

 YU LUNG LAU

Inborn Errors of Immunity – Beyond the Laboratory

LAU YU LUNG 劉宇隆

Department of Paediatrics & Adolescent Medicine
The University of Hong Kong

Never-ending Journey



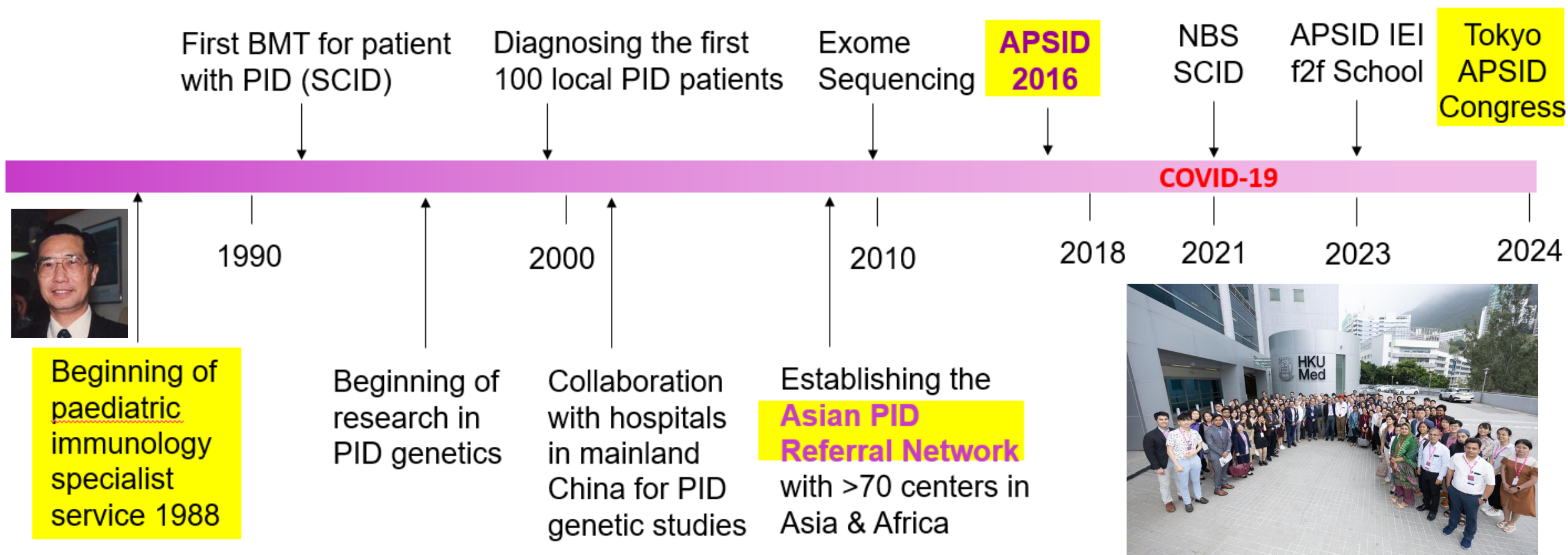
Croucher Summer Course 2024

All of us Be Linked Effectively (ABLE)

- To recognise and refer suspected IEI
- To evaluate undiagnosed IEI phenotypically and immunologically
- To identify potential disease-causing candidate genetic variants with bioinformatic pipeline
- To demonstrate causality of genetic variants with human cells and animal models
- To define disease mechanisms leading to target therapy
- To translate findings to treatment beyond IEI



PID Care & Research in Hong Kong – Historical Development



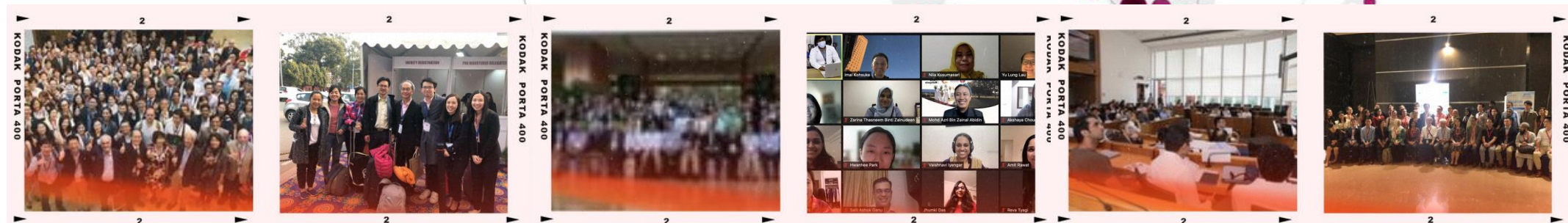


Leung, Chua et al. Front Immunol 2020

Asia Pacific Society for Immunodeficiencies



Tolerance to Balance
Creativity from Diversity



Current Perspectives and Unmet Needs of Primary Immunodeficiency Care in Asia Pacific

HDI	Diagnostics	Therapeutics
Medium	1. CBC 2. IgG/A/M/E 3. Lymphocyte subset (CD3, CD4, CD8, CD19/20, and CD16/56) 4. NBT test or DHR test 5. C3, C4, CH50, and AH50 6. Functional antibody response to tetanus, polio, and hepatitis B vaccine 7. Sanger sequencing for <i>BTK</i>, <i>WAS</i>, <i>IL2RG</i>, and <i>CYBB</i>	1. Antimicrobials 2. IVIG
High	1. Naive and memory T cell marker CD45RO/RA 2. TREC qPCR 3. Lymphocyte proliferation test 4. NK cytotoxicity study 5. C1 esterase inhibitor level and function 6. Targeted PID NGS panel 7. WES	1. Commonly used biologics 2. HSCT 3. SCIG
Very high	1. Comprehensive T or B cell subset with markers other than those mentioned (CD3, CD4, CD8, CD19/20, CD16/56, CD45RO/RA) 2. Protein expression of PID genes (e.g., WASP, BTK, CD40L by flow cytometry) 3. Assays of pathway activation (e.g., pSTAT3 by Western blot or flow cytometry) 4. Cytokine production (e.g., IFN-gamma level by ELISA) 5. SCID NBS (TREC qPCR) 6. WGS	1. Complete access to biologics 2. Gene therapy



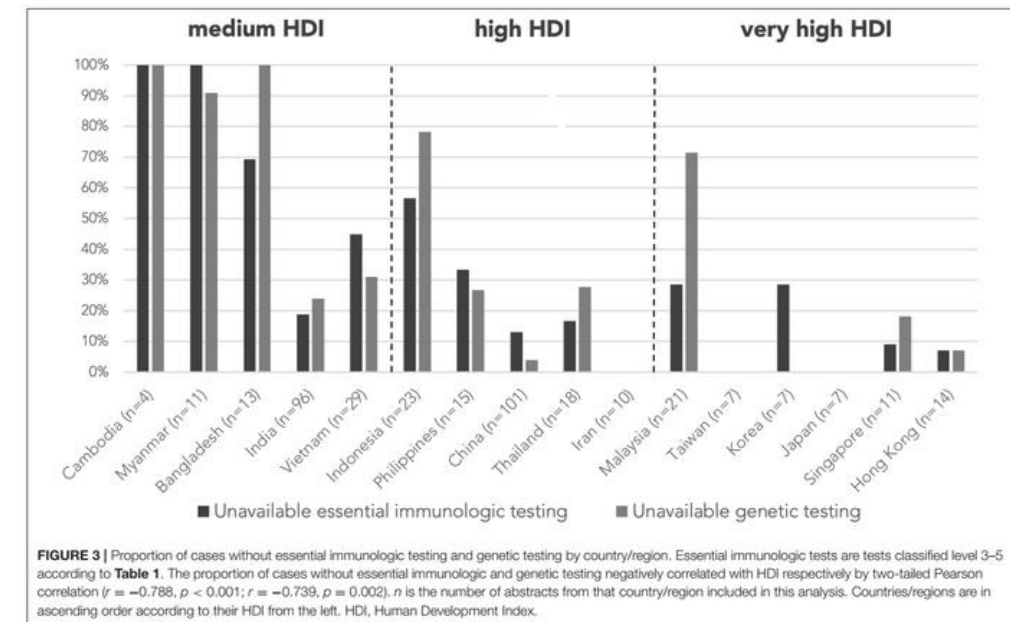
Human Development Index (HDI)



- 423 abstracts submitted to
- 9 APSID Schools from
- 99 centres
- 2015-2022

FIGURE 1 | Map showing 72 referring centres in 17 countries. (Created with Datawrapper).

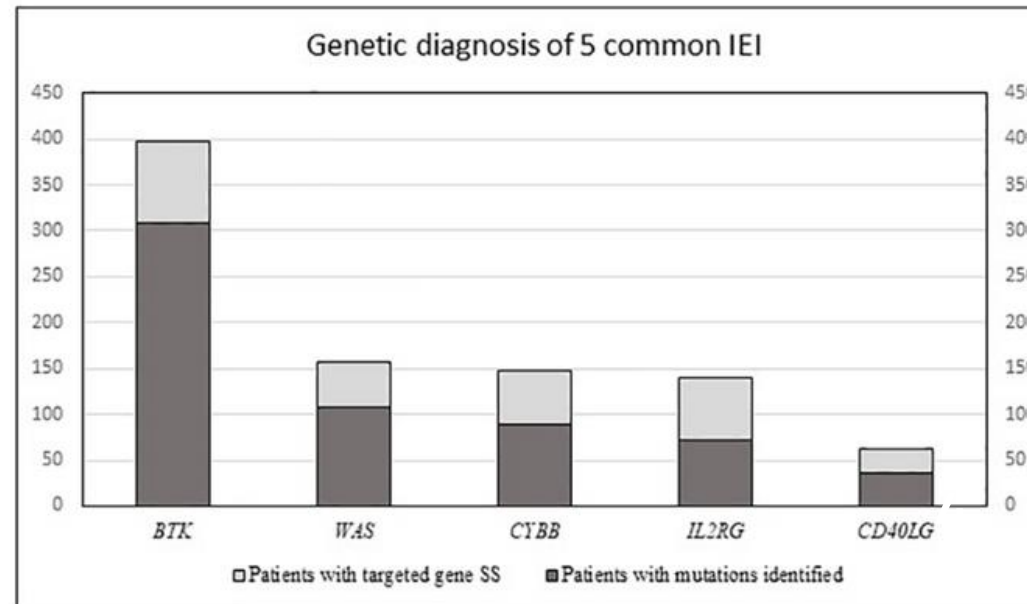
Front Immunol 2022;13:883446



Targeted Gene Sanger Sequencing Should Remain the First-Tier Genetic Test for Children Suspected to Have the Five Common X-Linked Inborn Errors of Immunity



- 72 referring centres in 17 countries

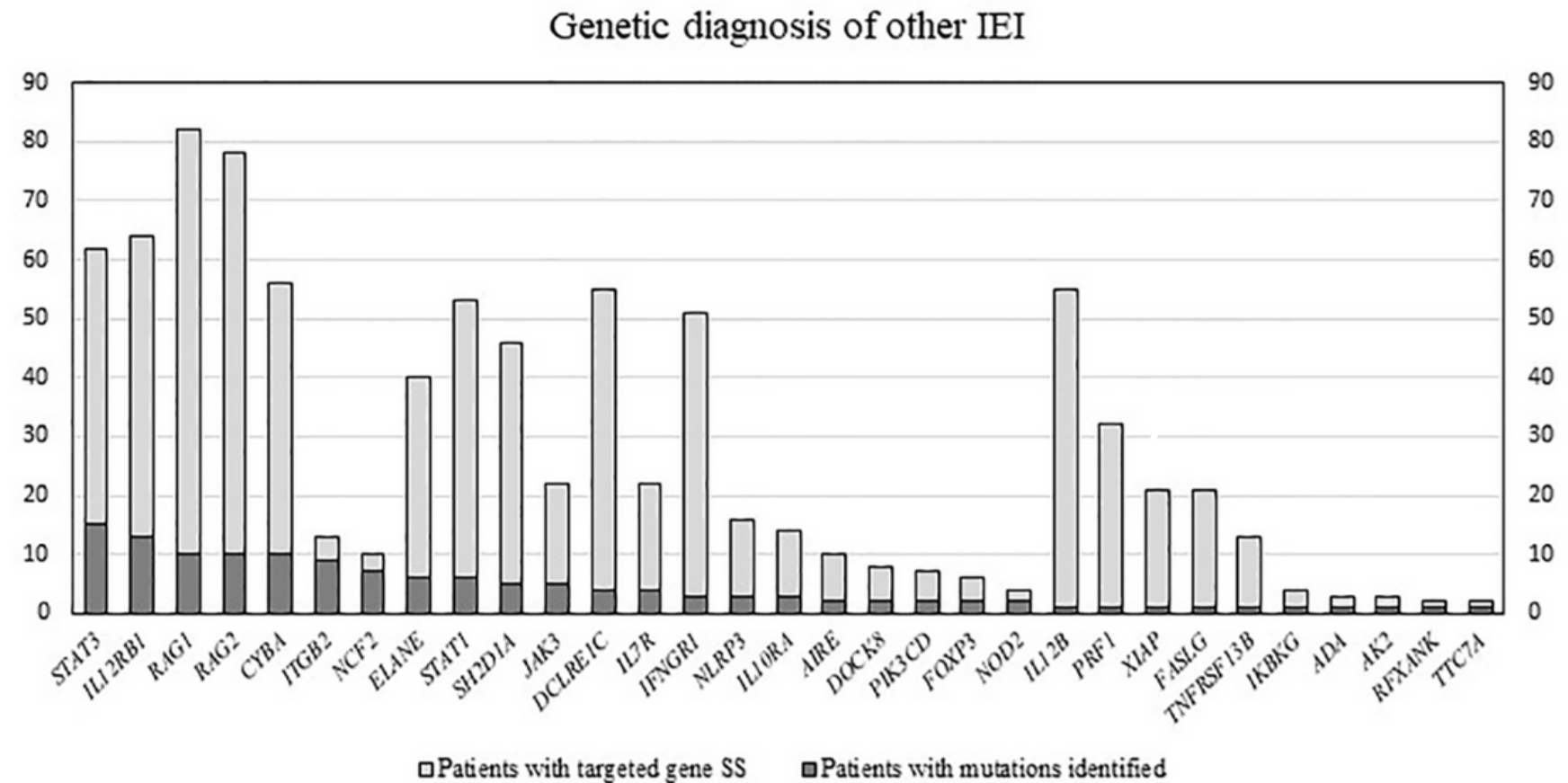


IEI genes	Patients with targeted gene SS	Patients with mutations identified	n/%
<i>BTK</i>	398	308	77.4
<i>WAS</i>	156	108	69.2
<i>CYBB</i>	148	88	59.5
<i>IL2RG</i>	139	71	51.1
<i>CD40LG</i>	62	36	58.1
Total	903	611	67.7

- 2024 IEI Sanger sequencing for 84 genes in 1,376 patients
- 744 (54%) identified to have IEI mutations
- from 2009, WES started and now preferred for IEIs other than these 5

Number of patients with targeted gene SS performed and number of patients with mutations identified

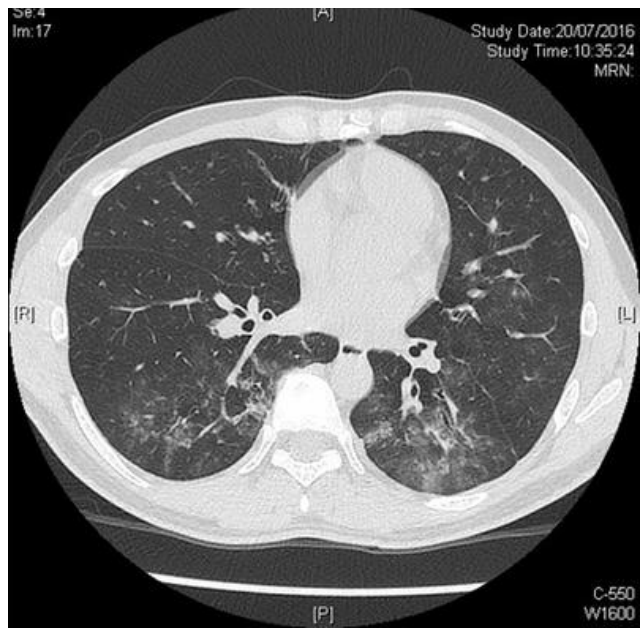
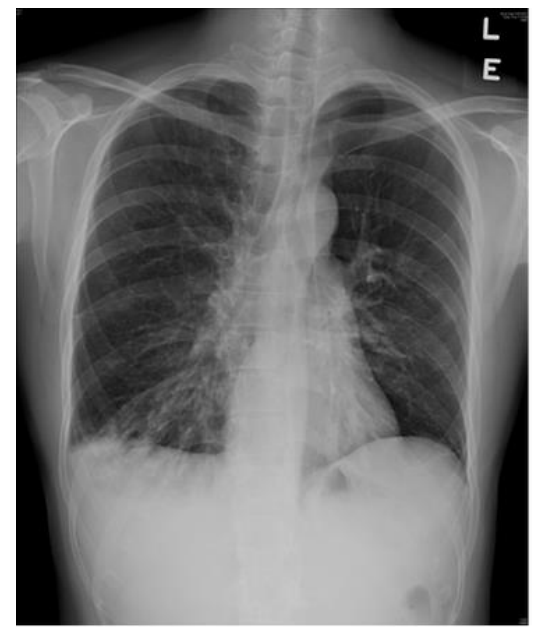
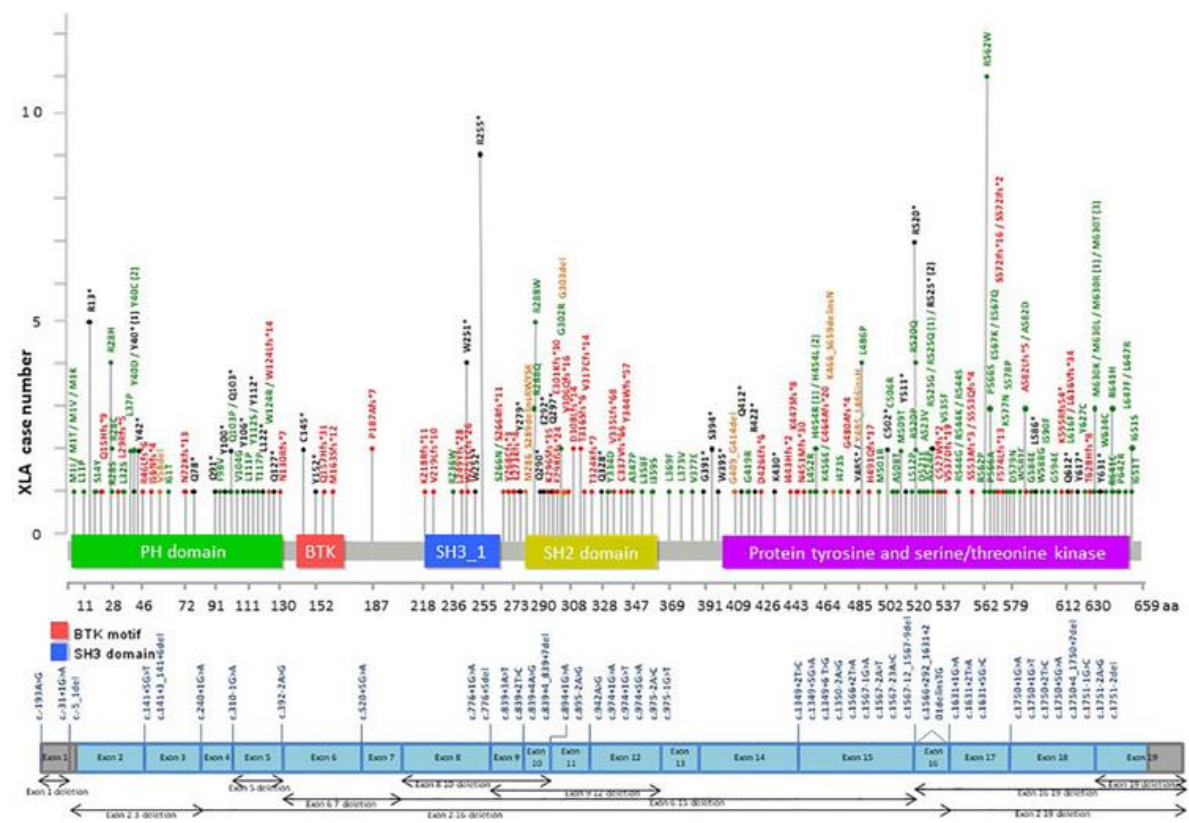
Not cost-effective to perform gene sequencing one by one other than the 5 most common XL IEI



Distribution of casual mutations in various exons, exon-intron junctions and corresponding domains of BTK gene

308
XLA

77%
success
rate



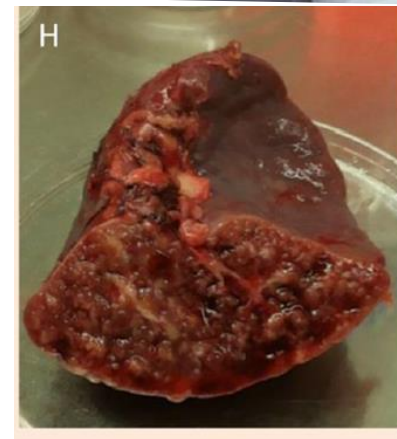
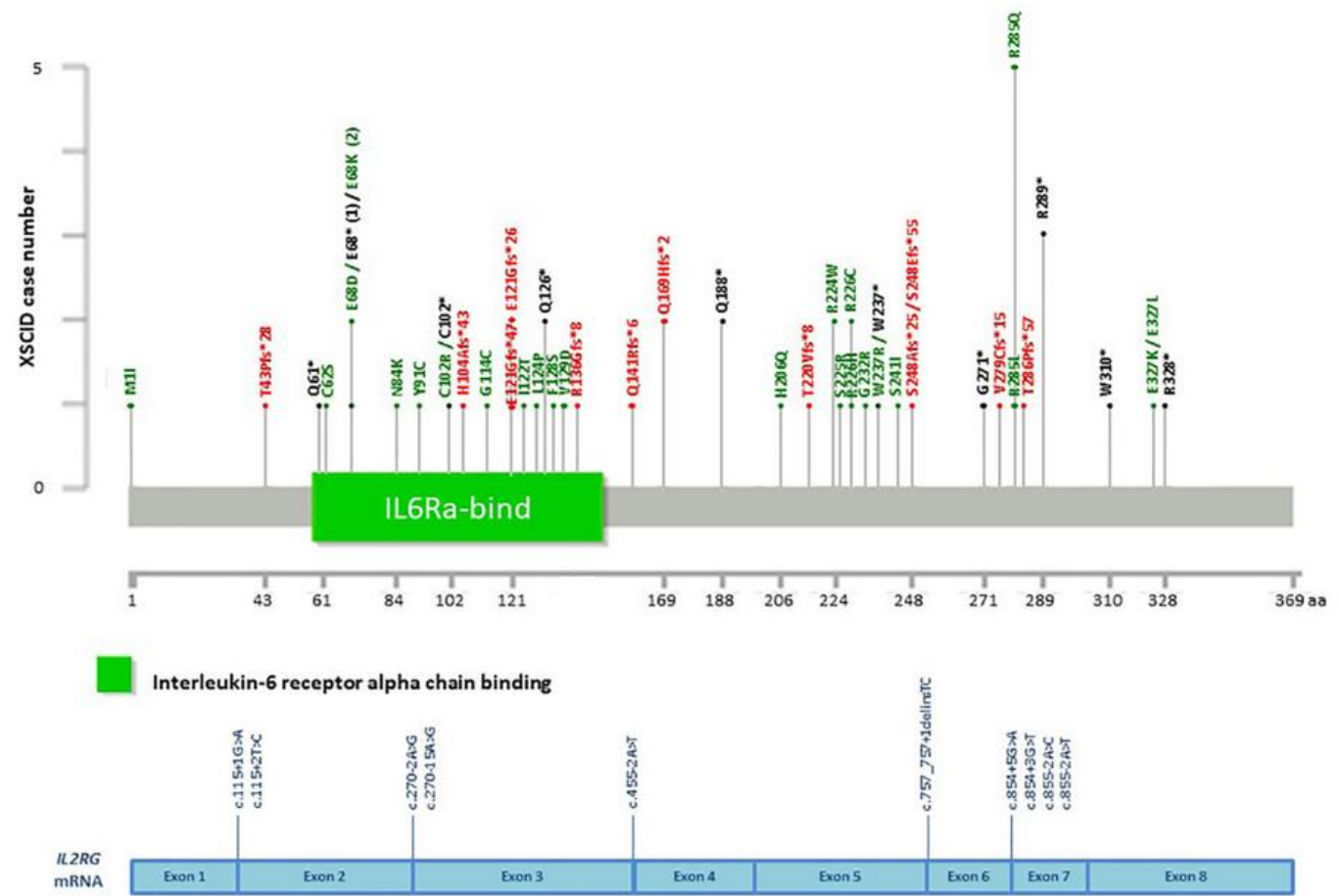
30 yo XLA ♂

- For medical students:
- Describe findings of CXR & CT
 - Symptoms to ask for confirmation of findings
 - Immune tests to order



Distribution of casual mutations in various exons, exon-intron junctions and corresponding domains of IL2RG gene

71
X-SCID

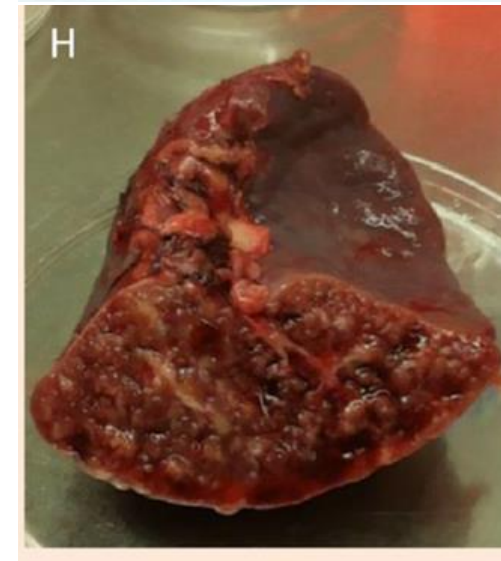
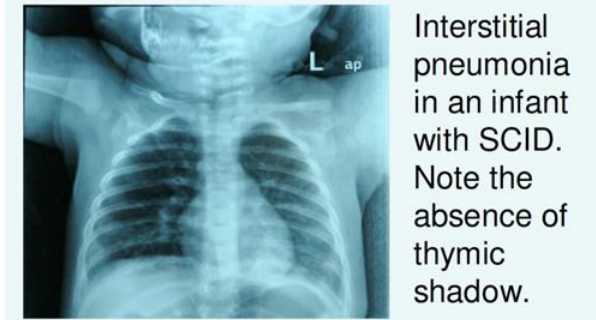
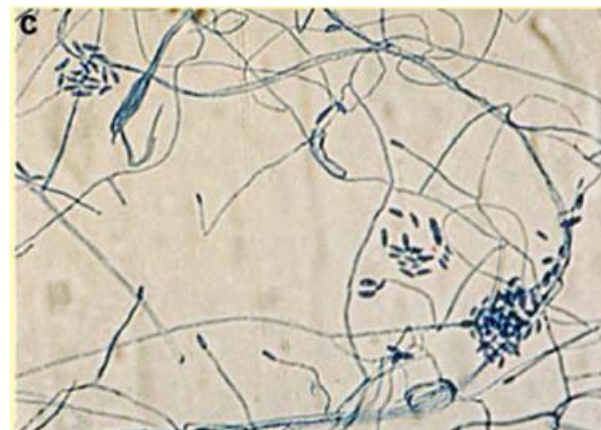
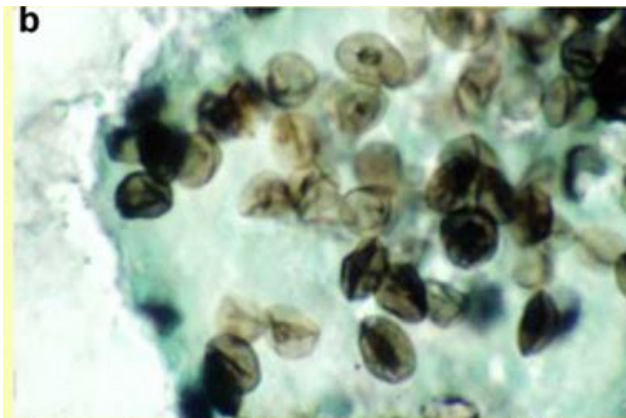


Disseminated
BCG infection



Family History of Early Infant Death Correlates with Earlier Age at Diagnosis But Not Shorter Time to Diagnosis for Severe Combined Immunodeficiency

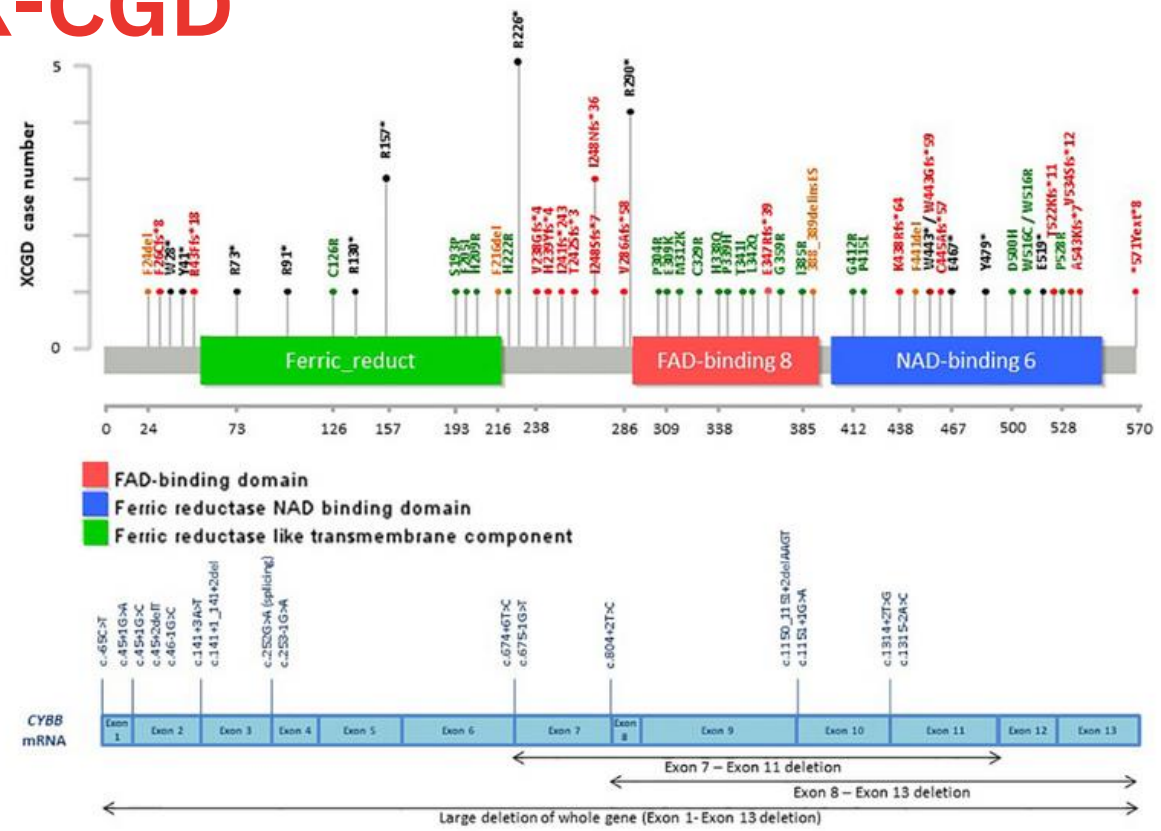
Conclusion: FH was useful to aid earlier diagnosis but was overlooked by clinicians and not by parents. Similarly, typical clinical features of SCID were not recognized by clinicians to shorten the time to diagnosis. We suggest that **lymphocyte subset** should be performed for any infant with one or more of the following four clinical features: **FH**, **candidiasis**, **BCG infections**, and **ALC below $3 \times 10^9/L$** .



- Acremonium
- BCG
- Candida
- Virus

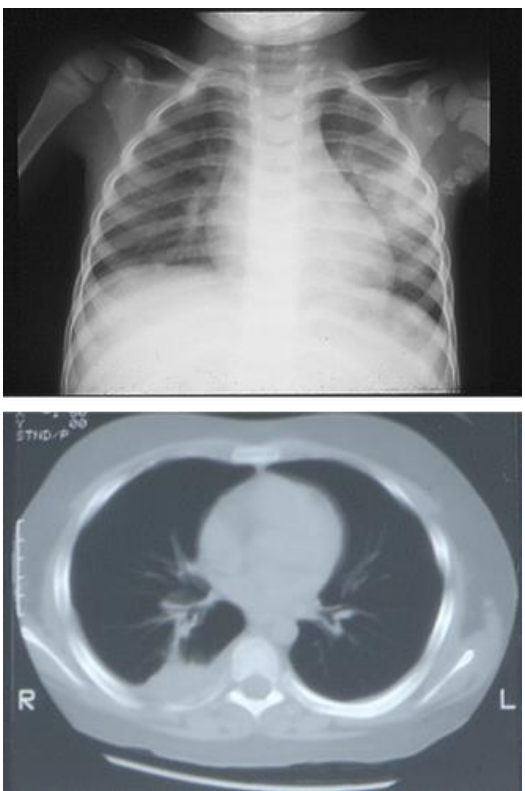
Distribution of casual mutations in various exons, exon-intron junctions and corresponding domains of CYBB gene

88
X-CGD

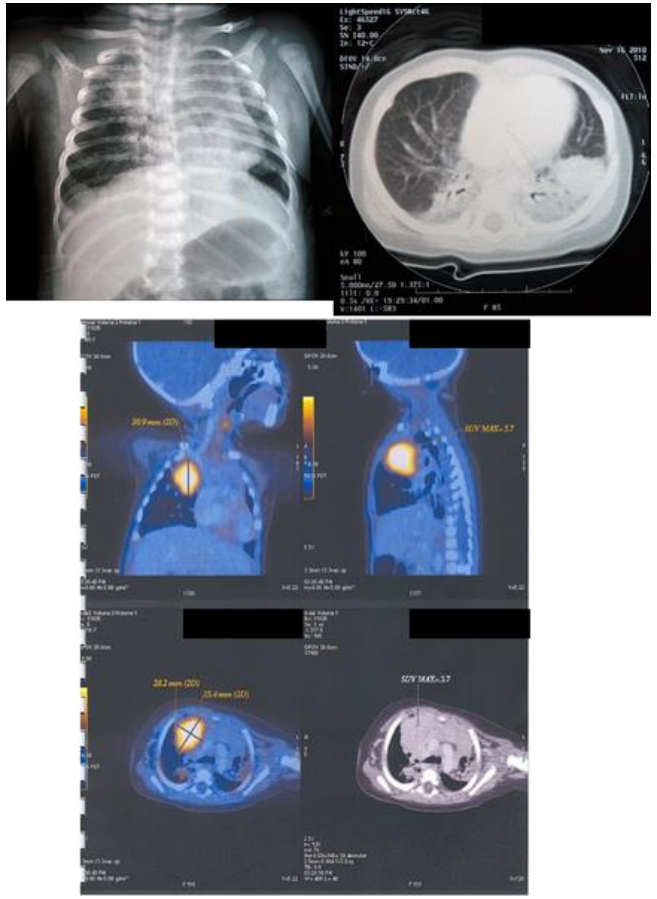


The Role of Phagocytic Respiratory Burst in Host Defense Against *Mycobacterium tuberculosis*

Clinical Infectious Diseases 1998;26:226-7



BCG & aspergellosis
in X-CGD



Granulomatous lesion
in AR-CGD (NCF-1)

Phenomic Analysis of Chronic Granulomatous Disease Reveals More Severe Integumentary Infections in X-Linked Compared With Autosomal Recessive Chronic Granulomatous Disease



Timothy Lok-Hin Chiu^{1†}, Daniel Leung^{1†}, Koon-Wing Chan¹, Hok Man Yeung¹, Chung-Yin Wong¹, Huawei Mao², Jianxin He³, Pandiarajan Vignesh⁴, Weiling Liang⁵, Woei Kang Liew⁶, Li-Ping Jiang⁷, Tong-Xin Chen⁸, Xiang-Yuan Chen⁹, Yin-Bo Tao⁹, Yong-Bin Xu¹⁰, Hsin-Hui Yu¹¹, Alta Terblanche¹², David Christopher Lung¹³, Cheng-Rong Li¹⁴, Jing Chen¹⁵, Man Tian¹⁶, Brian Eley¹⁷, Xingtian Yang¹, Jing Yang¹, Wen Chin Chiang⁶, Bee Wah Lee^{18,19}, Deepti Suri⁴, Amit Rawat⁴, Anju Gupta⁴, Surjit Singh⁴, Wilfred Hing Sang Wong¹, Gilbert T. Chua¹, Jaime Sou Da Rosa Duque¹, Kai-Ning Cheong²⁰, Patrick Chun-Yin Chong²¹, Marco Hok-Kung Ho²¹, Tsz-Leung Lee²⁰, Wanling Yang¹, Pamela P. Lee^{1*} and Yu Lung Lau^{1*}

- 117 CGD patients from **Asia & Africa**
- 90 with sufficient details for phenomic analysis
- Human Phenotype Ontology (HPO) - a computational bridge between genome biology & clinical medicine

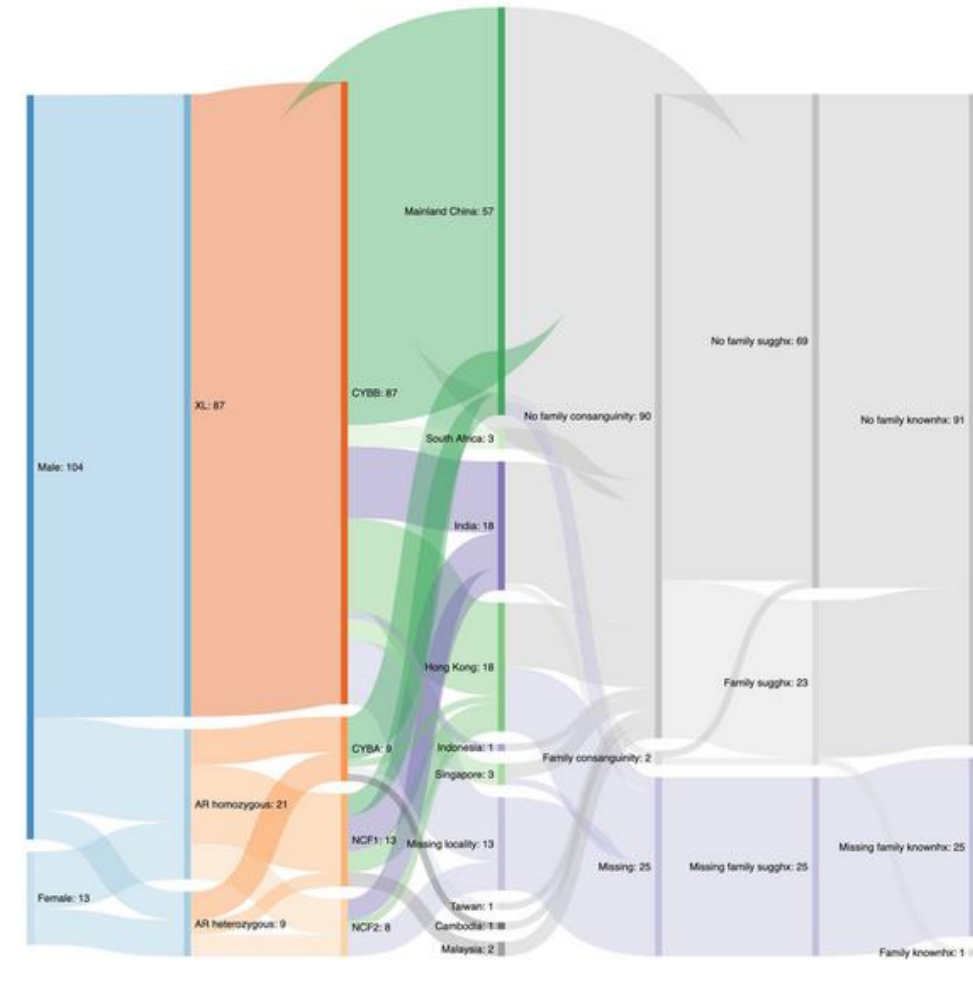


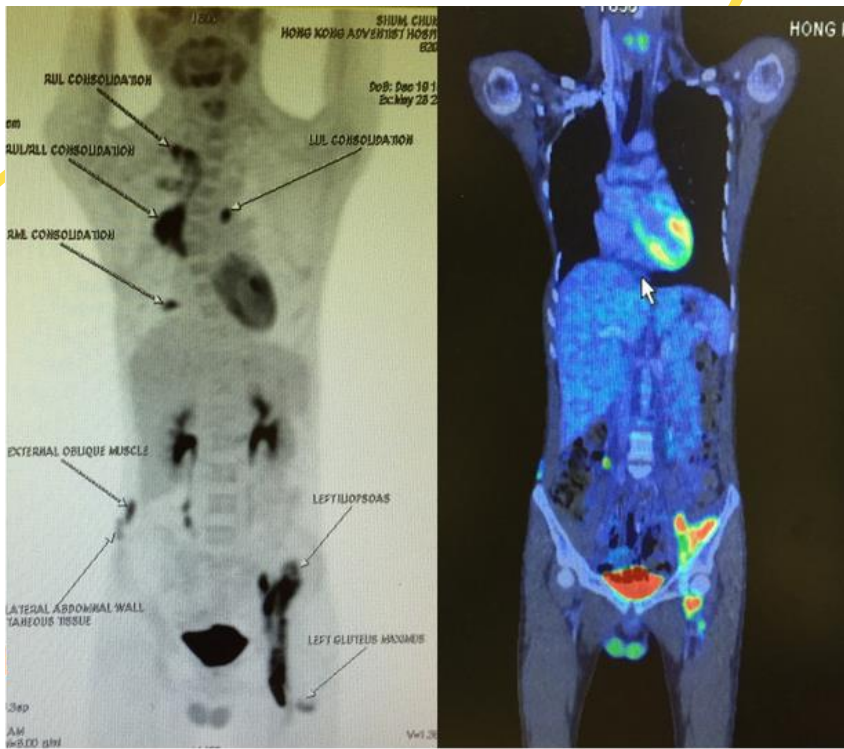
FIGURE 1 | A Sankey diagram describing demographics data of the CGD case series. XL, X-linked; AR, autosomal recessive; suggx, suggested history; knownx, known history.

TABLE 2 | Comparison between clinical characteristics between XL-CGD and AR-CGD using Fisher's exact test.

Parameter	XL (range) (<i>n</i> = 67)	AR (range) (<i>n</i> = 23)
Median age of onset*	0.2 (0–5) (<i>n</i> = 66)	0.4 (0–13.3) (<i>n</i> = 19)
Median age of referral to immunology centre*	0.75 (0–14) (<i>n</i> = 64)	3.5 (0.1–26.6) (<i>n</i> = 18)
Median age at clinical diagnosis*	1.4 (0–14) (<i>n</i> = 58)	4.8 (0.2–26.7) (<i>n</i> = 13)
Median age at genetic diagnosis*	2.2 (0.1–14.8) (<i>n</i> = 70)	4.7 (0.9–26.7) (<i>n</i> = 19)
Median delay in referral to immunology centre	0.3 (0–12) (<i>n</i> = 59)	0.25 (0–12) (<i>n</i> = 14)
Median delay in diagnosis of CGD	0 (–0.3–6.2) (<i>n</i> = 53)	0.3 (0–1) (<i>n</i> = 8)

*XL, X-linked; AR, autosomal recessive; CGD, chronic granulomatous disease. ** $p < 0.01$.*

- ***XL-CGD earlier onset, referral & diagnosis than AR-CGD**



- Disseminated aspergillosis
- 3rd HSCT at 18 years old

Biopsy of deep-seated lesion critical to identify pathogen

Whole body PET-CT: Hypermetabolic lesions over

- Left iliopsoas muscle
- Left gluteus maximus ms
- Right ext. oblique ms
- Right lat. abd wall
- Both lungs

Lung

- Aspergillus 16
- TB 15
- BCG 10

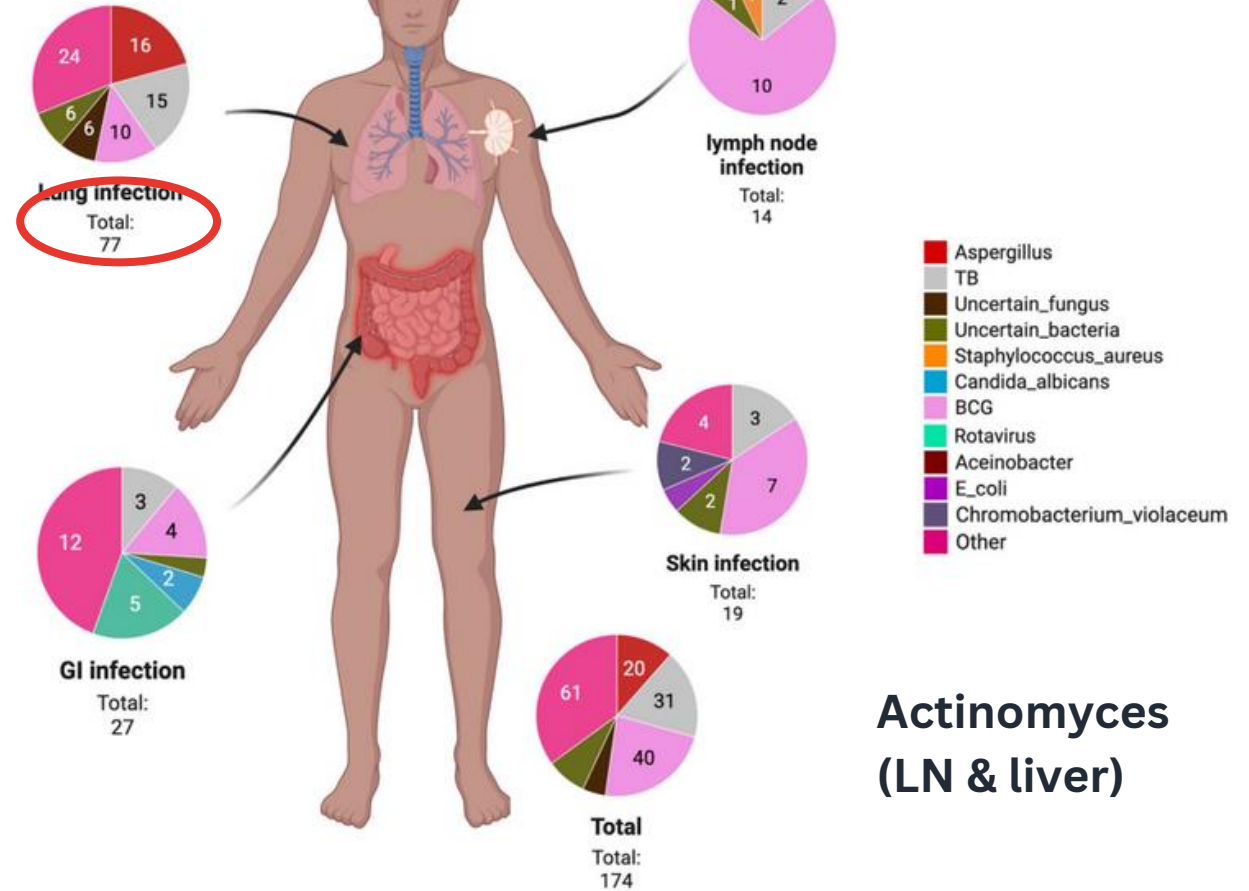


FIGURE 3 | A body map showing the infection location of pathogens in our CGD case series. GI, gastrointestinal; TB, *Mycobacterium tuberculosis*; *E. coli*, *Escherichia coli*; BCG, *Bacillus Calmette-Guérin*.

Actinomyces (LN & liver)

Front Immunol 2022;12:803763.

All of us **Be Linked Effectively (ABLE)**

- To recognise and refer suspected IEI
- To evaluate undiagnosed IEI phenotypically and immunologically
- To identify potential disease-causing candidate genetic variants with bioinformatic pipeline
- To demonstrate causality of genetic variants with human cells and animal models
- To define disease mechanisms leading to target therapy
- To translate findings to treatment beyond IEI

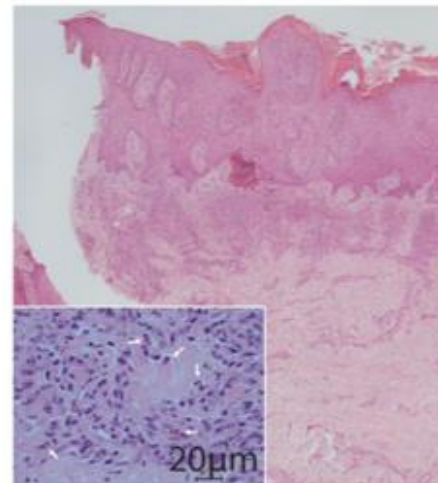


Unifying **clinical features** of the 16 patients with severe allergic disease

Severe eczema
(Hong Kong patient)

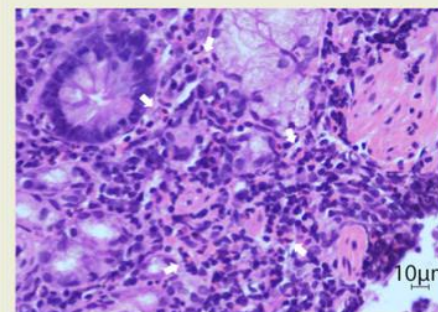


Skin Biopsy

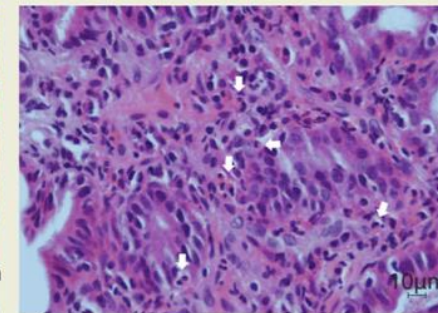


suggested
**lichen simplex
chronicus**

Duodenum Biopsy



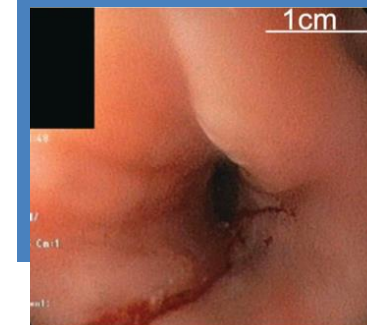
**abundant eosinophils
amongst lymphocytes**



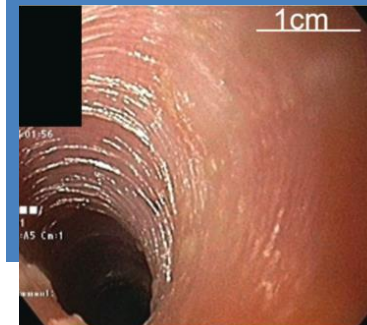
Gastric Antral Biopsy

Endoscopic images in middle esophagus

Furrowing

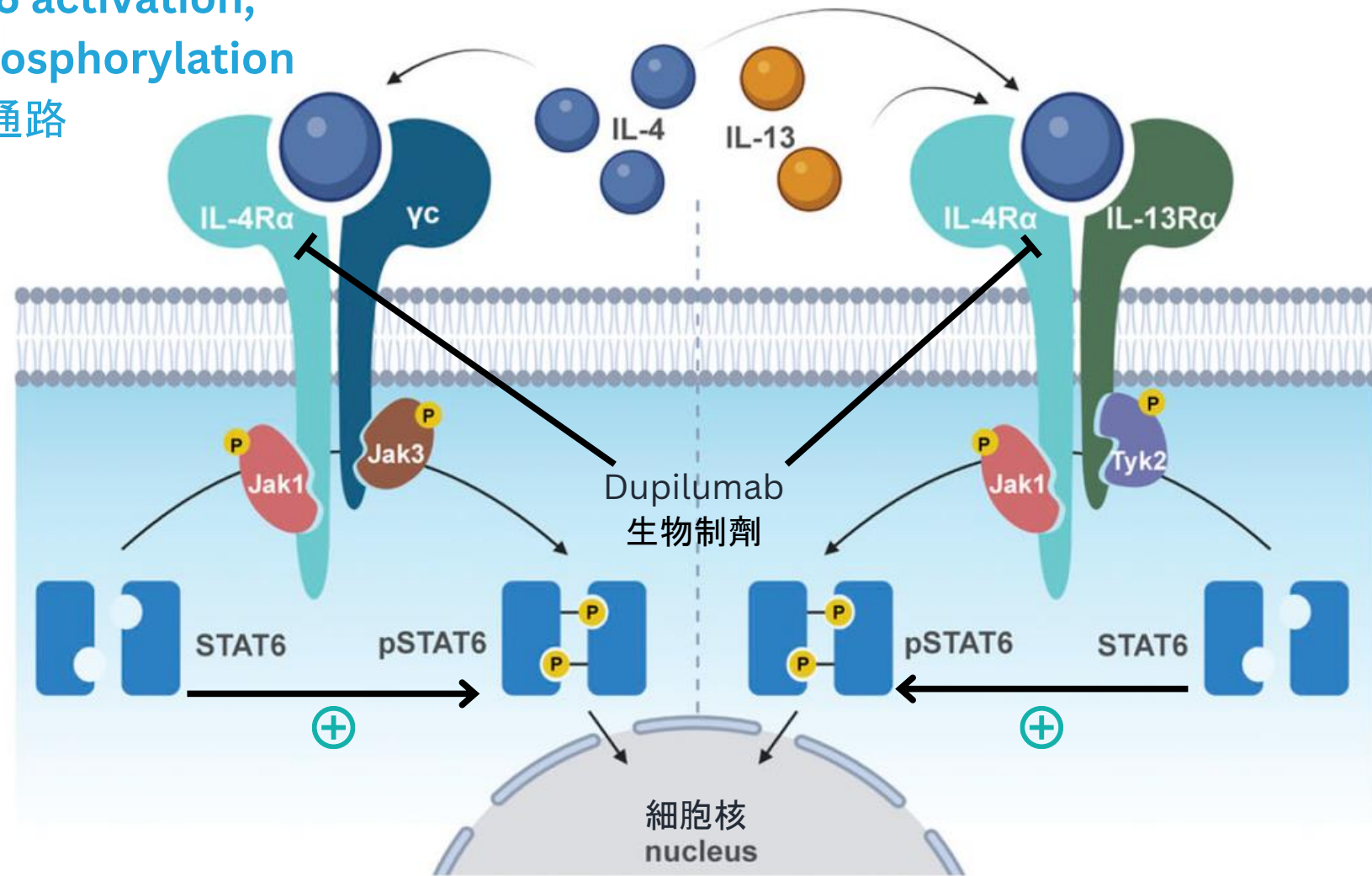


Trachealization

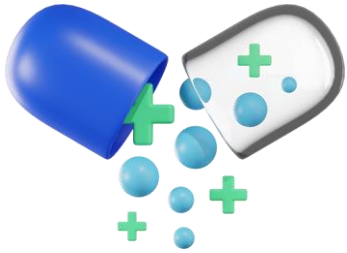


suggestive of eosinophilic esophagitis

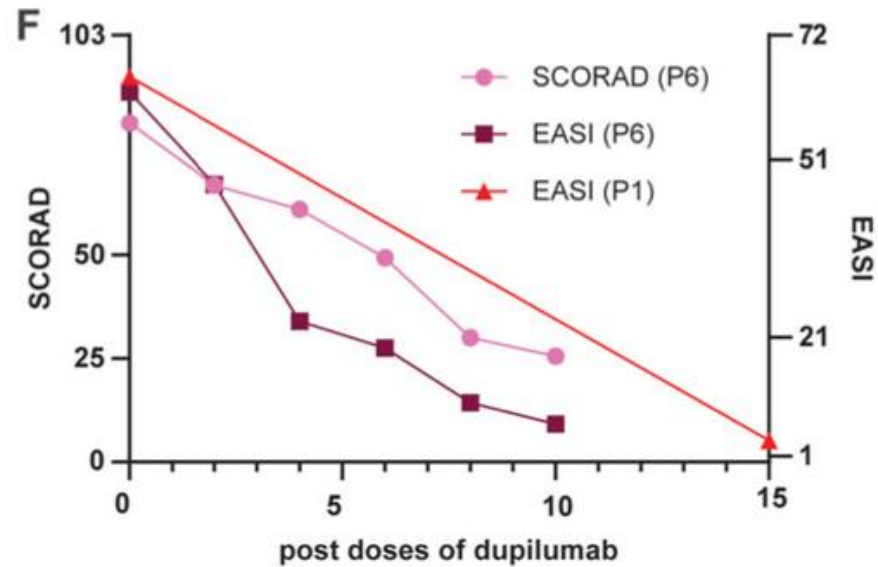
Schematic illustrating classical
IL-4-mediated STAT6 activation,
dimerization, and phosphorylation
STAT 6 免疫功能生物通路



嚴重濕疹、哮喘、多種食物/藥物過敏、過敏性休克、反覆皮膚/呼吸道/病毒感染等等
Severe Eczema, Asthma, Multiple food/drug allergies, Anaphylaxis, Recurrent skin/
respiratory/viral infections, etc

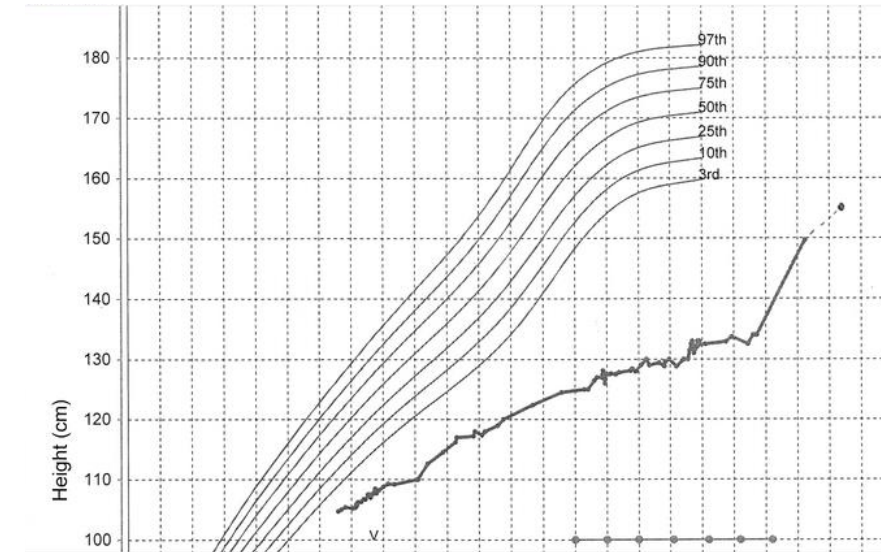


Clinical improvements of P6 after 2 years of dupilumab



Improved skin condition as quantified by SCORAD and EASI indices

Before



- No height gain on GH
- Height gain on dupilumab

After



For Resident:

- Why?



ARTICLE

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

- 16 patients from 10 families
- Germline AD GOF *STAT6* variants
- Sustained *STAT6* phosphorylation
- Increased *STAT6* target gene expression
- Th2 skewed transcriptional profile
- Dupilumab to block IL4Ra is effective treatment
- JAK inhibitors need more assessment

All of us Be Linked Effectively (ABLE)

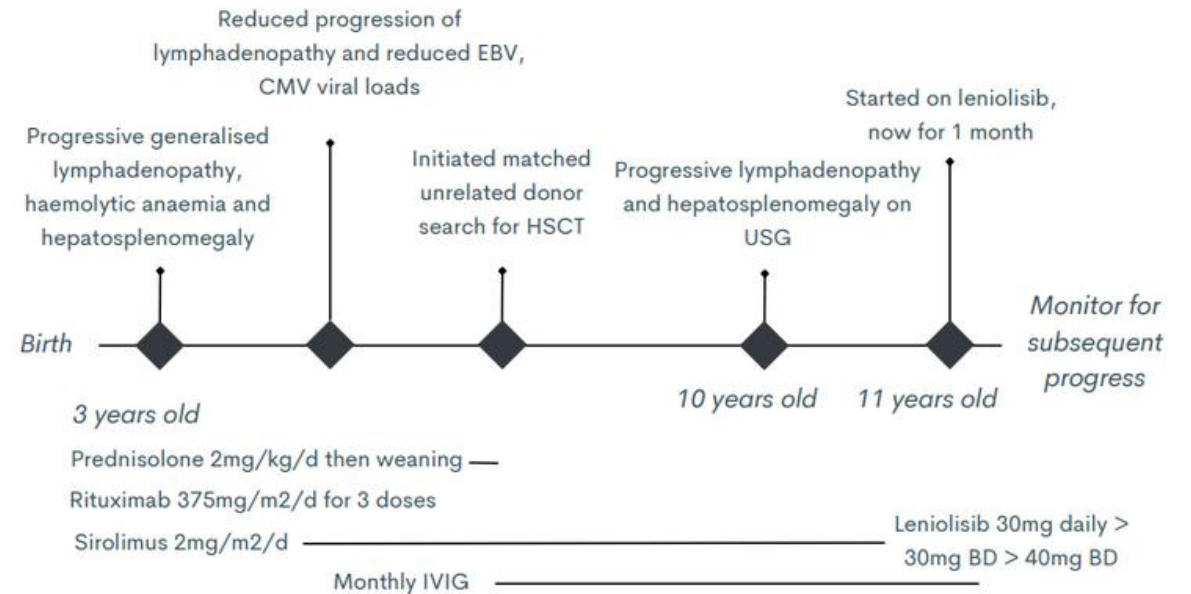
- To recognise and refer suspected IEI
- To evaluate undiagnosed IEI phenotypically and immunologically
- To identify potential disease-causing candidate genetic variants with bioinformatic pipeline
- To demonstrate causality of genetic variants with human cells and animal models
- To define disease mechanisms leading to target therapy
- To translate findings to treatment beyond IEI



Leniolisib Expanded Access Program (LE-EAP)- Hong Kong

- Activated Phosphoinositide 3-kinase delta syndrome (APDS)
- Lymphadenopathy, autoimmunity, frequent infections
- Leniolisib is an oral selective PI3K δ inhibitor, approved by Food and Drug Administration in 2023 for APDS

CASE PRESENTATION



Open-label extension study of leniolisib for patients with APDS

- 37 patients (median age, 20 years; 42.3% female)
- Of the 37 patients, 26, 9, and 2 patients had previously received leniolisib, placebo, or other PI3Kd inhibitors, respectively
- While on leniolisib, patients had reduced annualized infection rates ($P = .004$), and reductions in immunoglobulin replacement therapy occurred in 10 of 27 patients
- Reduced lymphadenopathy and splenomegaly, improved cytopenias, and normalized lymphocyte subsets
- Leniolisib was well tolerated and maintained durable outcomes with up to 5 years of exposure in 37 patients with APDS.



iapids 
INTERNATIONAL ALLIANCE OF
PRIMARY IMMUNODEFICIENCY SOCIETIES





兒童癌病基金
Children's Cancer Foundation

**The Children's Cancer Foundation
Peter Nash Paediatric Oncology
Research Grant (Hong Kong)**



**The Society for the
Relief of Disabled Children**



大學教育資助委員會
University Grants Committee



**The Shun Tak District
Min Yuen Tong**



Research Fund Secretariat
Food and Health Bureau
The Government of the Hong Kong Special Administrative Region



Jeffrey Model
Foundation

Curing PI.
Worldwide.

**Health and Medical
Research Fund (HMRF)**



YL Lau 2023