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Takeda

Genetic testing – what does it mean for patients?

Dr. Adiratna Mat Ripen (MD, PhD)
Head,
Primary Immunodeficiency Unit,
Allergy and Immunology Research Centre,
Institute for Medical Research (IMR),
National Institutes of Health (NIH),
Ministry of Health Malaysia.

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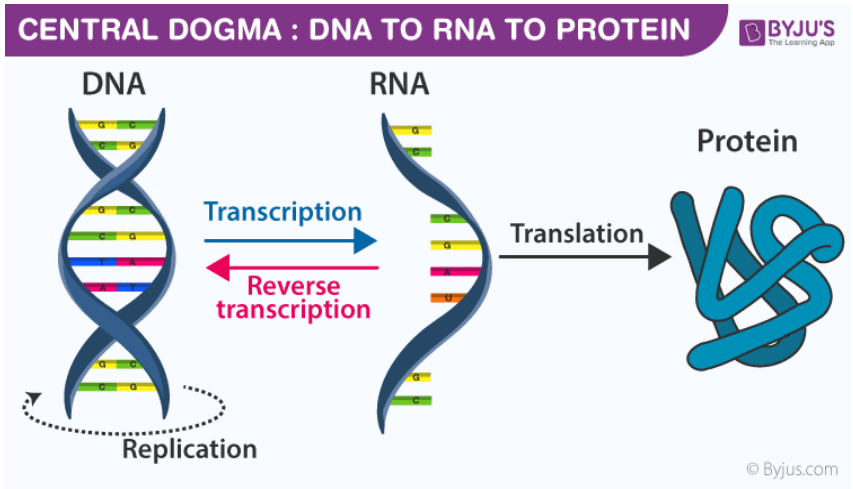
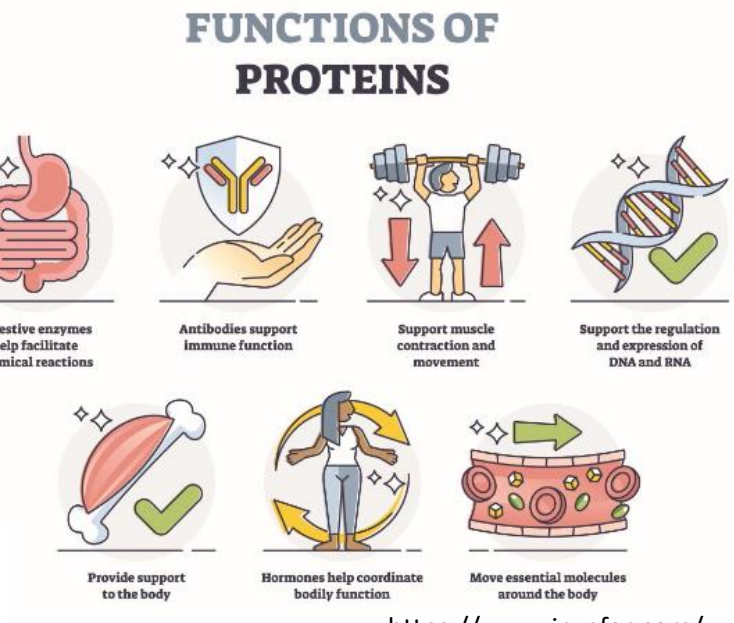
DNA: Blueprint of life

- **DNA** (deoxyribonucleic acid) is the molecule that carries genetic information for the development and functioning of an organism.
- A **gene** is a region of DNA that codes for a particular protein.
- Each protein carries out specific function.





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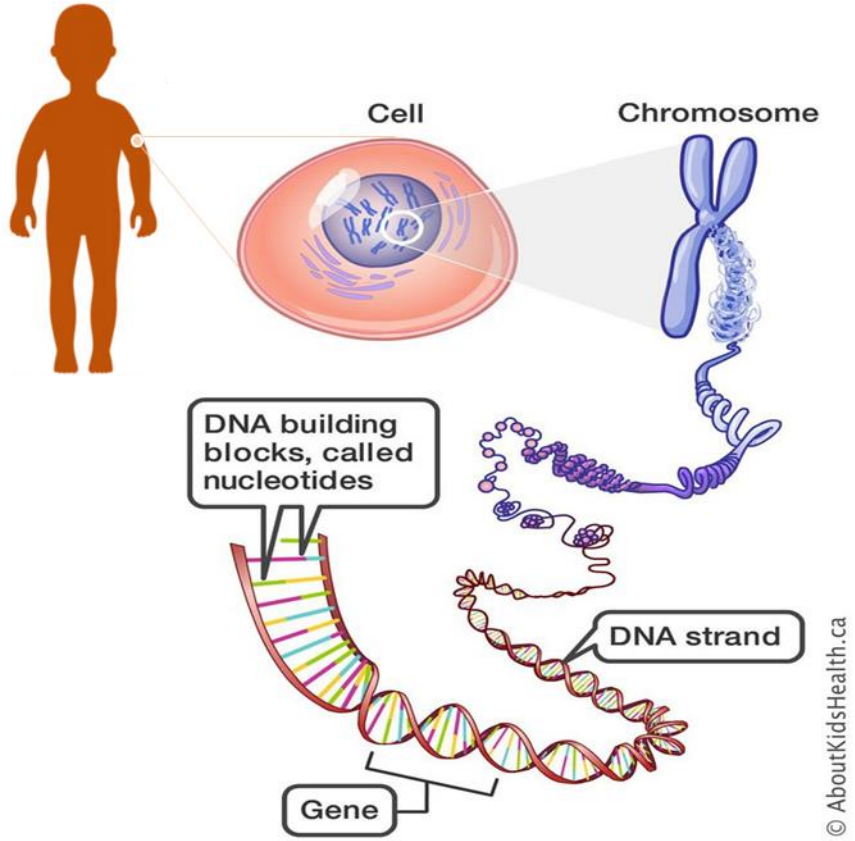
How does genetic disease occur?

- A genetic disease is caused by a change in the DNA sequence of a particular gene affecting its function.

- Genetic diseases can be:
  1. Genetically determined
  2. Environmentally determined
  3. Combination of gene mutations and environmental factors

- Genetic disease are hereditary (derived from parent(s)) or sporadic (not inherited from the parents).

- Not all genetic diseases are present or apparent at birth e.g. Huntington disease
  - ❖ degeneration of nerve cells in the brain
  - ❖ 3rd to 4th decade of life.



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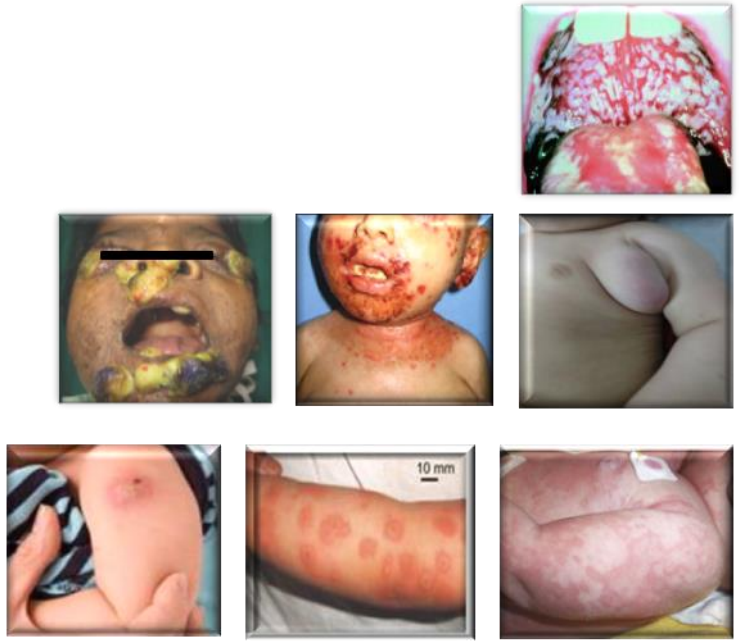
Inborn errors of immunity (IEI)

- Primary immunodeficiency (PID)

- are genetic disorders that result in the specific impairment of normal immune development and function.

- IEI present clinically as increased susceptibility to
  - ❖ infections, autoimmunity, autoinflammatory diseases, allergy, bone marrow failure and/ or malignancy (Tangye et al., 2022).

- 485 conditions (> 400 genes) (Tangye *et al.*, 2022)



Clinical presentations of some IEI patients

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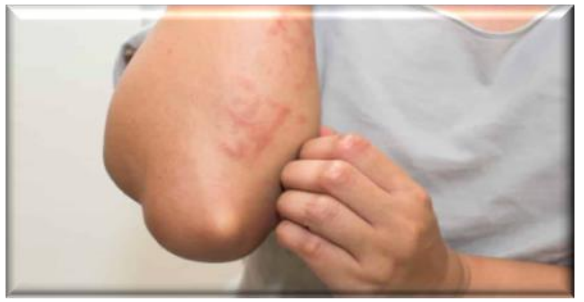
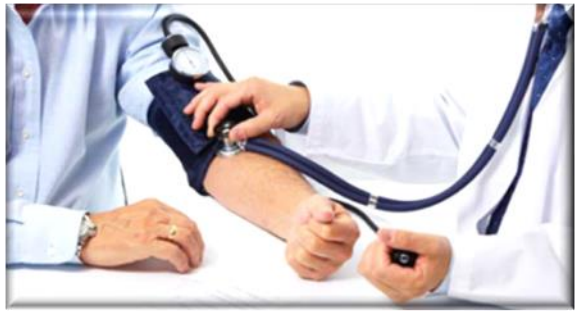
Disease diagnosis





- Identification of the nature of an illness

- Clinical diagnosis:
  - ❖ clinical signs and symptoms,
  - ❖ family history,
  - ❖ physical examinations,
  - ❖ laboratory diagnostic tests (Balogh *et al.*, 2015)

- Genetic testing:
  - ❖ PCR & Sanger sequencing
    - – identification of DNA mutation

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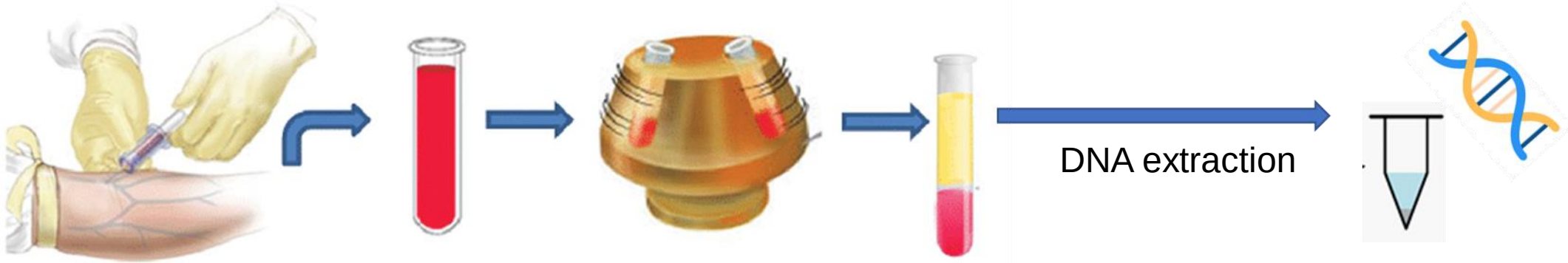
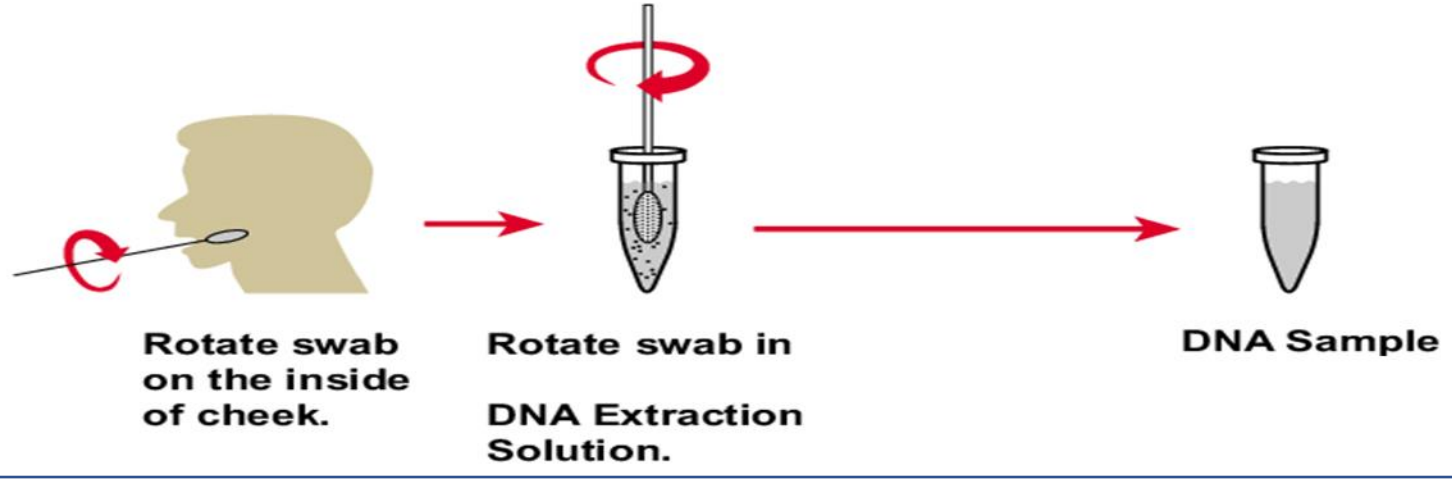
PCR: Polymerase Chain Reaction

Sample collection for genetic testing



Venipuncture | Whole blood | Centrifugation | Cell separation | DNA sample ready for genetic testing



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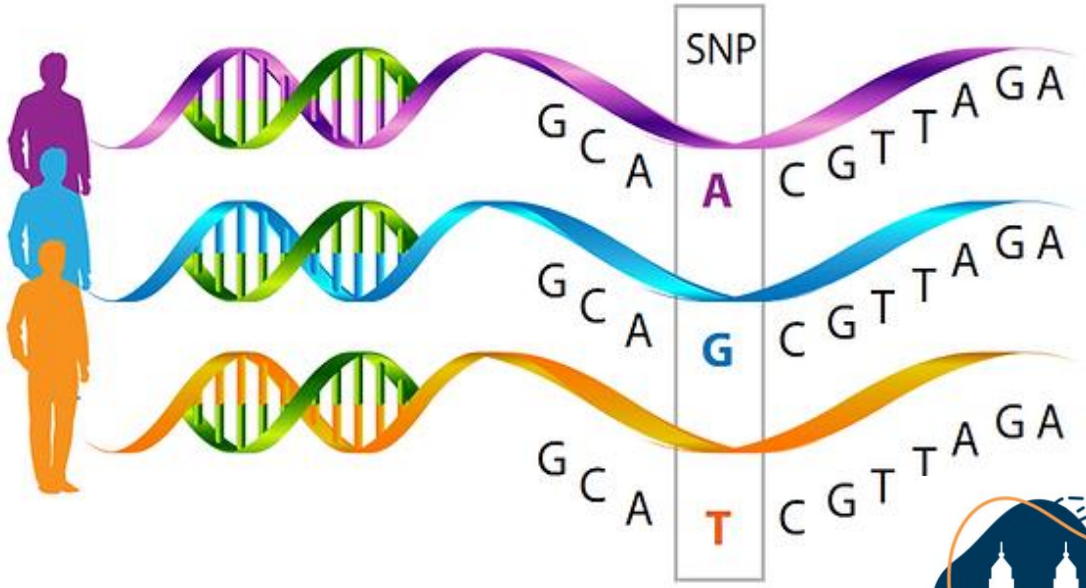
Workflow for Genetic Testing (1)

Genetic disease?

Known clinical manifestations

→ Single gene testing → PCR & Sanger sequencing → Genetic diagnosis



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SNP: Single Nucleotide Polymorphism

Publications

Case Report

X-linked chronic granulomatous disease in a male child with an X-CGD carrier, Klinefelter brother

Harvindar Kaur Gill,[1] Hemahwathy Chanthira Kumar,[1,2] Chan Kwai Cheng,[3] Choo Chong Ming,[4] Revathy Nallusamy,[3] Narazah Mohd Yusoff,[5] Saharuddin B Mohamad,[2] Adiratna Mat Ripen,[1] Jasbir Singh Dhaliwal[1] and Shahnaz Murad[6]

Summary

Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency (PID) caused by a dysfunctional respiratory burst enzyme NADPH-oxidase. The concurrence of Klinefelter's Syndrome (KS) and CGD would be extremely rare.

Objective: We describe the study of a family where the youngest male child had X-linked CGD (X-CGD) while his older brother was both an X-CGD carrier and a Klinefelter.

Methods: Flow cytometry was used to study respiratory burst and gp91-phox expression, while genetic investigation was done by RT-PCR, PCR and X-chromosome short tandem repeat (X-STR) analysis.

Results: The Dihydrorhodamine (DHR) assay showed the patient's neutrophils failed to produce a respiratory burst, while both the mother and an older brother showed a bimodal response. gp91-phox expression was absent in the patient's neutrophils, and bimodal in the mother's and brother's neutrophils. The patient's cDNA showed a C>T change at nucleotide 676 of the *CYBB* gene. The same change was seen in the patient's gDNA, while the brother and mother were heterozygous, with C and T, in this position. The c.676C>T is a nonsense mutation that leads to premature termination of the gp91-phox protein. The brother karyotyped as 47, XXY and X chromosome analysis showed that he had inherited both his mother's X chromosomes.

Conclusions: This study showed that the patient

Case report

Defining p47-phox deficient Chronic Granulomatous Disease in a Malay family

Harvindar Kaur Gill,[1] Hemahwathy Chanthira Kumar,[1] Jasbir Singh Dhaliwal,[1] Farizawati Zabidi,[1] Iean Hamzah Sendut,[2] Rahim Md Noah,[3] Lokman Mohammad Noh,[4] Amir Hamzah Abdul Latiff,[5] Shahnaz Murad[6]

Summary

Background: The most common autosomal form of Chronic Granulomatous Disease, p47-phox deficient CGD, generally features a GT (ΔGT) deletion in the GTGT sequence at the start of exon 2 on the *NCF-1* gene. This consistency is due to the coexistence of and the recombination between 2 homologous pseudogenes (ψs) and *NCF-1*. The GTGT: ΔGT ratio mirrors the *NCF-1*: *NCF-1ψ* ratio and is 2:4 in normal individuals.

Objective: To determine the molecular basis of the Autosomal-CGD in a family with 2 children, a male and female, affected by the disease. The female patient suffered recurrent infection, retinitis pigmentosa and discoid lupus.

Methods: Chemiluminescence (CL) was used to study the respiratory burst, while genetic analysis was done by RT-PCR, PCR, ΔGT and the 20bp gene scans.

Results: The CL response of the patient was profoundly low. The patient's p47-phox band was absent in the RT-PCR for NADPH-oxidase component mRNAs. The ΔGT scan showed that the patient's GTGT: ΔGT ratio was 0:6, the parents' and the younger brother's was 1:5 and the younger sister's was 2:4. Examination of other *NCF-1*/ *NCF-1ψs* differences showed that the father had a compound ΔGT allele *ie.* ΔGT-20bp, inherited by the patient, and that both parents had compound GTGT alleles with a single 30bp segment in intron 1.

Conclusions: The patient was a classic, homozygous ΔGT p47-phox deficient CGD with one allele harbouring a compound ΔGT-20bp gene. The ΔGT and 20bp gene scans offer a relatively simple and efficient means of defining a p47-phox deficient CGD patient. *(Asian Pac J Allergy Immunol 2012;30:313-20)*

Key words: Chronic Granulomatous Disease, Primary Immunodeficiency, NCF-1, p47-phox, NADPH-oxidase

Introduction

Patients with Chronic Granulomatous Disease (CGD), a primary immunodeficiency, suffer an enhanced susceptibility to bacterial and fungal infection.[1] The breach lies in the neutrophil where a functionally compromised enzyme fails to convert molecular oxygen to superoxide and other potent reactive oxygen intermediates that kill ingested pathogens.[1] The enzyme, nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase is a

Baharin *et al. Journal of Medical Case Reports* (2016) 10:188
DOI 10.1186/s13256-016-0944-1

Journal of Medical Case Reports

CASE REPORT Open Access

A rare case of Wiskott-Aldrich Syndrome with normal platelet size: a case report

Mohd Farid Baharin[1*], Jasbir Singh Dhaliwal[2], Smrdhi V. V. Sarachandran[3], Siti Zaharah Idris[4] and Seoh Leng Yeoh[5]

Abstract

Background: Wiskott-Aldrich syndrome is a rare X-linked disorder characterized by microthrombocytopenia, eczema, and recurrent infections. It is caused by mutations of the *WAS* gene. Microthrombocytopenia has been regarded as the key criteria in diagnosing this rare condition. However, in this case report, we describe a case of Wiskott-Aldrich syndrome with normal platelet size.

Case presentation: We report the case of a 9-month-old Malay boy who presented with persistent thrombocytopenia from birth. Serial blood investigations at birth showed he had normal platelet size. His family history revealed two early neonatal deaths in maternal uncles. Spontaneous bleeding was only seen at the age of 3 months. He was initially treated for immune thrombocytopenic purpura and was started on intravenously administered immunoglobulin. His clinical deterioration and poor response to the immunoglobulin raised suspicion for a different underlying pathology. Molecular analysis of the *WAS* gene revealed a missense mutation in exon 10. His parents refused further interventions and defaulted on subsequent follow-up appointments.

Conclusions: A diagnosis of Wiskott-Aldrich syndrome should be considered in any male infant who presents with early onset thrombocytopenia despite an absence of small platelet size, a characteristic feature of Wiskott-Aldrich syndrome.

Keywords: Wiskott-Aldrich syndrome, Thrombocytopenia, X-linked thrombocytopenia, Recurrent infection, Eczema

Malaysian J Pathol 2015; 37(2) : 153 – 158

CASE REPORT

Molecular characterization of two Malaysian patients with Wiskott-Aldrich syndrome

Mohd Farid BAHARIN *MD*, Sabeera Begum KADER IBRAHIM* *M.PAEDS*, YAP Song Hong** *MRCPCH*, Aina Mariana ABDUL MANAF** *MMED(PAEDS)*, Adiratna MAT RIPEN *PhD* and Jasbir Singh DHALIWAL *PhD*

*Allergy and Immunology Research Centre, Institute for Medical Research, Kuala Lumpur, *Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur and **Port Dickson Hospital, Negeri Sembilan, Malaysia*

Abstract

The Wiskott-Aldrich Syndrome (WAS) is an X-linked immunodeficiency condition characterized by microthrombocytopenia, eczema and recurrent infections. It is caused by mutations in the Wiskott-Aldrich Syndrome protein (*WASP*) gene. We investigated two Malay boys who presented with congenital thrombocytopenia, eczema and recurrent infections. Here we report two cases of *WASP* mutation in Malaysia from two unrelated families. One had a novel missense mutation in exon 1 while the other had a nonsense mutation in exon 2. Both patients succumbed to disease-related complications. A differential diagnosis of WAS should be considered in any male child who present with early onset thrombocytopenia, especially when this is associated with eczema and recurrent infections.

Gene 560 (2015) 245–248

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short communication

A novel *BTK* gene mutation creates a *de-novo* splice site in an X-linked agammaglobulinemia patient

Chai Teng Chear [a,*], Adiratna Mat Ripen [a], Sharifah Adlena Syed Mohamed [b], Jasbir Singh Dhaliwal [c]

[a] *Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, Kuala Lumpur, Malaysia*
[b] *Paediatric Department, Hospital Sultanah Aminah, Johor Bahru, Malaysia*
[c] *Allergy and Immunology Research Centre, Institute for Medical Research, Kuala Lumpur, Malaysia*

ARTICLE INFO

Article history:
Received 28 November 2014
Received in revised form 30 January 2015
Accepted 8 February 2015
Available online 11 February 2015

Keywords:
X-linked agammaglobulinemia
BTK mutation
Splice site
Arthritis

ABSTRACT

Bruton's tyrosine kinase (BTK), encoded by the *BTK* gene, is a cytoplasmic protein critical in B cell development. Mutations in the *BTK* gene cause X-linked agammaglobulinemia (XLA), a primary immunodeficiency with characteristically low or absent B cells and antibodies. This report describes a five year-old boy who presented with otitis externa, arthritis, reduced immunoglobulins and no B cells. Flow cytometry showed undetectable monocyte BTK expression. Sequencing revealed a novel mutation at exon 13 of the *BTK* gene which created a *de novo* splice site with a proximal 5 nucleotide loss resulting in a truncated BTK protein. The patient still suffered from ear infection despite intravenous immunoglobulin replacement therapy. In this study, mosaicism was seen only in the mother's genomic DNA. These results suggest that a combination of flow cytometry and *BTK* gene analysis is important for XLA diagnosis and carrier screening.

Case report

A novel Bruton's tyrosine kinase gene *(BTK)* invariant splice site mutation in a Malaysian family with X-linked agammaglobulinemia

Chai Teng Chear,[1,2] Harvindar Kaur Gill,[2] Nazatul Haslina Ramly,[3] Jasbir Singh Dhaliwal,[2] Noraini Bujang,[4] Adiratna Mat Ripen[2] and Saharuddin Bin Mohamad[1]

Summary

X-linked agammaglobulinemia (XLA) is a rare genetic disorder caused by mutations in the Bruton's tyrosine kinase (*BTK*) gene. These mutations cause defects in early B cell development. A patient with no circulating B cells and low serum immunoglobulin isotypes was studied as were his mother and sister. Monocyte BTK protein expression was evaluated by flow cytometry. The mutation was determined using PCR and followed by sequ... cytometry showed the patient... protein expression in his mono... mother and sister had 62% an... monocytes showing BTK prote... respectively. The patient had ... substitution in the first nucleotid... the *BTK* gene, and the ... IVS9+1G>C. This mutation resu... skipping. This defect rendere... susceptible to asthma, failure to t... pyogenic infections, otitis ... bronchopneumonia. His moth... were heterozygous for this mutation. The combination of flow cytometry and genetic study is necessary in the diagnosis of X-linked agammaglobulinemia and may be used for subsequent genetic counseling, carrier detection and prenatal diagnosis. *(Asian Pac J Allergy Immunol 2013;31:320-4)*

Key words: BTK gene, splice site mutation, X-linked agammaglobulinemia

Introduction

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Case study

- 7 year-old Malay boy

History of pyogenic infections since 1 year-old

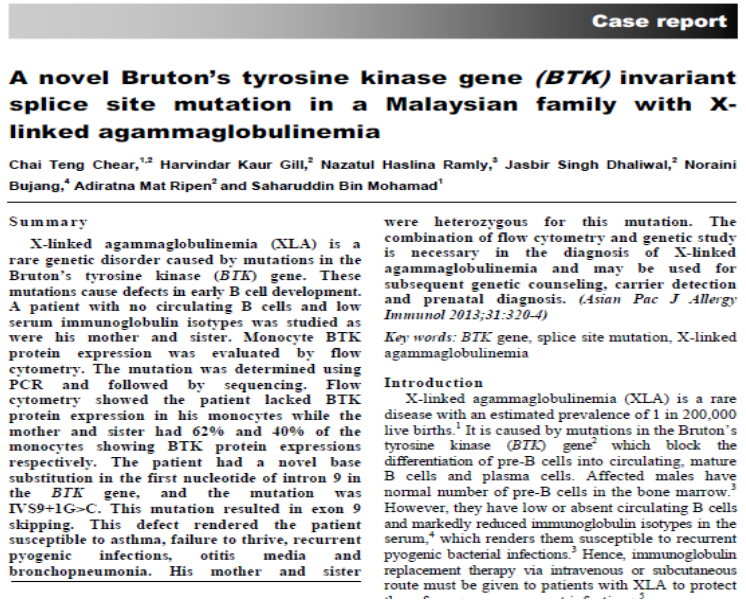
Recurrent otitis media

Recurrent bronchopneumonia

Asthma

Failure to thrive

Bronchiectasis



Case report

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Summary

X-linked agammaglobulinemia (XLA) is a rare genetic disorder caused by mutations in the Bruton's tyrosine kinase (*BTK*) gene. These mutations cause defects in early B cell development. A patient with no circulating B cells and low serum immunoglobulin isotypes was studied as were his mother and sister. Monocyte BTK protein expression was evaluated by flow cytometry. The mutation was determined using PCR and followed by sequencing. Flow cytometry showed the patient lacked BTK protein expression in his monocytes while the mother and sister had 62% and 40% of the monocytes showing BTK protein expressions respectively. The patient had a novel base substitution in the first nucleotide of intron 9 in the *BTK* gene, and the mutation was IVS9+1G>C. This mutation resulted in exon 9 skipping. This defect rendered the patient susceptible to asthma, failure to thrive, recurrent pyogenic infections, otitis media and bronchopneumonia. His mother and sister were heterozygous for this mutation. The combination of flow cytometry and genetic study is necessary in the diagnosis of X-linked agammaglobulinemia and may be used for subsequent genetic counseling, carrier detection and prenatal diagnosis. *(Asian Pac J Allergy Immunol 2013;31:320-4)*

Key words: BTK gene, splice site mutation, X-linked agammaglobulinemia

Introduction

X-linked agammaglobulinemia (XLA) is a rare disease with an estimated prevalence of 1 in 200,000 live births.[1] It is caused by mutations in the Bruton's tyrosine kinase (*BTK*) gene[2] which block the differentiation of pre-B cells into circulating, mature B cells and plasma cells. Affected males have normal number of pre-B cells in the bone marrow.[3] However, they have low or absent circulating B cells and markedly reduced immunoglobulin isotypes in the serum,[4] which renders them susceptible to recurrent pyogenic bacterial infections.[5] Hence, immunoglobulin replacement therapy via intravenous or subcutaneous route must be given to patients with XLA to protect

Chear *et al.,* 2013 (APJAI). doi: 10.12932/AP0304.31.4.2013.

- Routine immunology tests:
  - Patient had no B cells, low serum immunoglobulin isotypes
  - Suspected to have Predominant antibody deficiencies? (i.e. X-linked agammaglobulinemia)

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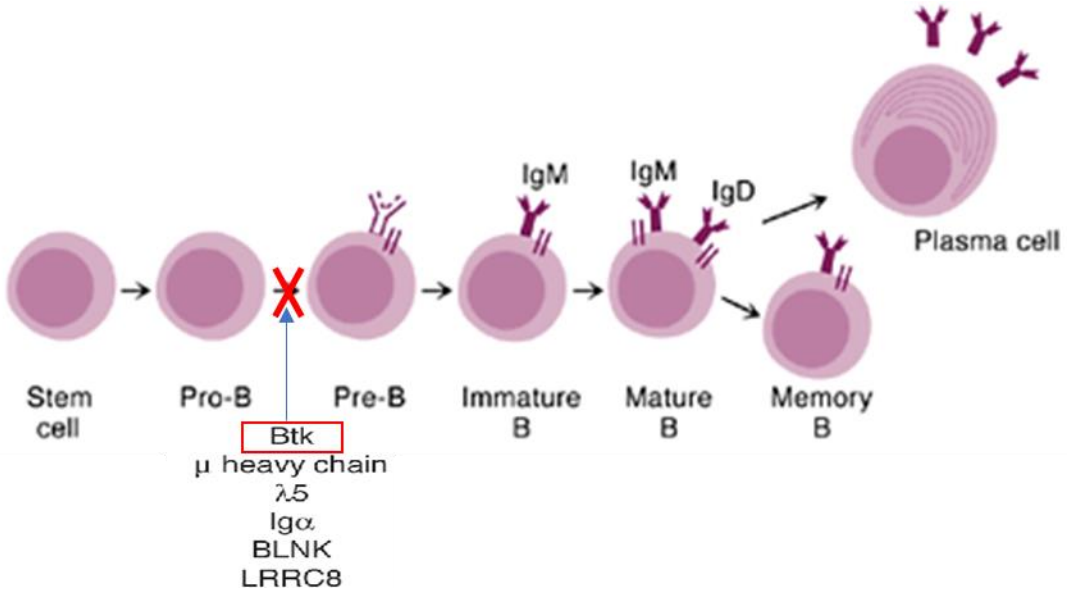
X-linked agammaglobulinemia (XLA)

- Bruton's agammaglobulinemia or Bruton's disease, is a rare, recessive genetic disorder caused by mutation in the Bruton’s tyrosine kinase (*BTK*) gene.
- XLA is characterized by the improper development of B cells, leading to a lack of mature B cells and antibodies



Genes required for B cell development

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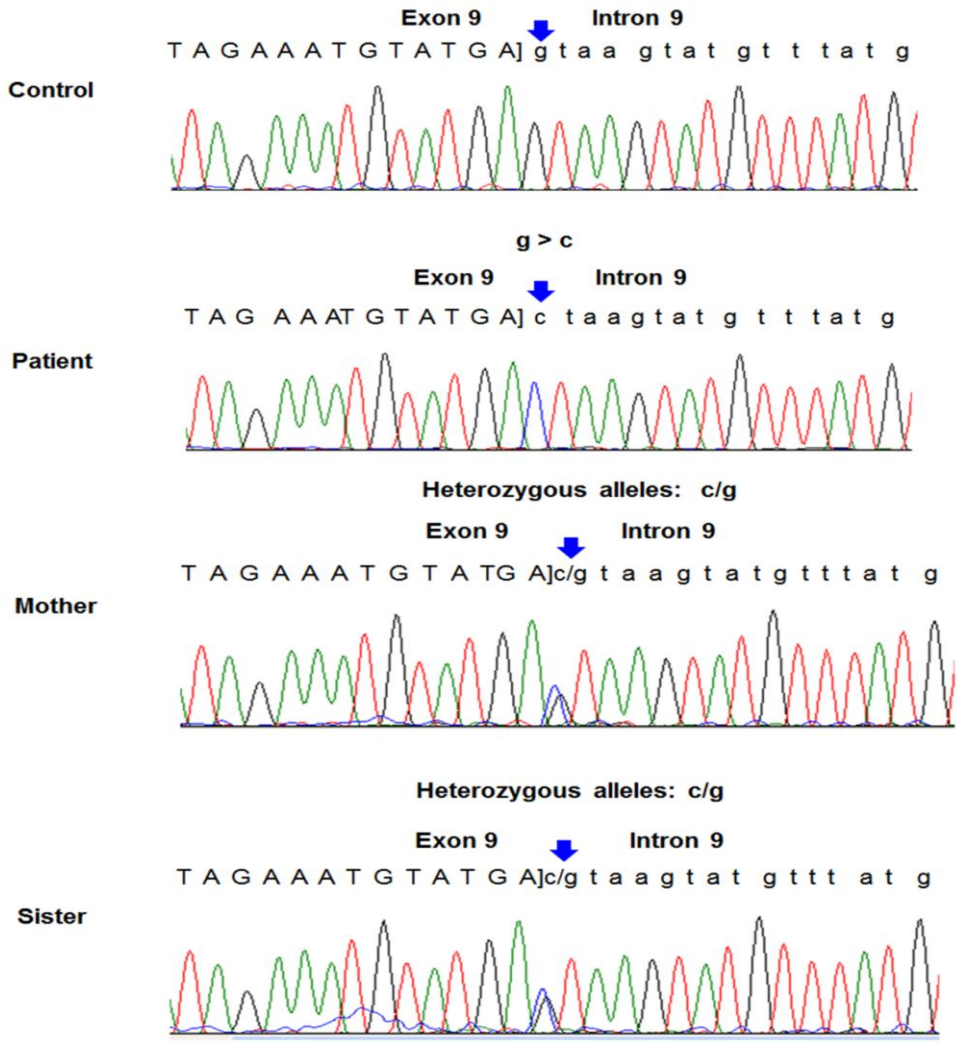
Genetic testing- Single gene testing



Sequencing of *BTK* gene

Genetic testing confirmed

i) Diagnosis of XLA for the patient

ii) Carrier status in the mother and sister

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Challenges

- Disease diagnosis remains difficult solely based on clinical phenotypes:
  - ❖ Common symptoms among different kind of diseases (Bousfiha *et al.,* 2020).
  - ❖ Complex or atypical clinical phenotypes (Gallo *et al.,* 2016).

- Other challenges in disease diagnosis:
  - ❖ Disease caused by multiple genes or variants (Tangye *et al.,* 2020).

- Patients exhibiting complex phenotypes without a pronounced candidate gene for testing, may have delayed disease diagnosis.
  - ❖ Single gene testing appears to be costly and inefficient when a serial testing of each candidate gene is required.
  - ❖ A confirmed molecular diagnosis can only be obtained after months, or even years (Haworth et al., 2016).

Whole-exome sequencing (WES) in rare genetic disease diagnosis

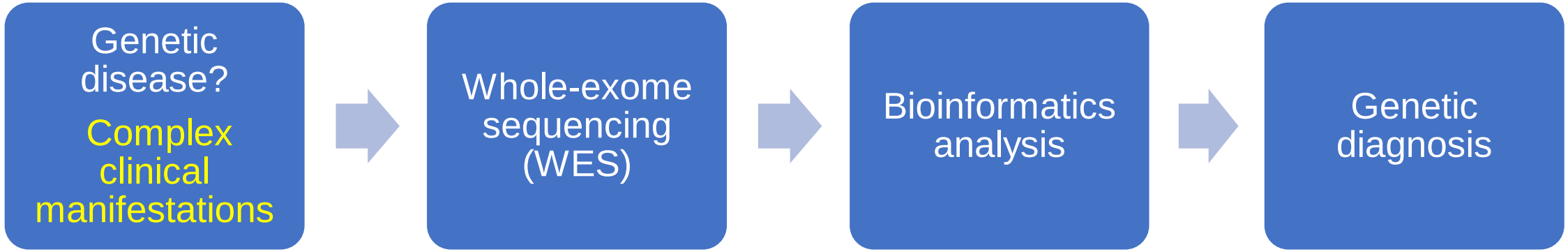
- Human genome: ~3 billion nucleotides (Hawkins, 2017)
- Protein coding region: ~1-2% of the human genome (Haworth et al., 2016)

- ~85% of disease-causing mutations occur at exonic region (Petersen et al., 2017).

- WES: sequencing ~20k protein-coding genes (Meyts et al., 2016)
  - ❖cost- and time-effective strategy

- Application in the molecular diagnosis of genetic disorders:
  - ❖ Complex clinical presentations (Gallo et al., 2016; Seleman et al., 2017)

Workflow for Genetic Testing (2)



Benefits of WES:

- WES is a large-scale, massively parallel DNA-sequencing technology that concurrently sequencing of thousands of genes (Resta et al., 2018).
- A virtual gene panel can be generated and applied to the analysis of DNA sequence data obtained from a whole-exome.
- Addition or removal of genes can be done for revisiting the investigation using virtual gene panel, without the need for a repeated sequencing (Haworth et al., 2016).

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Publications

Clinical Immunology 211 (2020) 108328

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

A novel *de novo NLRC4* mutation reinforces the likely pathogenicity of specific LRR domain mutation

Chai Teng Chear[a,b], Revathy Nallusamy[c], Scott W. Canna[d], Kwai Cheng Chan[c], Mohd Farid Baharin[a], Munirah Hishamshah[a], Hamidah Ghani[b], Adiratna Mat Ripen[a,1], Saharuddin Bin Mohamad[b,e,*,1]

[a] Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, Ministry of Health, Malaysia
[b] Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia
[c] Pediatric Department, Penang General Hospital, Ministry of Health, Malaysia
[d] Pediatrics and Immunology, University of Pittsburgh, Pittsburgh, PA, USA
[e] Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), University of Malaya, Kuala Lumpur, Malaysia

ORIGINAL RESEARCH article

Front. Immunol., 04 November 2021 | https://doi.org/10.3389/fimmu.2021.778133

Revealing Chronic Granulomatous Disease in a Patient With Williams-Beuren Syndrome Using Whole Exome Sequencing

Adiratna Mat Ripen[1*†], Mei Yee Chiow[2†], Prakash Rao Rama Rao[3] and Saharuddin Bin Mohamad[2,4*]

[1]Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health Malaysia, Selangor, Malaysia
[2]Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia
[3]Pediatrics Department, Keningau Hospital, Ministry of Health Malaysia, Sabah, Malaysia
[4]Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), University of Malaya, Kuala Lumpur, Malaysia

Received: 27 January 2021 | Revised: 18 May 2021 | Accepted: 18 May 2021

DOI: 10.1111/cei.13626

ORIGINAL ARTICLE

Clinical & Experimental Immunology

A single-center pilot study in Malaysia on the clinical utility of whole-exome sequencing for inborn errors of immunity

Adiratna Mat Ripen[1] | Chai Teng Chear[1,2] | Mohd Farid Baharin[1] | Revathy Nallusamy[3] | Kwai Cheng Chan[3] | Asiah Kassim[4] | Chong Ming Choo[5] | Ke Juin Wong[6] | Siew Moy Fong[6] | Kah Kee Tan[7] | Jeyaseelan P. Nachiappan[8] | Kai Ru Teo[9] | Mei Yee Chiow[2] | Munirah Hishamshah[1] | Hamidah Ghani[2] | Rikeish R. Muralitharan[1,10] | Saharuddin Bin Mohamad[2,11]

[1]Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, Ministry of Health, Selangor, Malaysia
[2]Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia
[3]Pediatric Department, Penang General Hospital, Ministry of Health, Penang, Malaysia
[4]Pediatric Department, Kuala Lumpur Hospital, Ministry of Health, Kuala Lumpur, Malaysia
[5]Pediatric Department, Sultan Abdul Halim Hospital, Ministry of Health, Kedah, Malaysia
[6]Pediatric Department, Likas Hospital, Ministry of Health, Sabah, Malaysia
[7]Pediatric Department, Tuanku Ja'afar Hospital, Ministry of Health, Seremban, Malaysia
[8]Pediatric Department, Raja Permaisuri Bainun Hospital, Ministry of Health, Perak, Malaysia
[9]Pediatric Department, Sultan Ismail Johor Bahru Hospital, Ministry of Health, Johor, Malaysia
[10]Hypertension Research Laboratory, School of Biological Sciences, Faculty of Science, Monash University, Melbourne, Victoria, Australia
[11]Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), University of Malaya, Kuala Lumpur, Malaysia

Correspondence
Adiratna Mat Ripen, Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Selangor, Malaysia.
Email: adiratna@moh.gov.my

Funding information
Kementerian Kesihatan Malaysia, Grant/Award Number: NMRR-16-892-31023

Abstract

Primary immunodeficiency diseases refer to inborn errors of immunity (IEI) that affect the normal development and function of the immune system. The phenotypical and genetic heterogeneity of IEI have made their diagnosis challenging. Hence, whole-exome sequencing (WES) was employed in this pilot study to identify the genetic etiology of 30 pediatric patients clinically diagnosed with IEI. The potential causative variants identified by WES were validated using Sanger sequencing. Genetic diagnosis was attained in 46.7% (14 of 30) of the patients and categorized into autoinflammatory disorders ($n = 3$), diseases of immune dysregulation ($n = 3$), defects in intrinsic and innate immunity ($n = 3$), predominantly antibody deficiencies ($n = 2$), combined immunodeficiencies with associated and syndromic features ($n = 2$) and immunodeficiencies affecting cellular and humoral immunity ($n = 1$). Of the 15 genetic variants identified, two were novel variants. Genetic findings differed from the provisional clinical diagnoses in seven cases (50.0%). This study showed that WES enhances the capacity to diagnose IEI, allowing more patients to receive appropriate therapy and disease management.

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01017-3

ORIGINAL ARTICLE

Atypical Presentation of Severe Fungal Necrotizing Fasciitis in a Patient with X-Linked Agammaglobulinemia

Chai Teng Chear [1] · Revathy Nallusamy [2] · Kwai Cheng Chan [2] · Ratna Mohd Tap [3] · Mohd Farid Baharin [1] · Sharifah Nurul Husna Syed Yahya [1] · Prasobhan Bala Krishnan [1] · Saharuddin Bin Mohamad [4,5] · Adiratna Mat Ripen [1]

Received: 12 December 2020 / Accepted: 2 March 2021

[1] Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Selangor, Malaysia
[2] Pediatric Department, Penang General Hospital, Ministry of Health, Penang, Malaysia
[3] Medical Mycology Laboratory, Infectious Diseases Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health, Selangor, Malaysia
[4] Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia
[5] Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), University of Malaya, Kuala Lumpur, Malaysia

genes

MDPI

Article

A Novel De Novo *NFKBIA* Missense Mutation Associated to Ectodermal Dysplasia with Dysgammaglobulinemia

Chai Teng Chear [1,†], Bader Abdul Kader El Farran [2,†], Marina Sham [3], Kavetha Ramalingam [4], Lokman Mohd Noh [3], Intan Hakimah Ismail [5], Mei Yee Chiow [2], Mohd Farid Baharin [1], Adiratna Mat Ripen [1,*] and Saharuddin Bin Mohamad [2,6,*]

[1] Primary Immunodeficiency Unit, Allergy and Immunology Research Centre, Institute for Medical Research, National Institutes of Health, Ministry of Health Malaysia, Setia Alam 40170, Malaysia
[2] Institute of Biological Sciences, Faculty of Science, Universiti Malaya, Kuala Lumpur 50603, Malaysia
[3] Pediatric Department, Kuala Lumpur Hospital, Ministry of Health Malaysia, Kuala Lumpur 50586, Malaysia
[4] Pediatric Department, Taiping Hospital, Ministry of Health Malaysia, Taiping 34000, Malaysia
[5] Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Malaysia
[6] Centre of Research in Systems Biology, Structural Bioinformatics and Human Digital Imaging (CRYSTAL), Universiti Malaya, Kuala Lumpur 50603, Malaysia
* Correspondence: adiratna@moh.gov.my (A.M.R.); saharuddin@um.edu.my (S.B.M.); Tel.: +603-33627744 (A.M.R.); +603-79674118 (S.B.M.)
† These authors contributed equally to this work.

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Citation: Chear, C.T.; El Farran, B.A.K.; Sham, M.; Ramalingam, K.; Noh, L.M.; Ismail, I.H.; Chiow, M.Y.; Baharin, M.F.; Ripen, A.M.; Mohamad, S.B. A Novel De Novo *NFKBIA* Missense Mutation Associated to Ectodermal Dysplasia with Dysgammaglobulinemia. *Genes* **2022**, *13*, 1900. https://doi.org/10.3390/genes13101900

Academic Editor: Stefania Zampatti

Received: 15 September 2022
Accepted: 11 October 2022
Published: 19 October 2022

Abstract: Background: Inborn errors of immunity (IEIs) are comprised of heterogeneous groups of genetic disorders affecting immune function. In this report, a 17-month-old Malay patient suspected of having Hyper IgM syndrome, a type of IEIs, was described. However, the diagnosis of Hyper IgM syndrome was excluded by the normal functional studies and the mild features of ectodermal dysplasia observed from a further clinical phenotype inspection. Methods: Whole-exome sequencing (WES) was performed to unravel the causative mutation in this patient. Results: The variant analysis demonstrated a novel missense mutation in *NFKBIA* (NM_020529:c.94A > T,NP_065390:p.Ser32Cys) and was predicted as damaging by in silico prediction tools. The *NFKBIA* gene encodes for IκBα, a member of nuclear factor kappa B (NF-κB) inhibitors, playing an important role in regulating NF-κB activity. The mutation occurred at the six degrons (Asp31-Ser36) in IκBα which were evolutionarily conserved across several species. Prediction analysis suggested that the substitution of Ser32Cys may cause a loss of the phosphorylation site at residue 32 and a gain of the sumoylation site at residue 38, resulting in the alteration of post-translational modifications of IκBα required for NF-κB activation. Conclusion: Our analysis hints that the post-translational modification in the *NFKBIA* Ser32Cys mutant would alter the signaling pathway of NF-κB. Our findings support the usefulness of WES in diagnosing IEIs and suggest the role of post-translational modification of IκBα.

Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 8: 1–8

DOI: 10.1177/2050312120922652
journals.sagepub.com/home/smo

SAGE

Whole exome sequencing identifies compound heterozygous variants of *CR2* gene in monozygotic twin patients with common variable immunodeficiency

Adiratna Mat Ripen[1], Hamidah Ghani[2], Chai Teng Chear[1], Mei Yee Chiow[2], Sharifah Nurul Husna Syed Yahya[1], Asiah Kassim[3] and Saharuddin Bin Mohamad[2,4]

IPOPI 4TH REGIONAL ASIAN PID MEETING
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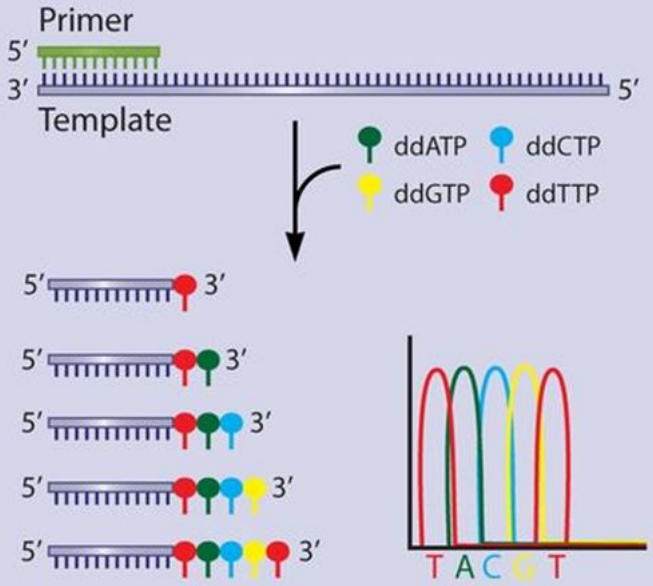
an IPOPI event

Evolution and future of genetic testing

First Generation
Shotgun Sequencing

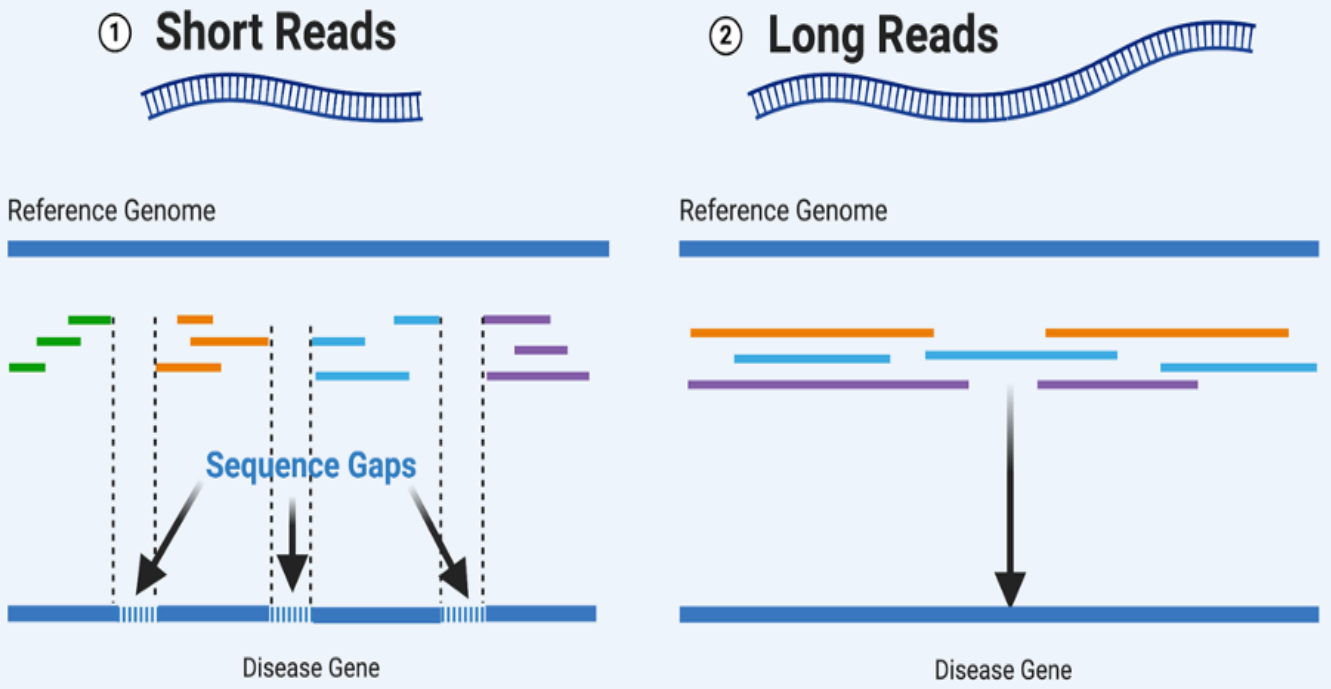


- Sequencing by synthesis
- High accuracy
- Long read lengths
- Relatively small amount of data generated

e.g., ABI capillary sequencer (ABI)

Second Generation
Massively Parallel Sequencing

Third Generation
Single-molecule Sequencing



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