遺傳性血管性水腫處置新發展

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Introduction

- Recent advances in the **field of medical immunology**, **molecular biology** and **molecular genetics** have greatly enhanced our understanding of the **pathogenesis** of various **immunodeficiency** diseases at the **molecular and DNA level**.
- Now it is clear to us that **different gene mutations** may result in the **same clinical syndrome** and **different clinical symptoms** may result from the **same gene mutation**.

Introduction

- A correct **diagnosis at the DNA level** in immunodeficiency diseases is **critically important** because of the real possibility of **correcting the underlying abnormalities**.
- Most patients with **primary immunodeficiency** present with **recurrent serious or unusual infections, except hereditary angioedema (HAE)**.
- In this report, I will review the **Taiwan experience of HAE** to impart a better understanding of their pathogenesis and to describe the **new diagnostic** and **therapeutic** modalities that are available now.

Introduction

- Primary care **physicians** must have a **high index of suspicion** if **defects of the immune** system are to be **diagnosed early** enough that **appropriate treatment** can be instituted **before irreversible damage** or **life-threatening** event develops.

Primary immunodeficiency

- Predominant antibody deficiency
- Predominant T cell immunodeficiency
- Combined immunodeficiency
- Immunodeficiency with phagocyte defect
- Immunodeficiency with complement defect

IUIS: 2017 Phenotypic Classification of PID

- The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in London in Feb. 23-24, 2017 to update the phenotypic classification of human primary immunodeficiencies (PIDs). (354 distinct disorders
- with 344 different gene defects)
- **I. Immunodeficiencies affecng cellular and humoral immunity.**
- (a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia
- (b) **Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency**
- **IIa. CID with associated or syndromic features**
- **IIb. CID with associated or syndromic features**
- **III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia**
- **b: Other Anbody deficiencies**
- **IV. Diseases of immune dysregulaon.**
- **a : Hemophagocyc Lymphohisocytosis HLH & EBV suscepbility**
- **b: Sd with Autoimmunity and Others**

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- **V. Congenital defects of phagocyte number, function, or both.**
- **a : Neutropenia**(without an-PMN)
- **b : Funconal defects**
- **VI. Defects in Intrinsic and Innate immunity. a : Bacterial and Parasitic Infections**
- **b : MSMD and Viral infection**
- **VIIa. Auto-inflammatory disorders**
- **VIIb. Auto-inflammatory disorders**
- **VIII. Complement deficiencies**
- **IX. Phenocopies of PID**

J Clin Immunol (2018) 38:129–143

VIII. Complement deficiencies

VIII. Complement deficiencies

Susceptibility to infections

High

Disseminated Neisserial infections

Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity.

C5 def. *C5*

C6 def. *C6*

C7 def . *C7.*
+ Vasculitis

C8 def.
C8A, C8B, C8G

C9 def. *C9.*
Mild susceptibility.

Normal CH50. Absent AH50 hemolytic activity

Properdin def.
PFC. XL

Factor D def.
CFD. AR.

Recurrent pyogenic infections

C3 LOF. *C3.* AR.
Absent CH50 and AH50 hemolytic activity, defective opsonization and humoral response

MASP2 def.
MASP2. AR.
Inflammatory lung disease, autoimmunity

Ficolin 3 def.
FCN3. AR.
Infections mainly in the lungs; abscesses, necrotizing entero-colitis in infancy; selective antibody defect to Pneumo-coccal polysaccharides. Absence of complement activation by the Ficolin 3 pathway

Factor B. *CFB LOF.*
AR. Infections with encapsulated organisms. Deficient activation of the alternative pathway

Low

SLE-like syndrome.

Infections with encapsulated organisms
Absent CH50 hemolytic activity

C1q def. *C1QA, C1QB, C1QC.*

C1r def. *C1R.* Ehlers Danlos phenotype

C1s def.*C1S.*
Multiple autoimmune diseases; Ehlers Danlos phenotype

C2 def. *C2.*
Vasculitis, Polymyositis, atherosclerosis

C4 def .C4A, C4B.AR.
Partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense

Atypical Hemolytic Uremic Syndrome

C3 GOF. *C3.* AD.
Infections , glomerulonephritis. Increased activation of complement

Factor B GOF. *CFB.* AD. Increased spontaneous AH50

Factor H def. *CFH.* AR or AD.
Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3

Factor H –related protein deficiencies. *CFHR1-5.* AR or AD.
Later onset, disseminated neisserial infections. Normal CH50, AH50, autoantibodies to Factor H.

Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3

Thrombomodulin def. *THBD.*
AD. Normal CH50, AH50

Membrane Cofactor Protein deficiency. *CD46.*AD,Glomerulone-phritis. Infections, preeclampsia . Inhibitor of complement alternate pathway, decreased C3b binding

Others

C1 inhibitor. *SERPING1.*
AD, Hereditary angioedema. Spontaneous activation of the complement pathway with consumption of C4/C2

Membrane Attack Complex Inhibitor deficiency. *CD59.*
Hemolytic anemia. Polyneuropathy.

CD55 deficiency (CHAPLE disease). *CD55.* AR. Protein losing enteropathy, thrombosis

VIII. Complement deficiencies Suscepbility to infecons-Low

Others

C1 inhibitor.

SERPING1.

AD, Hereditary angioedema.

Spontaneous activation of the complement pathway with consumption of C4/C2

Complement deficiency- Hereditary angioedema

Table 8 (continued)

Disease	Genetic defect; presumed pathogenesis OMIM gene	Inheritance	Laboratory features	Associated Features	Phenotype OMIM number
MASP2 deficiency	*MASP2*: Cleavage of C4 605102	AR	Deficient activation of the lectin activation pathway	Pyogenic infections; Inflammatory lung disease, autoimmunity	613791
Ficolin 3 deficiency	*FCN3:* Activates the classical complement pathway 604973	AR	Absence of complement activation by the Ficolin 3 pathway.	Respiratory infections, abscesses	613860
2) Complement Regulatory defects					
C1 inhibitor deficiency	*SERPING1*: regulation of kinins and complement activation	AD	Spontaneous activation of the complement pathway with consumption of C4/C2 Spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema	106100
Factor B	*CFB*: Activation of the alternative pathway 138470	AD	Gain-of-function mutation with increased spontaneous AH50		
Factor D deficiency	*CFD*: Regulation of the alternative complement pathway 134350				613912
Properdin deficiency	*CFP*: Regulation of the alternative complement pathway 300383				312060
Factor I deficiency	*CFI*: Regulation of the alternative complement pathway 217030				610984 612923
Factor H deficiency	*CFH*: Regulation of the alternative complement pathway 134370				609814 235400
Factor H –related protein deficiencies	*CFHR1-5*: Bind C3b 134371 600889 605336 605337 608593	AR/AD	Normal CH50, AH50, autoantibodies to Factor H. Linked deletions of one or more CFHR genes leads to susceptibility autoantibody-mediated aHUS	aHUS, Neisserial infections	235400
Thrombomodulin	*THBD*: Regulates complement and coagulant activation 188040	AD	Normal CH50, AH50	aHUS	612926
Complement Receptor 3 (CR3) deficiency	*ITGAM* 120980	AR	CR3 expression is lost in LAD1. See LAD1 in Table 5	Infections	609939
Membrane Cofactor Protein (CD46) deficiency	*CD46*: Dissociates C3b and C4b 120920	AD	Inhibitor of complement alternate pathway, decreased C3b binding	aHUS, infections, preeclampsia	612922
Membrane Attack Complex Inhibitor (CD59) deficiency	*CD59:* Regulates the membrane attack complex formation 107271	AR	Erythrocytes highly susceptible to complement-mediated lysis	Hemolytic anemia, polyneuropathy	612300

C1 inhibitor deficiency

Hereditary angioedema

Spontaneous activation of the complement pathway with consumption of C4/C2

Spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen

J Clin Immunol (2015) 35:696–726

IUIS PID VIII
Suscepbility to infecons-Low Hereditary angioedema

- Sex: Female
- 16 Y/O
- Chief Complaint:

  Recurrent swelling 3 times over head and neck in recently 2 years

Hereditary angioedema

A 16-year-old girl suffered from 3 attacks of angioedema over face and neck in recently 2 years.

Tracing back her family history, her uncle was dead due to asphyxia by recurrent laryngeal edema with facial angioedema.

C1 inhibitor 6.5 mg/dL

C3 118 mg/dL

C4 <10 mg/dL

C1 inhibitor gene mutation at p.c.628delA,I210fsX210

Introduction

- Hereditary angioedema is an ***autosomal dominant*** disease caused by low levels or function of the plasma protein C1 inhibitor (C1-INH).
  - **50%** chance of inheritance to **offspring** when one parent is affected.
  - 25% of cases arise from spontaneous mutations
- It accounts for approximately 2% of clinical angioedema cases and occurs in 1 per 50,000-150,000 population in western coutry.

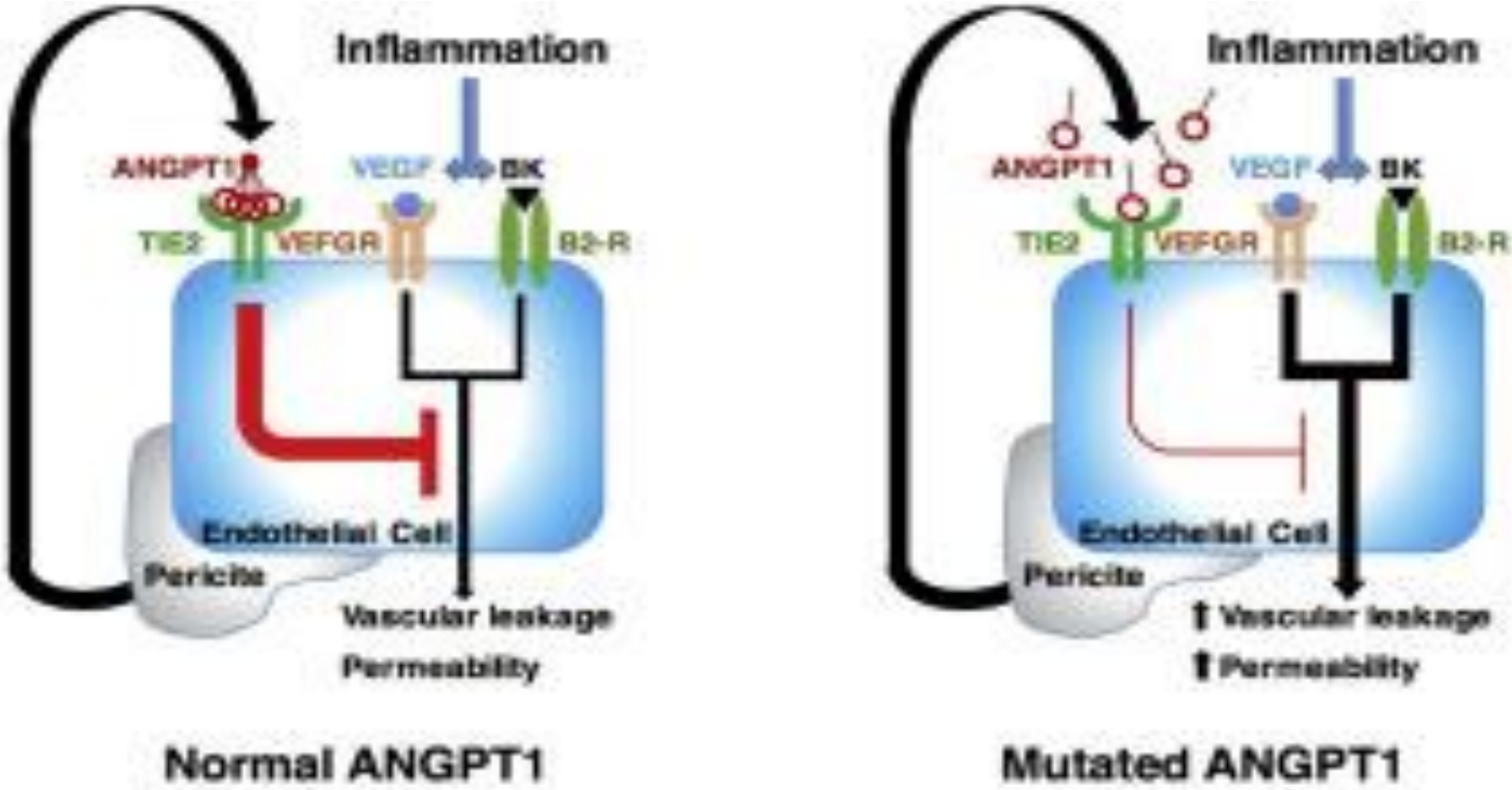
Introduction

- Classification:
- Type I HAE :
  - low C1-INH protein and function (85% of cases)
- Type II HAE :
  - normal level but low C1-INH function (15%)
- HAE nC1-INH :
  - HAE nC1-INH, hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in factor XII (FXII)，angiopoietin (ANGPTI) or plasminogen (PLG).
- AAE-C1-INH:
  - AAE-C1-INH, acquired angioedema due to C1-inhibitor deficiency

Mutation of the angiopoietin-1 gene *(ANGPT1)* associates with a new type of hereditary angioedema

Valeria Bafunno, et al. J Allergy Clin Immunol 2018;141:1009-1017.

Mutation of the angiopoietin-1 gene *(ANGPT1)* associates with a new type of hereditary angioedema



ANGPT1: angiopoietin 1
BK: bradykinin
VEGF: vascular endothelial growth factor
B2-R: bradykinin type 2 receptor
TIE2: tunica interna endothelial cell kinase-2
VEGFR: vascular endothelial growth factor receptor

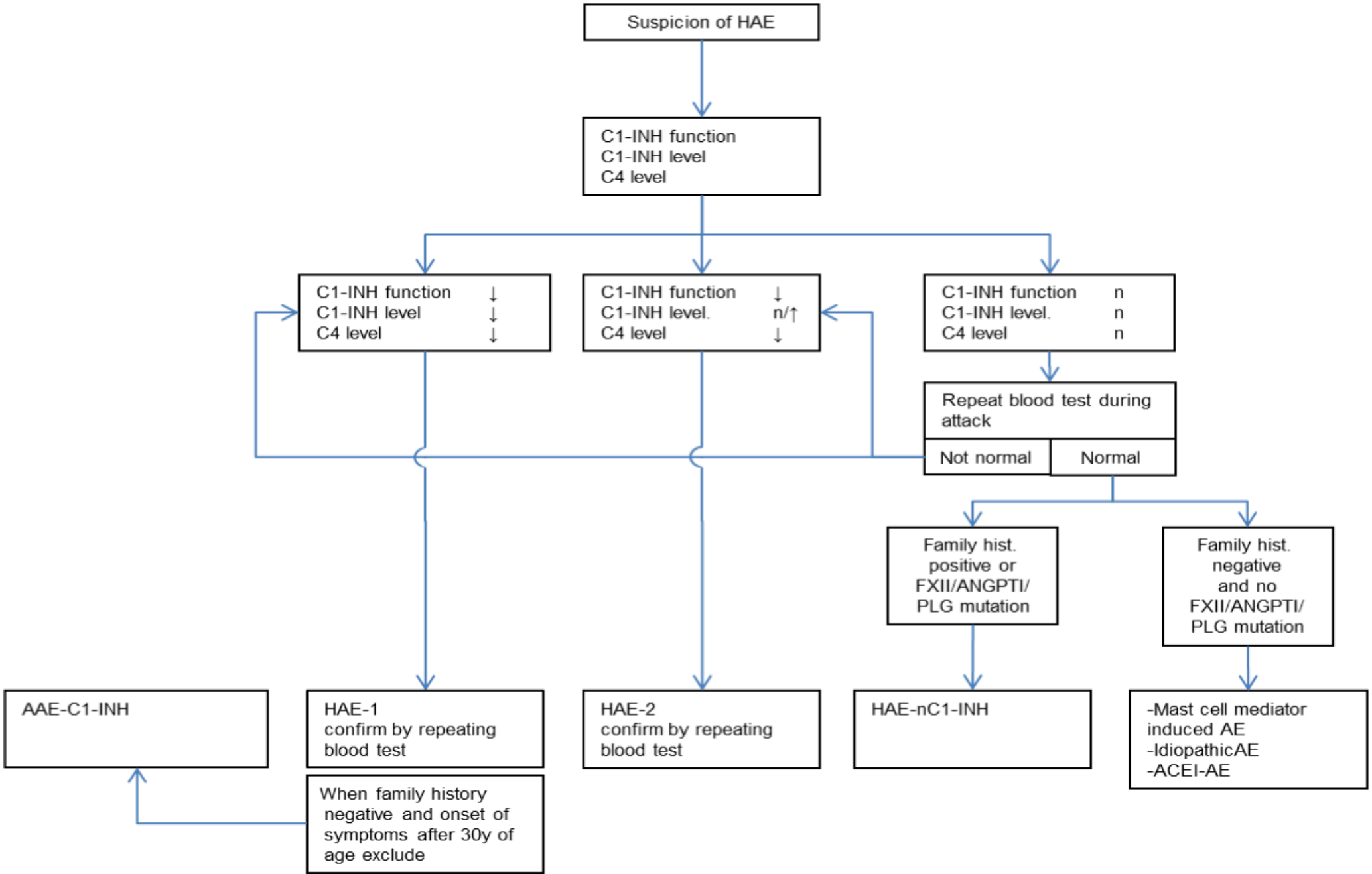
Hereditary angioedema caused by missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy

Konrad Bork, et al. J Allergy Clin Immunol 2009;124:129-34

Hereditary angioedema with a mutation in the plasminogen gene

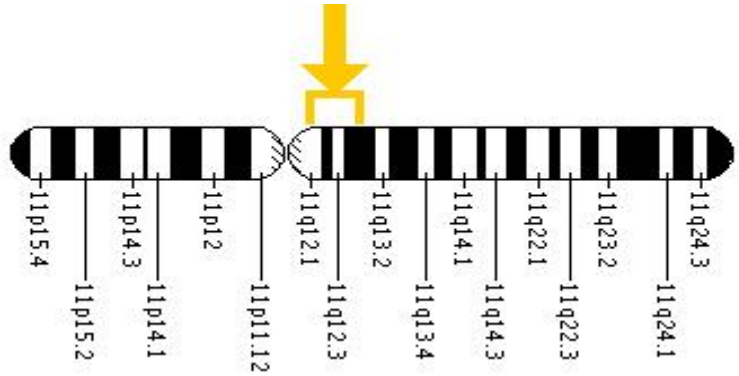
K. Bork, et al. Allergy. 2018;73:442–450.

Diagnostic workup in patients suspected to have HAE



Introduction

- A positive family history of angioedema is present in most patients
- The genetic bases of Type I and II HAE are *mutations in the C1 inhibitor gene*
- The gene encoding C1-INH : chromosome 11q12-q13

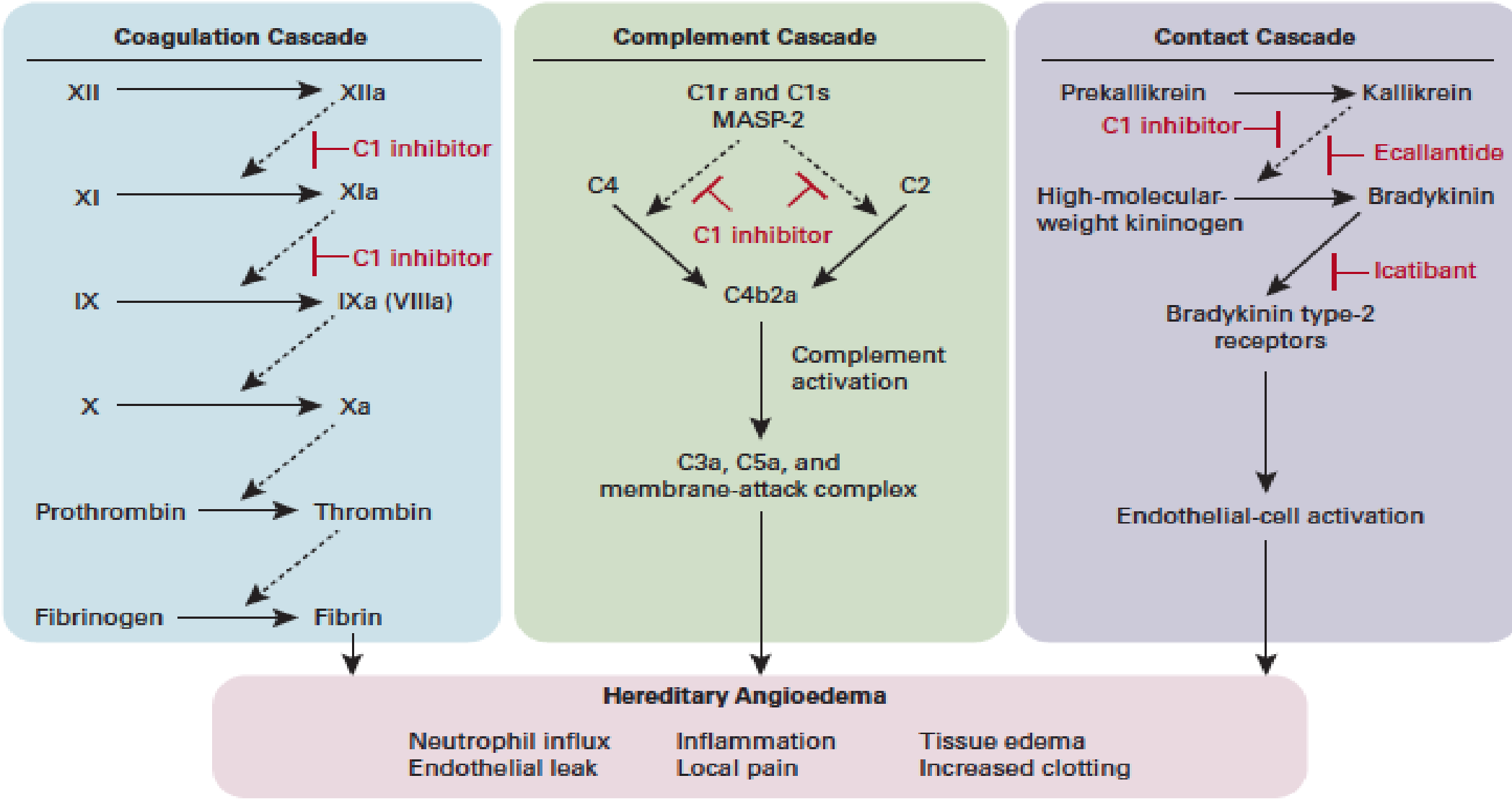


- More than 150 different mutations reported

Pathogenesis of HAE

- HAE主要的致病機轉為病人先天上抗原性C1-INH和/或功能缺乏或低下造成：
- Coagulation cascade：凝血因子XI和IX的持續活化，產生大量的fibrin。
- Complement cascade：補體C4和C2的持續活化，產生大量的C3a、C5a和membrane attack complex。
- Contact cascade：Kallikrein持續活化High-molecular-weight kininogen，間接產生大量的Bradykinin。
- 因而造成病人血管擴張，微血管通透性增加，血管外水分滲出及皮下水腫。(如下圖)

Figure 1. Dysregulation of Coagulation, Complement, and Contact Cascades in Hereditary Angioedema[2]



C1 inhibitor controls activation in the coagulation, complement, and contact cascades, and all 3 cascades are dysregulated in hereditary angioedema. Replacement of C1 inhibitor restores homeostasis. Ecallantide and icatibant specifically inhibit the contact cascade but have no direct effect on the complement or coagulation cascade. Dashed arrows indicate enzyme-cleavage steps, and T bars points of inhibition.
MASP-2 indicates mannose-binding lectin–associated serine protease 2.
Reprinted with permission from Morgan BP. *N Engl J Med*. 2010;363:581-583.

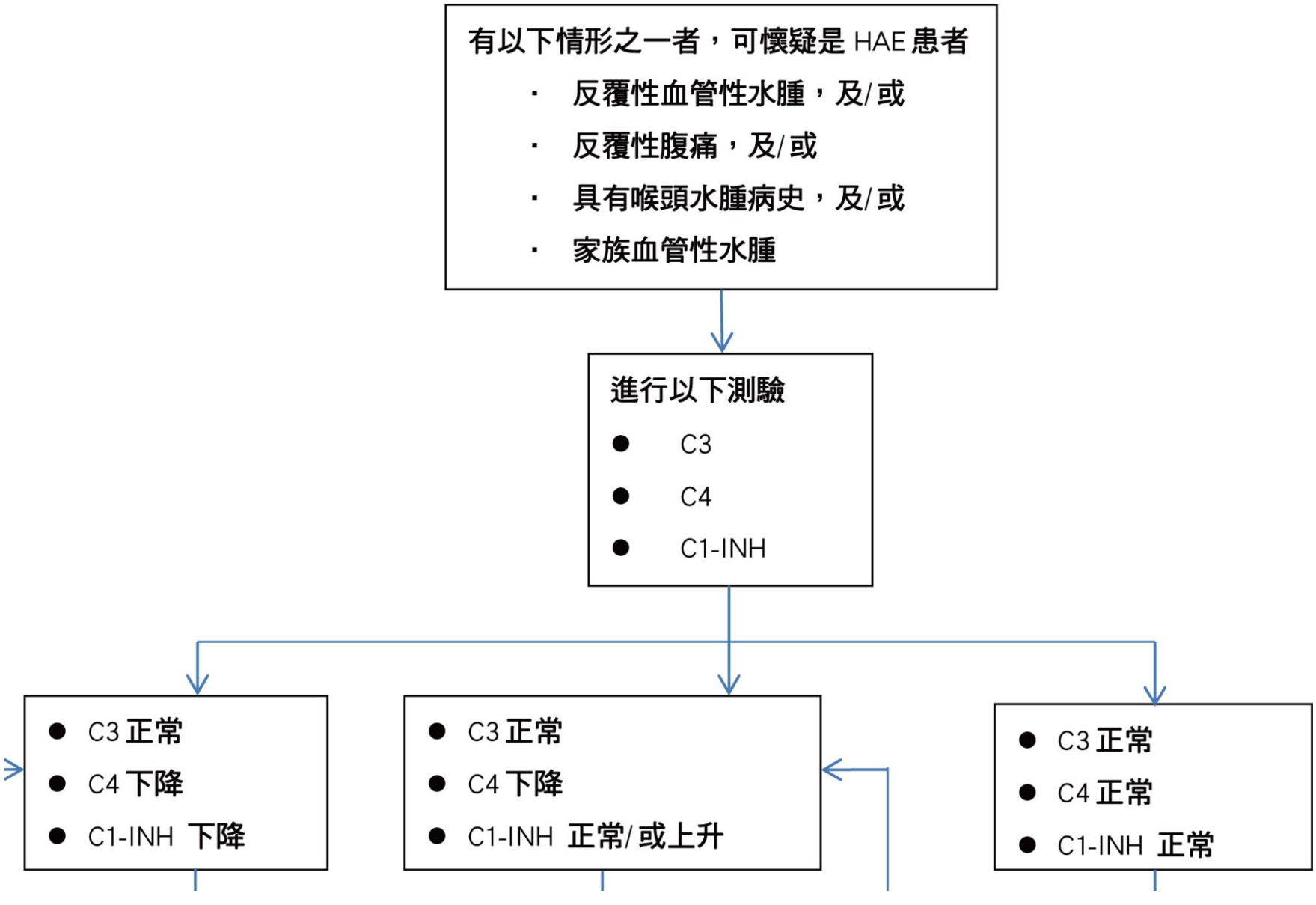
Epidemiology of HAE in Taiwan

- In Taiwan, until year 2018 hereditary angioedema is still a very rare genetic disease (**prevalence 1/639000**) and only **11 mutations** were found. **Thirty six patients (19 male and 17 female)** from **12 families** in Taiwan area (7,4,2,3,8,1,1,2,1,1,2,4 members, respectively) who had suffered from **subcutaneous angioedema, laryngeal edema or gastrointestinal tract edema with ascites** were diagnosed of HAE by **laboratory** study and/or **gene** analysis were enrolled in this report.

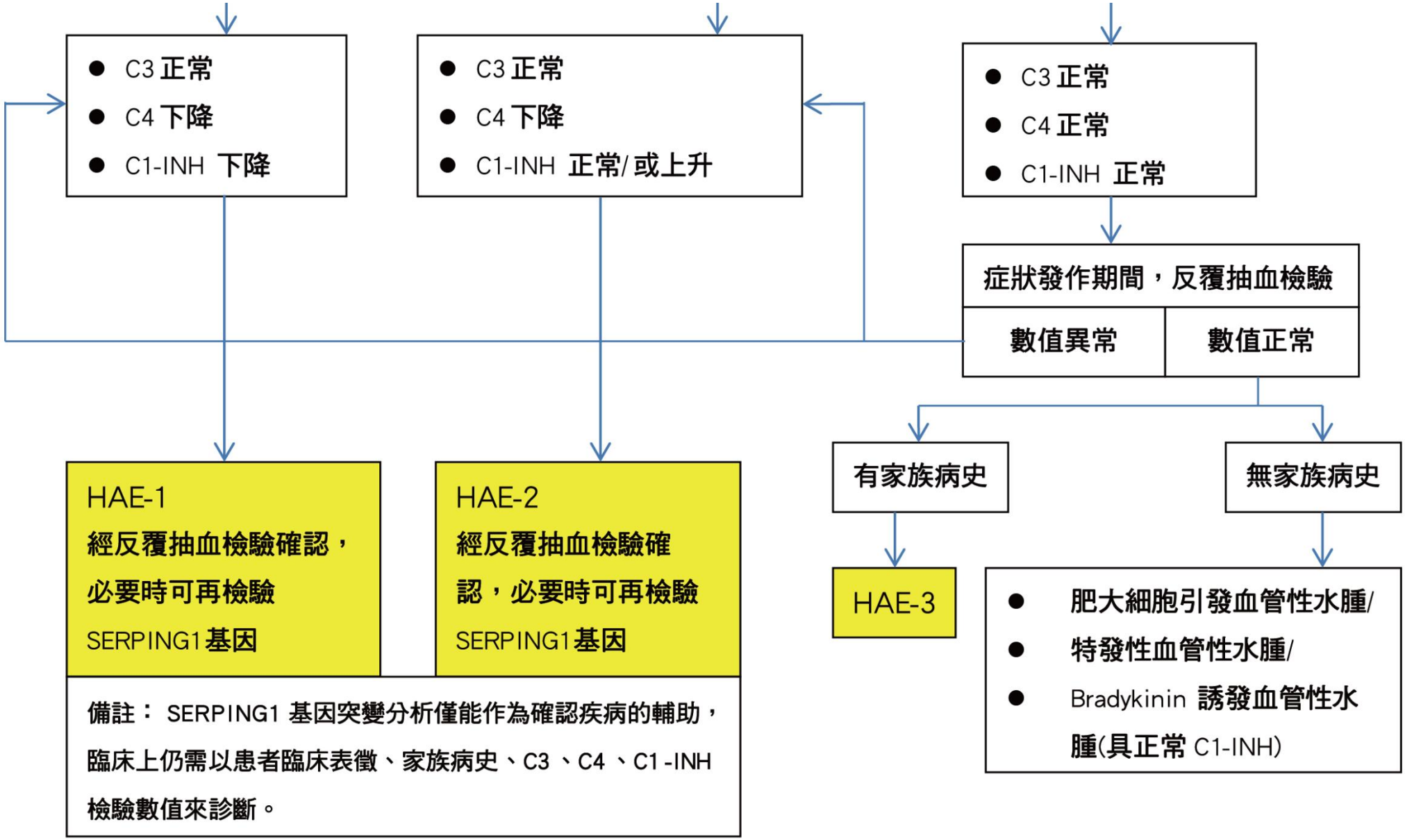
Clinical manifestations of HAE

- Hereditary angioedema clinically characterized by **recurrent face, skin or extremity and scrotum swelling**, without urticaria or pruritus, as well as **gastrointestinal** and **respiratory** system involvement. Although the swelling is always self-limited, **laryngeal involvement** may cause **fatal asphyxiation**.

遺傳性血管性水腫診斷流程



遺傳性血管性水腫診斷流程



HAE experience in Taiwan

HAE experience in Taiwan

Sex	No.	%
M	19	52.78%
F	17	47.22%

Age, range	Age(y)	(mean)
At start of clinical symptom	4-34	21.70
At diagnosis	4-69	30.61
delay in diagnosis	0-52	11.21

HAE experience in Taiwan

Family hx	No.	%
positive	34	94.44%
negative	2	5.56%

Clinical manifestations	No.	%
Asymptomatic	10	27.78%
Symptomatic	26	72.22%
Skin/limbs/trunk	25	96.15%
abdomen	9	34.62%
Face/larynx	18	69.23%
Motality	4	11.11%

HAE experience in Taiwan

HAE type	No.	%
type I	34	93.75%
type II	2	6.25%

Genomic mutation		No.	%
	Exon 3	4+1(Mosaicism)	12.82%(5/39)
	Exon 4	4	10.26%(4/39)
	Exon 5	8	20.51%(8/39)
	Exon 6	3	7.69%(3/39)
	Exon 6 + 8	1	2.56%(1/39)
	Exon 8 (type II)	4	10.26%(4/39)
	Exon 8 (type I)	4	10.26%(4/39)

#No gene mutation or gross deletion 2 persons 5.13%(2/39)
 # Gene not checked 8 persons 20.51%(8/39)

Management of HAE in Taiwan

藥物	優點	缺點	最佳使用	認證批准狀態
Plasma-derived C1-INH(血清製成的 C1-INH)	Extensive clinical experience Replaces deficient C1-INH Long half-life	Infectious risk Needs IV access Limited supply Expensive as prophylaxis	Acute attacks Short-term Long-term prophylaxis Prodromes	Berinert: FDA approved for acute attacks Cinryze: FDA approved for prophylaxis Cetor in the EU
Recombinant C1-INH(基因重組製成的 C1-INH)	Replaces deficient C1-INH No human virus risk Scalable supply	Needs IV access Short half-life Potential for allergic reactions	Acute attacks Short prophylaxis Prodrome	rhC1-INH: approved for acute attacks
Ecallantide (Contact system modulators)(激肽通路調節劑)	No infectious risk Subcutaneous administration	Antibodies may cause allergic reaction or neutralization Short half-life Box warning for anaphylaxis	Acute attacks in office or at home with a health care provider	Kalbitor: FDA approval for administration by health care provider
Icantibant (Contact system modulators)(激肽通路調節劑)	No infectious risk Stable at room temperature Subcutaneous	Short half-life Repeat dosing Local pain or irritation	Home treatment of acute attacks Ease to use during travel	Firazyr: approved in Europe and recently in the Unites States
Antifibrino-lytics(抗纖維蛋白溶解藥)	Inexpensive Oral administration	Adverse effect profile Minimal to no effect	Not recommended	Not recommended
FFP(新鮮冷凍血清)	Inexpensive	Higher risk of viral transmission May worsen HAE attacks No controlled studies have demonstrated effectiveness	Short-term prophylaxis and for attacks	Used for acute attacks and short-term prophylaxis in HAE
Androgens(雄激素)	Inexpensive, oral and effective	Adverse effects are frequent Risk might outweigh benefits for doses above 200 mg a day	Short- and long-term prophylaxis	Danazol: approved for HAE

資料來源： Modified from Xu YY, et al. Clinical & Experimental Allergy 2013;43: 395–405

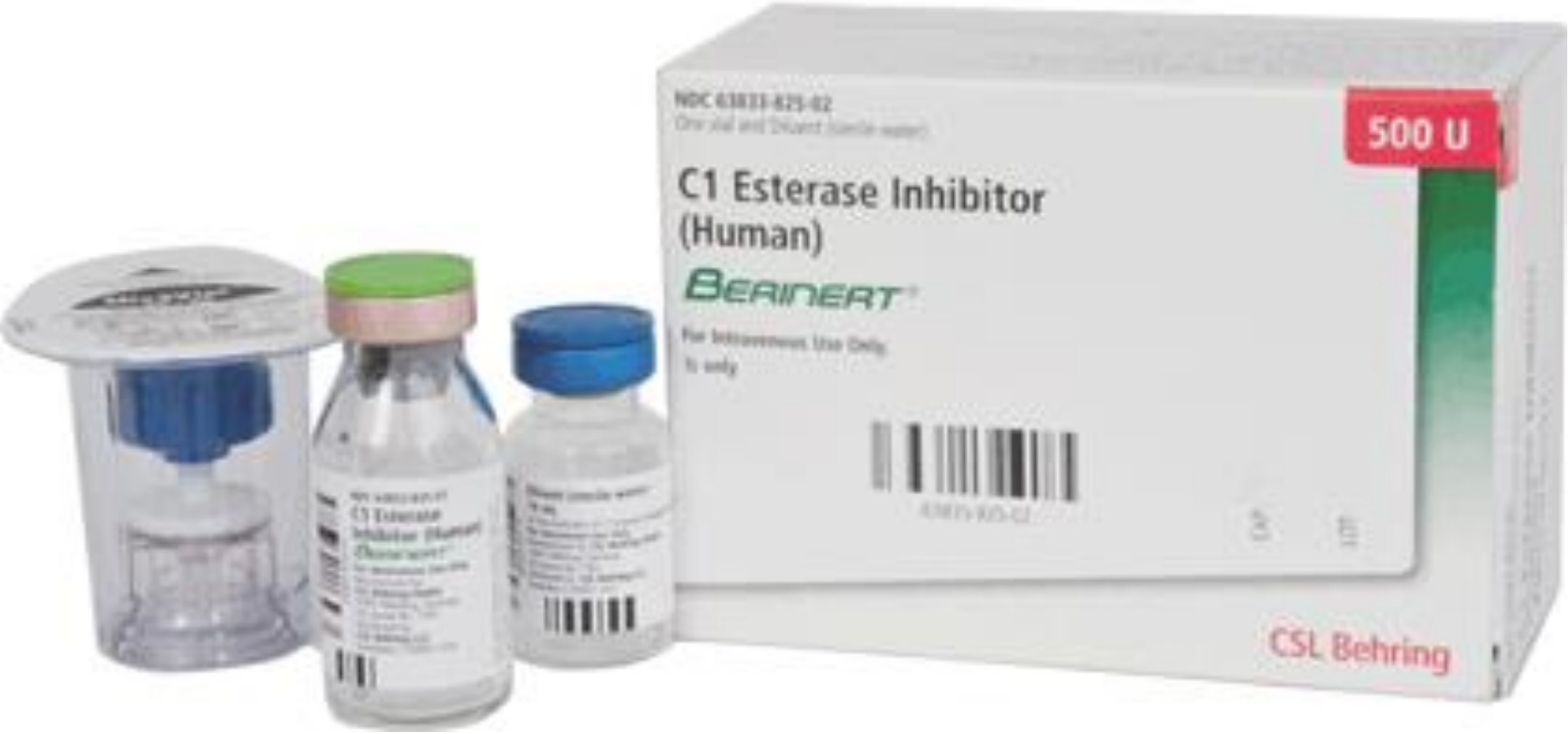
目前台灣可以引進FDA認證的HAE治療藥物

- C1-INH(血清製成的C1-INH)：BERINERT® IV; HAEGARDA® SC; CINRYZE® IV
- **適應症**：BERINERT® IV 500 IU/10mL, 20IU/kg, 4 mL/min; 是一人體血漿純化的濃縮C1酯酶抑制劑，用於治療急性腹部、面部或喉部的遺傳性血管性水腫(HAE)發作的病患。 **HAEGARDA® SC** 2000 IU/4mL,3000 IU/6mL,60IU/kg,2/Wk 循環部位注射。用於長期預防12歲以上HAE發作。**CINRYZE® IV 500 U/8mL**, 每3或4天靜脈注射1000U,循環部位注射。用於定期預防青少年和成人遺傳性血管性水腫發作血管性水腫（HAE）。
- Contact system modulators (**激肽通路調節劑**；Ecallantide)：KALBITOR® SC 10mg/mL/vial, 30 mg st, ≦2 doses within 24 hours.
- 適應症：**KALBITOR®** (ecallantide) 係用於治療 12 歲以上遺傳性血管性水腫(hereditary angioedema, HAE) 病患之急性發作。
- Contact system modulators (**激肽通路調節劑**；Icatibant)：FIRAZYR® SC 30 mg/vial q6h,≦3 doses within 24 hours.
- 適應症：FIRAZYR® (icatibant 注射劑) 是一種緩激肽B2受體拮抗劑，用於治療18 歲以上成人的遺傳性血管性水腫（HAE）急性發作。

目前台灣可以引進FDA認證的HAE治療藥物

- **基因重組製成的C1-抑製劑：** rhC1-INH; Ruconest® IV
- **適應症：** rhC1-INH; Ruconest®，來源於轉基因兔子的乳汁，用於治療急性遺傳性血管性水腫(HAE)發作的12歲以上HAE發作病患，與血漿衍生的C1-抑製劑相比，基因重組製成的C1-抑製劑具有較短的半衰期（3小時VS24小時）。 50 U/kg，最高劑量4200 U ，靜脈注射5分鐘。 ≦2 doses within 24 hours 。
- **Contact system modulators (激肽通路調節劑)：** Lanadelumab; Takhzyro ® 300 mg SC 2 to 4 weeks
- **適應症：** 單株抗體Lanadelumab (Takhzyro ®), 用於長期預防12歲以上第一型與第二型HAE發作。Lanadelumab是一種血漿激肽釋放酶抑製劑(plasma kallikrein inhibitor)。 Lanadelumab是一種完全的人IgG1單株抗體，由重組中國倉鼠卵巢細胞製成。

BERINERT® IV



HAEGARDA® SC


NDC 63833-828-02
One vial and Sterile Water for Injection, USP
2000 IU
C1 Esterase Inhibitor
Subcutaneous (Human)
HAEGARDA®
For Subcutaneous Administration Only
℞ only
CSL Behring
NDC 63833-829-02
One vial and Sterile Water for Injection, USP
3000 IU
C1 Esterase Inhibitor
Subcutaneous (Human)
HAEGARDA®
For Subcutaneous Administration Only
℞ only
CSL Behring

CINRYZE® IV


CINRYZE
C1 inhibitor (human)
Reconstitution Demonstration Kit
For demonstration purposes only—not for administration or resale.
CINRYZE

BERINERT® IV
HAEGARDA® SC

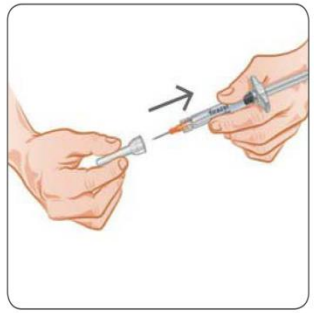
KALBITOR® SC

Image courtesy of Business Wire

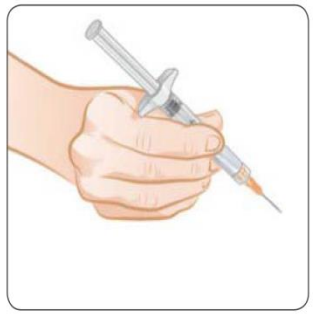
FIRAZYR® SC

FIRAZYR® SC and KALBITOR® SC

A. Remove the needle from the needle cap by holding the needle cap and carefully pulling the syringe. Do not pull up on the plunger

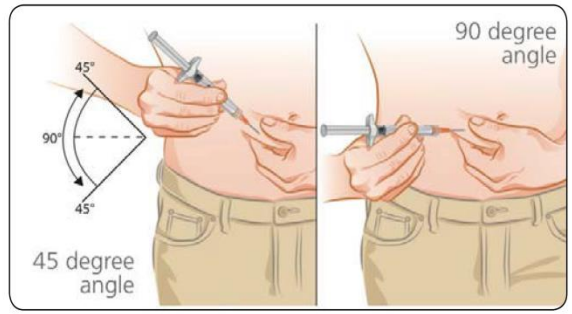


B. Hold the FIRAZYR prefilled syringe in 1 hand, between your fingers and thumb

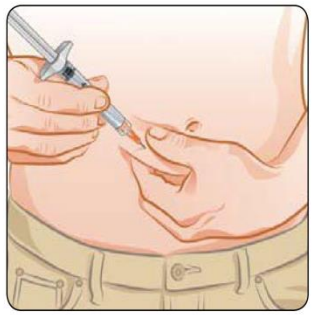


C. Use your other hand to gently pinch the fold of skin you cleaned with the alcohol wipe between your thumb and fingers for your injection

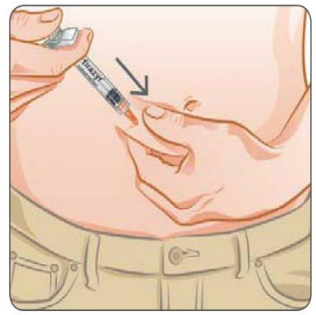
D. Hold the syringe between a 45 to 90 degree angle to your skin with the needle facing the fold of skin you are holding



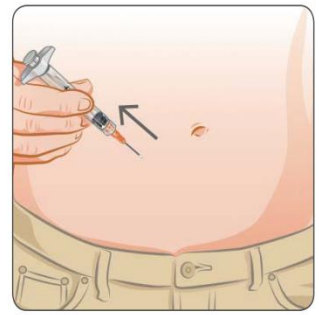
E. Hold the fold of skin. Bring the syringe to the skin and quickly insert the needle into the skin fold



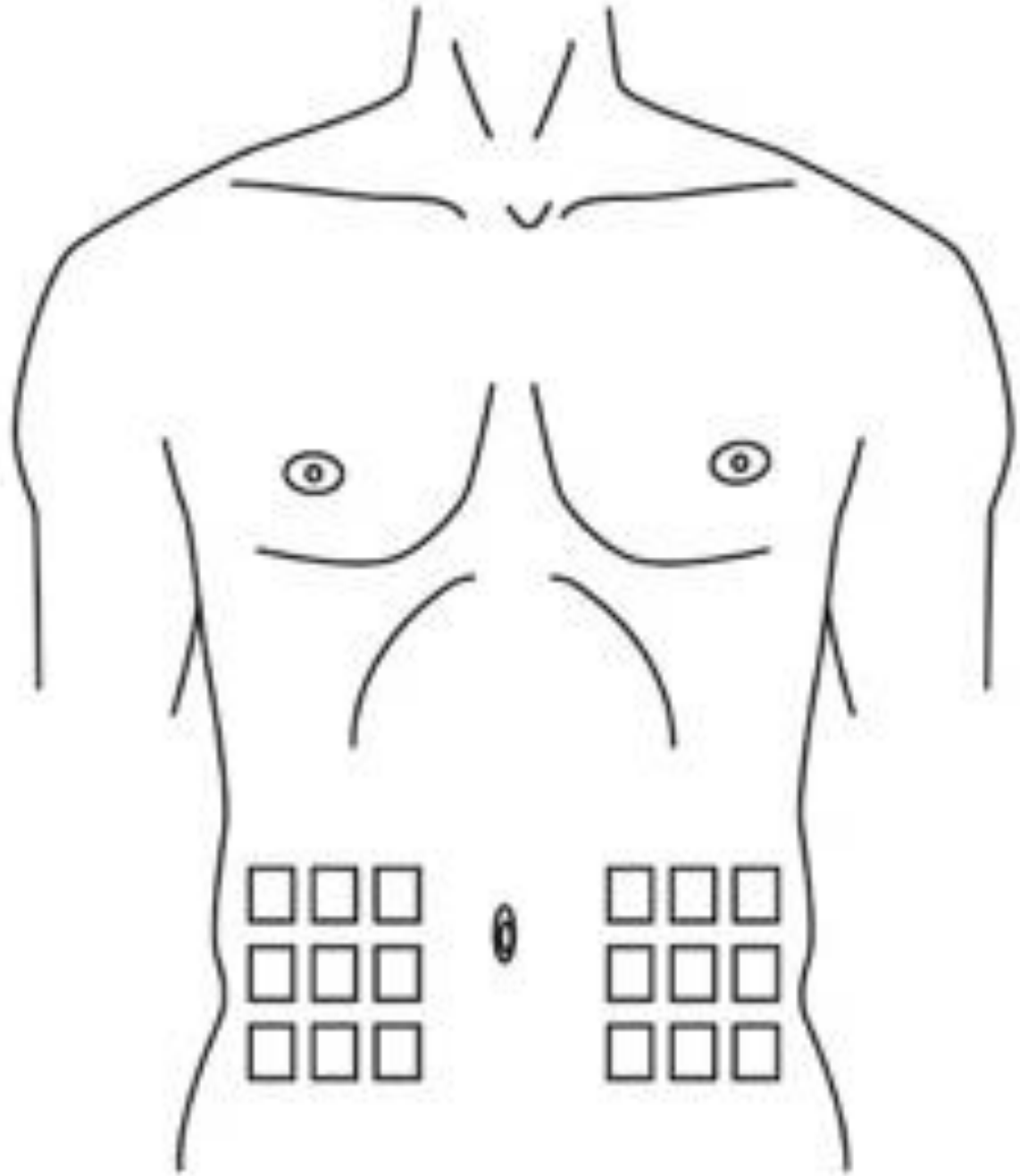
F. Push the plunger, at the top of the syringe, over at least 30 seconds until no FIRAZYR is in the syringe



G. Release the skin fold and gently pull the needle out



HAEGARDA® SC
循環部位注射



Ruconest® IV


RUCONEST™ 2100 U
Powder for solution
for injection
Conestat alfa
For intravenous use.
One vial contains 2100 U of conestat alfa, corresponding to 2100 U/14 ml after reconstitution, or a concentration of 150 U/ml.
Excipients: Sucrose, Sodium citrate (E331), Citric acid (E330).
Do not store above 25°C. Store in the original package in order to protect from light. Keep out of the reach and sight of children.
Medicinal product subject to medical prescription. Read the package leaflet before use.
1 vial.
PHARMING

Lanadelumab（Takhzyro ®）SC

目前台灣可以處方的HAE治療藥物

雄激素(Danazol)，抗纖維蛋白溶解藥和新鮮冷凍血清(FFP)

- 對於急性期遺傳性血管水腫的治療：先給予兩個單位的FFP治療。此劑量可以重複每兩至四個小時，直到有臨床改善。
- 對於短期預防：應避免接觸誘發因子（但是大多發作時並沒有接觸誘發因子），誘發因子包括牙科手術、外科手術和緊張壓力性生活事件。對於短期的預防，我們平時使用Danazol每天200 - 400毫克於接觸誘發因子5-7天前即事件發生後2天。
- 對於長期預防治療：Danazol用量可高達200毫克，每日三次。如果臨床穩定，我們會逐漸將Danazol減少至每兩天200毫克 。Danazol的劑量是根據臨床反應調整，而不是根據C4或其他實驗室測試結果調整。

HAE
短期與長期預防治療

Need for short-term prophylaxis

- May be indicated before medical, surgical, or dental procedures; however, relatively little is known about risk of swelling after these procedures

Need for long-term (routine) prophylaxis

- Factors to consider: attack frequency, attack severity, comorbidities, access to emergent treatment, patient experience and preference

Attenuated Androgens

- Most common agents: Danazol, Stanozolol
- Mechanism
  - Increase levels of aminopeptidase P
    - enzyme that inactivate kinins
  - Increase hepatic production of C1INH

Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities.

Gelfand JA, Sherins RJ, Alling DW, Frank MM

N Engl J Med. 1976;295(26):1444.

Danazol, an androgen derivative, was evaluated for its effectiveness in preventing attacks of hereditary angioedema in a double-blind study with nine patients. Of 47 placebo courses, 44 ended with attacks, but during 46 danazol courses only one attack occurred. Side effects were minimal, and virilization was not observed in the women studied. C1 esterase inhibitor levels increased three to four times, and levels of the fourth component of complement (C4) increased 15 times. These changes began during the first day of therapy and were maximal by one to two weeks. After therapy was stopped, C1 esterase inhibitor and C4 levels rapidly decreased. Danazol effectively prevents attacks in hereditary angioedema and acts to correct the underlying biochemical abnormality.

Adverse Effects of Attenuated Androgens

- Short term (< 2wks) is well tolerated
  - Children can also be treated short term with androgens
- Adverse Effects include
  - Lipid abnormalities, HTN, virilization, weight gain..etc
  - Elevated liver enzymes, if >400mg/daily
  - Rare reports of hepatocellular adenomas/carcinomas with years of use
- Daily dose > 200mg/daily is not recommended
- Contraindications
  - Short term: pregnancy
  - Long term: childhood, pregnancy, lactation, liver disease, nephrotic syndrome, breast or prostate cancer

Take home message

- The clinical manifestations of HAE in Taiwan are not completely match to the literature described.
- The **prevalence** of hereditary angioedema in Taiwan is low (**1:639,000** versus 1:50,000 to 1:150,000) .
- **De novo mutation was 5.56%** (2/36) in Taiwan.
- Persons with low levels or function of C1 INH who were **clinically symptomatic** accounted for only **72.22 %** of the cases in our study, which is far lower than previous reports from other countries(95%).

Take home message

- **Abdominal attack** is the 2nd most common symptom in HAE (93% of patients) in other journal, but abdominal attack in our study is **low**(**34.62%** of patients) in Taiwan.
- **Graves' disease** in one patient with **c.685+1G>T mutation in 4th extron** of C1-INH gene, which is **never reported** previously.

Take home message

- **Parental mosaicism** is a possible explanation for **normal C1 INH plasma concentrations in both parents** despite **clinically apparent HAE in the children**.
- Further studies may be needed to elucidate the **genetic penetrance** of C1 INH deficiency in Taiwan.

感謝您的聆聽!

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