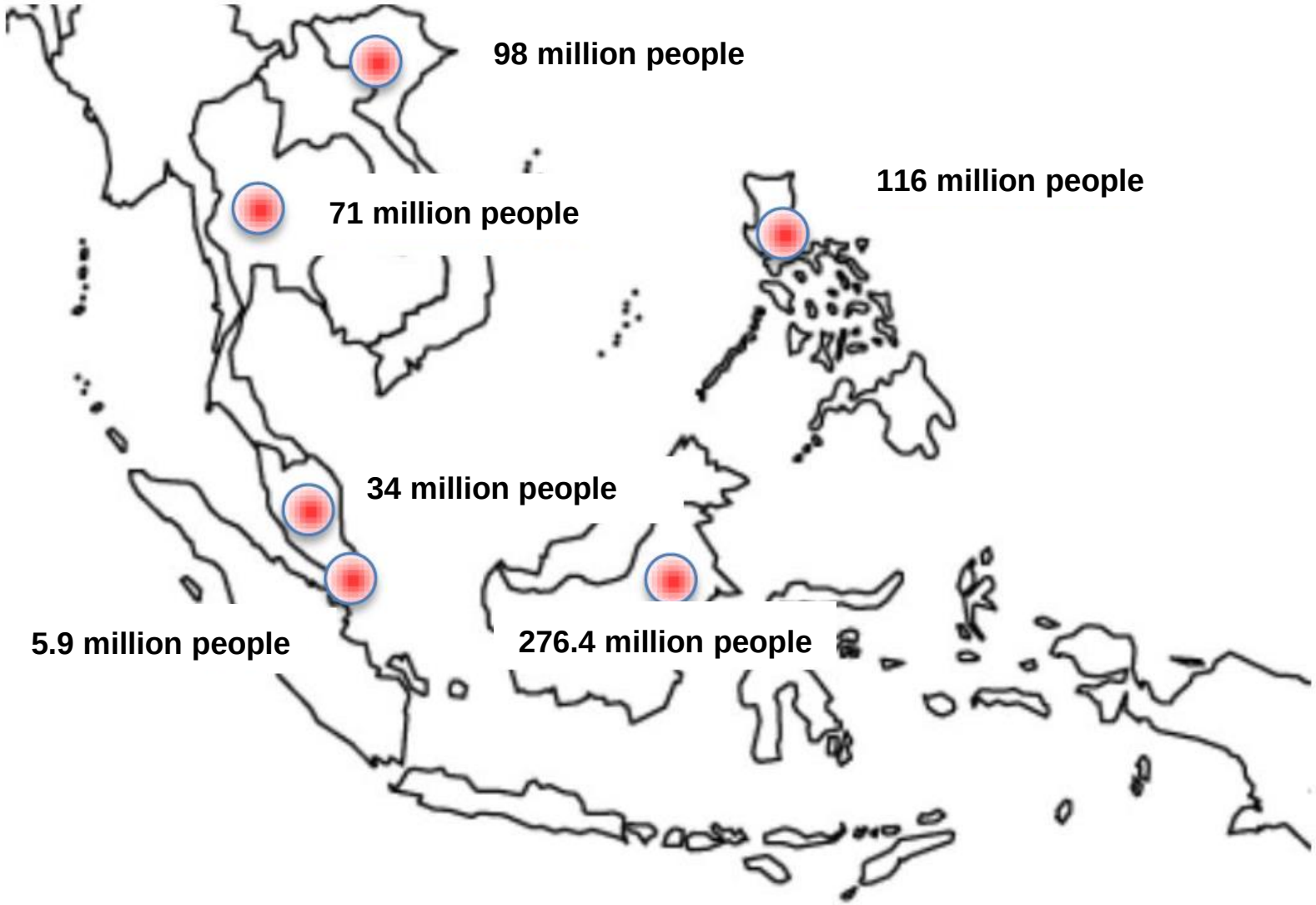
Regional Diagnosis & Clinical Challenges

Narissara Suratannon, MD., PhD. on behalf of

SEAPID
South East Asia Primary Immunodeficiency Network

9th November 2023

Southeast Asia: 600 million population (update 2023)

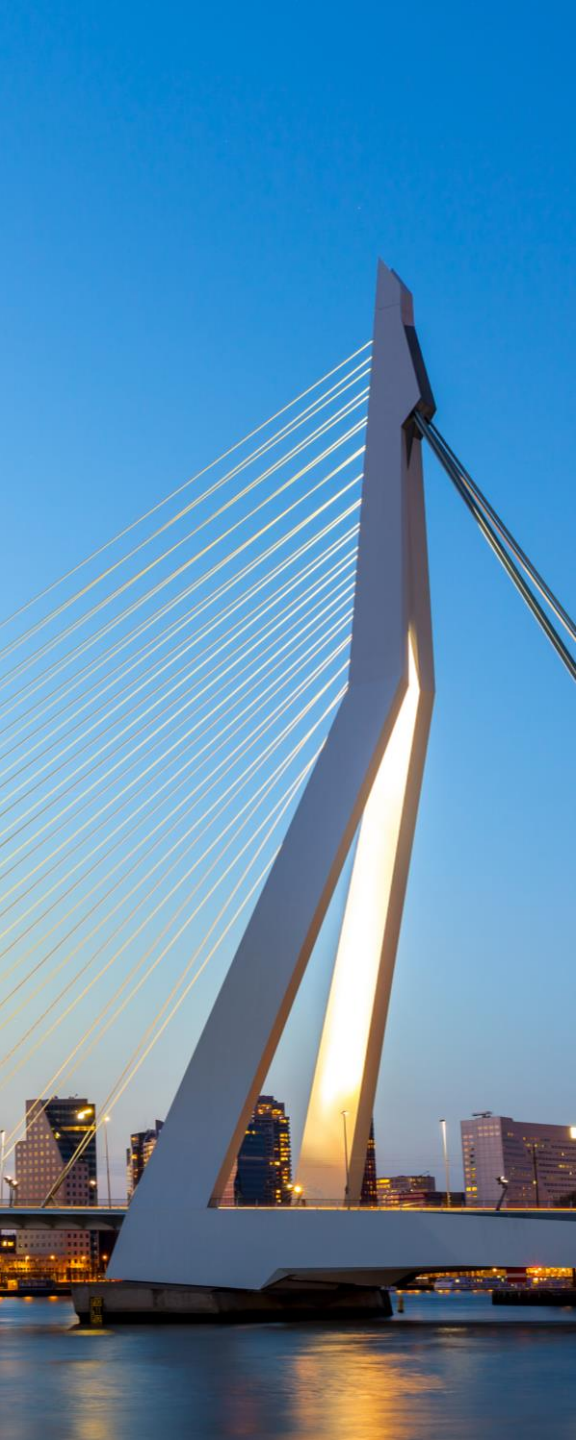


Disease awareness

NGS technology

Networking

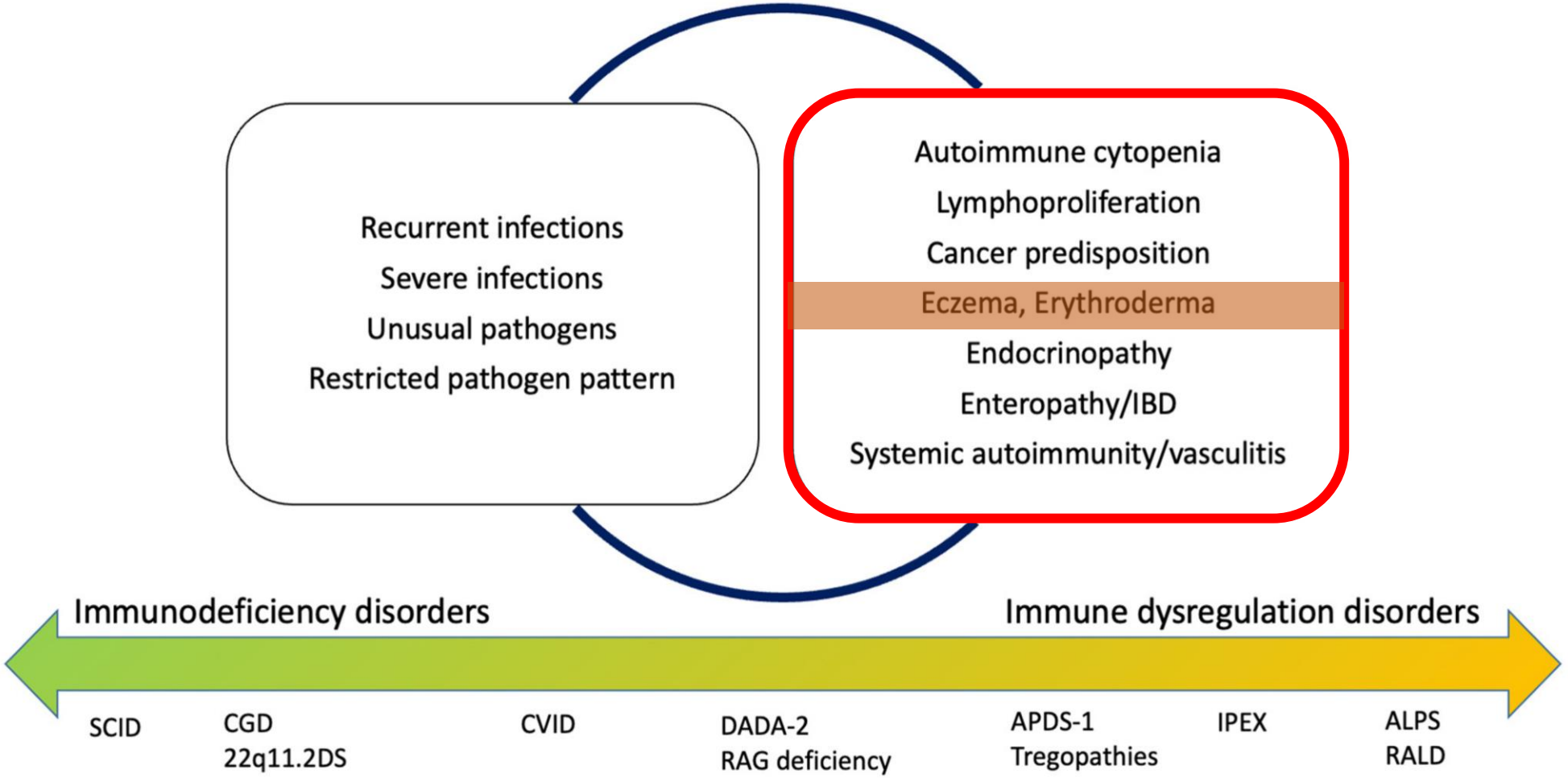
Picture from Flaticon & Linkedin.com



Success:

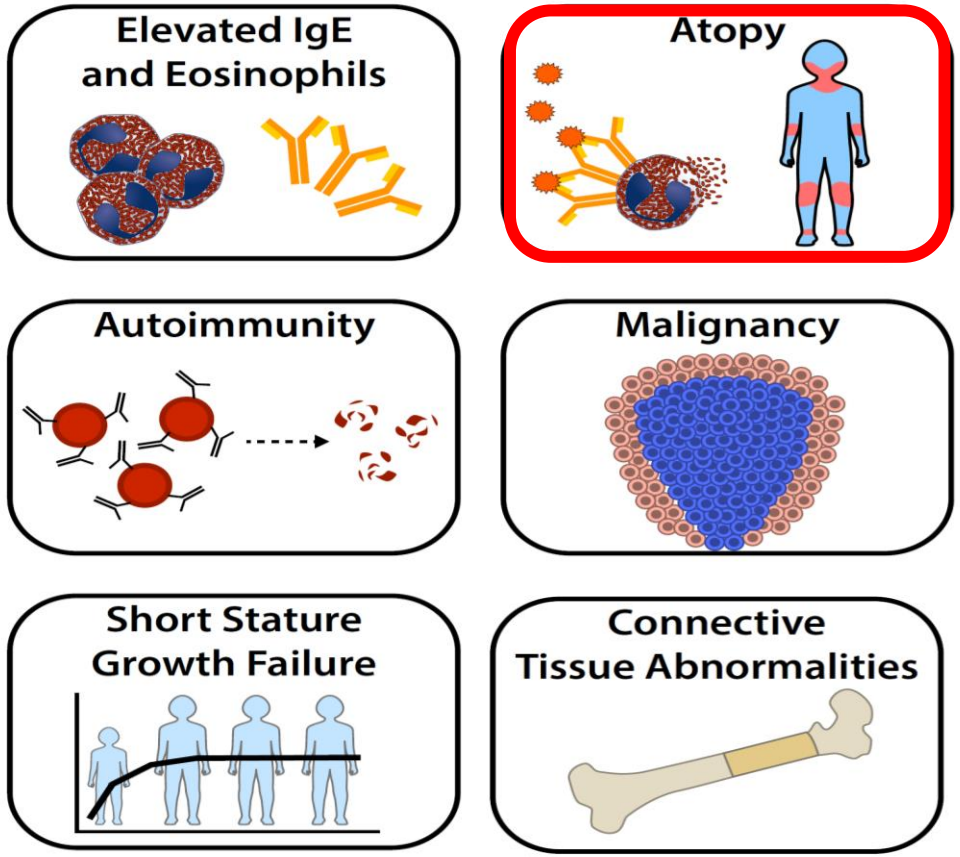
Novel Primary atopic disorders

Beyond Infections: New warning signs of Inborn errors of immunity



Costagliola G, et al. Front. Pediatr 2022. 10:855445.

“Primary atopic disorders”



“No recurrent/severe infection”

Vaseghi-Shanjani et al. JACI 2021;148:1130-9.

The index patient

Six episodes of anaphylaxis with unknown causes

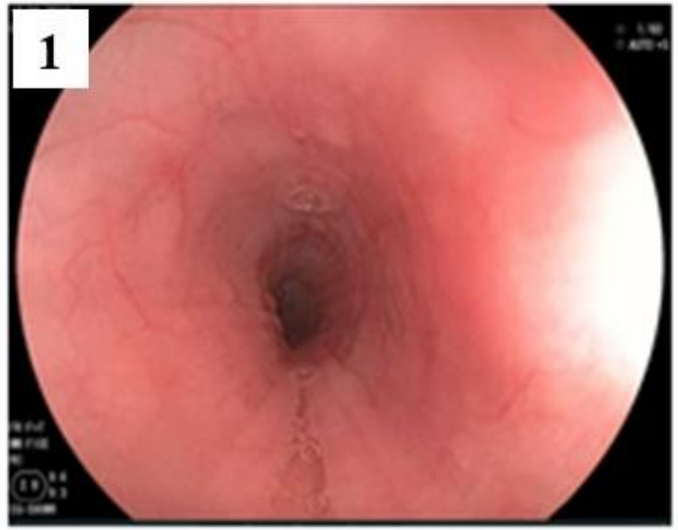
His younger sister

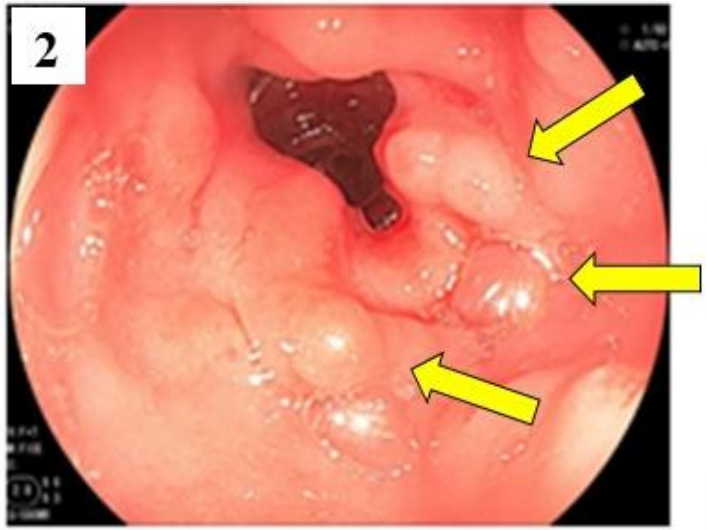
Severe eczema

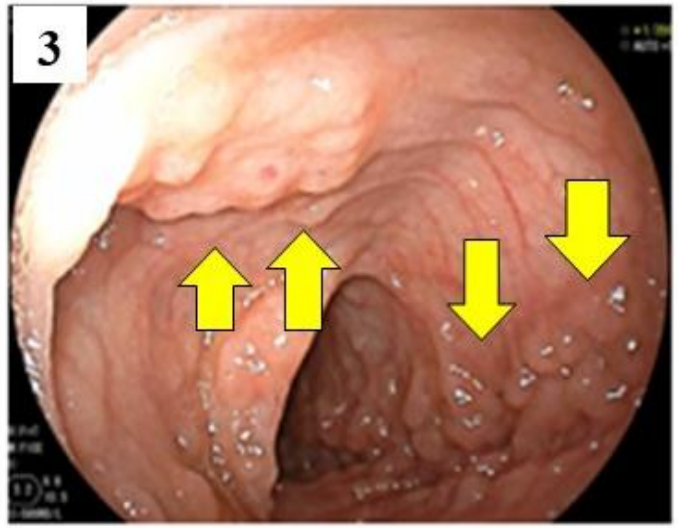
Swelling abdomen (ascites) due to too much fluid leakage in your abdomen, related to food allergies

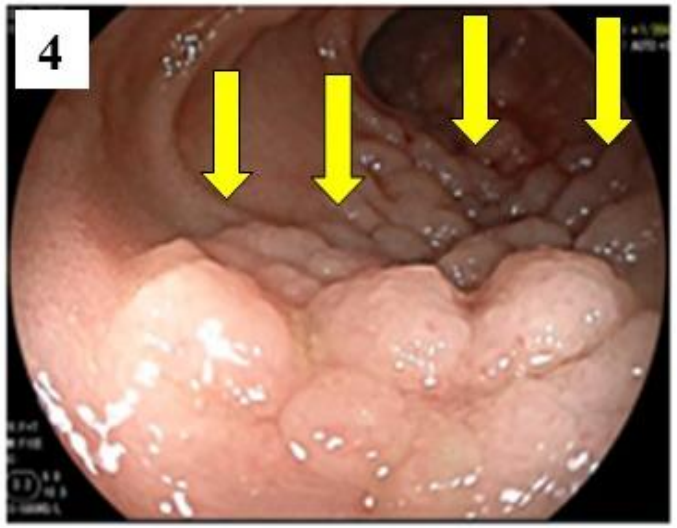
The pictures are shown with the parents' consent

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.







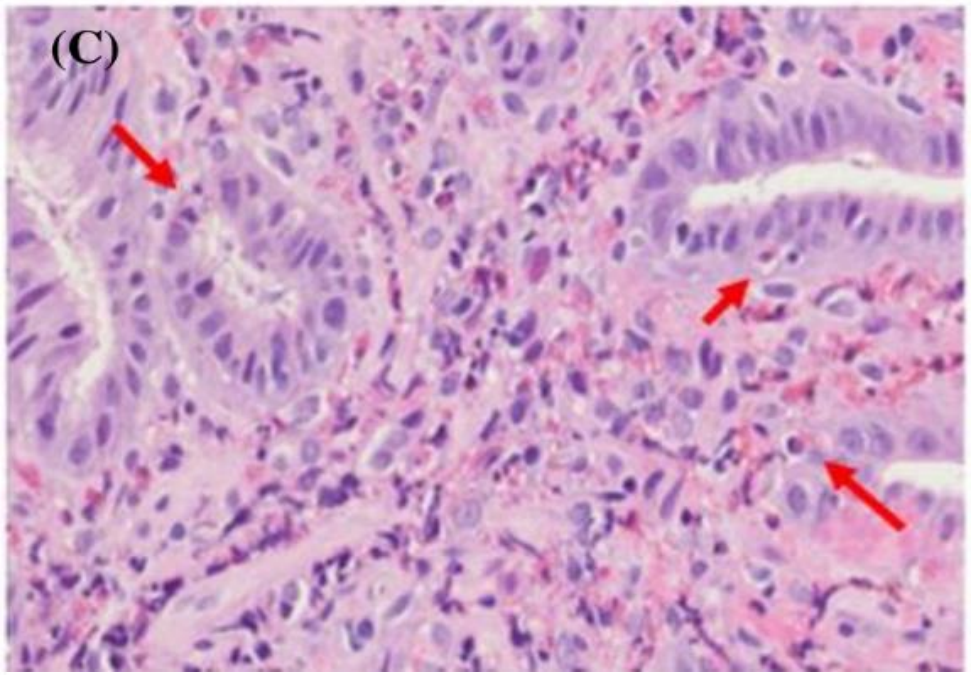


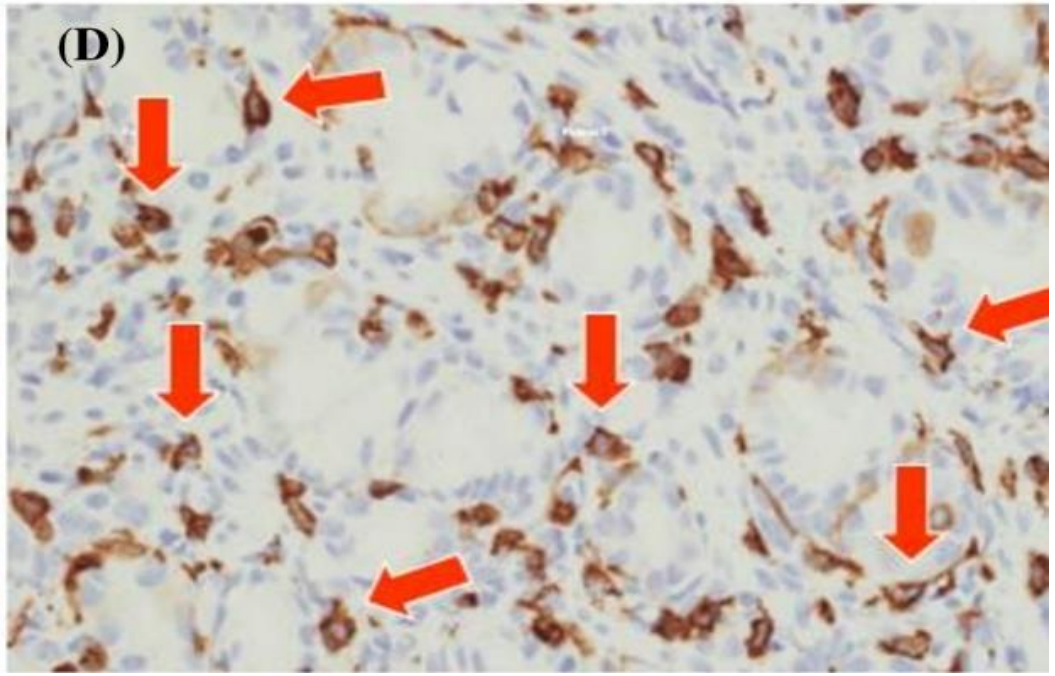
Upper endoscopy shows (1) longitudinal furrows at esophagus

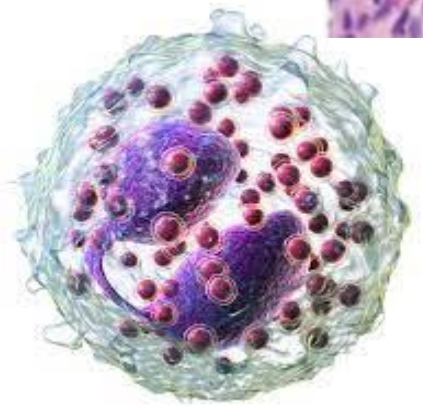
(2) polypoid-like lesions of the antrum (3) transverse colon, and (4) terminal ileum (yellow arrow).

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

Allergic eosinophilic gastroenteritis (AEG) with protein-losing enteropathy



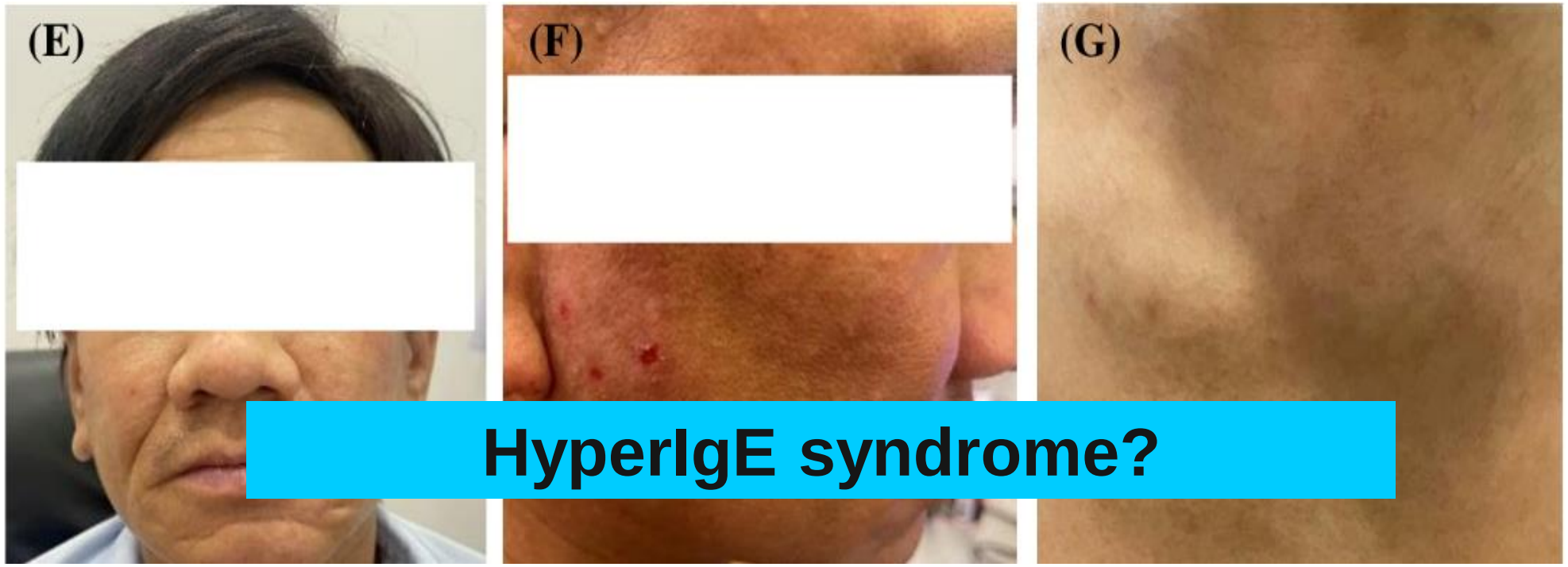




Eosinophilic infiltration in gastric tissues

Mast cells infiltrating gastric mucosa

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.



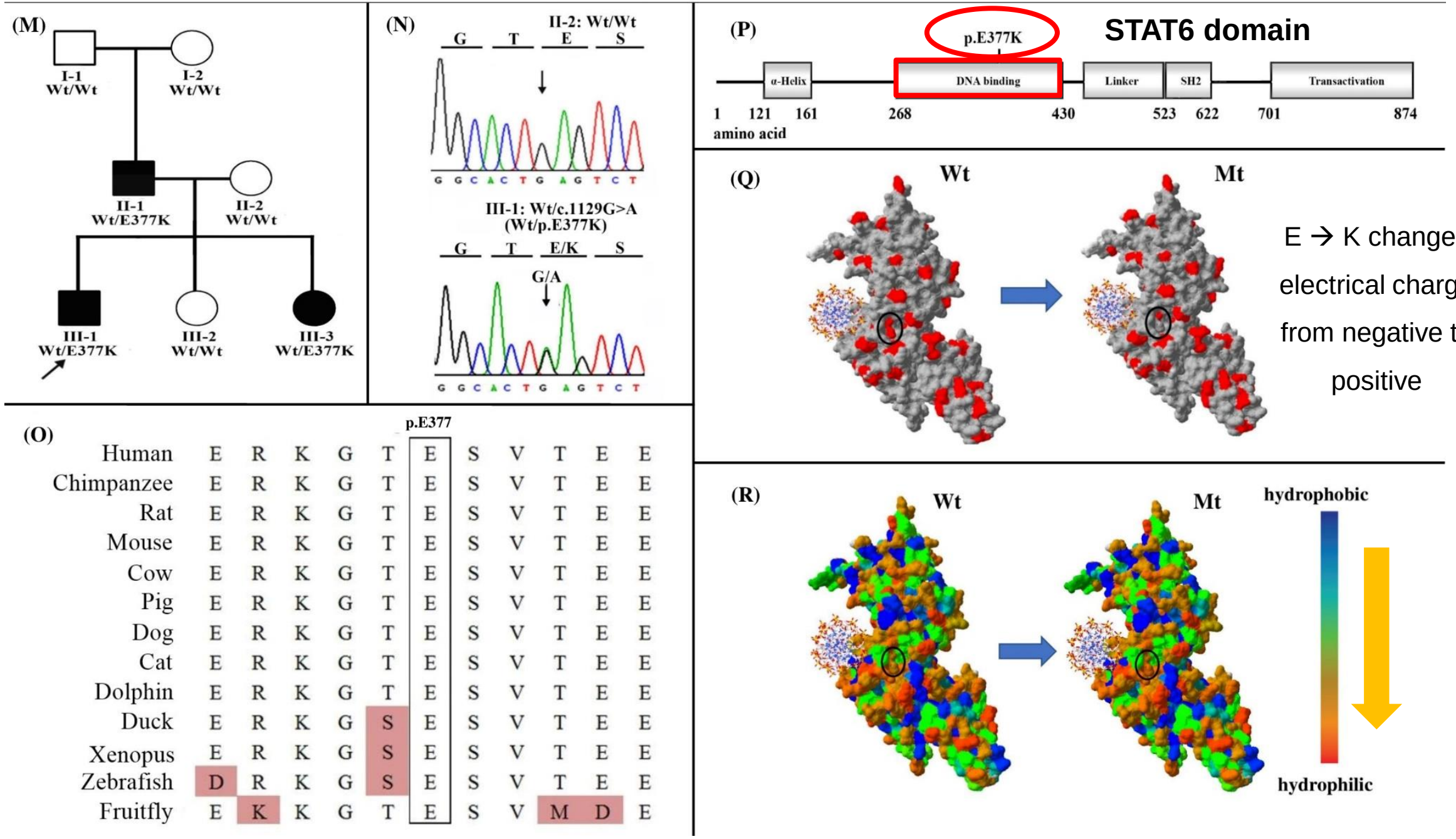
HyperIgE syndrome?

His father:

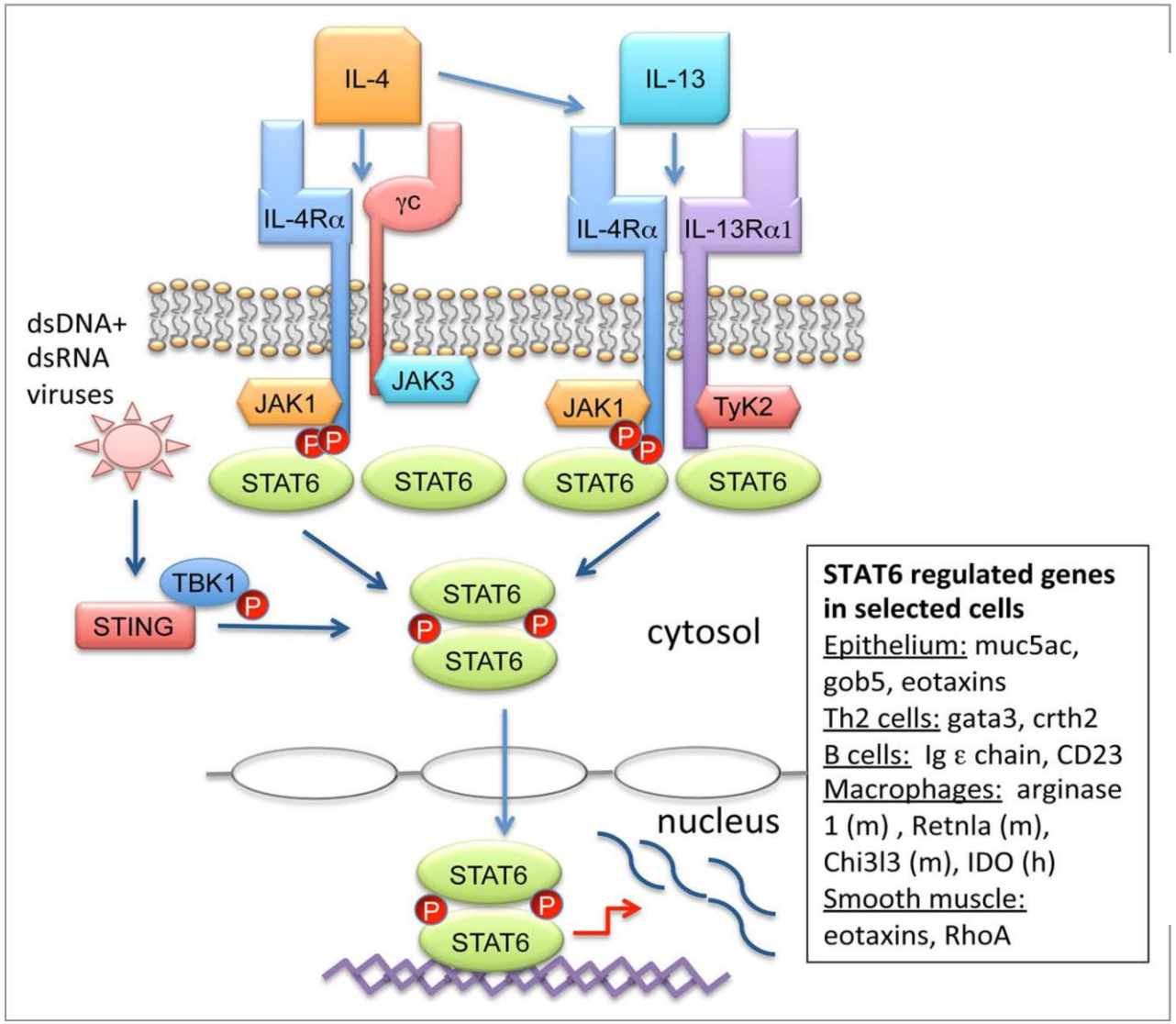
- Multiple food allergies (cow's milk, shrimp, cashew), dry skin, and moderate AD
- Coarse facies and hypotrichosis (lack of hair, axillary hair)
- Chronic renal failure of unknown cause was diagnosed in his adolescent years

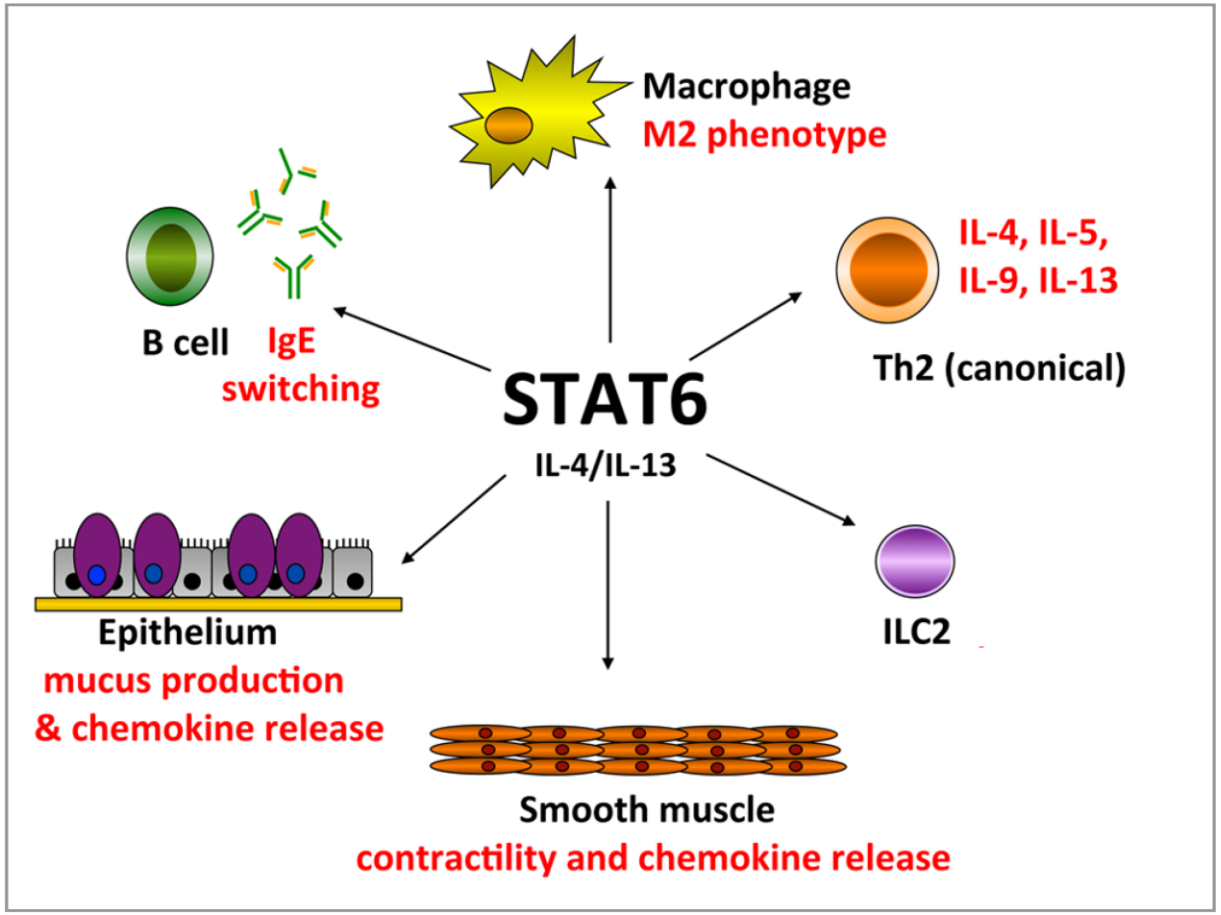
The pictures are shown with patient' consent

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.


(M)
I-1
Wt/Wt
I-2
Wt/Wt
II-1
Wt/E377K
II-2
Wt/Wt
III-1
Wt/E377K
III-2
Wt/Wt
III-3
Wt/E377K
(N)
II-2: Wt/Wt
G T E S
G G C A C T G A G T C T
III-1: Wt/c.1129G>A
(Wt/p.E377K)
G T E/K S
G/A
G G C A C T G A G T C T
(O)
p.E377
Human E R K G T E S V T E E
Chimpanzee E R K G T E S V T E E
Rat E R K G T E S V T E E
Mouse E R K G T E S V T E E
Cow E R K G T E S V T E E
Pig E R K G T E S V T E E
Dog E R K G T E S V T E E
Cat E R K G T E S V T E E
Dolphin E R K G T E S V T E E
Duck E R K G S E S V T E E
Xenopus E R K G S E S V T E E
Zebrafish D R K G S E S V T E E
Fruitfly E K K G T E S V M D E
(P)
p.E377K
STAT6 domain
α-Helix
DNA binding
Linker
SH2
Transactivation
1 121 161 268 430 523 622 701 874
amino acid
(Q)
Wt
Mt
E → K changes electrical charge from negative to positive
(R)
Wt
Mt
hydrophobic
hydrophilic

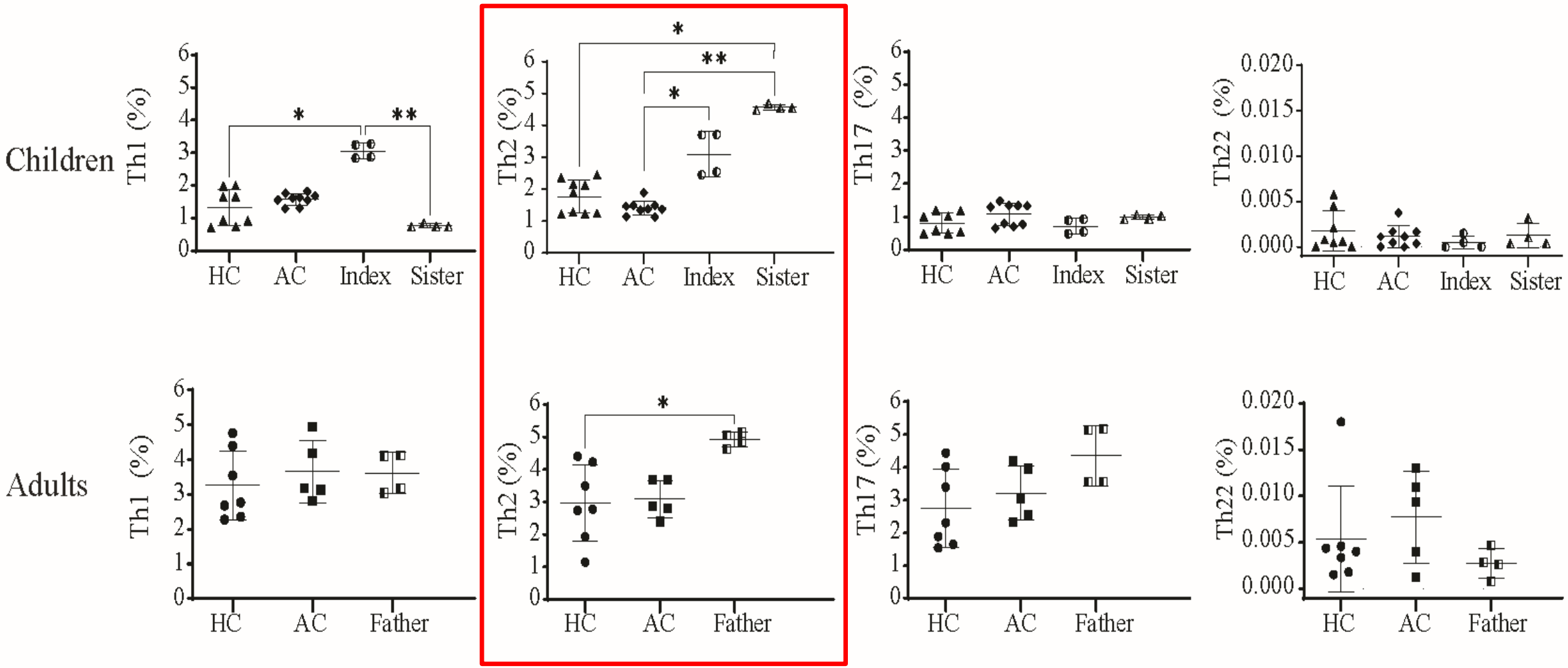
Effector functions mediated by STAT6 in many cell types





Walford et al. JAKSTAT 2013.1;2(4):e25301.

Increase Th2 cells in the index patient, sister and father



HC; age-matched healthy controls, AC; age-matched allergic controls without STAT6 variant

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

"First description of *STAT6* variant in human"

Brief report

A germline *STAT6* gain-of-function variant is associated with early-onset allergies

Narissara Suratannon, MD,[a,j,n] Chupong Ittiwut, PhD,[b,l] Willem A. Dik, PhD,[k,n,q] Rungnapa Ittiwut, PhD,[b,l] Kornvalee Meesilpavikkai, MD, PhD,[c,n] Nipan Israsena, MD, PhD,[d] Praewphan Ingrungruanglert, PhD,[d] Virgil A. S. H. Dalm, MD, PhD,[n,o,q] Paul L. A. van Daele, MD, PhD,[n,o,q] Anapat Sanpavat, MD,[e] Nataruks Chaijitraruch, MD, PhD,[f,m] Benjamin Schrijver, Bsc,[k,n,o,q] Supranee Buranapraditkun, PhD,[g] Thantrira Porntaveetus, PhD,[h] Sigrid M. A. Swagemakers, BS,[p,q,r] Hanna IJspeert, PhD,[k,n,q] Tanapat Palaga, PhD,[c,i] Kanya Suphapeetiporn, MD, PhD,[b,l] Peter J. van der Spek, PhD,[p,q,r] Nattiya Hirankarn, MD, PhD,[c] Pantipa Chatchatee, MD,[a,j] P. Martin van Hagen, MD, PhD,[a,j,n,o,q] and Vorasuk Shotelersuk, MD[b,l]

Bangkok, Thailand, and Rotterdam, The Netherlands

Background: The signal transducer and activator of transcription 6 (STAT6) signaling pathway plays a central role in allergic inflammation. To date, however, there have been no descriptions of

displayed a strong preference for nuclear localization, increased DNA binding affinity, and spontaneous transcriptional activity. Moreover, gastric organoids showed constitutive activation of

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

Brief report

STAT6 gain-of-function variant exacerbates multiple allergic symptoms

Ichiro Takeuchi, MD,[a,b]* Kumiko Yanagi, DDSc, PhD,[c]* Shuji Takada, PhD,[d] Toru Uchiyama, MD, PhD,[e] Arisa Igarashi, PhD,[c,f] Kenichiro Motomura, MD, PhD,[f] Yuka Hayashi, MD,[f] Naoko Nagano, MD,[f] Ryo Matsuoka, MD, Hiroki Sugiyama, MD,[f] Takako Yoshioka, MD, PhD,[g] Hirohisa Saito, MD, PhD,[f] Toshinao Kawai, MD, PhD,[e] Yumiko Miyaji, MD, PhD,[h] Yusuke Inuzuka, MD,[h] Yoichi Matsubara, MD, PhD,[i] Yukihiro Ohya, MD, PhD,[h] Toshiaki Shimizu, MD, PhD,[b] Kenji Matsumoto, MD, PhD,[f] Katsuhiro Arai, MD, PhD,[a,h] Ichiro Nomura, MD, PhD,[h,j] Tadashi Kaname, MD, PhD,[c] and Hideaki Morita, MD, PhD[f,h] *Tokyo, Japan*

Severe allergic dysregulation due to a gain of function mutation in the transcription factor STAT6

Safa Baris, MD,[a,b,c]* Mehdi Benamar, PhD,[d,e]* Qian Chen, PhD,[d,e] Mehmet Cihangir Catak, MSc,[a,b,c] Mónica Martínez-Blanco, PhD,[d,e] Muyun Wang, BA,[d,e] Jason Fong, BSc,[d,e] Michel J. Massaad, PhD,[f,g] Asena Pinar Sefer, MD,[a,b,c] Altan Kara, PhD,[h] Royala Babayeva, MD,[a,b,c] Sevgi Bilgic Eltan, MD,[a,b,c] Ayse Deniz Yucelten, MD,[i] Emine Bozkurtlar, MD,[j] Leyla Cinel, MD,[j] Elif Karakoc-Aydiner, MD,[a,b,c] Yumei Zheng, PhD,[k,l] Hao Wu, PhD,[k,l] Ahmet Ozen, MD,[a,b,c] Klaus Schmitz-Abe, PhD,[d,e,m] and Talal A. Chatila, MD, MSc[d,e] *Istanbul and Gebze, Turkey; Boston, Mass; and Beirut, Lebanon*

Human germline heterozygous gain-of-function *STAT6* variants cause severe allergic disease

Mehul Sharma[1*], Daniel Leung[2*], Mana Momenilandi[3,4*], Lauren C.W. Jones[1**], Lucia Pacillo[5,6,7**], Alyssa E. James[8**], Jill R. Murrell[9**], Selket Delafontaine[10,11**], Jesmeen Maimaris[12,13**], Maryam Vaseghi-Shanjani[1**], Kate L. Del Bel[1**], Henry Y. Lu[14,15,16**], Gilbert T. Chua[2,17], Silvia Di Cesare[5,7], Oriol Fornes[18,19], Zhongyi Liu[2], Gigliola Di Matteo[6,7], Maggie P. Fu[20,21], Donato Amodio[6], Issan Yee San Tam[2], Gavin Shueng Wai Chan[22], Ashish A. Sharma[23], Joshua Dalmann[1], Robin van der Lee[18,19], Géraldine Blanchard-Rohner[1,24], Susan Lin[1], Quentin Philippot[3,4], Phillip A. Richmond[1,18], Jessica J. Lee[18,25], Allison Matthews[18,26], Michael Seear[1], Alexandra K. Turvey[1], Rachael L. Philips[27], Terri F. Brown-Whitehorn[28], Christopher J. Gray[29], Kosuke Izumi[29], James R. Treat[30], Kathleen H. Wood[9], Justin Lack[31], Asya Khleborodova[31], Julie E. Niemela[32], Xingtian Yang[2], Rui Liang[2], Lin Kui[2,33], Christina Sze Man Wong[34], Grace Wing Kit Poon[35], Alexander Hoischen[36], Caspar I. van der Made[36], Jing Yang[2], Koon Wing Chan[2], Jaime Sou Da Rosa Duque[2], Pamela Pui Wah Lee[2], Marco Hok Kung Ho[2,37], Brian Hon Yin Chung[2], Huong Thi Minh Le[38], Wanling Yang[2], Pejman Rohani[39], Ali Fouladvand[40], Hassan Rokni-Zadeh[41], Majid Changi-Ashtiani[42], Mohammad Miryounesi[43], Anne Puel[3,4,60], Mohammad Shahrooei[44], Andrea Finocchi[5,7], Paolo Rossi[5,45], Beatrice Rivalta[5,6,7], Cristina Cifaldi[7], Antonio Novelli[46], Chiara Passarelli[46], Stefania Arasi[47], Dominique Bullens[48,49], Kate Sauer[50,51], Tania Claeys[52], Catherine M. Biggs[1], Emma C. Morris[12,13], Sergio D. Rosenzweig[32], John J. O'Shea[27], Wyeth W. Wasserman[18], H. Melanie Bedford[26,53], Clara D.M. van Karnebeek[18,54], Paolo Palma[5,6], Siobhan O. Burns[12,13***], Isabelle Meyts[10,11***], Jean-Laurent Casanova[3,4,55,56,60***], Jonathan J. Lyons[8***], Nima Parvaneh[57***], Anh Thi Van Nguyen[58***], Caterina Cancrini[5,7***], Jennifer Heimall[28***], Hanan Ahmed[59***], Margaret L. McKinnon[19***], Yu Lung Lau[2****], Vivien Béziat[3,4,60****], and Stuart E. Turvey[1****]

Journal of Clinical Immunology (2023) 43:1611–1622
https://doi.org/10.1007/s10875-023-01530-7

ORIGINAL ARTICLE

Autosomal Dominant STAT6 Gain of Function Causes Severe Atopy Associated with Lymphoma

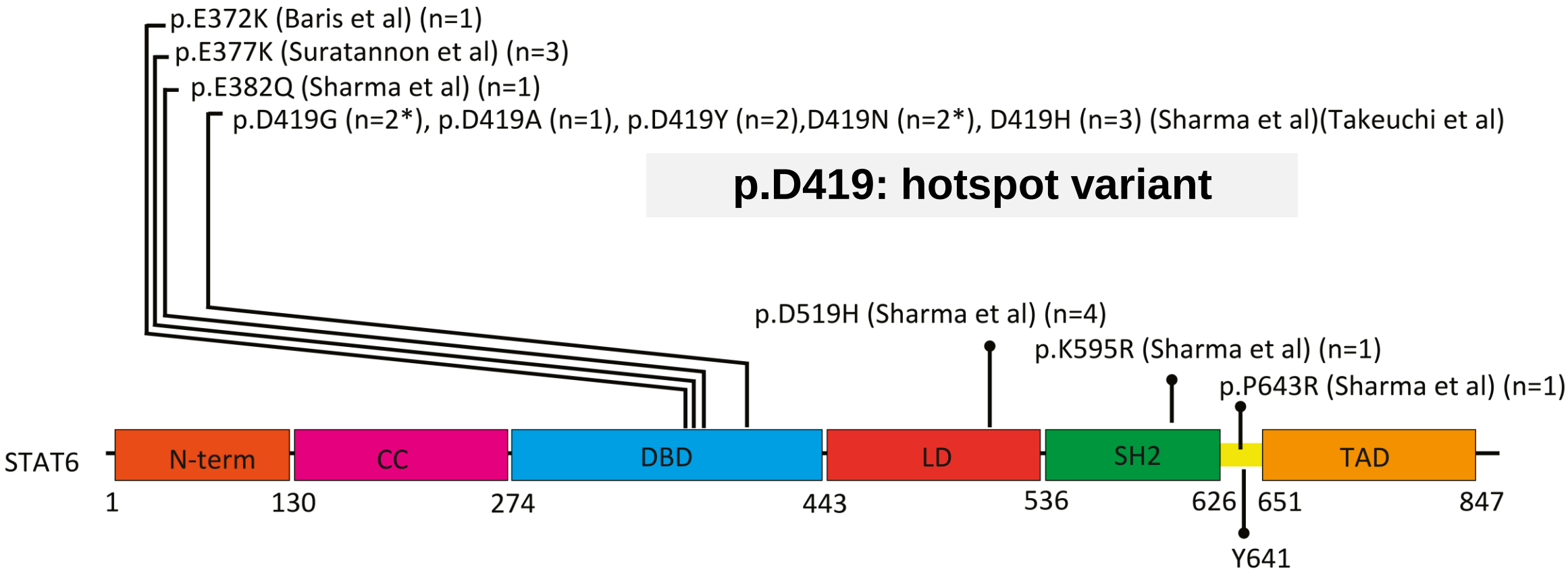
Ekaterina Minskaia[1] · Jesmeen Maimaris[1,2] · Persephone Jenkins[1] · Adriana S. Albuquerque[1] · Ying Hong[3] · Despina Eleftheriou[3,4] · Kimberly C. Gilmour[5] · Richard Grace[6] · Fernando Moreira[2] · Bodo Grimbacher[7] · NIHR Bioresource-Rare Diseases Consortium · Emma C. Morris[1,2] · Siobhan O. Burns[1,2]

Baris S, JACI 2023 Feb 8., Takeuchi I, JACI 2023;151:1402-9.e6.

Sharma et al. J. Exp. Med. 2023 Vol. 220 No. 5 e20221755.

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

21 affected patients from 13 families were reported worldwide



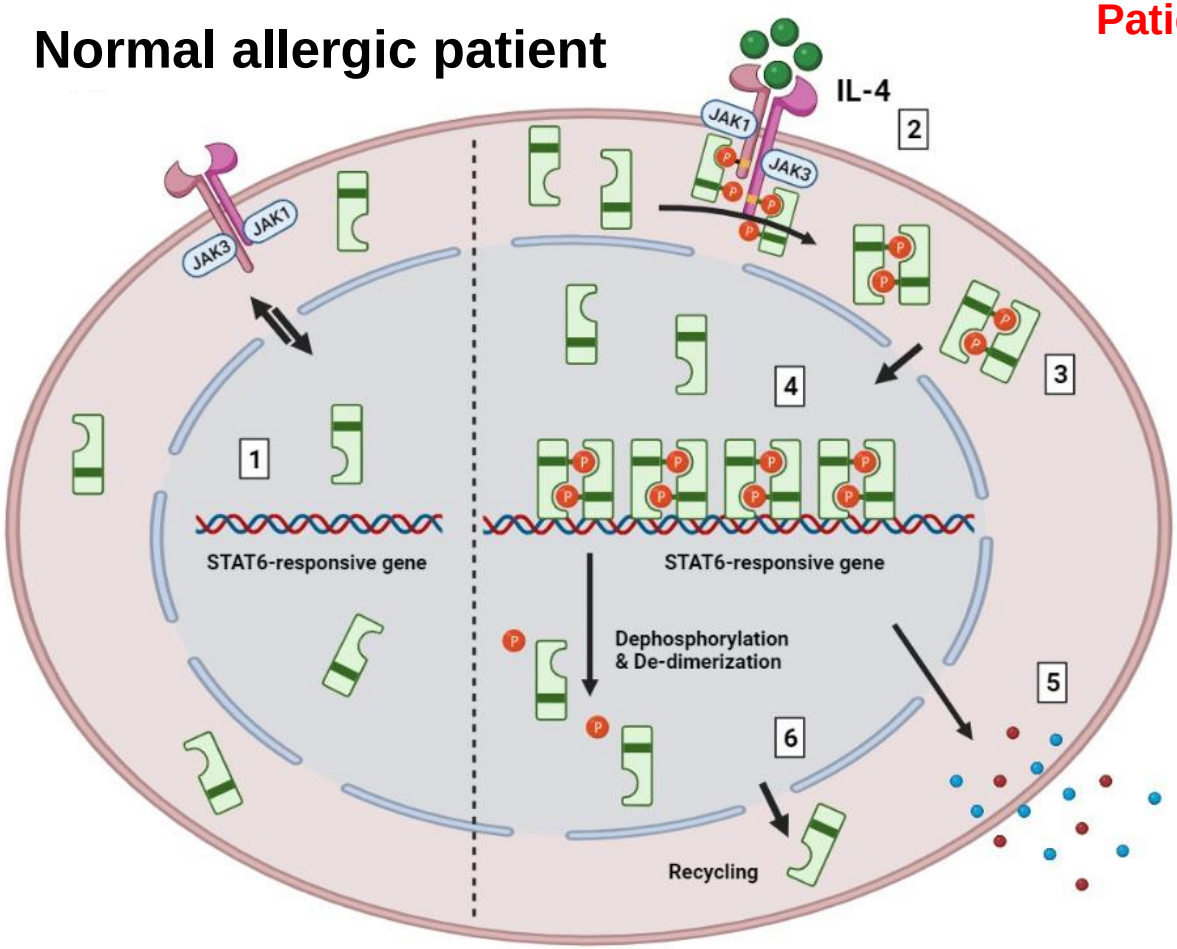
Baris S, JACI 2023 Feb 8., Takeuchi I, JACI 2023;151:1402-9.e6.

Sharma et al. J. Exp. Med. 2023 Vol. 220 No. 5 e20221755.

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

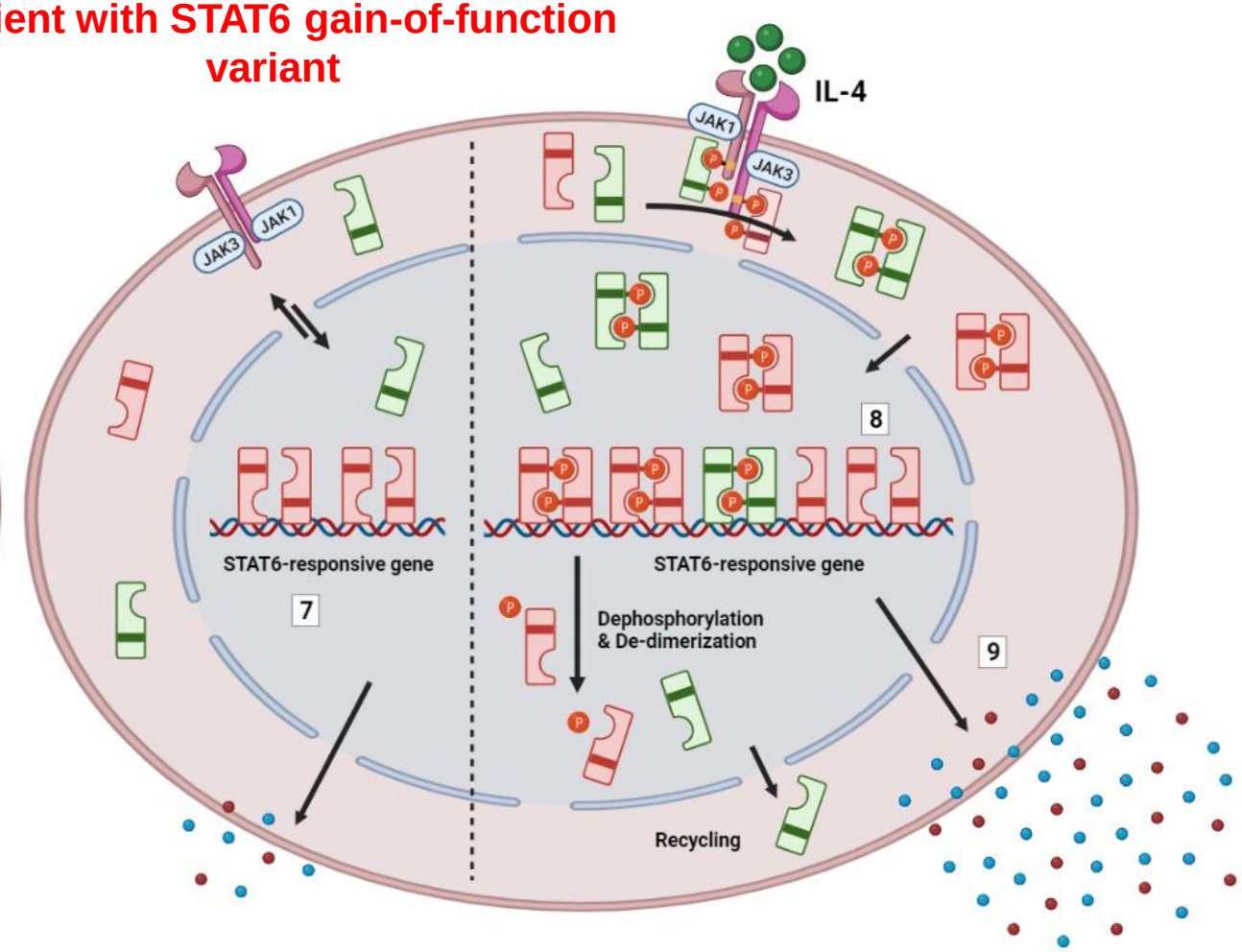
Chen et al. JACI 2023 May 14;S0091-6749(23)00593-6.

Normal allergic patient



Normal allergic response

Patient with STAT6 gain-of-function variant



Persistent and exaggerated allergic inflammation

↑ *XBP1, EPS1, BCL6, CISH, IL4R in* T cell ↑ IL-4 producing TH lymphocytes

↑ STAT-6 related molecules (eotaxin-1, 2, 3, MCP-1)

↑ TH2, TH2-like TFH, TH2-like Tregs, IgE-secreting B lymphocytes B cell IgE IgE

↑ fibrosis- and GC formation-related molecules

↑ Eosinophil

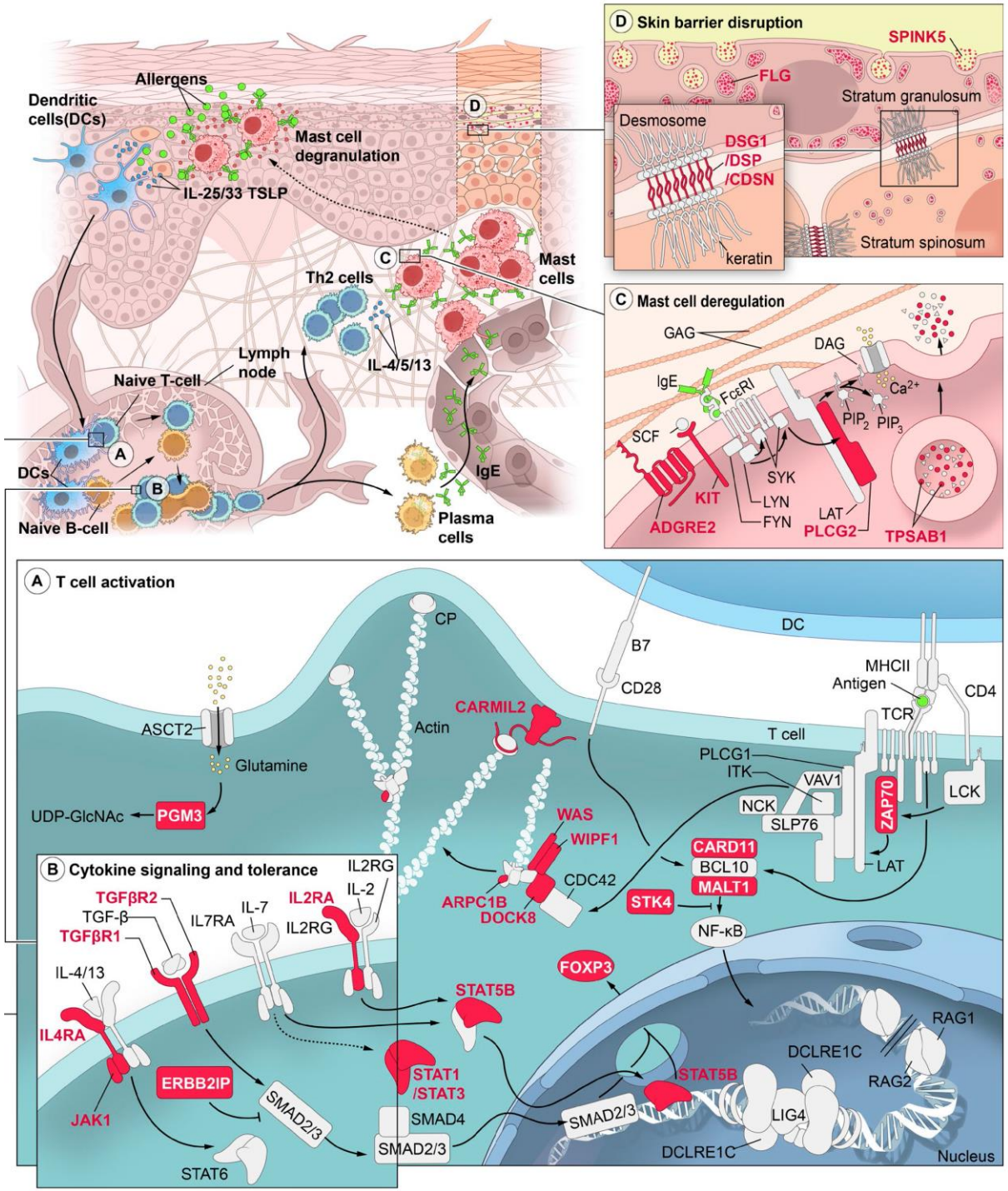
Baris S, JACI 2023 Feb 8., Takeuchi I, JACI 2023;151:1402-9.e6.

Sharma et al. J. Exp. Med. 2023 Vol. 220 No. 5 e20221755.

Suratannon N, et al. JACI 2022.7;S0091-6749(22)01334-3.

Key pathways and molecules involved in monogenic and polygenic allergic diseases

J Allergy Clin Immunol Pract 2022;10:1737-56.



Lyon et al. J. Exp. Med. 2018 Vol. 215 No. 4. 100

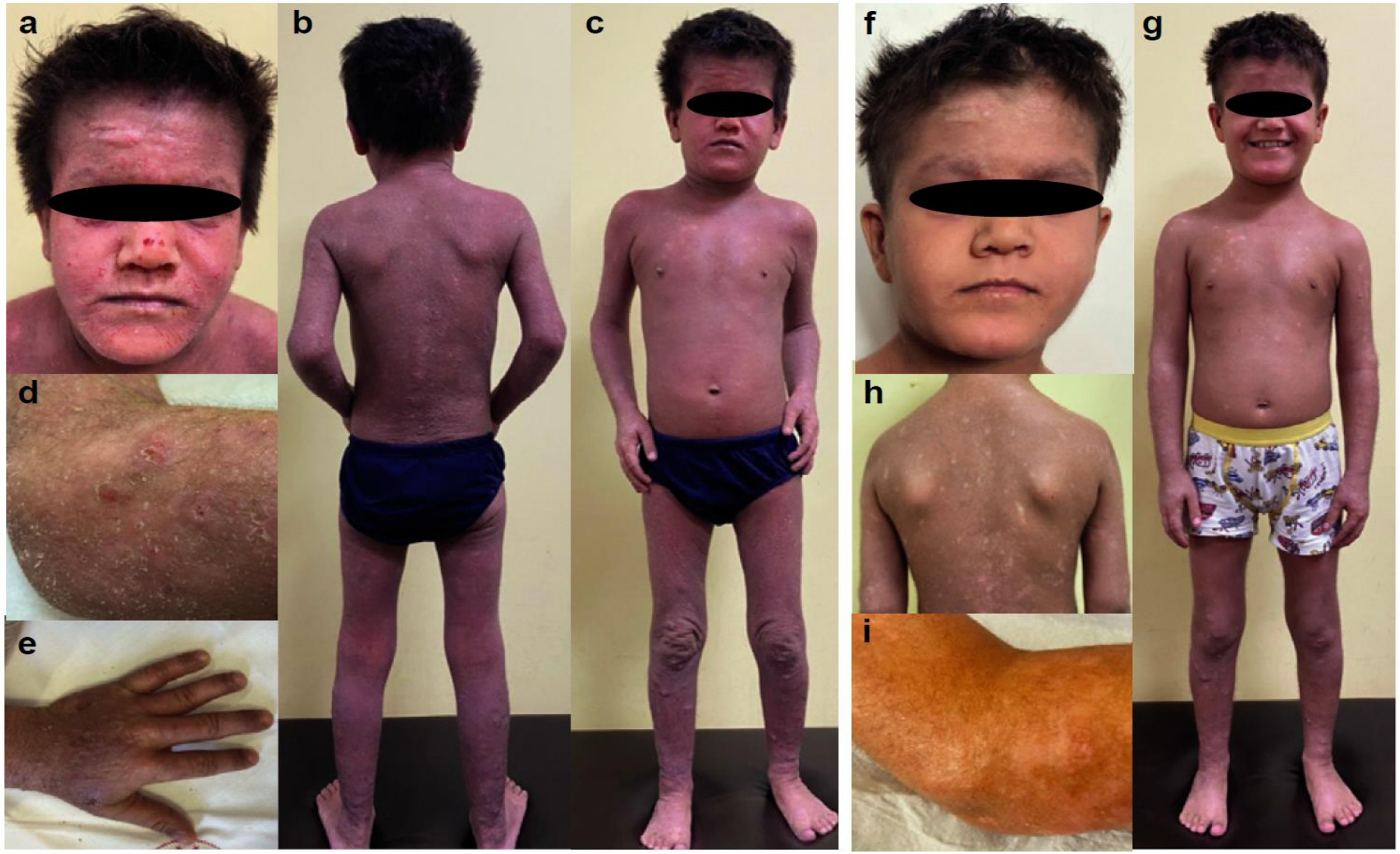
What’s the matter to identify allergic patients with mendelian inheritance?

The patients with *STAT6* GOF variants after IL-4Rα antibody

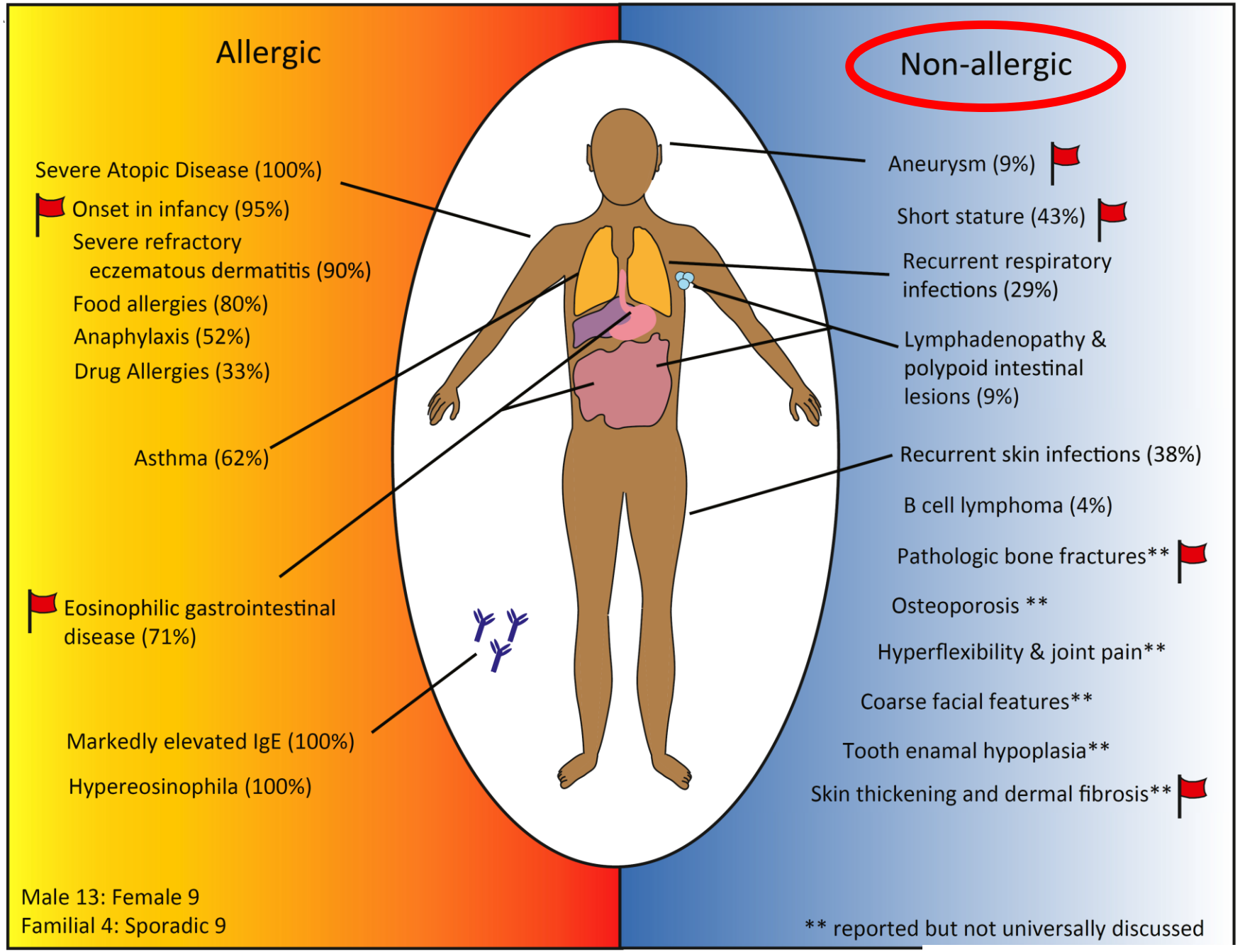
Sharma et al. J. Exp. Med. 2023 Vol. 220 No. 5 e20221755.

Before Ruxolitinib

On Ruxolitinib



Baris et al. J Allergy Clin Immunol 2023.



Chen et al. JACI 2023 May 14;S0091-6749(23)00593-6.

Extra-allergy manifestations

- A patient from Sharma et al. had recurrent B-cell lymphomas.

- Baris et al. noted significant lymphadenopathy in the patient.

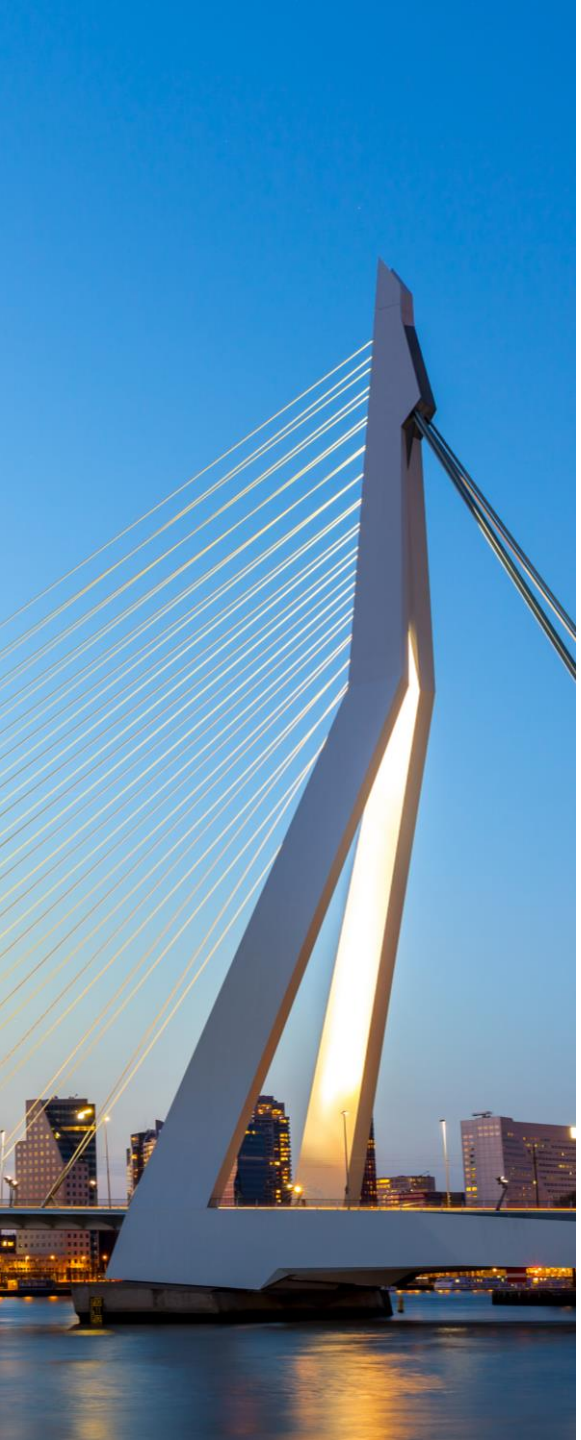
Baris S, JACI 2023 Feb 8.

Sharma et al. J. Exp. Med. 2023 Vol. 220 No. 5 e20221755.

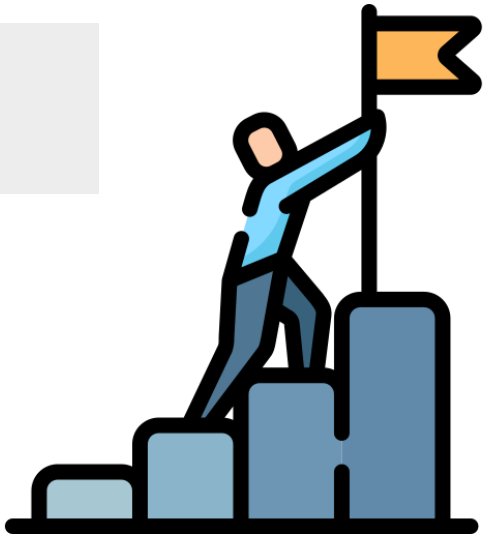
Conclusion:

- **Treatment-refractory early onset allergies (AD, eosinophilic gastroenteritis): key factors to investigate for the monogenic atopic disorders**

- **Different long-term follow-up and early-targeted therapies might be considered.**



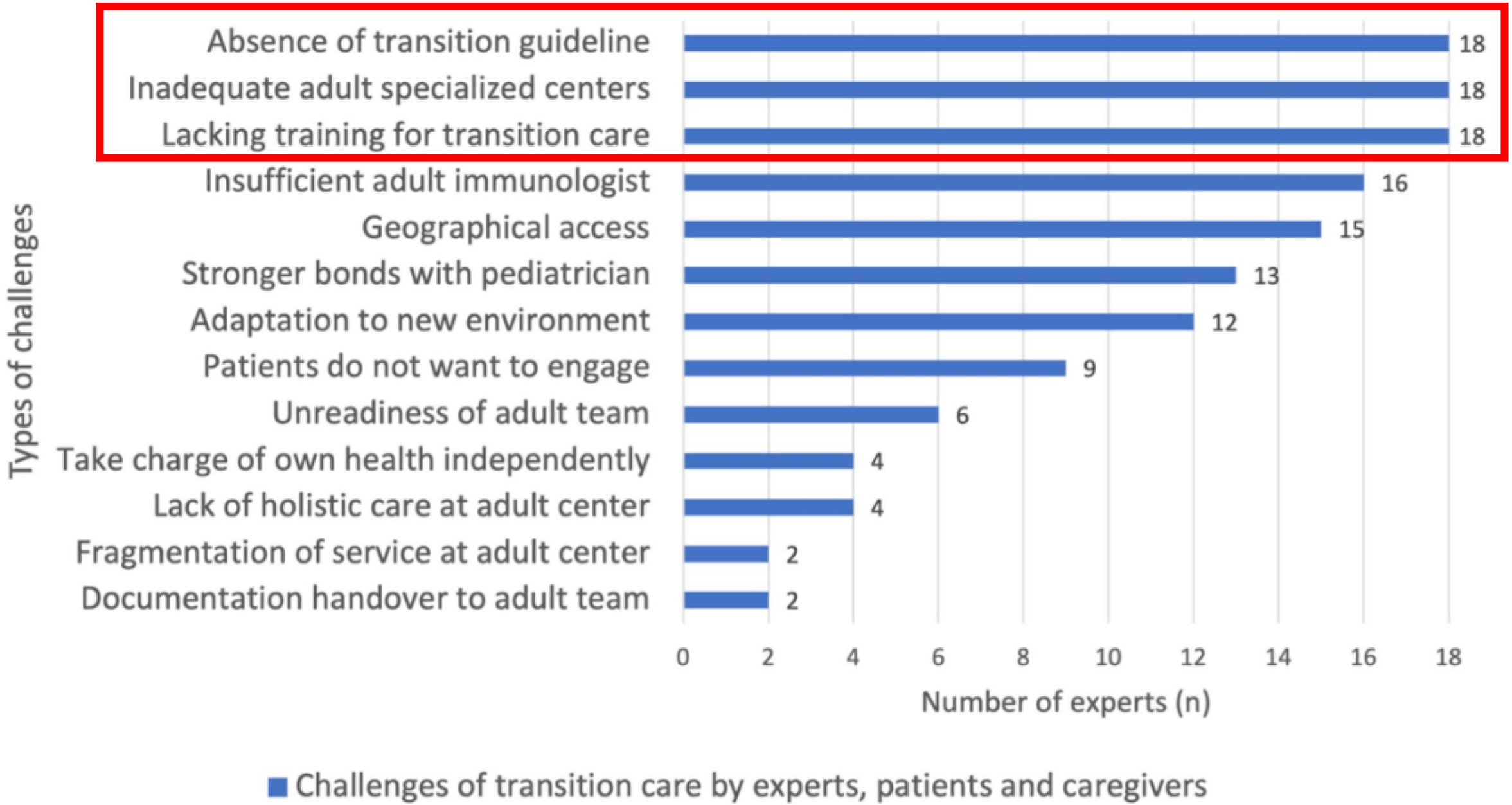
Challenge



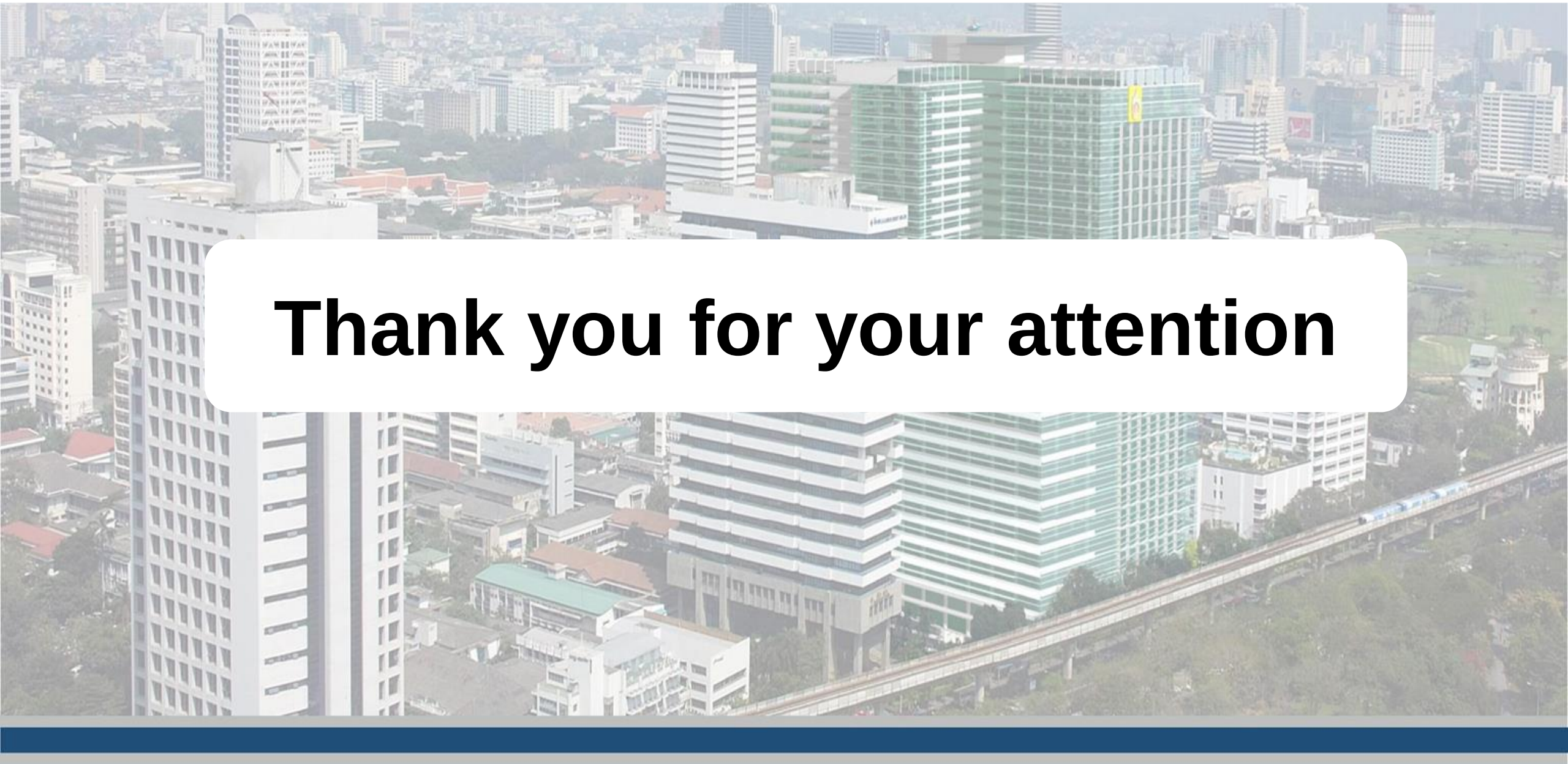
Transition practice for primary immunodeficiency diseases in Southeast Asia: a regional survey

Chee Mun Chan[1,2], Amir Hamzah Abdul Latiff[3], Lokman Mohd Noh[4], Intan Hakimah Ismail[5], Intan Juliana Abd Hamid[6], Woei Kang Liew[7], Youjia Zhong[8], Narissara Suratannon[9], Rapisa Nantanee[9,10], Fatima Johanna Santos-Ocampo[11], Mary Anne R. Castor[12], Le Nguyen-Ngoc-Quynh[13], Anh Thi Van Nguyen[14], Huyen Thanh Thuc[15], Nguyen Minh Tuan[16], Dina Muktiarti[17], Rizqi Amalia[17], Sophâl Chean[18], Lytheang Try[18] and Adli Ali[1,2,19,20]* on behalf of the South East Asia Primary Immunodeficiencies (SEAPID) Consortium

Chan CM, et al. Front. Immunol 2023. 14:1209315.



Chan CM, et al. Front. Immunol 2023. 14:1209315.



Thank you for your attention