

wellcome
connecting
science

Translational approach: GWAS in congenital heart defect

Dr Sathiya Maran

14 June 2022



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Visual settings



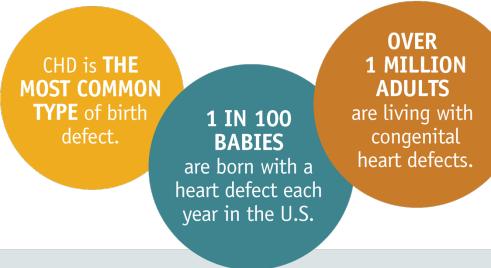
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CONGENITAL HEART DEFECTS (CHD)

are present **AT BIRTH** and occur when a baby's **HEART**
DOES NOT DEVELOP OR WORK THE WAY IT SHOULD.



THE GOOD NEWS IS...



...**9 OUT OF 10** children born with a heart defect now **SURVIVE INTO ADULTHOOD** thanks to medical advances.

LONG-TERM CHD CHALLENGES



- | | | | |
|---|--|---|--|
|  Heart Valve Problems |  Pulmonary Hypertension |  Abnormal Heart Rhythms (arrhythmias) |  Anxiety and Depression |
|  Heart Infections (endocarditis) |  Heart Failure |  Need for Repeat Surgeries or Procedures |  Stroke |

How to LIVE WELL with CHD

- | | | | | |
|--|--|--|---|--|
|  Understand your heart defect and ask questions |  Ask if it is safe for you to get pregnant |  Keep all follow-up medical appointments - even if you are feeling well |  Meet with a heart (or CHD) specialist when reaching adulthood |  Maintain regular dental checkups |
|  Seek emotional support as needed |  Know your health insurance options |  | | |

Information provided for educational purposes only. Please consult your health care provider regarding your specific health needs.

For more information, visit CardioSmart.org/CHD

If you would like to download or order additional posters on various topics, visit CardioSmart.org/Posters

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SUSTAINABLE DEVELOPMENT GOALS

17 GOALS TO TRANSFORM OUR WORLD

1 NO POVERTY



2 ZERO HUNGER



3 GOOD HEALTH AND WELL-BEING



4 QUALITY EDUCATION



5 GENDER EQUALITY



6 CLEAN WATER AND SANITATION



7 AFFORDABLE AND
CLEAN ENERGY



8 DECENT WORK AND
ECONOMIC GROWTH



9 INDUSTRY, INNOVATION
AND INFRASTRUCTURE



10 REDUCED INEQUALITIES



11 SUSTAINABLE CITIES
AND COMMUNITIES



12 RESPONSIBLE
CONSUMPTION
AND PRODUCTION



13 CLIMATE ACTION



14 LIFE BELOW WATER



15 LIFE ON LAND



16 PEACE, JUSTICE
AND STRONG INSTITUTIONS



17 PARTNERSHIPS
FOR THE GOALS



 SUSTAINABLE
DEVELOPMENT
GOALS

Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017

GBD 2017 Congenital Heart Disease Collaborators*



South Asia

South Asia	75 091 (38 351 to 109 094)	66 984 (50 484 to 81 590)	-10·8% (-38·2 to 34·5)	154·8 (76·6 to 223·5)	138·5 (95·5 to 176·6)	-10·6% (-38·3 to 29·4)	4·8 (2·5 to 7·0)	4·0 (3·0 to 4·9)	-17·0% (-42·1 to 21·0)
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(Table 1 continues on next page)

Number of deaths (all ages)

Mortality per 100 000 children younger than 1 year

Age-standardised mortality per 100 000 individuals

1990

2017

Percentage change,
1990–2017

1990

2017

Percentage change,
1990–2017

1990

2017

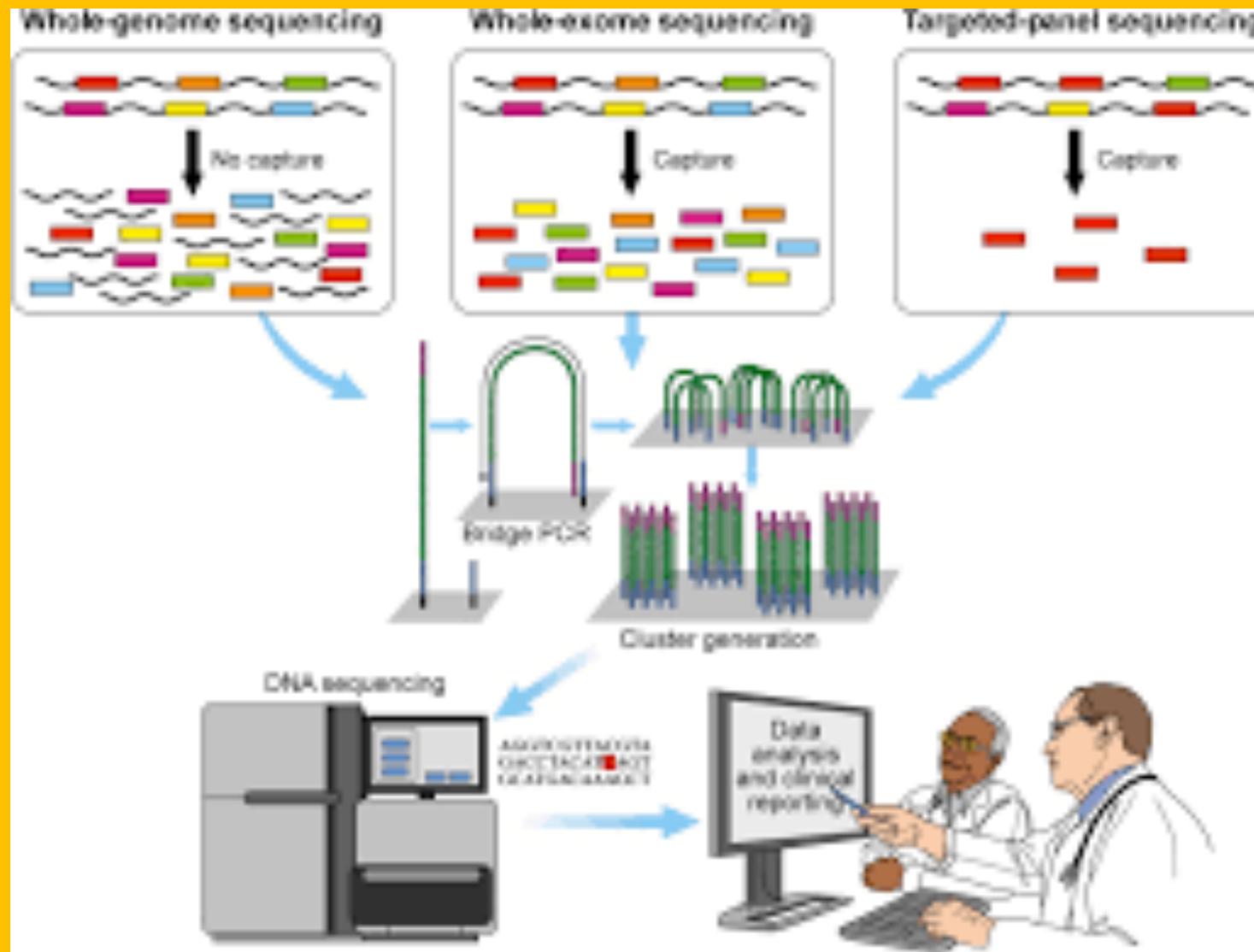
Percentage change,
1990–2017

(Continued from previous page)

Southeast Asia, east Asia, and Oceania

East Asia	93 878 (80 522 to 113 589)	31 885 (29 266 to 35 408)	-66·0% (-72·5 to -58·2)*	254·8 (217·6 to 312·0)	112·5 (103·0 to 125·7)	-55·9% (-66·0 to -46·2)*	7·4 (6·3 to 8·9)	3·4 (3·1 to 3·7)	-54·5% (-63·6 to -44·1)*
Oceania	775 (440 to 1071)	1 307 (790 to 1793)	68·8% (23·8 to 126·7)*	244·2 (137·7 to 348·0)	226·4 (126·0 to 327·7)	-7·3% (-35·6 to 32·8)	8·3 (4·9 to 11·2)	7·7 (4·8 to 10·5)	-6·7% (-30·5 to 23·6)
Southeast Asia	42 680 (25 044 to 55 932)	23 976 (19 721 to 27 605)	-43·8% (-56·5 to -19·3)*	268·3 (151·0 to 352·8)	153·1 (120·2 to 181·0)	-42·9% (-55·3 to -17·6)*	7·3 (4·3 to 9·6)	4·4 (3·6 to 5·1)	-40·4% (-53·8 to -15·3)*

Next-Generation Sequencing as a Tool for CHD





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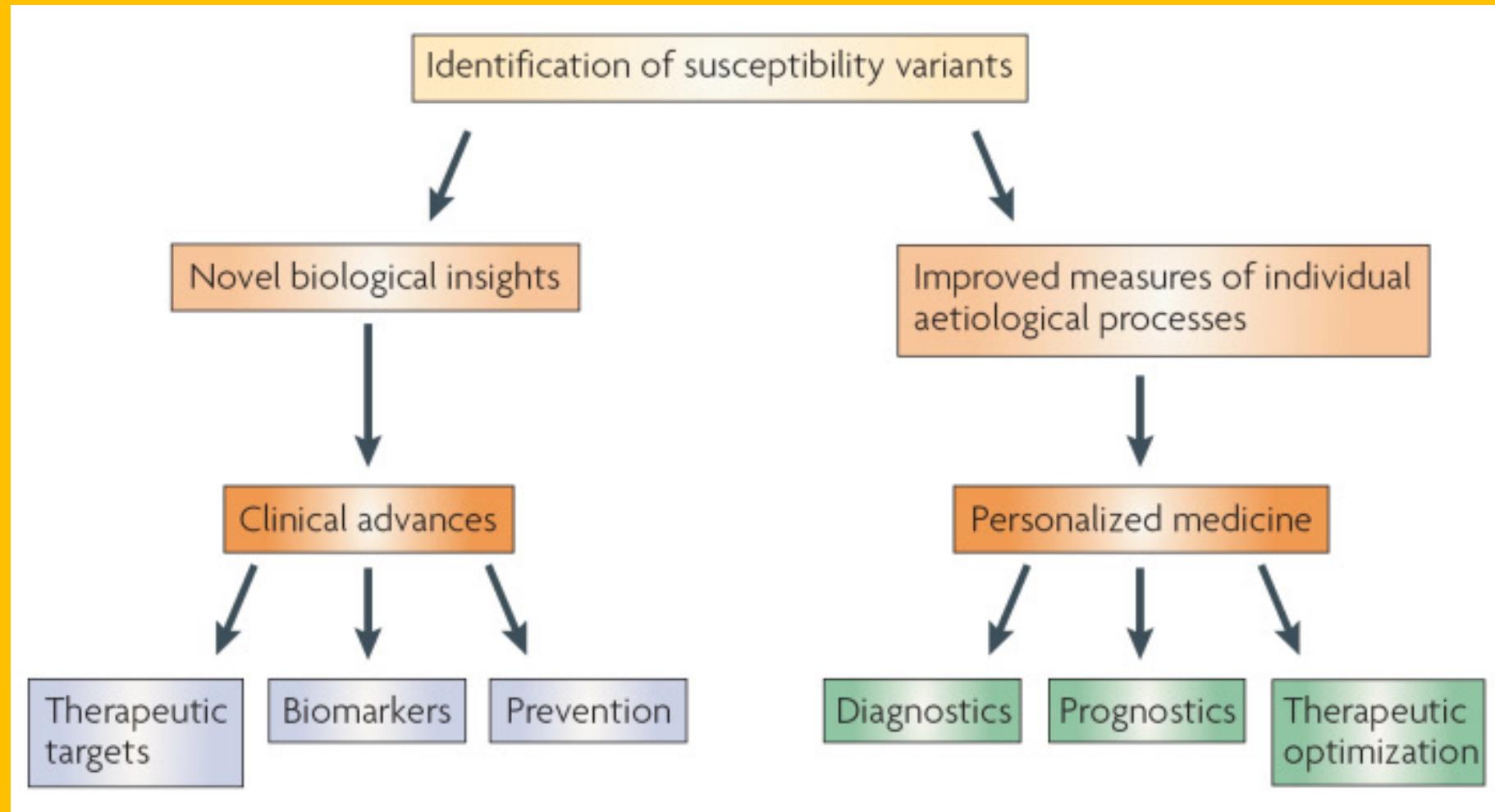
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How to link GWAS towards translational approach?

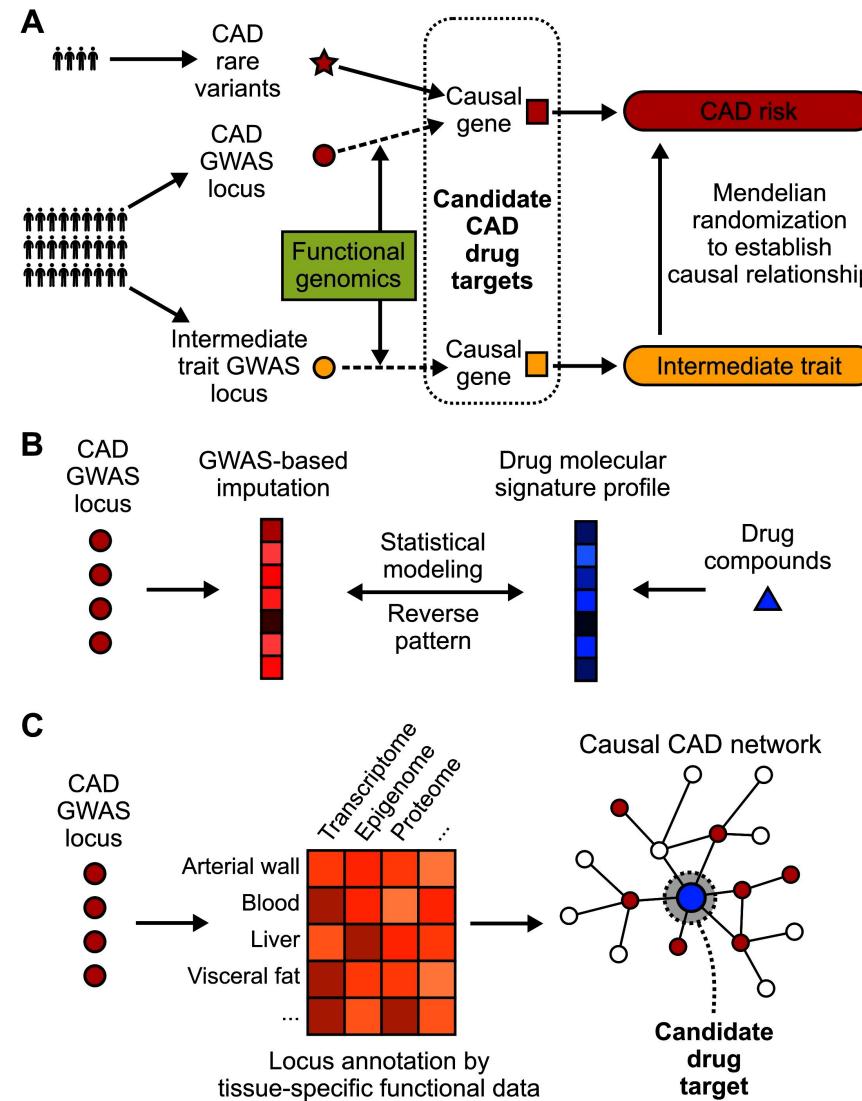


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Goals of GWAS



Therapeutic targets



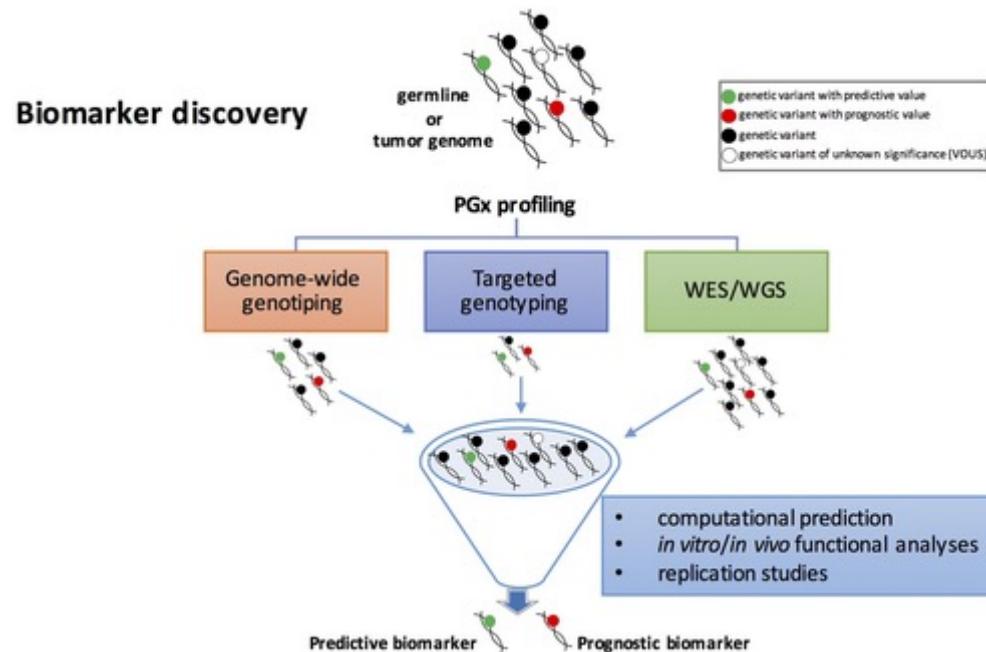
Network-Based Drug Discovery Approaches

“one drug → one target → one disease”

to the network mode

“multi-drugs → multi-targets → multi-diseases”

Biomarker discovery



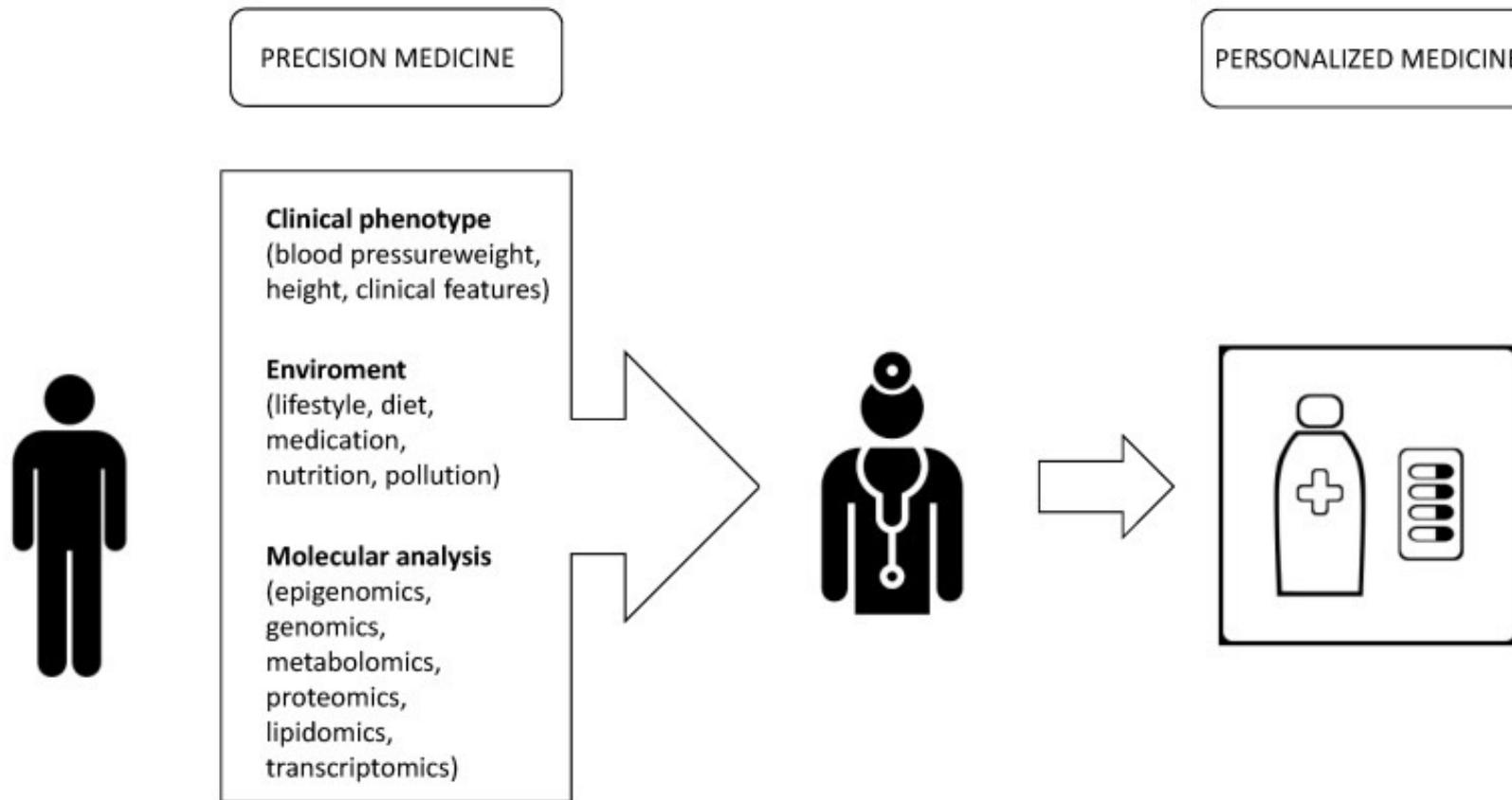
Biomarker translation



PGx assay assessment process



Personalised medicine- Diagnostics



RESEARCH ARTICLE

Mutations in the tail domain of *MYH3* contributes to atrial septal defect

Sathiya Maran^{1,2*}, Robson Ee³, Siti Aisyah Faten², Choi Sy Bing⁴, Kooi Yeong Khaw¹, Swee-Hua Erin Lim^{5†}, Kok-Song Lai^{5†}, Wan Pauzi Wan Ibrahim^{6‡}, Mohd Rizal Mohd Zain^{7‡}, Kok Gan Chan^{3,8‡}, Siew Hua Gan^{1‡}, Huay Lin Tan²

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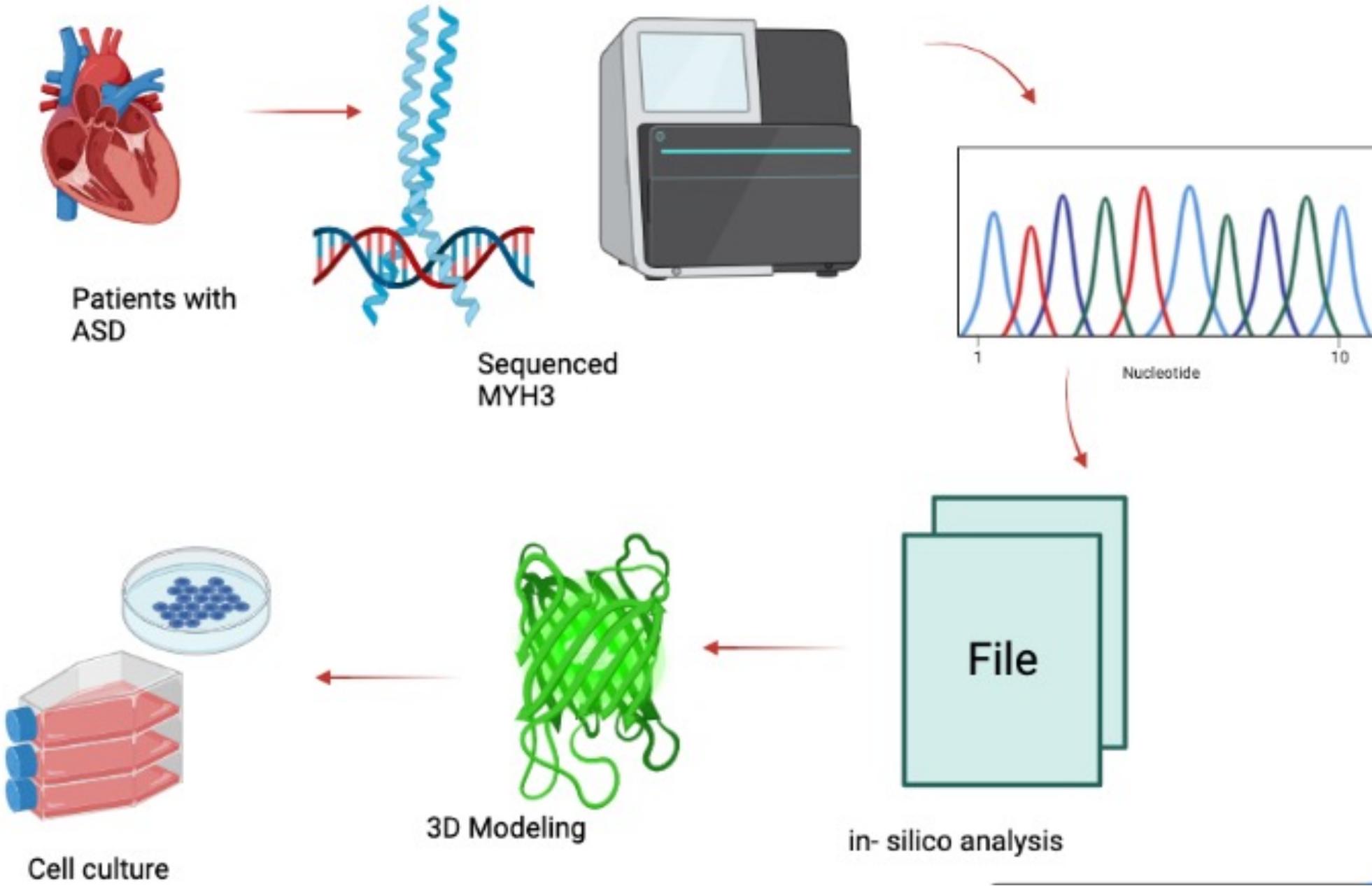
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Data Availability Statement: The original uncropped and unadjusted images of gel blot and

Abstract

Atrial septal defect (ASD) is one of the most common congenital heart defects diagnosed in children. Sarcomeric genes has been attributed to ASD and knockdown of *MYH3* functionally homologues gene in chick models indicated abnormal atrial septal development. Here, we report for the first time, a case-control study investigating the role of *MYH3* among non-syndromic ASD patients in contributing to septal development. Four amplicons which will amplifies the 40 kb *MYH3* were designed and amplified using long range-PCR. The amplicons were then sequenced using indexed paired-end libraries on the MiSeq platform. The STREGA guidelines were applied for planning and reporting. The non-synonymous c. 3574G>A (p.Ala1192Thr) [p = 0.001, OR = 2.30 (1.36–3.87)] located within the tail domain indicated a highly conserved protein region. The mutant model of c. 3574G>A (p. Ala1192Thr) showed high root mean square deviation (RMSD) values compared to the wild model. To our knowledge, this is the first study to provide compelling evidence on the pathogenesis of *MYH3* variants towards ASD hence, suggesting the crucial role of non-synonymous variants in the tail domain of *MYH3* towards atrial septal development. It is hoped that this gene can be used as panel for diagnosis of ASD in future.



Our findings

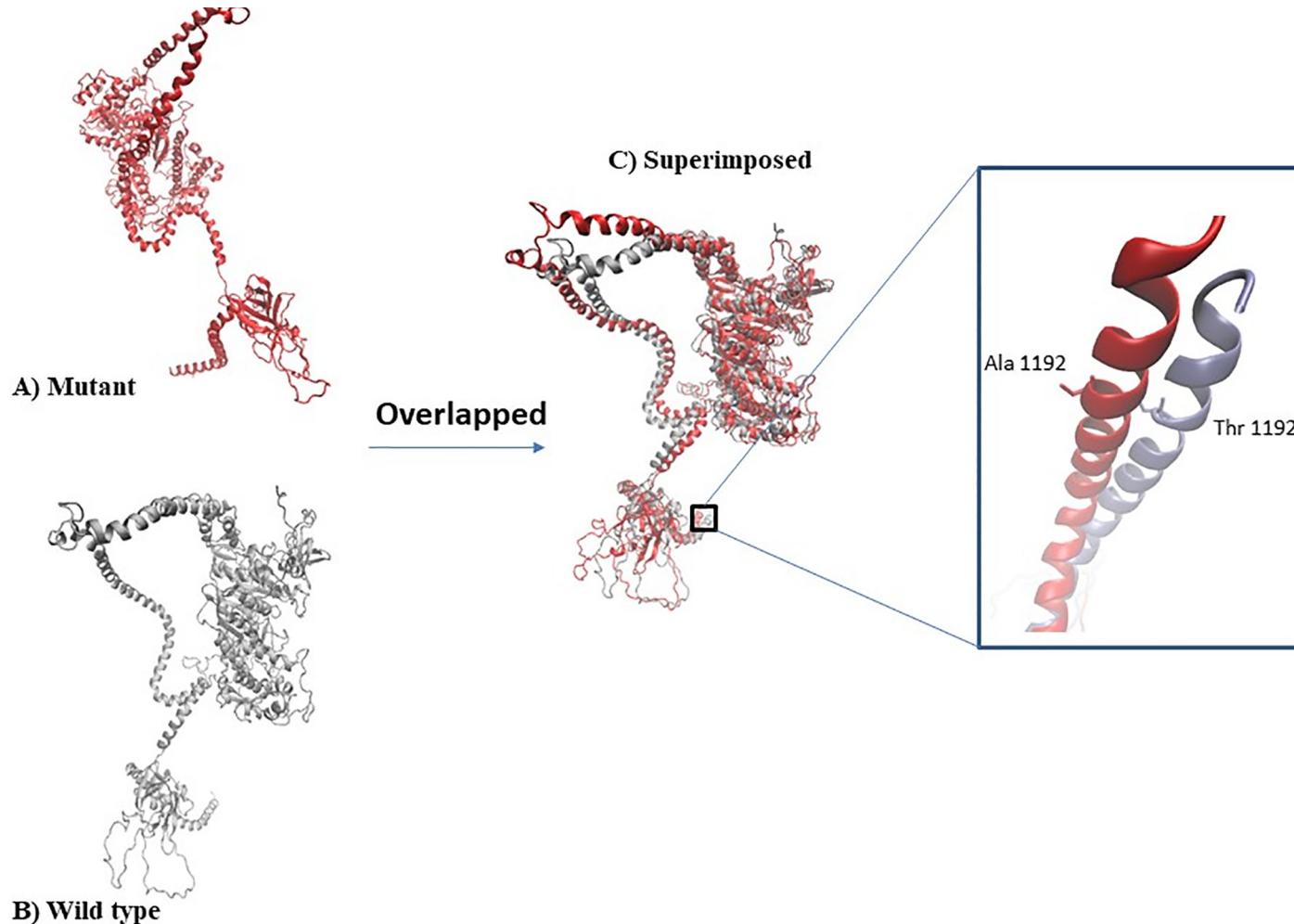


Fig 4. Structural comparison via RMSD analysis (a) Wild type built model (b) Mutant type built model (c) Superimposition of wild and mutant type model with RMSD value of 5.4 \AA .



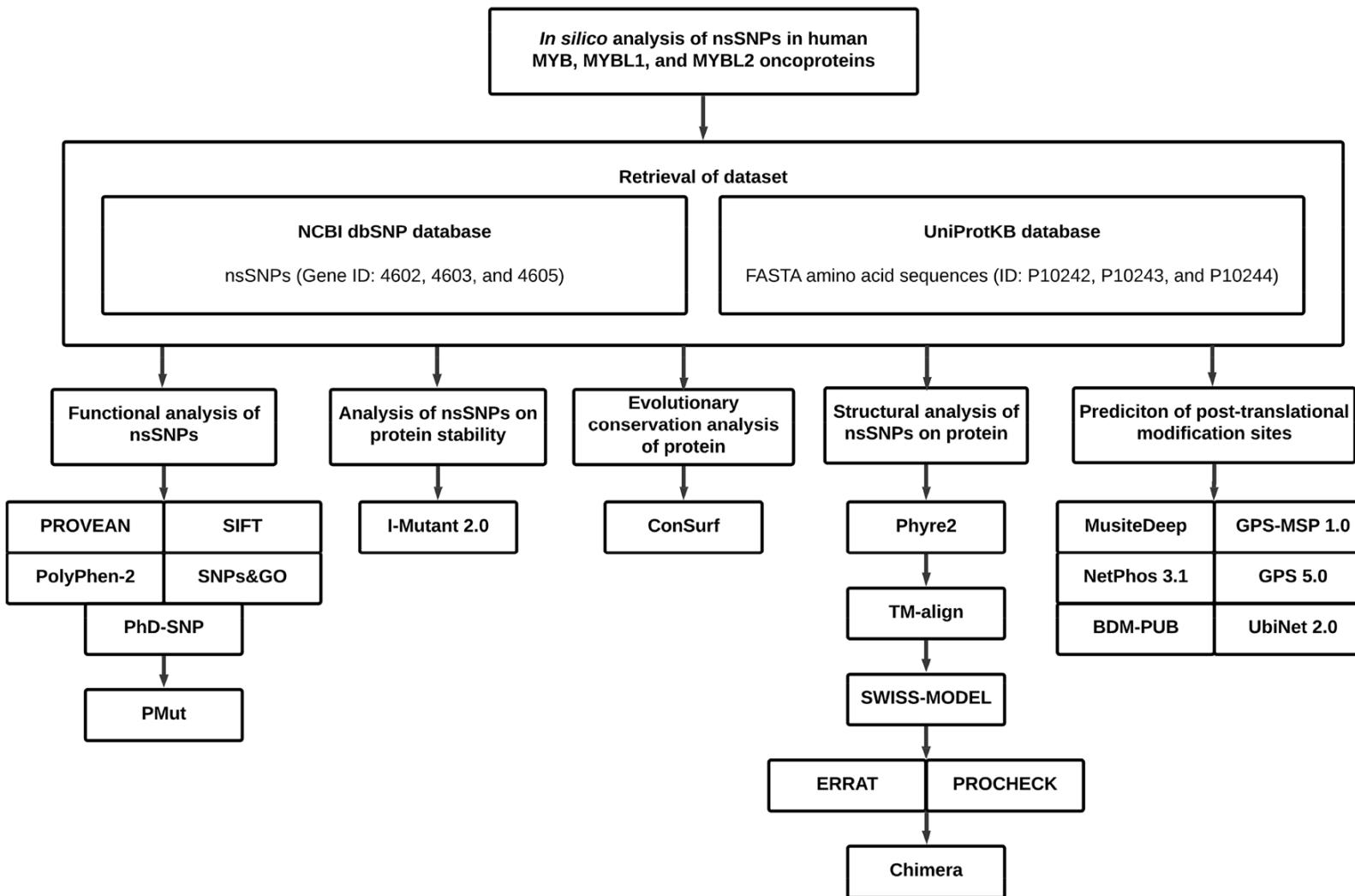
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Functional and structural analysis of non-synonymous single nucleotide polymorphisms (nsSNPs) in the MYB oncoproteins associated with human cancer

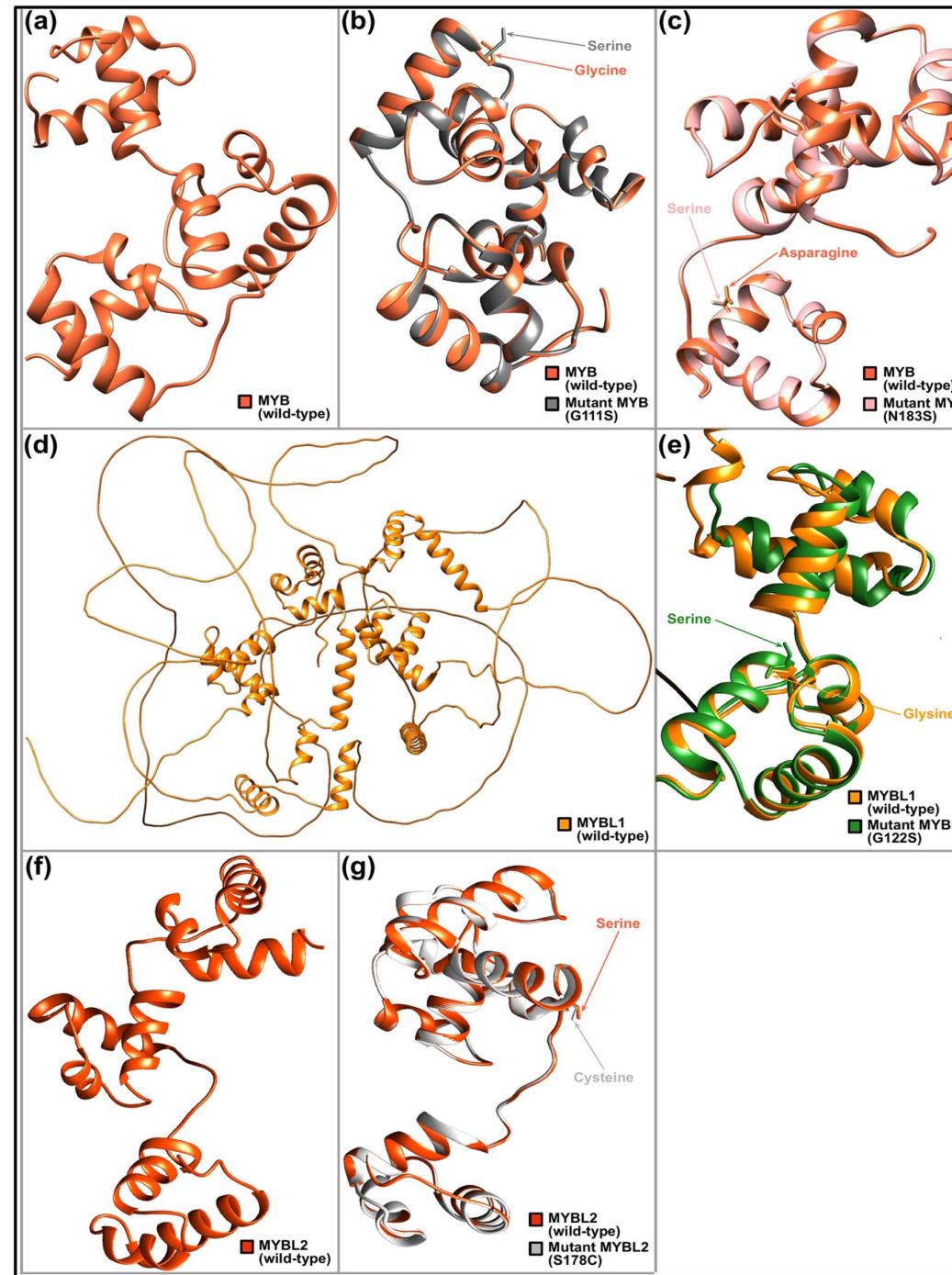
Shu Wen Lim², Kennet JunKai Tan², Osman Mohd Azuraidi¹, Maran Sathiya³, Ee Chen Lim², Kok Song Lai⁴, Wai-Sum Yap^{2✉} & Nik Abd Rahman Nik Mohd Afizan^{1✉}

MYB proteins are highly conserved DNA-binding domains (DBD) and mutations in MYB oncoproteins have been reported to cause aberrant and augmented cancer progression. Identification of MYB molecular biomarkers predictive of cancer progression can be used for improving cancer management. To address this, a biomarker discovery pipeline was employed in investigating deleterious non-synonymous single nucleotide polymorphisms (nsSNPs) in predicting damaging and potential alterations on the properties of proteins. The nsSNP of the MYB family; *MYB*, *MYBL1*, and *MYBL2* was extracted from the NCBI database. Five *in silico* tools (PROVEAN, SIFT, PolyPhen-2, SNPs&GO and PhD-SNP) were utilized to investigate the outcomes of nsSNPs. A total of 45 nsSNPs were predicted as high-risk and damaging, and were subjected to PMut and I-Mutant 2.0 for protein stability analysis. This resulted in 32 nsSNPs with decreased stability with a DDG score lower than -0.5, indicating damaging effect. G111S, N183S, G122S, and S178C located within the helix-turn-helix (HTH) domain were predicted to be conserved, further posttranslational modifications and 3-D protein analysis indicated these nsSNPs to shift DNA-binding specificity of the protein thus altering the protein function. Findings from this study would help in the field of pharmacogenomic and cancer therapy towards better intervention and management of cancer.

Methodology



Findings





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