港大醫學院發現常見於香港華人但罕被記載而與藥物有關的基因變異

HKUMed identifies rarely documented pharmacogenetic variants commonly found among Hong Kong Chinese

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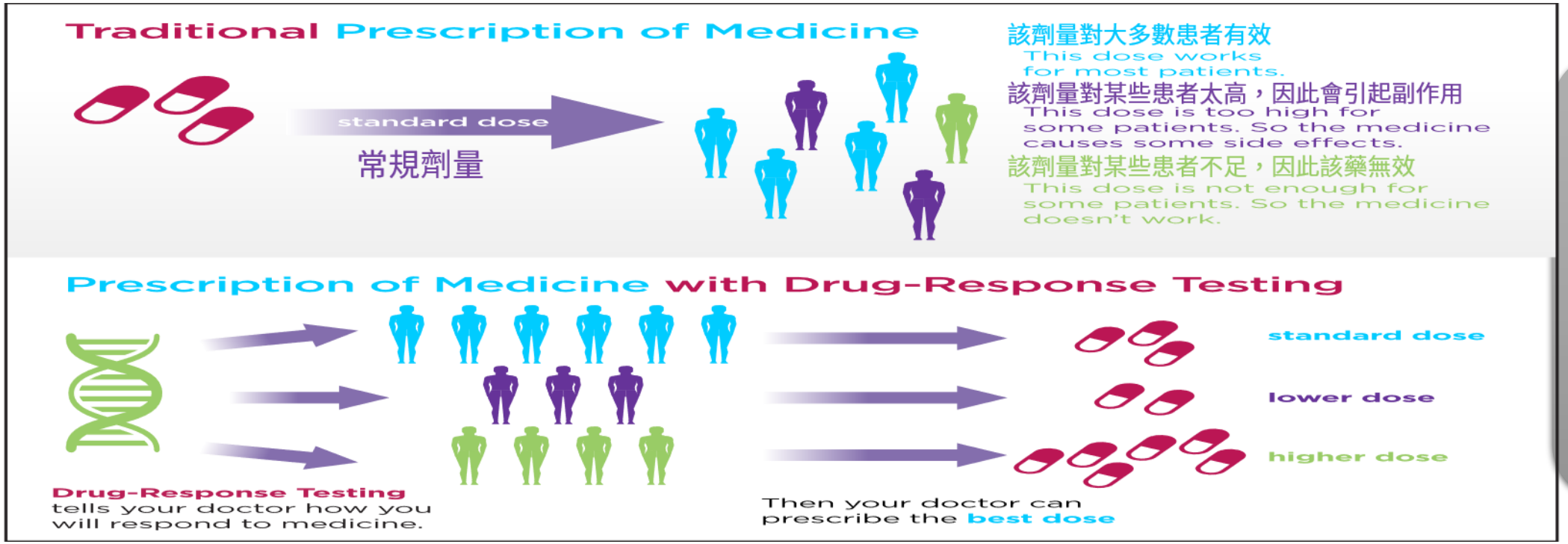
什麼是藥物基因組學？ What is pharmacogenomics (PGx)?

藥物基因組學分析你的遺傳構成如何影響你對藥物的反應。
Pharmacogenomics is the study of how your genetics change your response to medicine.

常規處方模式　Conventional prescription



劃一劑量未必適合所有人
One-size-fits-all approach may not suit everyone needs

以美國的情況為例（每年）　Issues in US (annually)

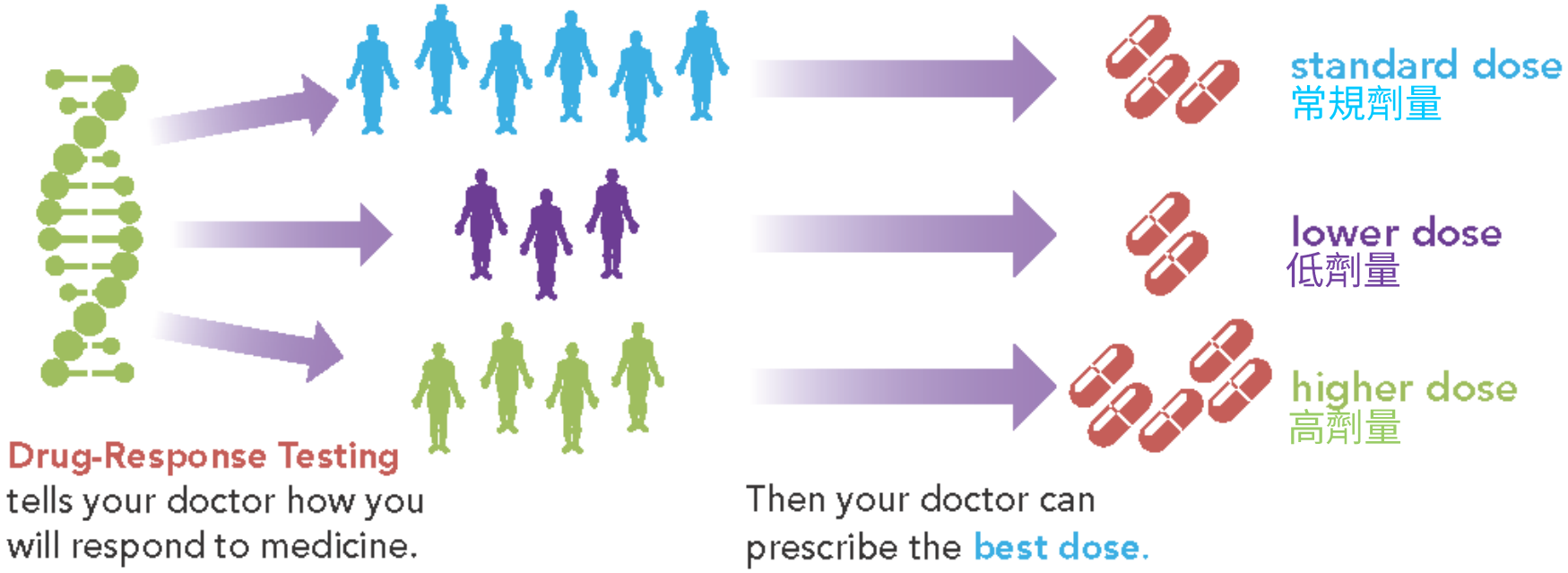
超過二百萬宗 Over 2 Million	嚴重藥物不良反應 serious ADR	十萬宗 100,000	不良反應引起的死亡 Death due to ADR	第四大死因 4th	Adverse drug reaction is the 4th leading cause of death

https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions

從被動到主動　From reactive to pre-emptive

主動測試指用藥前事先了解患者與藥物有關的基因變異。
Pre-emptive testing means testing before commencement of prescription.

藥物基因測試引導處方　Prescription of medicine with testing



個人化治療
Personalised medicine approach

優點 Benefits

- 事先預測患者對藥物的反應
- Predict the drug response of patients before dispensing
- 精準計算藥物劑量，避免引起不良反應
- Optimising drug dose and avoiding adverse events

研究目的 Research objectives

1. 鑒定香港華人群體裡已知會影響藥物治療效果而與藥物有關的基因變異

   Identify the pharmacogenetic variants that are known to affect drug responses in Hong Kong Chinese

2. 推算藥物基因組學對公共醫療系統處方藥物的影響（以2019年數據為例）
   Project prescription impact by PGx of HK public healthcare system using electronic health record data of 2019 as example

   - 利用醫院管理局臨床數據分析與報告系統（CDARS）獲取不含個人資料的公共醫療服務數據，當中包括藥物處方紀錄
     All public healthcare service data, including drug prescriptions, are available in the Clinical Data Analysis and Reporting System (CDARS) database in an unlisted and anonymous manner
   - 索取患者人數、藥物數量與藥物單價，以推算對處方藥物及相關開支之影響
     The number of subjects, drug quantity, and unit cost of drugs were retrieved for the estimation of prescription impact and drug expenditure

已知會影響藥物療效的基因變異
Medically actionable pharmacogenetic variants

CACNA1S	*CFTR*	*CYP2B6*	*CYP2C19*
CYP2C9	*CYP2D6*	*CYP3A5*	*CYP4F2*
DPYD	*IFNL3*	*NUDT15*	*RYR1*
SLCO1B1	*TMPT*	*UGT1A1*	*VKORC1*
HLA-A	*HLA-B*	*G6PD*	

額外添加特別影響華人臨床用藥的基因
Addition of gene strongly implicated in Chinese
CPIC - Level C
PharmGKB - Level 3

129 variants & 4 HLA alleles from 19 pharmacogenes
19個藥物基因中的129個變異與4個HLA等位基因

(Level A)

指引 Guideline

CPIC® Clinical Pharmacogenetic Implementation Consortiu

轉化基因研究成果為臨床處方規範的指引
Translating genetic laboratory test results into actionable prescribing decisions for affected drugs with detailed **gene/drug clinical practice guidelines**

(Level 1)

資料庫 Knowledge base

PharmGKB

聯繫基因變異與藥物反應的專業知識平台
A **comprehensive resource** that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

港大全外顯子組群 – 樣本收集
HKU exome cohort – sample recruitment

- 來自兒童及青少年科學系及外科學系的1,116個全外顯子數據組
- Collection of exome cohorts (n=1,116) from Department of Paediatrics & Adolescent Medicine and Department of Surgery

- 皆報稱為華人
- Self-reported Han Chinese

- 個體間無基因關係
- Genetically unrelated individuals

研究方法　Methodology

全外顯子測序
Exome
Pipeline

數據質素檢查
Quality check

基因數據庫
Genomic
repository

篩選與藥物有關的基因
Pharmacogenes
curation

分析基因變異
Gene variants
interpretation

處理、整合基因數據
Processing of aggregated data

個別分析
Specific analysis

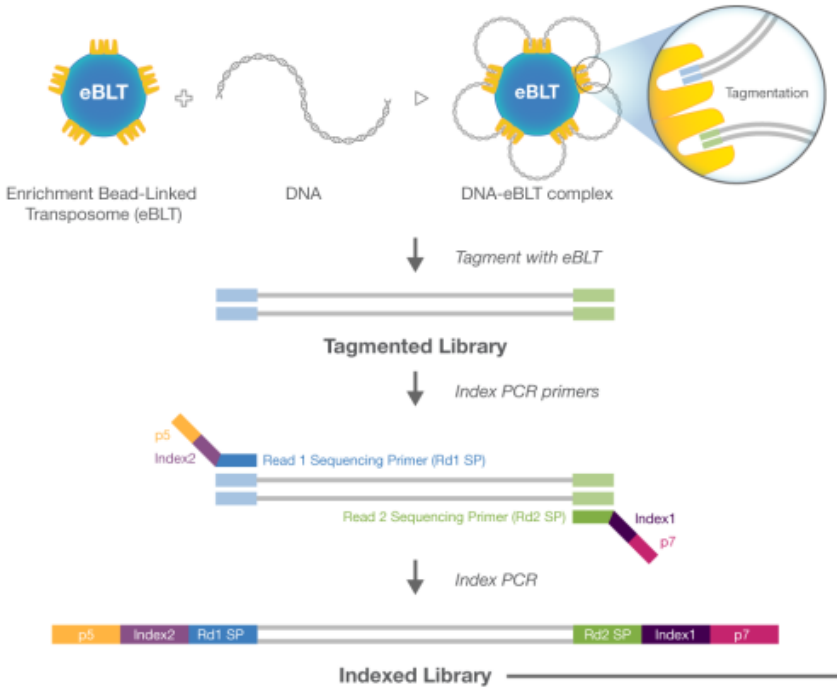
全外顯子測序　Whole exome sequencing pipeline

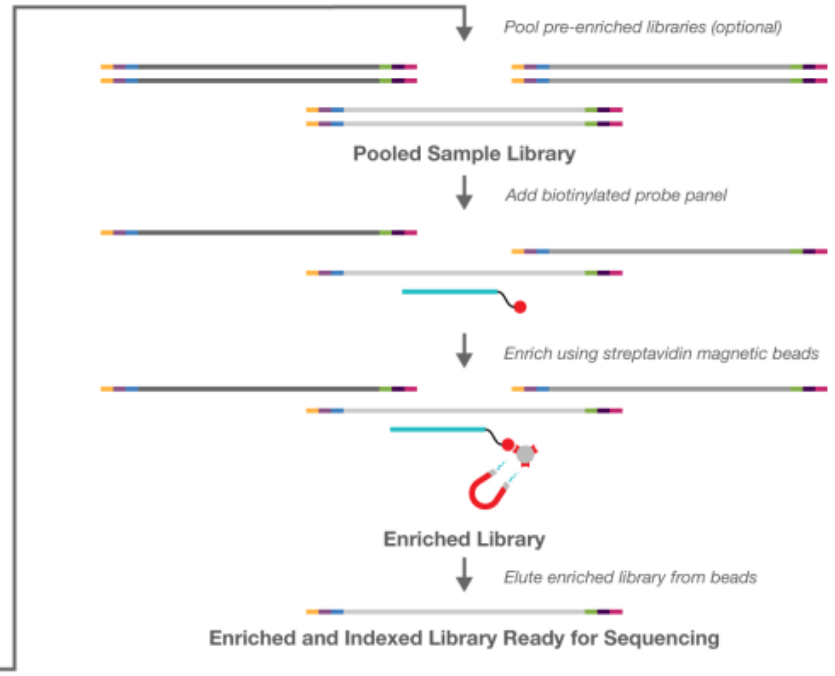
提取DNA
DNA extraction

構建測序文庫
Library preparation

富集外顯子
Exome capture and enrichment

全外顯子測序
Exome sequencing





桌上型測序儀
Benchtop sequencing machine

- 以GATK最佳規範(v3.4-46)進行內部生物信息學分析
- In-house bioinformatics pipeline based on GATK best practices (v3.4-46)

Read Alignment
與參考基因組序列比對

Removal of PCR duplication
刪除聚合酶鏈鎖反應重覆序列

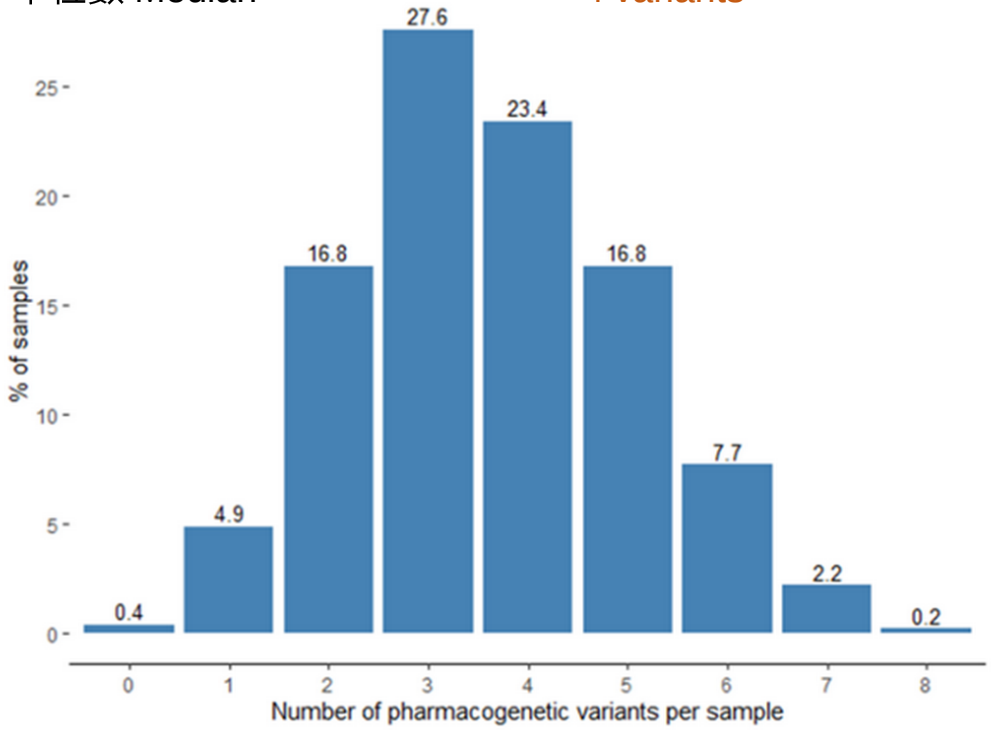
Variant calling
辨認基因變異

Variant annotation
與資料庫比對分析

與藥物有關的基因變異非常普遍
Pharmacogenetic variants are common

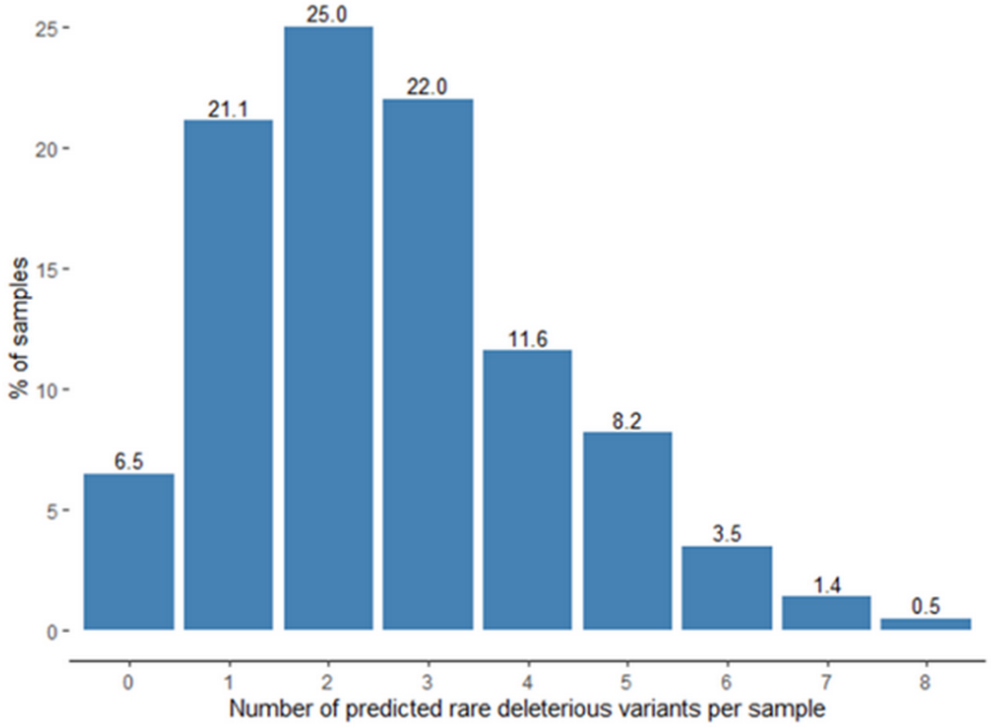
會影響藥物治療效果的基因變異
pharmacogenetic variant known to affect drug response in patients

擁有至少一個 Carry at least one：**99.6%**
中位數 Median： 4 variants

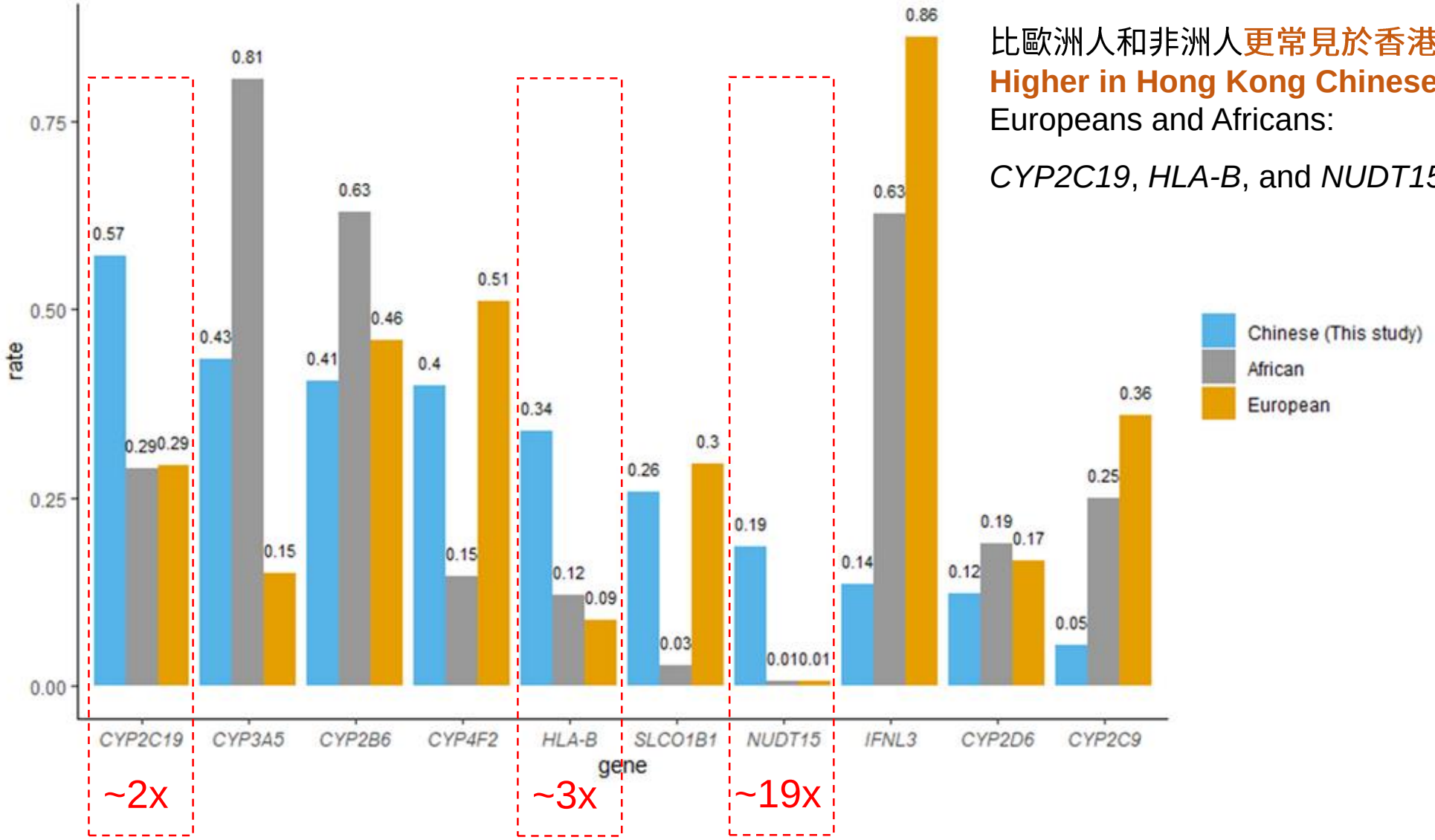


罕見且預測有害、與藥物有關的基因變異
Rare deleterious pharmacogenetic variant

擁有至少一個 Carry at least one：**93.6%**
中位數 Median： 2 variants



於香港華人中最常見的十大與藥物有關的基因表型
Top 10 pharmacogenetic phenotypes in HK Chinese

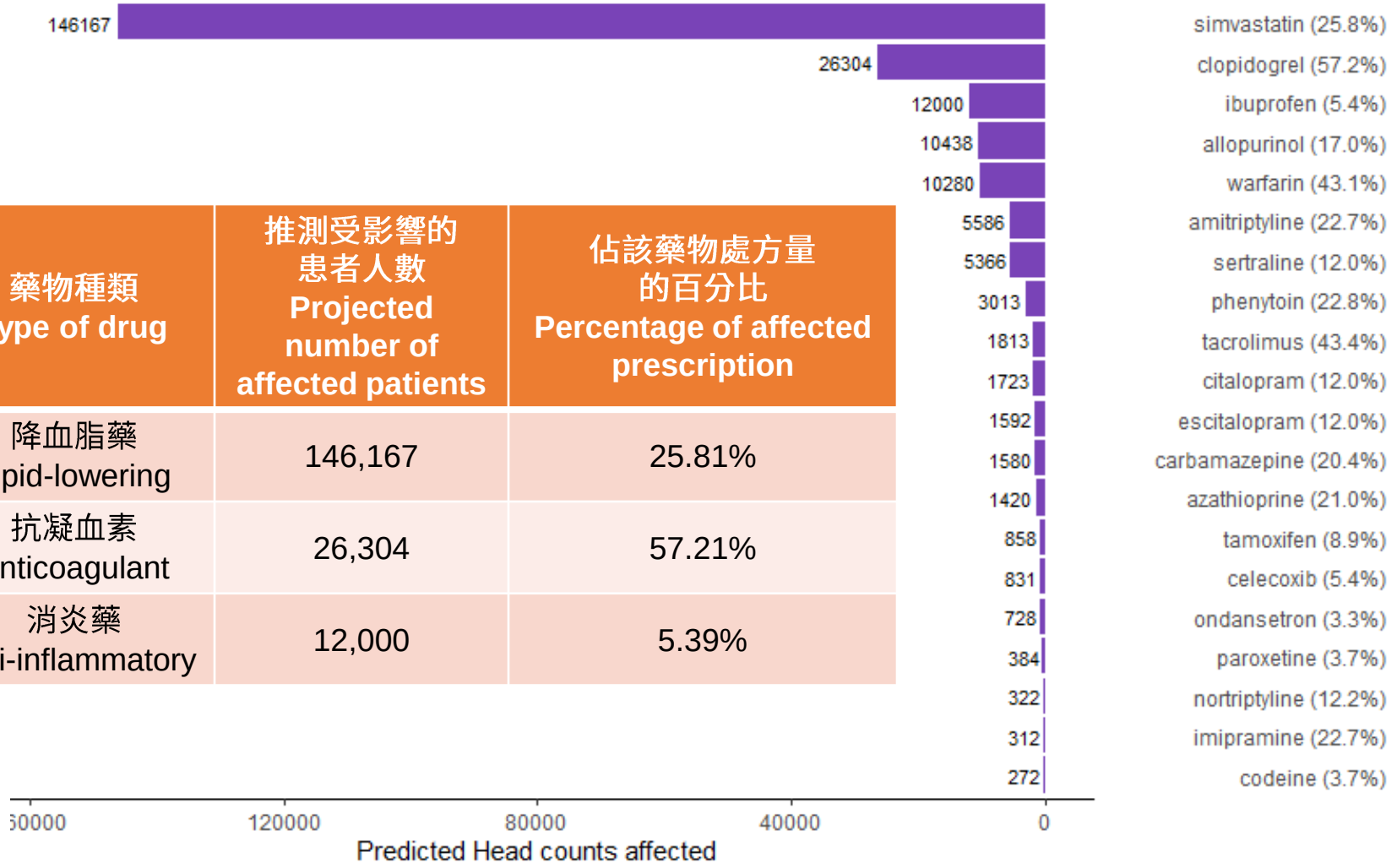


比歐洲人和非洲人**更常見於香港華人**：
Higher in Hong Kong Chinese than in Europeans and Africans:

CYP2C19, *HLA-B*, and *NUDT15*

推測影響最多患者的首二十種藥物
Top 20 drugs with the highest estimated prescription impact on headcount

	處方藥名 Prescription Drug Name	藥物種類 Type of drug	推測受影響的患者人數 Projected number of affected patients	佔該藥物處方量的百分比 Percentage of affected prescription
1	辛伐他汀 simvastatin	降血脂藥 Lipid-lowering	146,167	25.81%
2	氯吡多 clopidogrel	抗凝血素 Anticoagulant	26,304	57.21%
3	布洛芬 ibuprofen	消炎藥 Anti-inflammatory	12,000	5.39%



分析流程 – 以*SLCO1B1*與辛伐他汀引起的肌肉病變爲例
Analysis workflow – illustration with *SLCO1B1* and simvastatin-induced myopathy

星號等位基因
Star Allele

*SLCO1B1**15,*17

可影響藥效之基因表型
Actionable phenotype

Low function CC /
intermediate function CT

預計終生風險
Lifetime risk estimate [1]

Low function: 18%
Intermediate function: 3%

基因型
Genotype

SLCO1B1:c.521T>C
(Frequency = 13.87%)

相關不良藥物反應
Associated ADR

Statin-induced
myopathy

2019 CDARS prescription data
處方數據

獲處方辛伐他汀之患者人數
Total number of patients prescribed with simvastatin = **566,223**

低藥物代謝的表型
CC phenotype = Low function (freq = 1.92%)

566223*0.0192*0.18

中等藥物代謝的表型
CT phenotype = Intermediate function (freq = 23.89%)

566223*0.2389*0.03

146,167 patients receiving simvastatin has an actionable phenotype 會影響藥效的基因表型
6,019 cases of myopathy preventable by genotype-guided prescription
可避免的藥性肌肉病變

1. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. 2008;359(8):789-99. Epub 2008/07/25. doi: 10.1056/NEJMoa0801936. PubMed PMID: 18650507.

根據藥物基因組學推算對處方藥物的影響
Projected prescription impact based on local PGx data

- 在2019年總共有超過100萬(1,006,046)名香港華人患者接受了36種受基因變異影響的藥物，佔香港人口的13.4%。
- More than 1 million(1,006,046) Hong Kong Chinese patients had received prescriptions of the 36 drugs that are affected by actionable pharmacogenetics variants in 2019, accounting for 13.4% of HK population.
    - 獲處方的病人中有約23.1%的人擁有會影響藥物治療效果的藥物基因表型，應該根據國際臨床指引調整處方。
    - Among the patients receiving the prescribed drugs , 23.1% of them have actionable pharmacogenetic phenotypes, which should have prescription adjustment according to the international clinical guidelines.
- 總值約6,400萬港元($64,108,000)的藥物可以根據患者與藥物有關的基因變異，調節劑量或改善處方。
- Around HK$64 million(HK$64,108,000) worth of drugs were prescribed to patients with an implicated actionable phenotype for drug usage and dosage adjustment.

總結　Summary

- 研究團隊根據1,116個香港華人的全外顯子測序，分析133個已知會影響藥物治療效果的基因變異，以及存在於108個基因中的罕有變異。
- The research team studied the spectrum of 133 pharmacogenetic variants known to affect drug response in patients and rare deleterious variants in 108 pharmacogenes using an exome sequencing consisting of 1,116 Hong Kong Chinese subjects.

- 幾乎所有香港華人皆帶有最少一個會影響藥物治療效果的基因變異，以及一個罕有且推測有害的變異。
- Nearly all individuals carried at least one pharmacogenetic variants known to affect drug response and one rare, predicted deleterious pharmacogenetic variant.

- 每七名香港華人就有一人曾接受過根據臨床藥物基因指引處方的36種藥物的其中一種。
- One-seventh of the Hong Kong population received at least one of the 36 drugs with clinical pharmacogenetics guideline recommendations.

- 此研究展示了與藥物有關的基因測試對改善患者護理及指引醫療資源分配的潛力。研究數據為於華人族群中發展藥物基因組學的臨床實踐提供支持。
- The findings demonstrated the potential of pharmacogenetic testing in improving patient care and medical resource allocation in Chinese. The cohort dataset also supports clinical implementation of pharmacogenetics in the Chinese population.

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