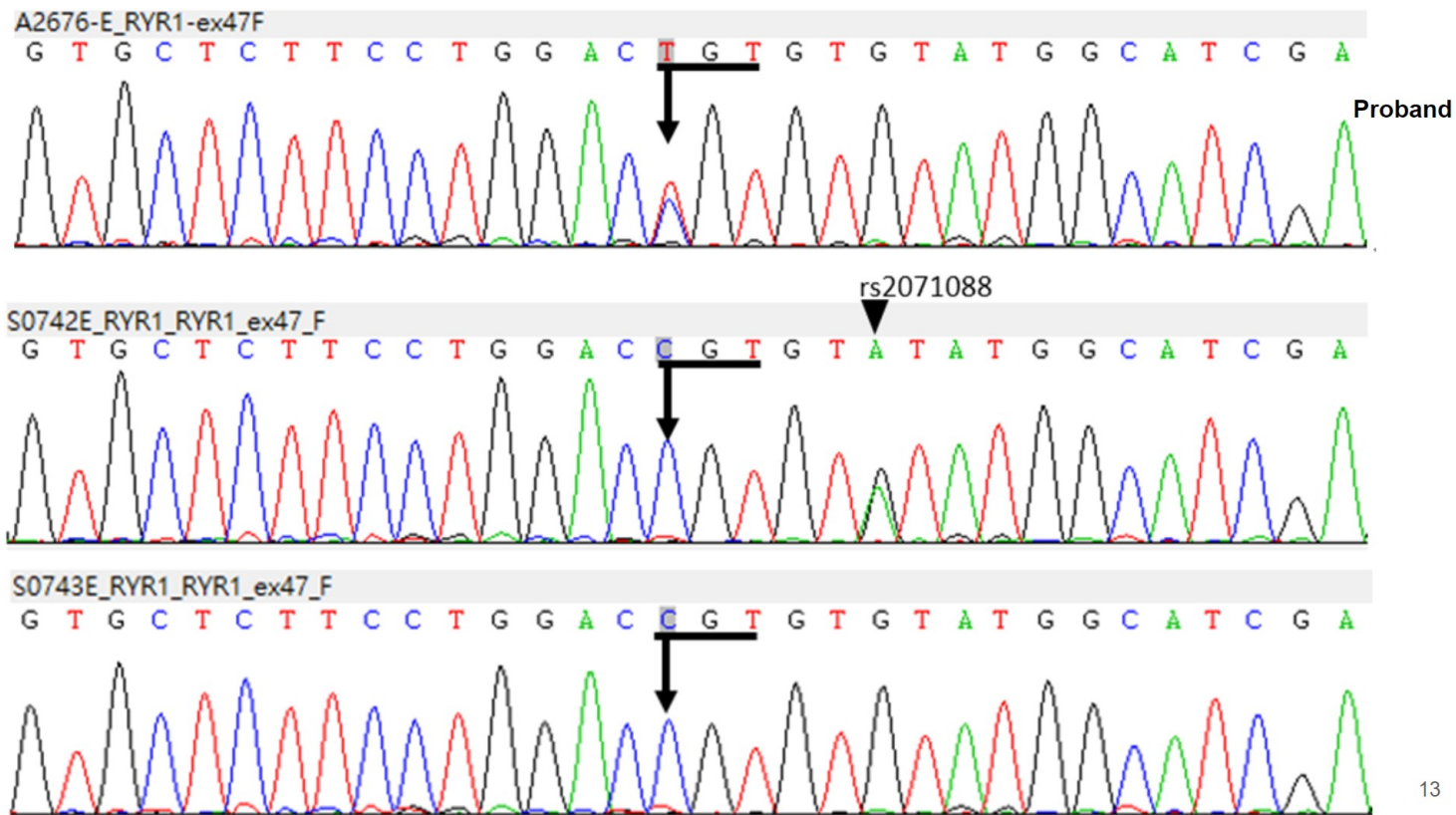
Result: database

- Establish **REDCap**: a secure web application for building and managing online surveys and databases.

Analyses of *RYR1* variants reported as pathogenic by the European Malignant Hyperthermia Group.

Nucleotide change	Amino acid change	No. of Asian families			
		Japan	South Korea	Singapore	Taiwan
c.487C>T	p.R163C	1			1
c.742G>A	p.G248R		1		
c.1021G>A	p.G314R	1			
c.1021G>C	p.G314R	1			
c.1565A>G	p.Y522C				2
c.1840C>T	p.R614C				1
c.1841G>T	p.R614L	4			
c.6502G>A	p.V2168M				1
c.7007G>A	p.R2336H	1			
c.7304G>A	p.R2435H		1		
c.7373G>A	p.R2458H		1	1	4
c.7522C>T	p.R2508C		1		1
c.7523G>A	p.R2508H	1			
c.8026C>T	p.R2676W		1		
c.9310G>A	p.E3104K	2			
c.14512C>G	p.L4838V	2	1		

- Demographic
 - Age
 - Gender
 - MH onset year
 - Height/weight
 - Ethnic
 - Specific underlying
- Surgical type
 - Number of times of anes.
- On set timing
 - After anes., intraOP, postOP
- Symptoms and signs
 - Fever degree, more detail
- Clinical grading scale
 - Larach, M G et al. 1994
- Treatments
 - Stop trigger agents
 - Active cooling
 - Dantrolene
 - Alive/died
- Diagnosis
 - IVCT
 - CHCT
 - CICR
 - DNA sequencing



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Case	Age	Gender	Spec.	Underlying dz	Onset	DNA	IVCT	Ethnic	Surgery	Clinical grading scale	Outcome	Stop trigger	active cooling	Dantrolene
TW01-01	9	F		Scoliosis	2022	p.R2508C	nil	chinese	Posterior correction	33	alive	Sevoflurane	cold saline	nil
TW01-02	37	F		TW 01-01	nil	wnl	nil	chinese						
TW01-03	41	M		TW 01-01	nil	wnl	nil	chinese						

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