46 文献およびゲノム解析データベースを利用したヒト疾患原因変異の解析例

ナンセンス変異：一塩基置換により、翻訳領域中に終止コドンが出現する変異

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Introduction

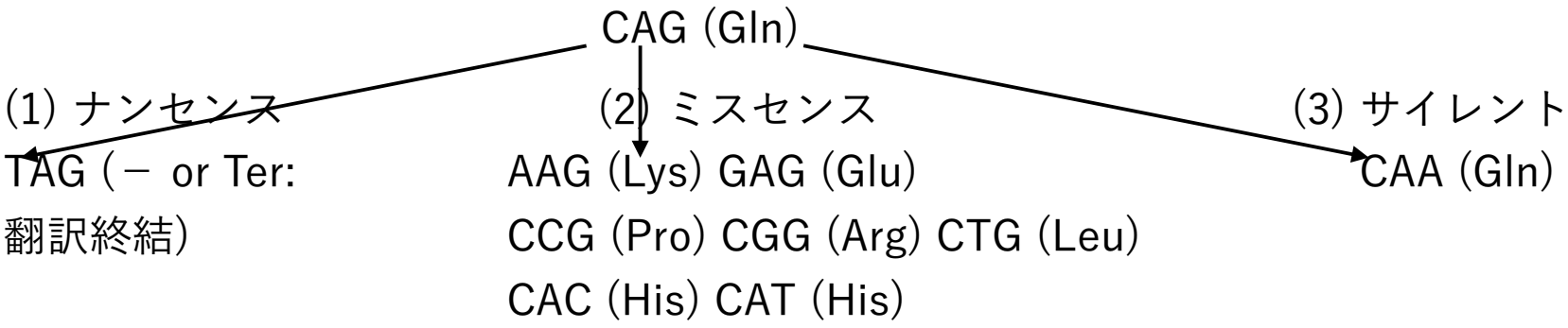
生物の「変異」

・病気の原因にもなるが、変異が起こらなければ生物の進化もない
・変異の数が最も調べられている生物　ヒト

太古から続く医学の歴史
近代・近年の科学の進歩

「変異」の中で最も多いのは、一塩基置換

・わずか１塩基の置換だから、頻度が多い。
・わずか１塩基の置換だけれども、種類が多い。
　１つには変異が起こる場所の影響を受けるから。
・翻訳領域の中にあるものだけで、３種類



大腸菌のナンセンス変異

Garen (1968)

Sense and Nonsense in the Genetic Code

Three exceptional triplets can serve as both chain-terminating signals and amino acid codons.

Alan Garen

TAA, TAG, TGAの３通り

タンパク質合成が途中で終結
＞影響はsevere

ナンセンス変異から表現型を回復する一塩基置換

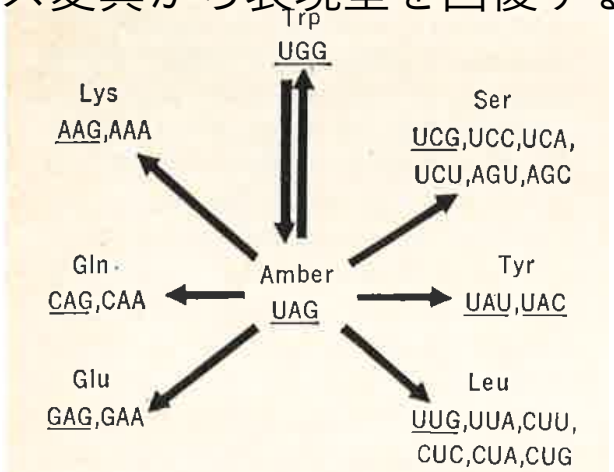


Fig. 3. Identification of an *amber* nonsense triplet as UAG. The diagram summarizes the pattern of amino acid substitutions in the alkaline phosphatases produced by re-

TAA: ７通り　　のうちの１つ
TAG: ８通り（左図）
TGA: ８通り
＊(Tyr Cys Argは２つ)

目的はヒト

ナンセンス変異の解消には元コドン情報が必須
＞データベースによる解析

ヒトの変異：ヒトの染色体は46,XY

・男性のX,Y以外は遺伝子は２つ

一つの遺伝子上の塩基配列の変化(=変異)が、疾患に直結するわけではない

モデル生物で使用されて来たナンセンス変異とは違いが…

使用語句について

今まで述べてきた「変異」＝DNAの塩基配列の変化：

塩基変化（またはnucleotide change）と呼ぶことにします

患者検体から同定された病気の原因となる塩基変化：

mutation（または患者mutation）

健康人中の塩基変化：variation（物質上mutationと同じものでも!）

対象遺伝子：原発性高アンモニア血症（尿素サイクル異常症）

enzymes: NAGS CPS1 OTC ASS1 ASL ARG1

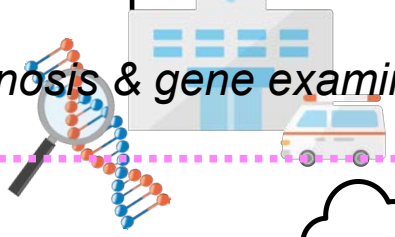
transporters: ORNT1/SLC25A15 CITRIN/Citrin/SLC25A13

Introd.~
Methods

Two different approaches to characterize nonsense nucleotide change

1. Bottom-up approach 'mutations' in patients

Medical diagnosis & gene examination



2. Bird's-eye view approach 'variations' in healthy population

Togovar

Publication

NCBI
ClinVar
dbSNP

jMorp 38K JPN
Japanese Multi Omics Reference Panel.

gnomAD 3.1.2
gnomAD
Genome Aggregation Database

Others

HGMD
HGMD®
The Human Gene Mutation Database

50 YEARS OMIM
Human Genetics Knowledge for the World

Databases

download & literature search

search & filtering 'stop_gained'

Datasets

Dataset 1 ('nucleotide change') L (location) =194

Dataset 2 (patient mutations) L=152, n=352

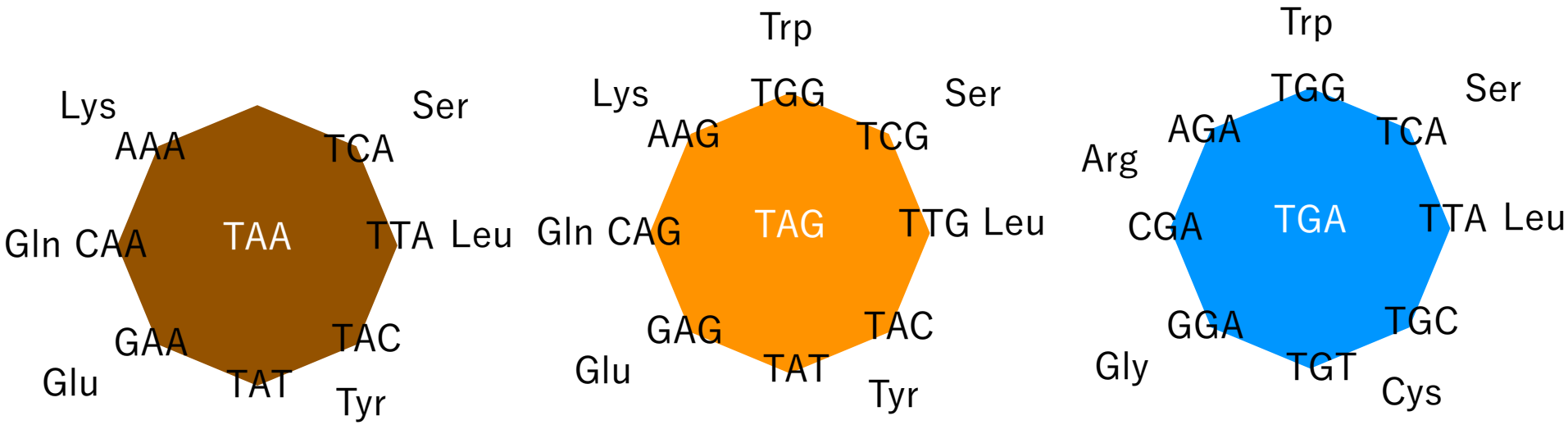
Dataset 3 (variations) L=60

(1) Position & sequence change; (2) Frequency

Results 1

Location of patient mutations: asymmetry among 23 changes

Among 152 locations (in 4562 codons), all 23 types of changes were observed.



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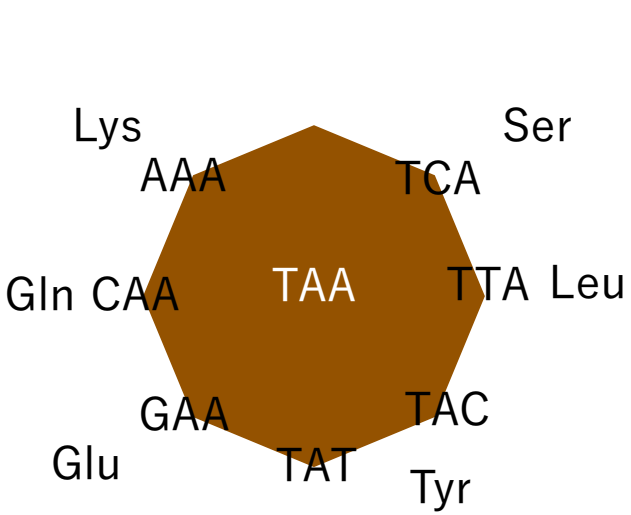

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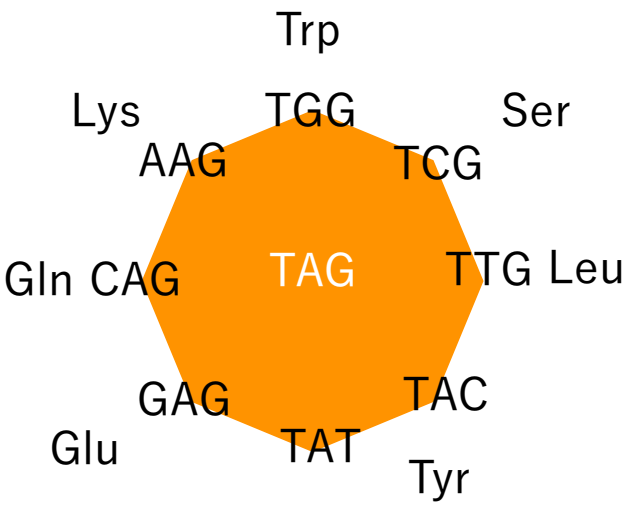

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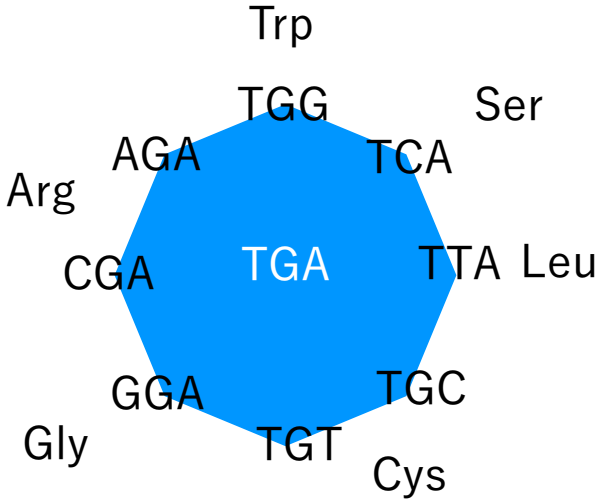

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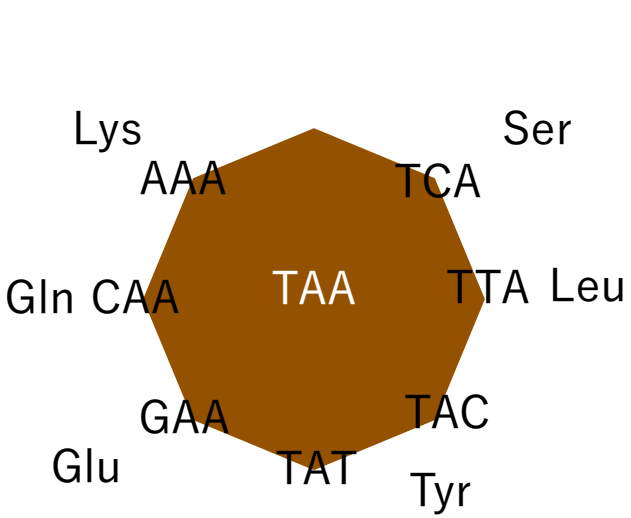

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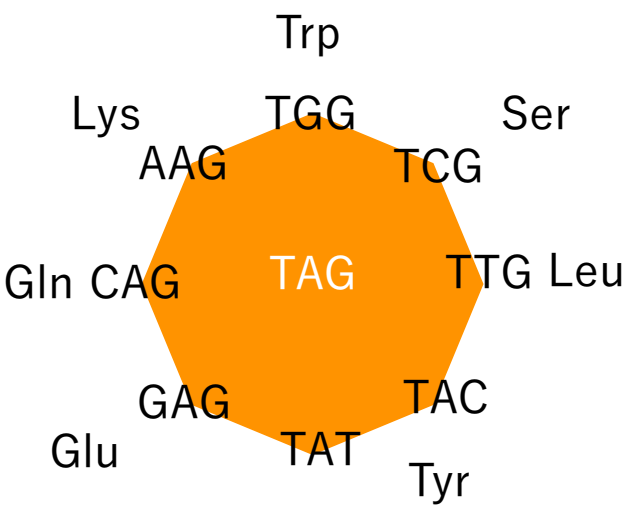

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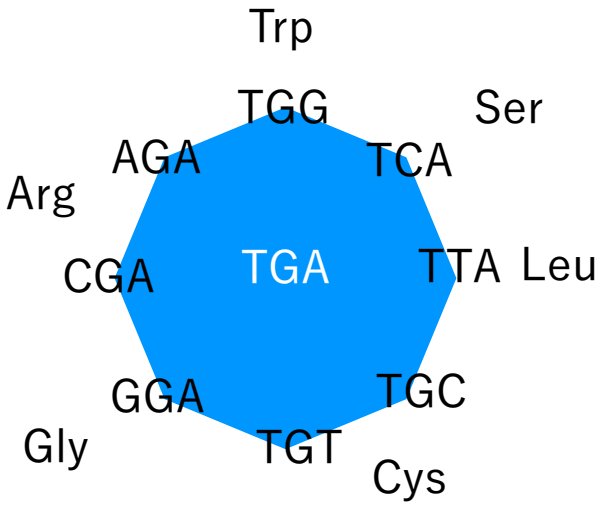

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base transition
C⇄T; A⇄G

88

base transversion
CorT⇄AorG

64

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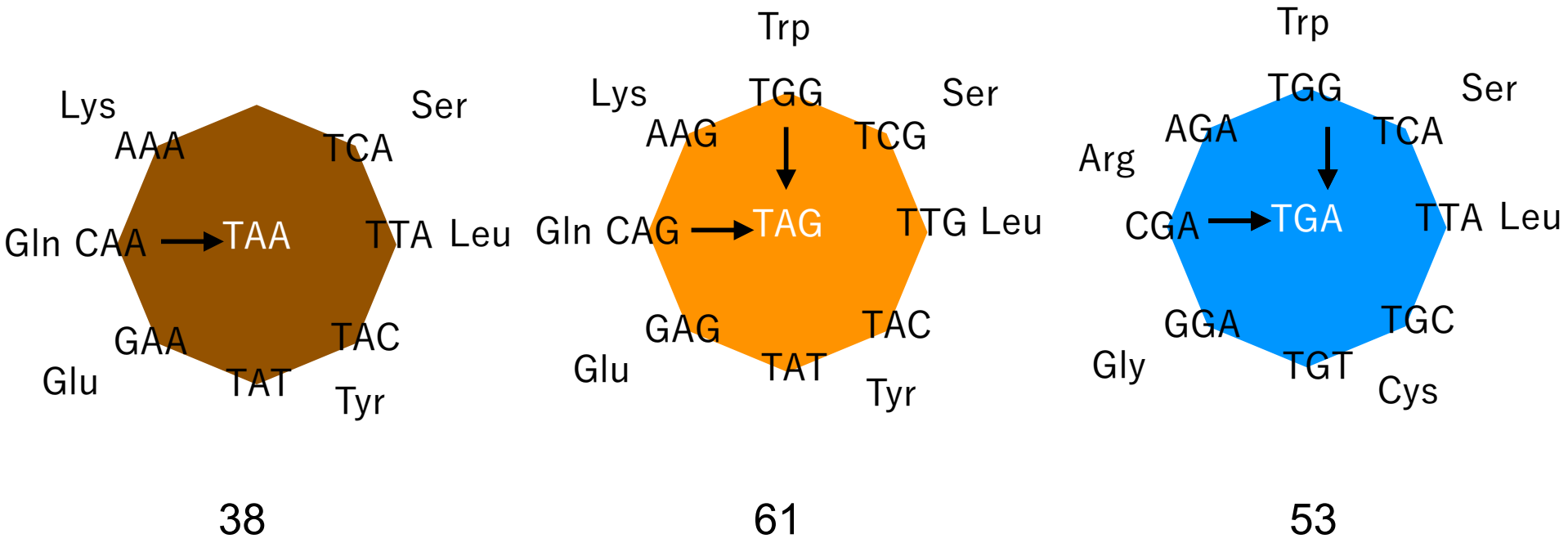

38 61 53

base transition → 88

base transversion 64

C⇄T; A⇄G

CorT⇄AorG

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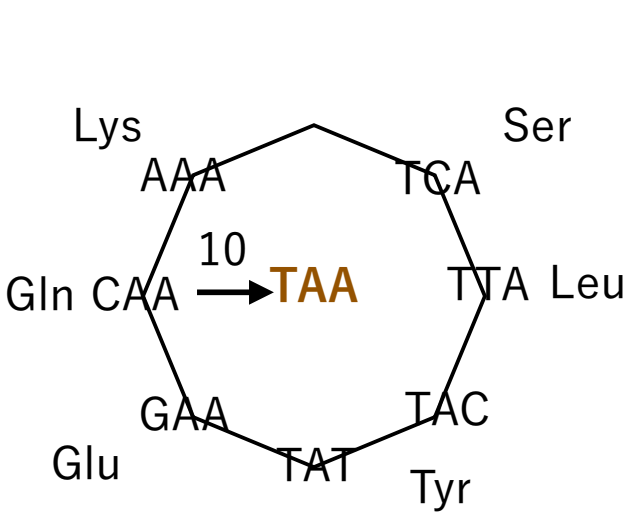

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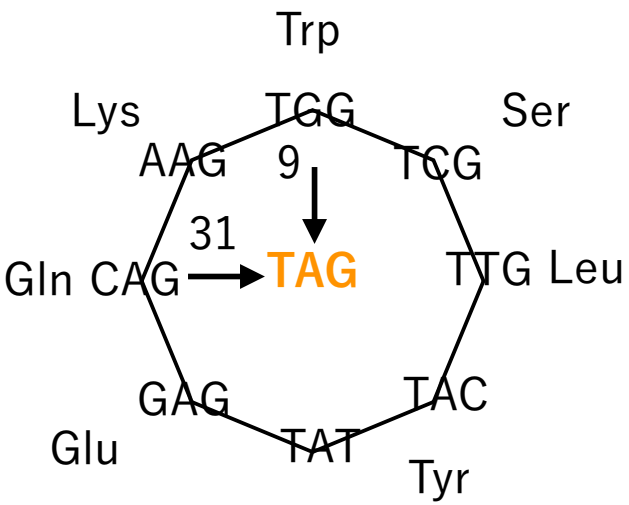

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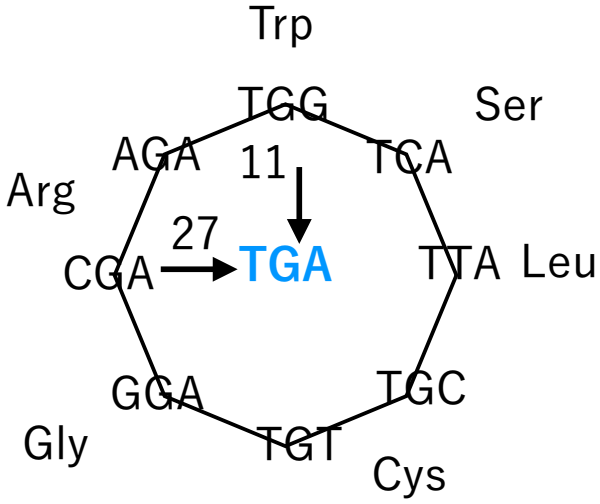

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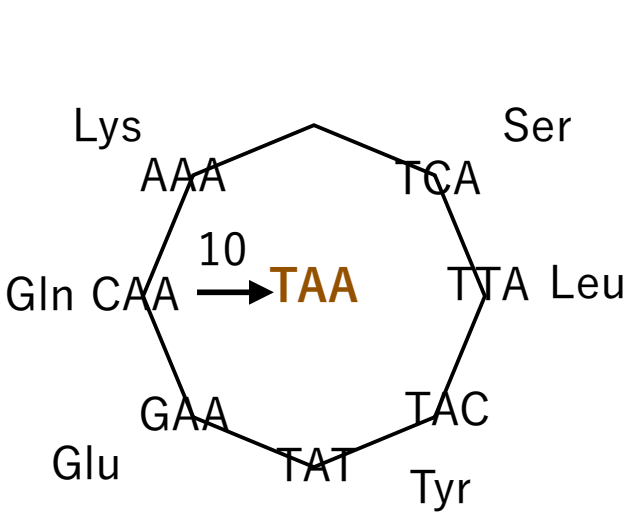

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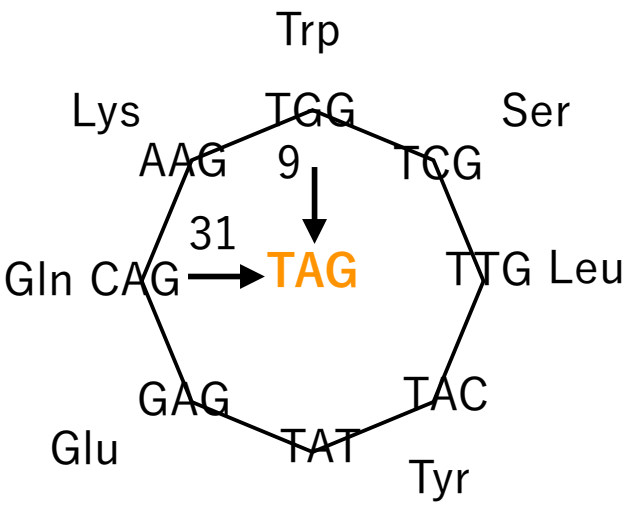

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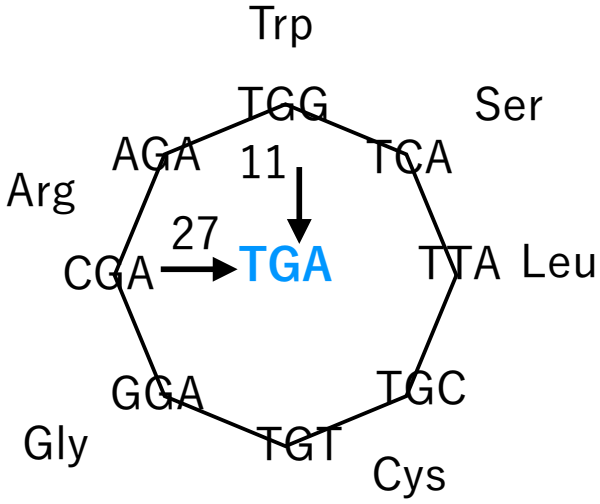

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When codon frequency is considered,

Results 1

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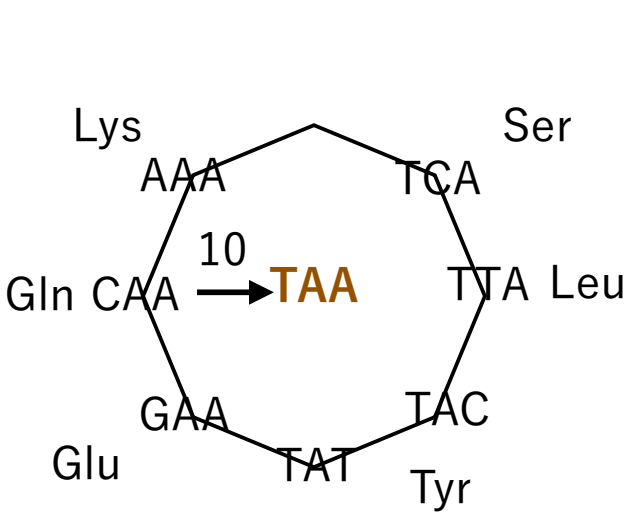

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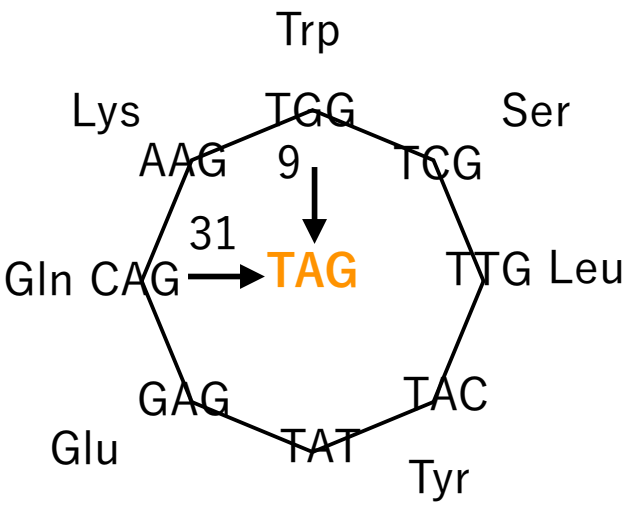

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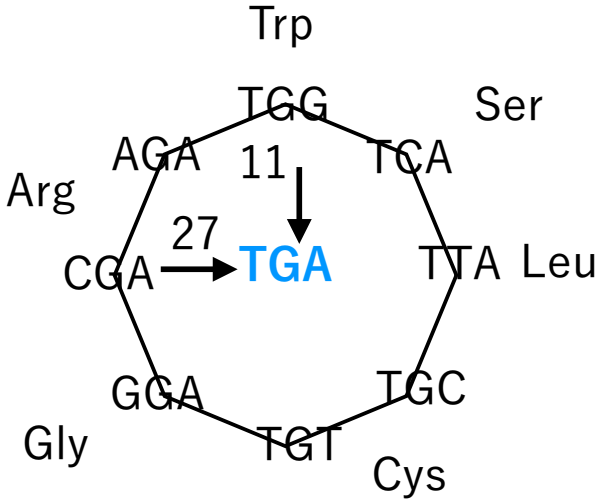

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When codon frequency is considered, CGA>TGA is by far the hot spot.

CAA → TAA
10/ 43

CAG → TAG
31/132

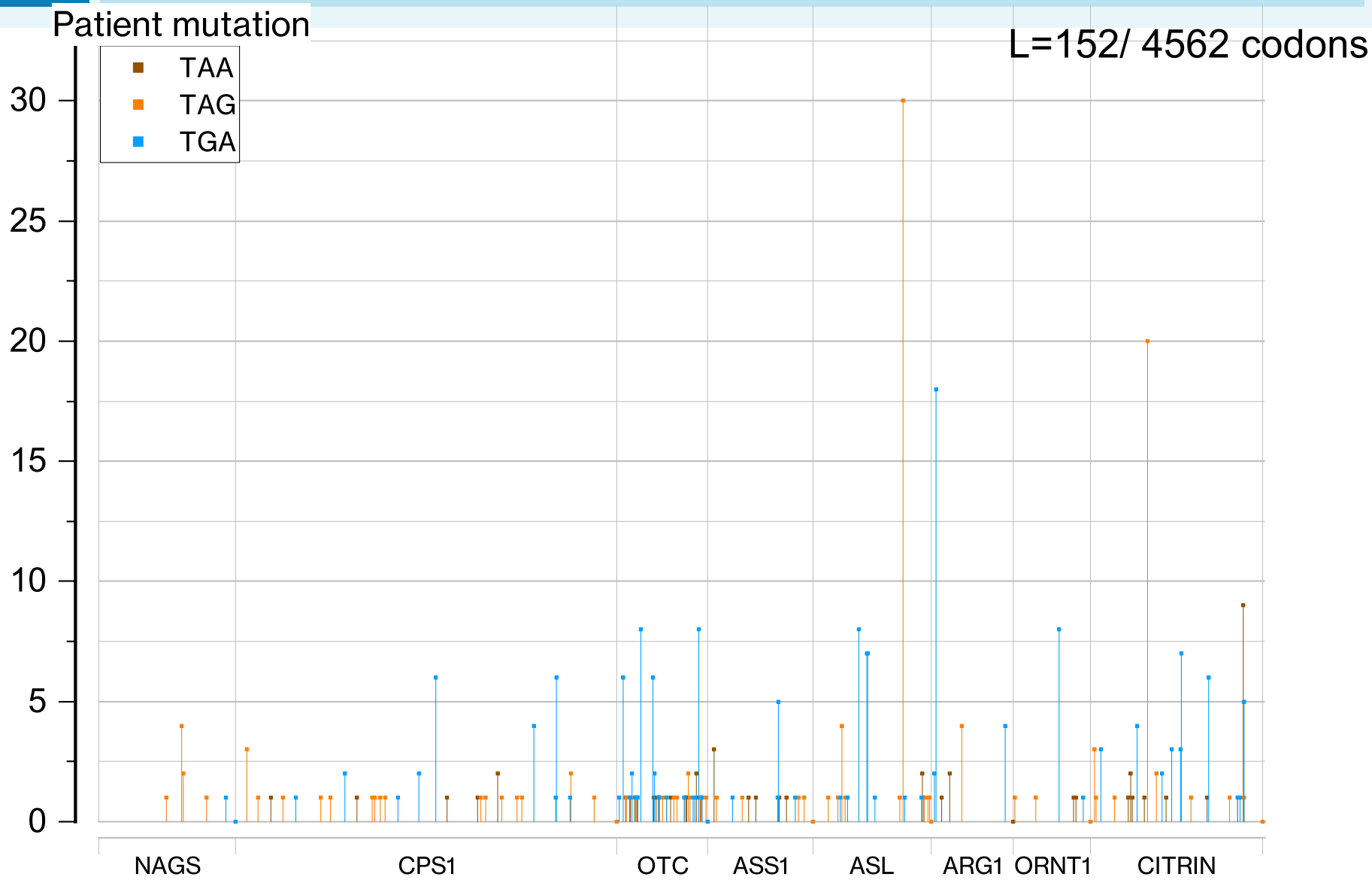
TGG → TAG
9/ 53

CGA → TGA
27/ 30 90%!

TGG → TGA
11/ 53

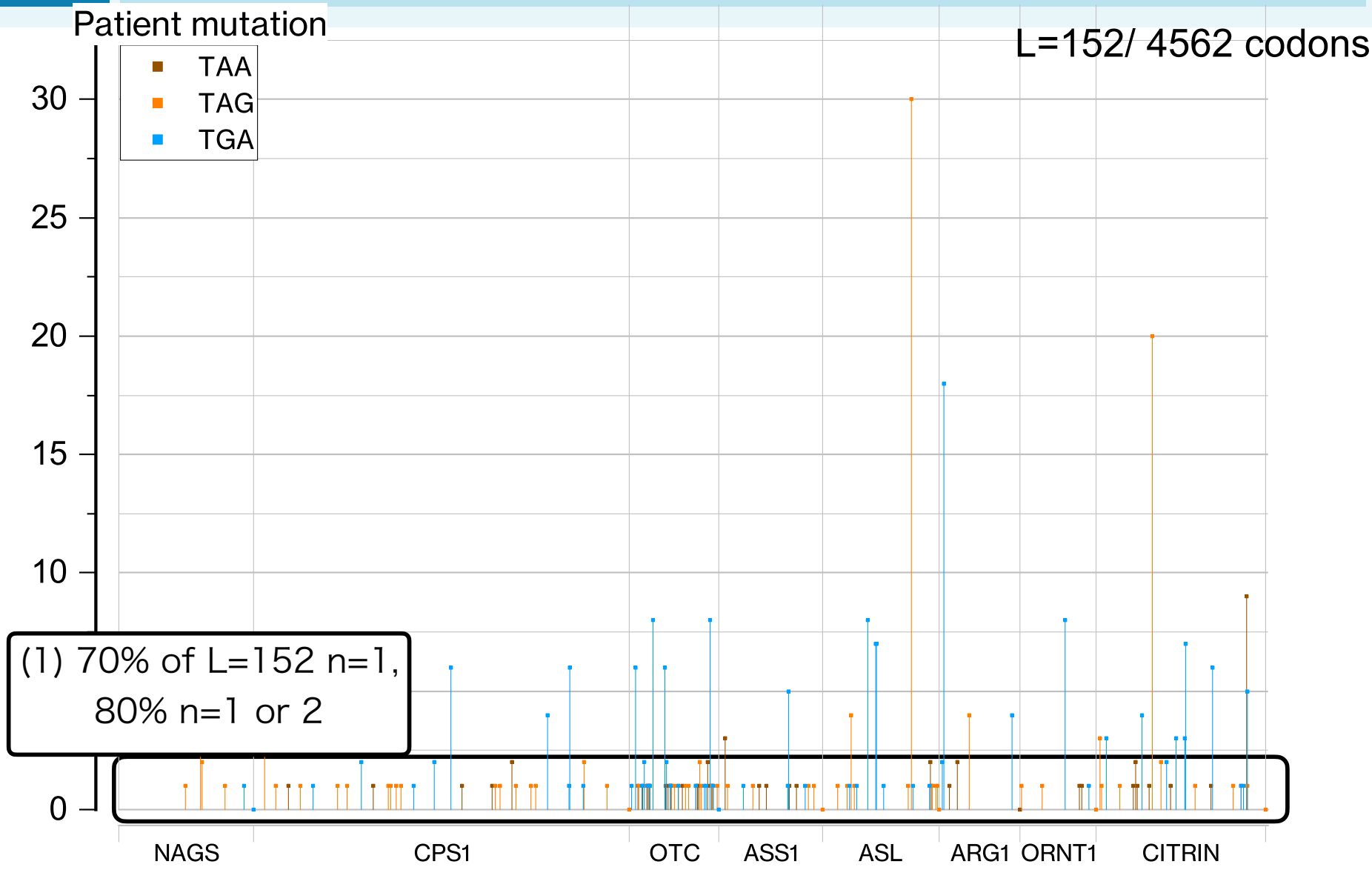
Results
2

Frequency of patient mutations



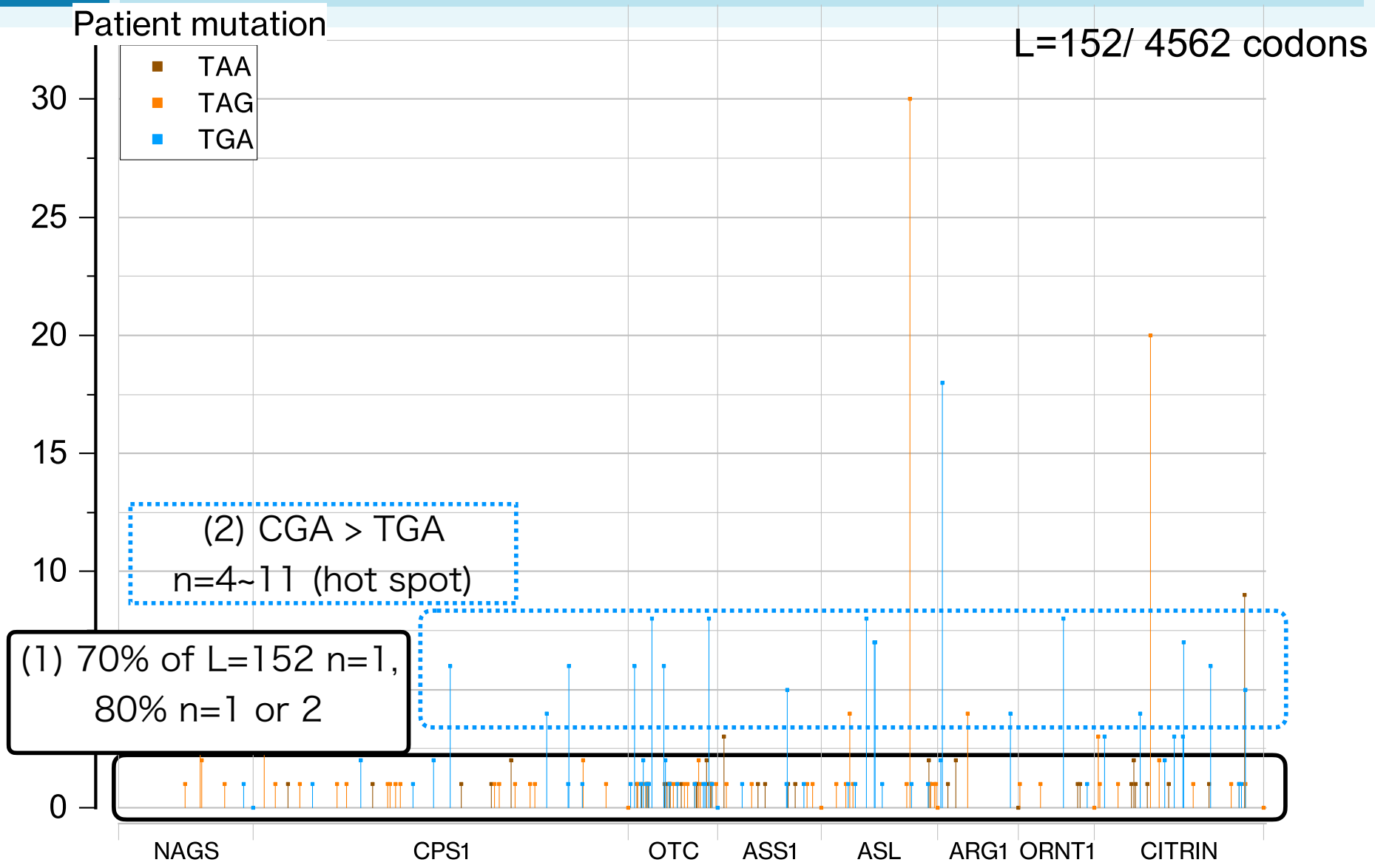
Results 2

Frequency of patient mutations



Results
2

Frequency of patient mutations



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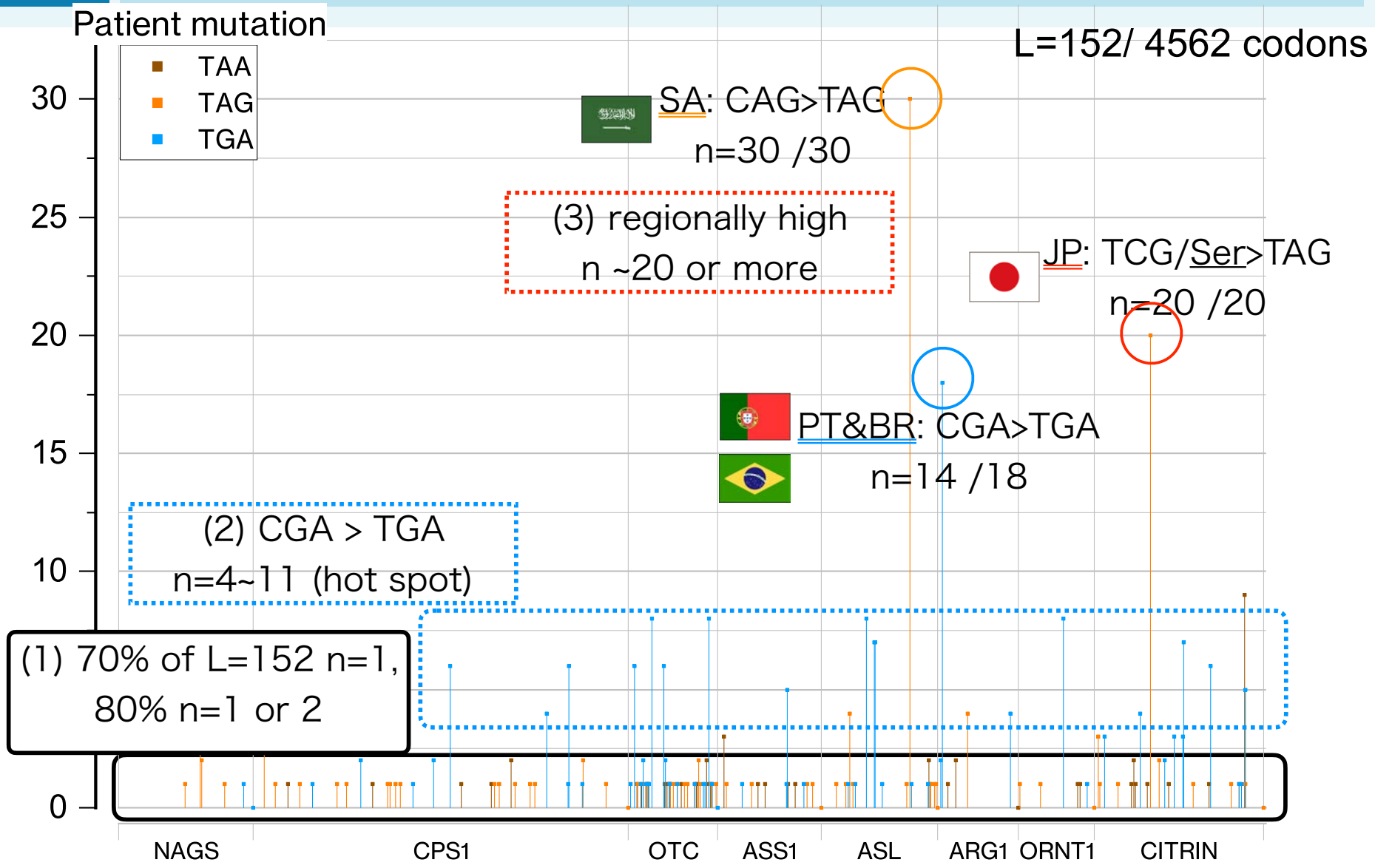
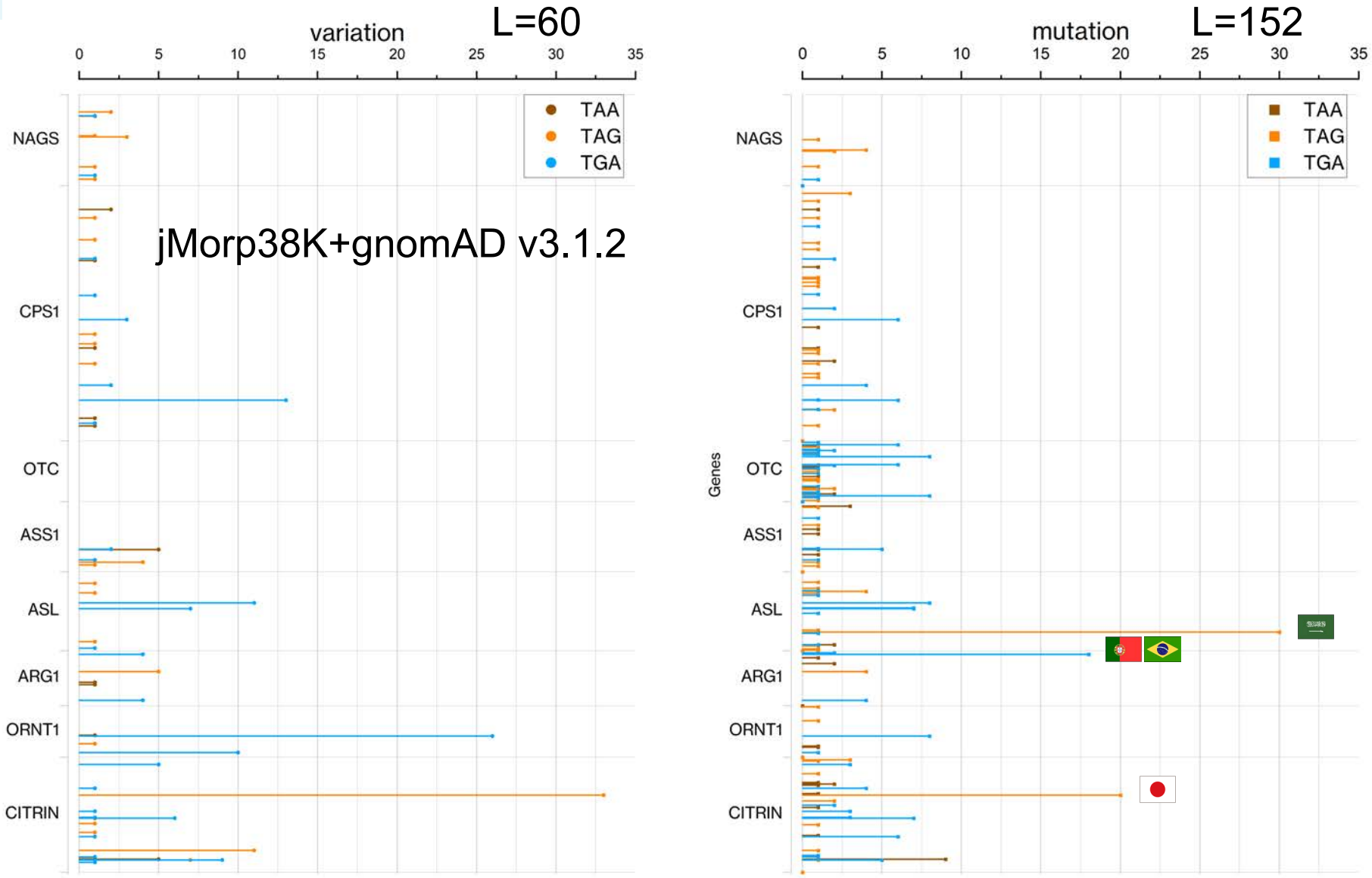


Results
3

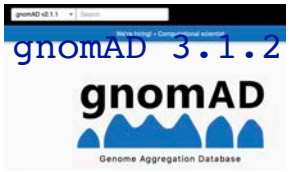
Nonsense variation & mutation



Methods

Populations in genomics study

'variations' in healthy population



gnomAD v3.1.2

- NFE 34,029
- AFR 20,744
- AMR 7,647
- FE 5,316
- EAS 2,604
- SAS 2,419
- ASJ 1,736
- OTH 1,047
- AMI 456
- ME 158

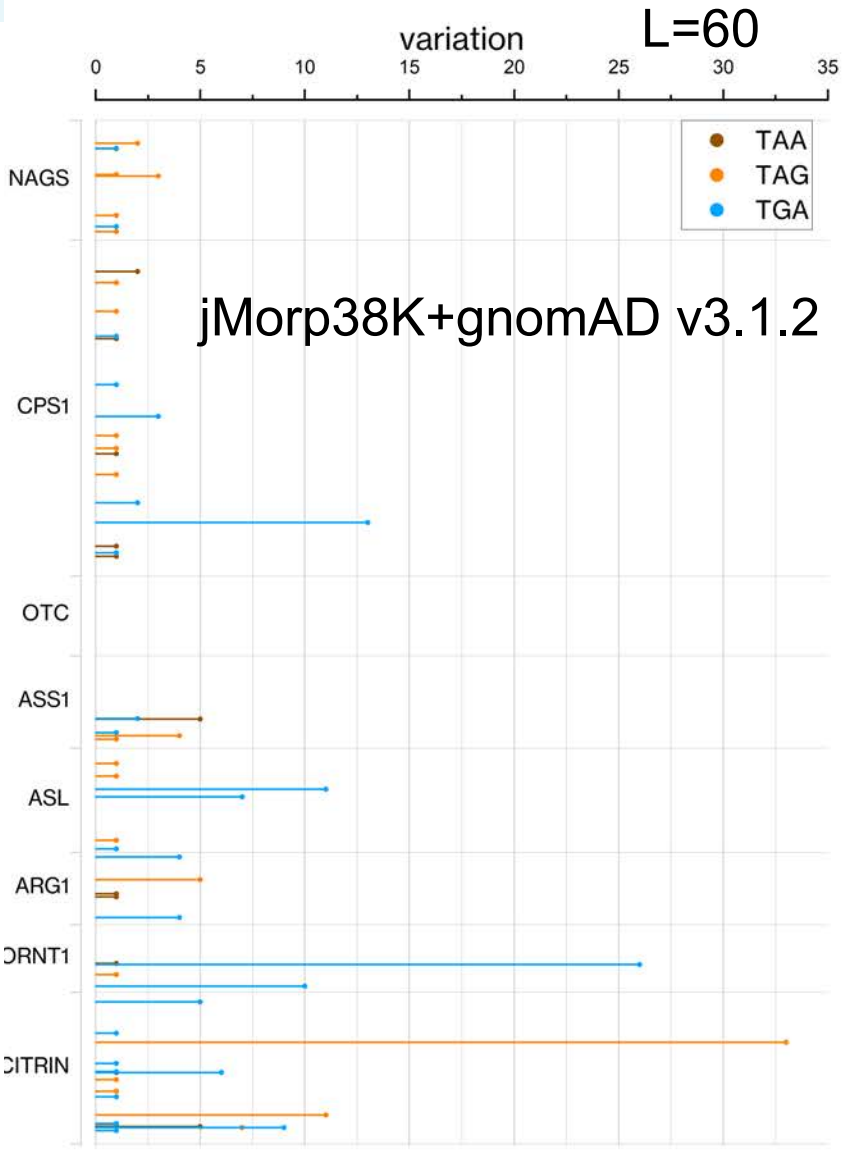
jMorp38K

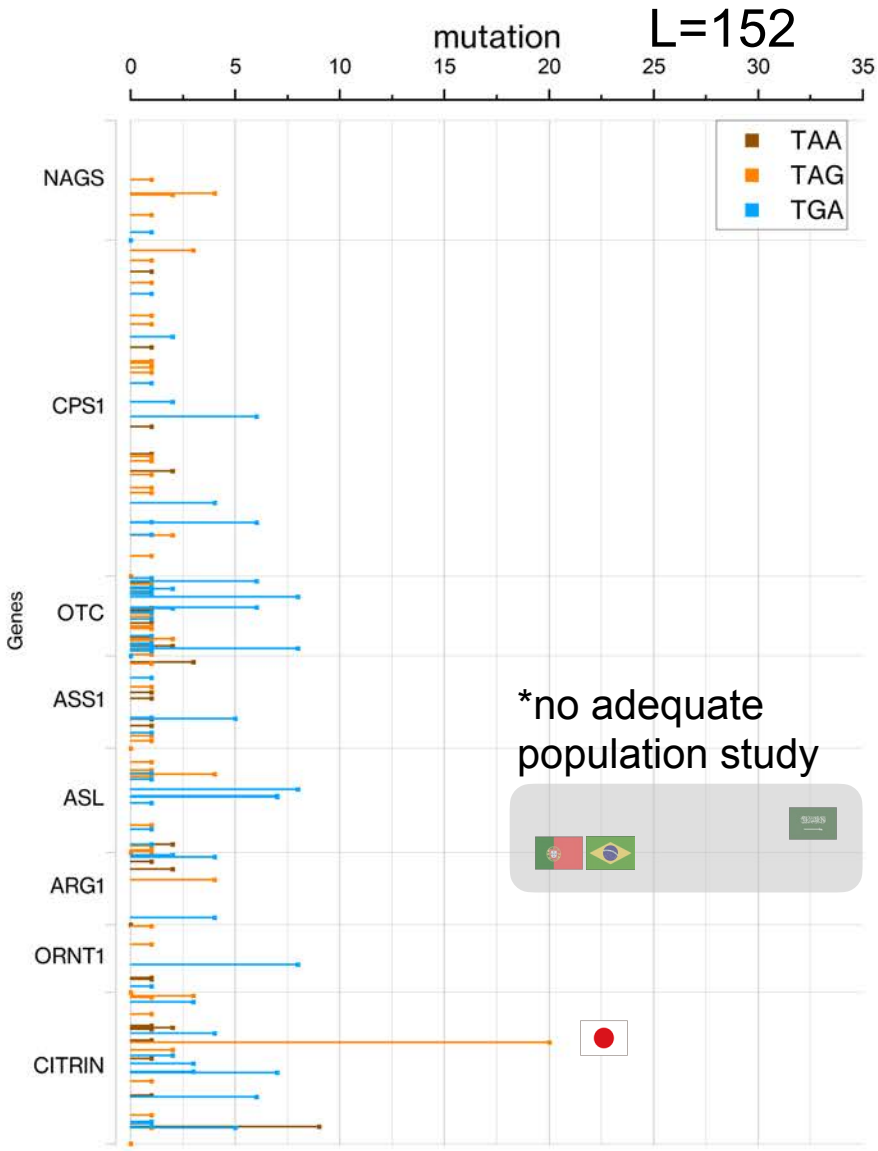
JPN 38,722

JPN Japanese
NFE non-Finnish European, AFR Africa/ African American,
AMR Latino/ Admixed American, FE Finnish European, EAS East Asian,
SAS Southern Asian, ASJ Ashkenazi Jewish, OTH others,
AMI Amish, ME Middle East

Results
3’

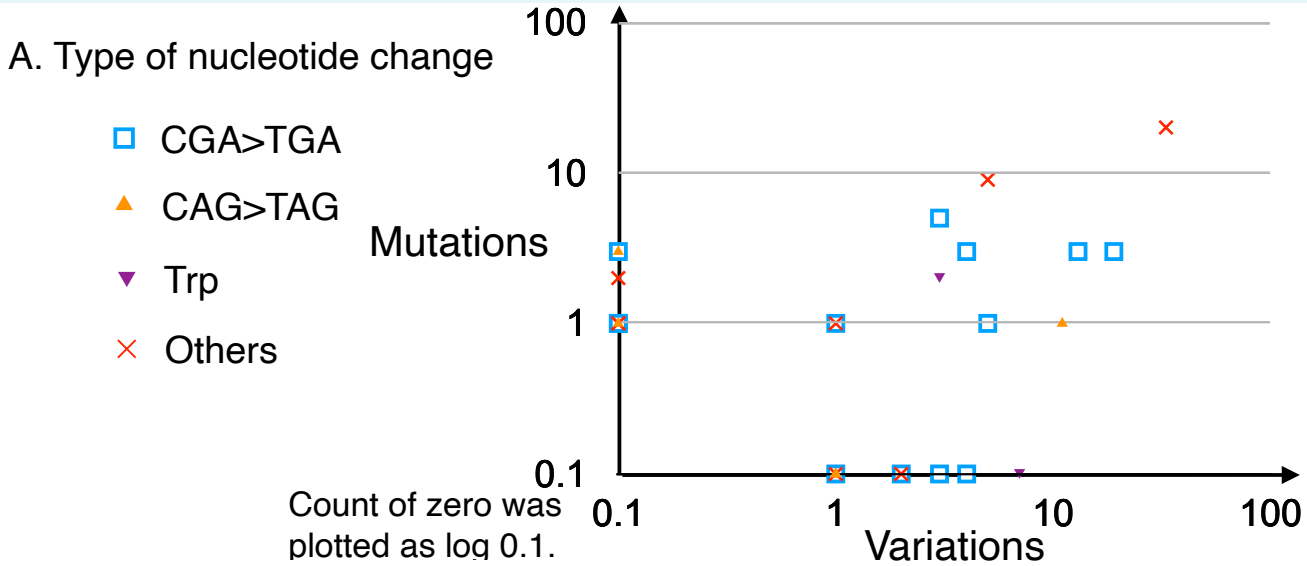
Nonsense variation & mutation

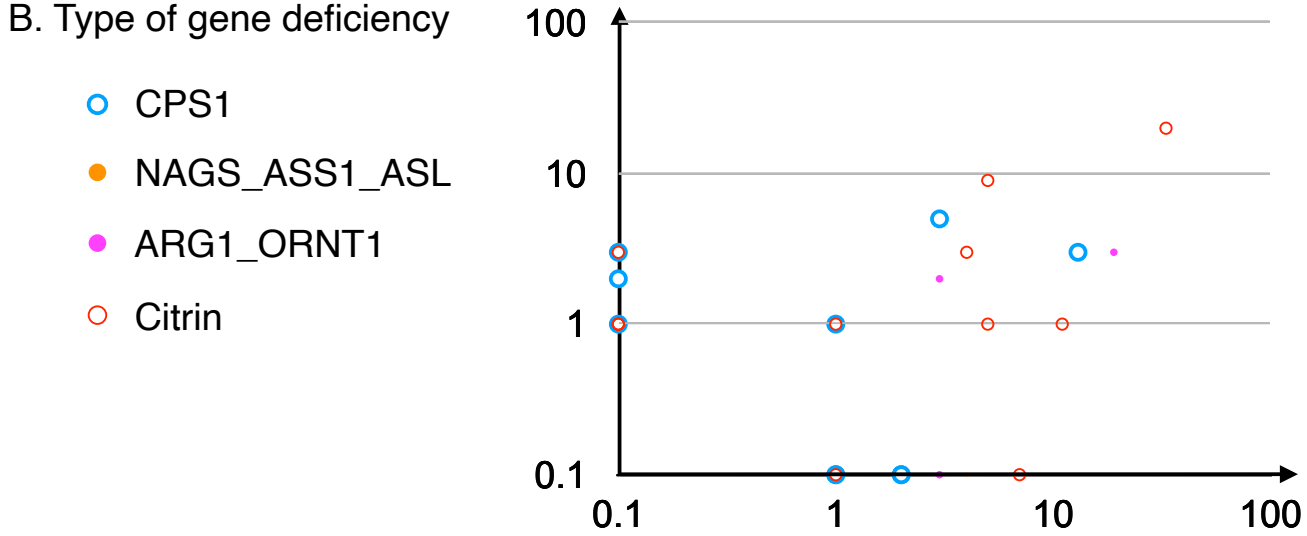




Results
4

Nonsense variation vs mutation in Japan





Nonsense nucleotide changes in patients and healthy populations are…

Diverse and can be dynamic

1. Most changes are sporadic.
   80% of mutations and 70% of variations occur at most twice (in the current search level).
2. CGA> TGA is a hot spot.
3. Frequency of some mutations and variations can become regionally high.

科研費 KAKENHI