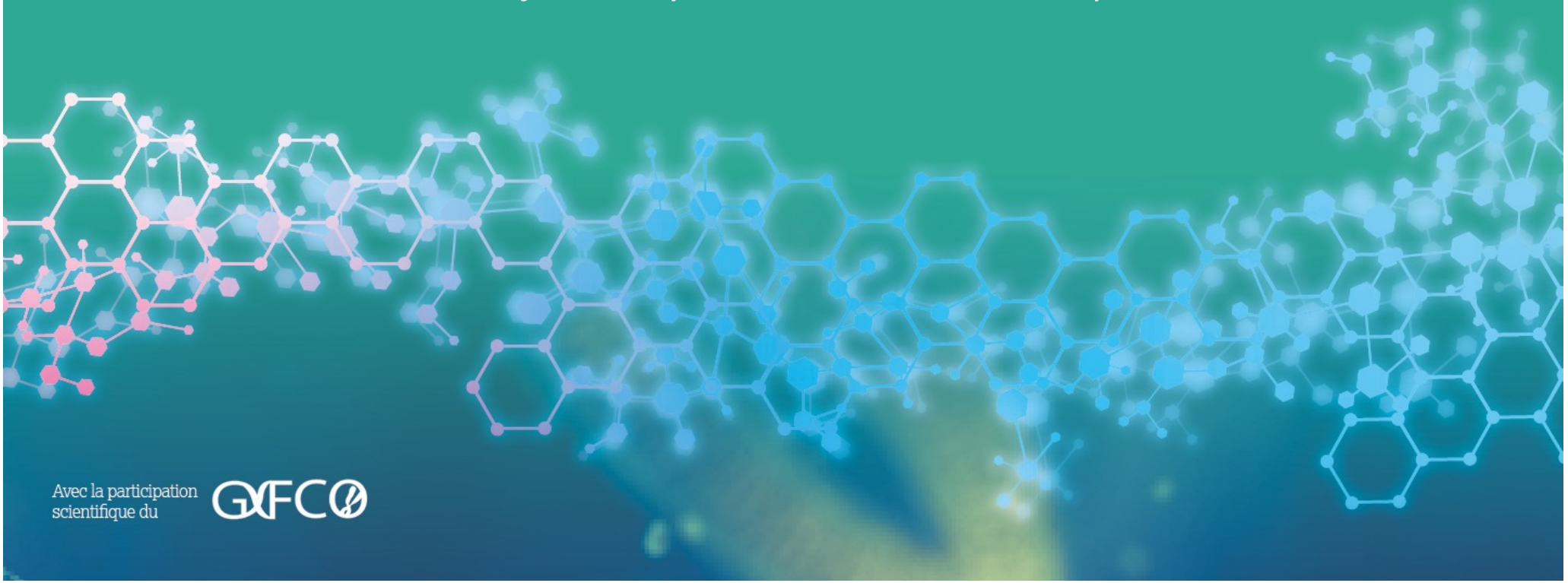

JOURNÉES DU
GFCO
10e ÉDITION
Biomarqueurs et analyses moléculaires en oncologie
Avec la participation scientifique du
GFCO

Apport d'outils d'interprétation : AlphaMissense & Mobidetails

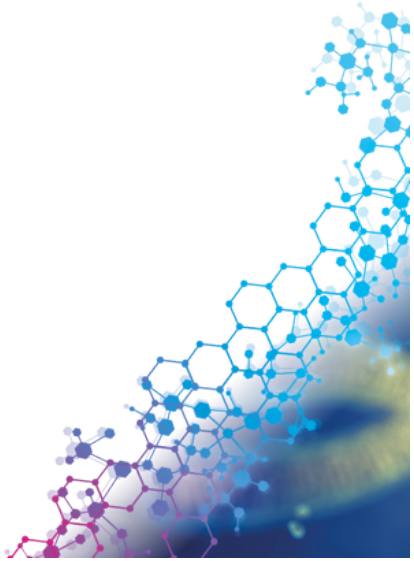
Pierre Sujobert, Lyon & David Baux, Montpellier



Avec la participation scientifique du GFCO

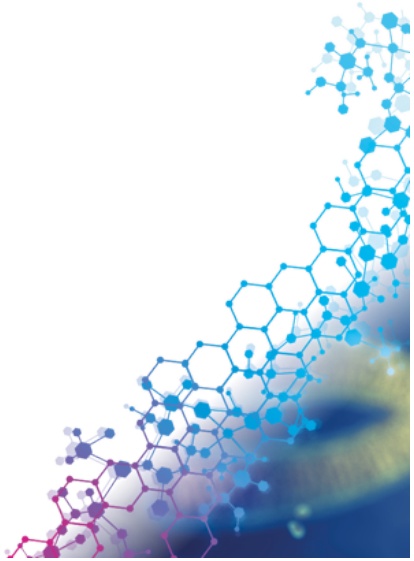
LIENS D'INTÉRÊT - Pierre Sujobert

- **AstraZeneca : financement d'un programme de recherche (2020-22)**
- **Gilead/Kyte : conférences rémunérées, participation à un board (2017-2023)**
- **Janssen-Cilag : financement d'un programme de recherche (2017-19), participation à un « board » (2017-22)**
- **Astellas : participation à un board, conférences rémunérées (2020-21)**
- **Kephren : conférences rémunérées (2019, 2021)**
- **Celgene : conférences rémunérées (2016, 2017, 2021)**
- **Daiichi Sankyo : participation à un board (2019-20)**
- **Sandoz : conférence rémunérée (2018-19)**
- **Abbvie : conférence rémunérée (2017, 2022)**
- **Servier : financement d'un programme de recherche (2023-26)**



LIENS D'INTÉRÊT – David Baux

- **AstraZeneca (GFCO, JEBM)**

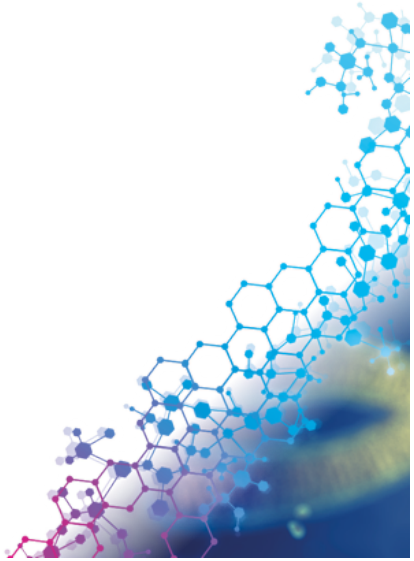


URLs

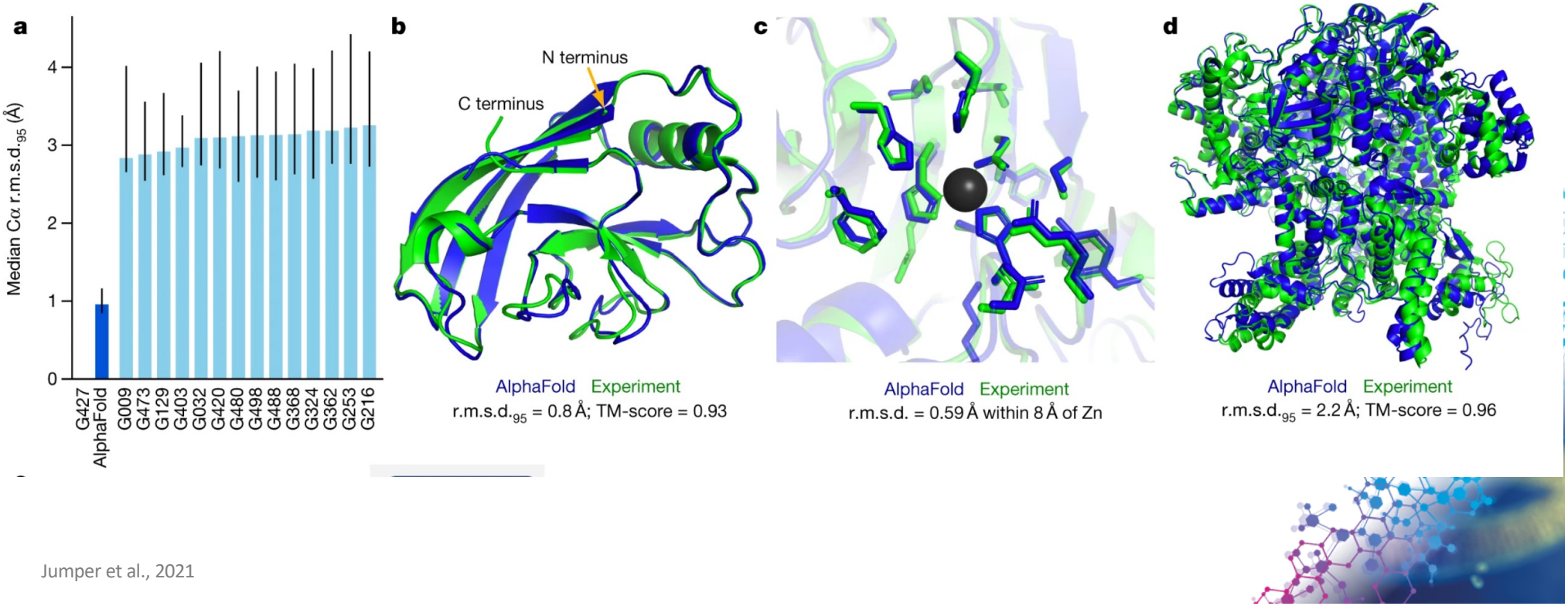
- MobiDetails https://mobidetails.iurc.montp.inserm.fr/MD/
  (google mobidetails)

- alphaFold EBI https://alphafold.com
  (google alphafold)

- MIZTLI https://miztli.biokerden.eu/
  (google miztli biokerden)



AlphaFold

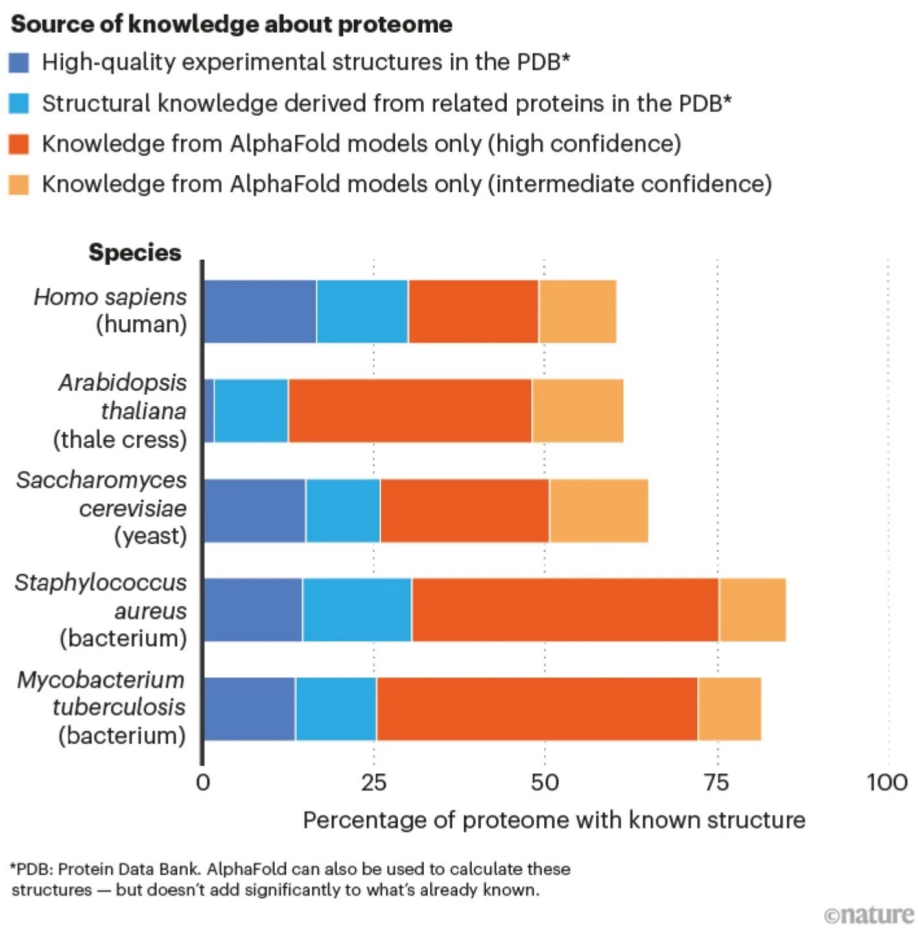


Jumper et al., 2021

AlphaFold

WHAT'S KNOWN ABOUT PROTEOMES

AlphaFold's predictions have greatly increased the proportion of confidently known structures in the human proteome — the collection of all human proteins. The software is even more useful for other species.



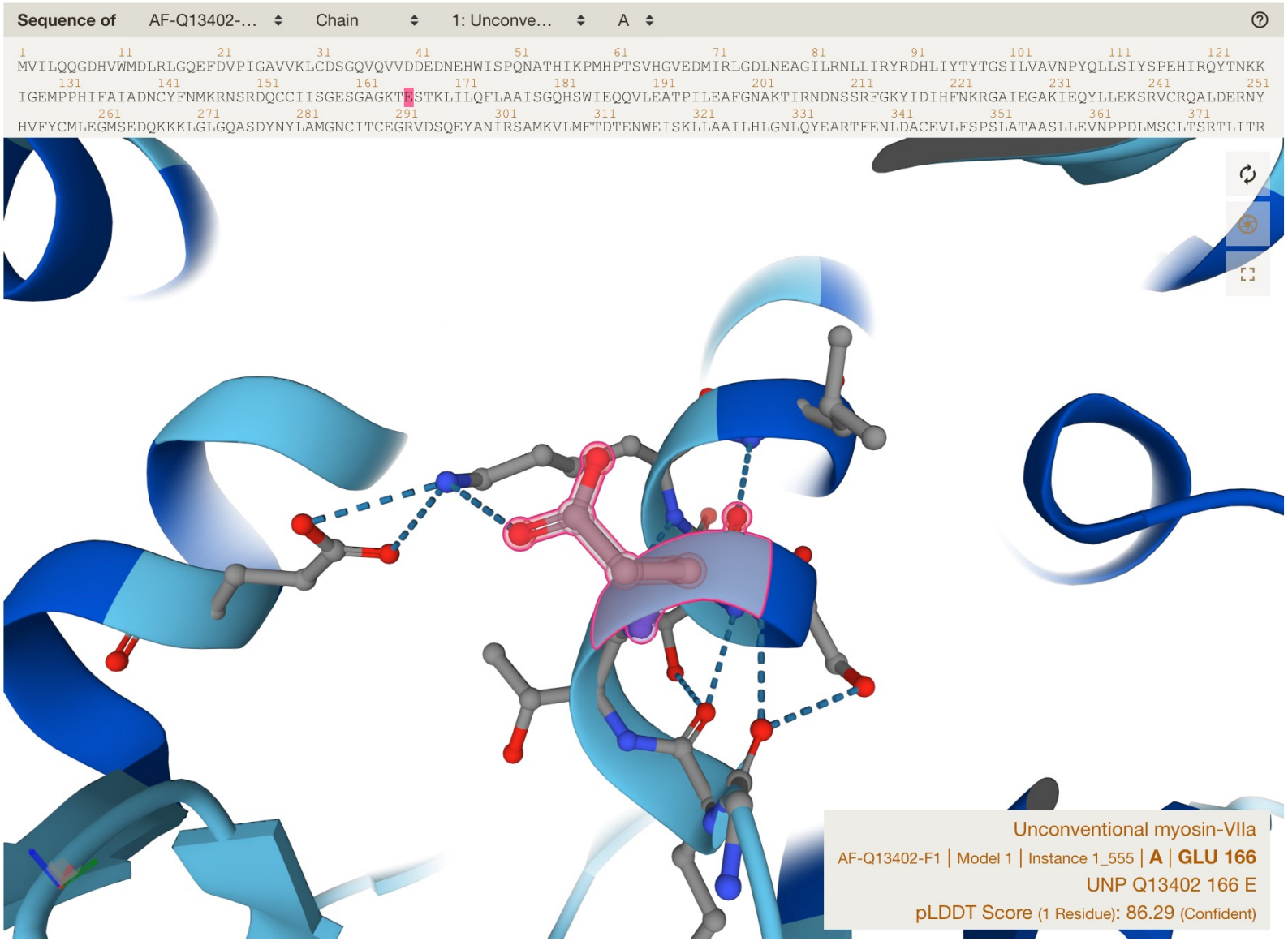
*PDB: Protein Data Bank. AlphaFold can also be used to calculate these structures — but doesn't add significantly to what's already known.

©nature

Source: E. Porta-Pardo *et al. PLoS Comput. Biol.* **18**, e1009818 (2022).

Callaway E, 2022

AlphaFold


Sequence of AF-Q13402-... Chain 1: Unconve... A
MVILQQGDHVWMDLRLGQEFDVPIGAVVKLCDSGQVQVVDDEDNEHWISPQNATHIKPMHPTSVHGVEDMIRLGDLNEAGILRNLLIRYRDHLIYTYTGSILVAVNPYQLLSIYSPEHIRQYTNKK
IGEMPPHIFAIADNCYFNMKRNSRDQCCIISGESGAGKTESTKLILQFLAAISGQHSWIEQQVLEATPILEAFGNAKTIRNDNSSRFGKYIDIHFNKRGAIEGAKIEQYLLEKSRVCRQALDERNY
HVFYCMLEGMSEDQKKKLGLGQASDYNYLAMGNCITCEGRVDSQEYANIRSAMKVLMFTDTENWEISKLLAAILHLGNLQYEARTFENLDACEVLFSPSLATAASLLEVNPPDLMSCLTSRTLITR
Unconventional myosin-VIIa
AF-Q13402-F1 | Model 1 | Instance 1_555 | A | GLU 166
UNP Q13402 166 E
pLDDT Score (1 Residue): 86.29 (Confident)

AlphaFold

The Nobel Prize in Chemistry 2024

Ill. Niklas Elmehed © Nobel Prize Outreach

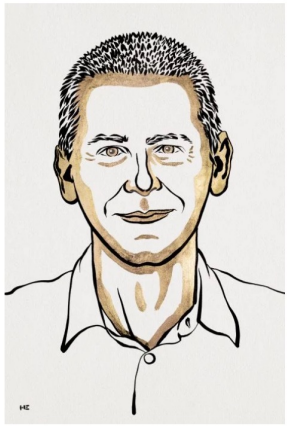
David Baker

Prize share: 1/2

Ill. Niklas Elmehed © Nobel Prize Outreach

Demis Hassabis

Prize share: 1/4



Ill. Niklas Elmehed © Nobel Prize Outreach

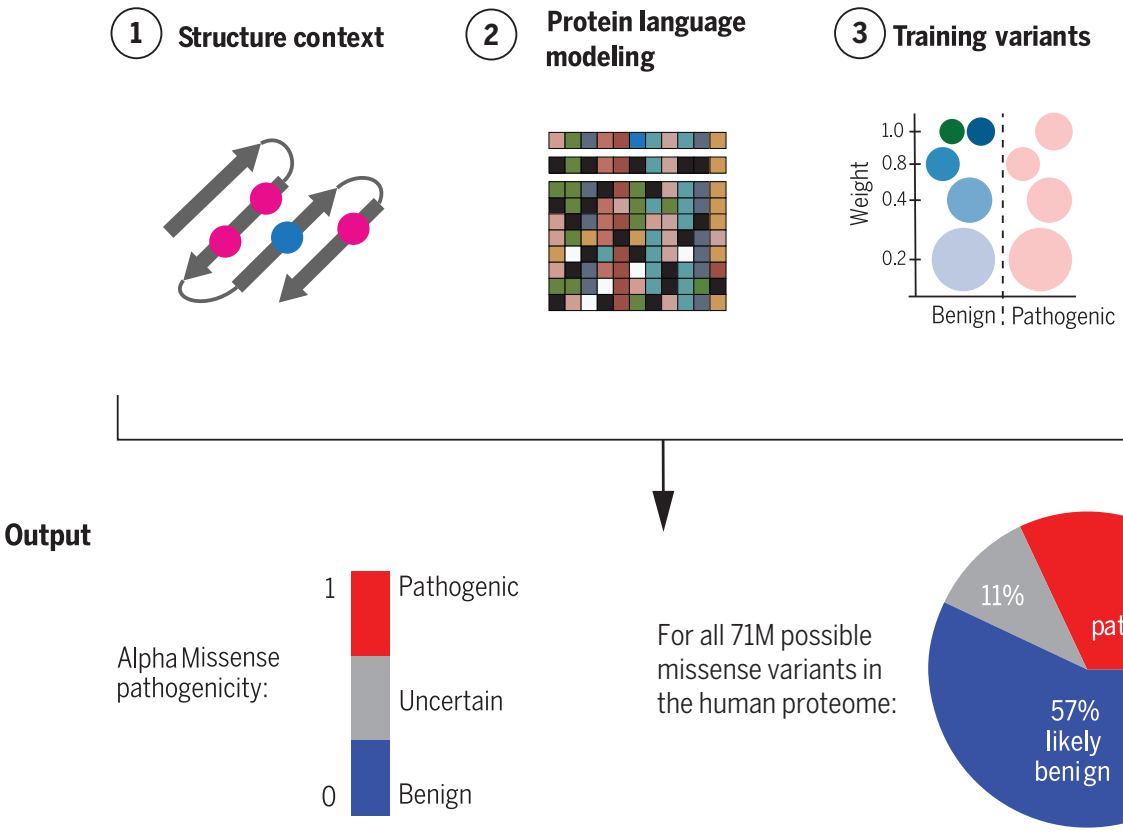
John M. Jumper

Prize share: 1/4

The Nobel Prize in Chemistry 2024 was divided, one half awarded to David Baker "for computational protein design", the other half jointly to Demis Hassabis and John M. Jumper "for protein structure prediction"

To cite this section
MLA style: The Nobel Prize in Chemistry 2024. NobelPrize.org. Nobel Prize Outreach AB 2024. Thu. 10 Oct 2024. <https://www.nobelprize.org/prizes/chemistry/2024/summary/>

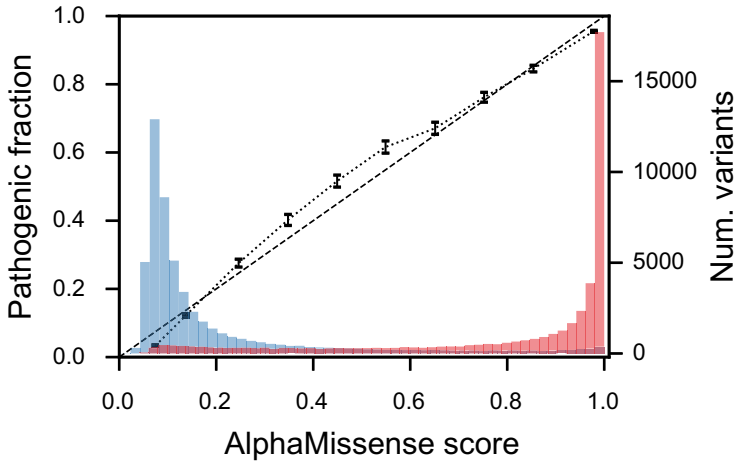
AlphaMissense: Sur les 71 millions de variants missense possibles, 4 millions ont été observés, parmi lesquels 97,5 % de VUS…

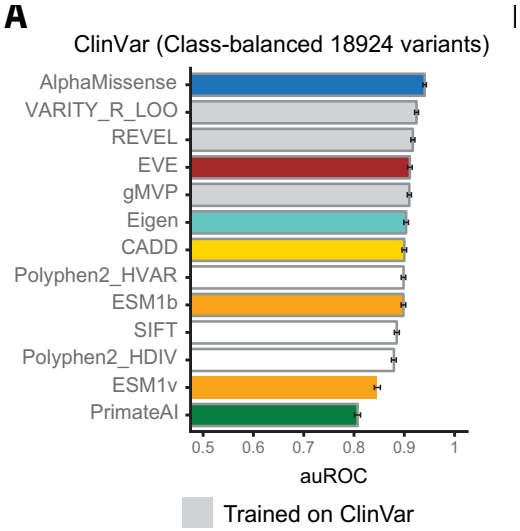


+ population frequency

Cheng, Science 2023

AlphaMissense

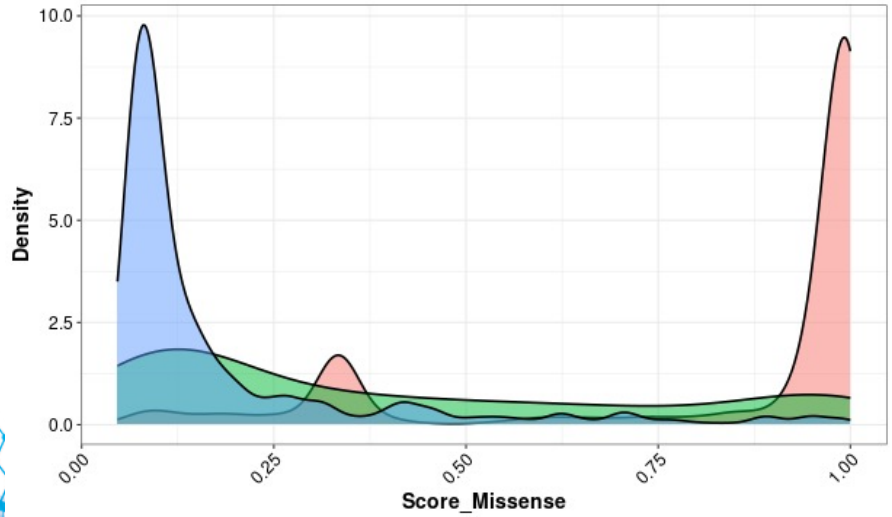


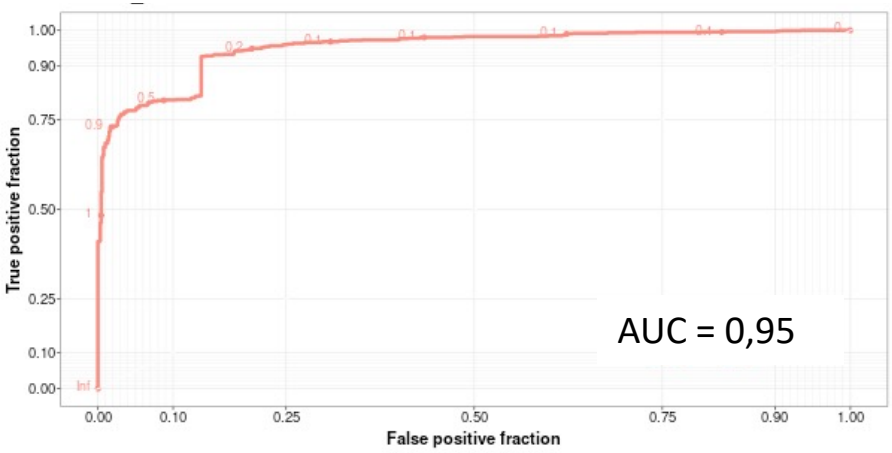


Cheng, Science 2023

AlphaMissense

686 samples (MDS/AML (326), MPN (302), lymphomas (32), ALL (25)
2222 missense variants, 93% with Alphamissense score

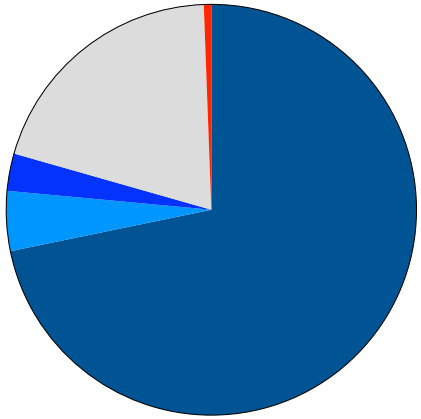




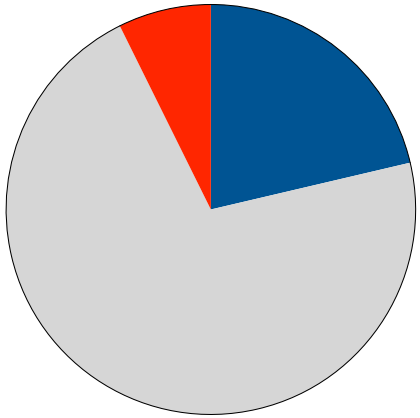
Chabane, Leukemia 2024

AlphaMissense

170 Alphamissense wrongly (?) benign



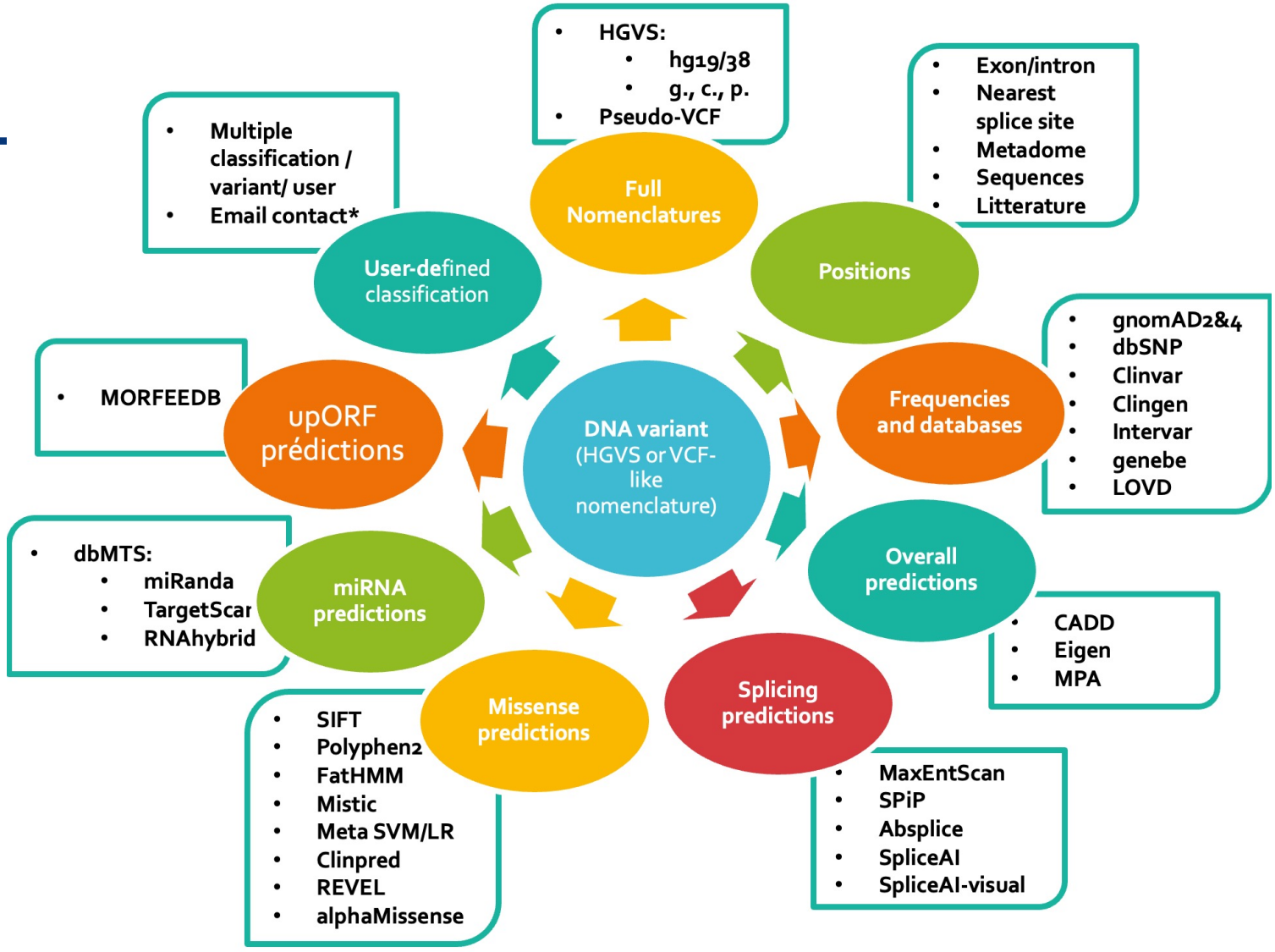
155 Alphamissense wrongly (?) pathogenic



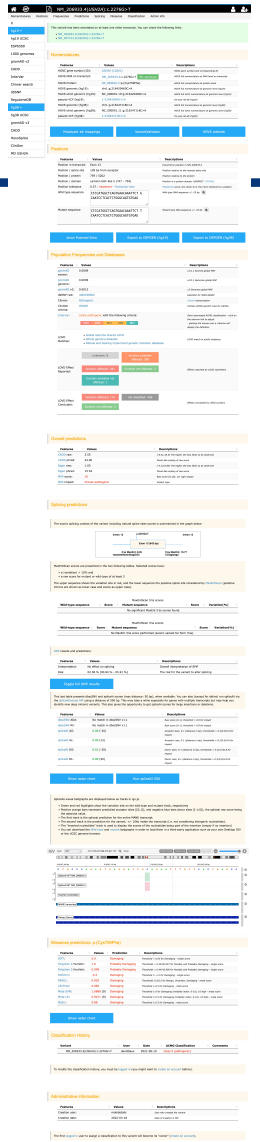
Chabane, Leukemia 2024

MobiDetails

Annotation platform



MobiDetails



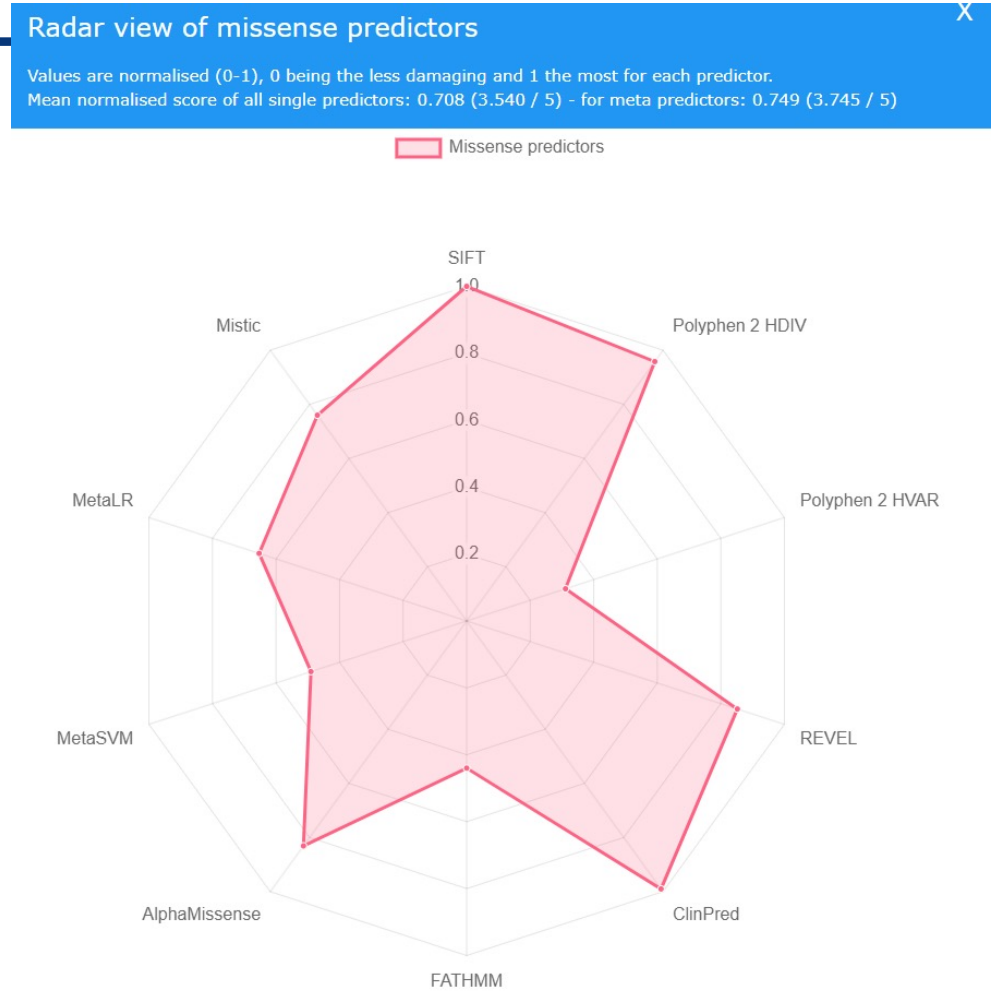
- **Up to 9 interpretation sections:**
  - Nomenclatures: hg19, hg38, genomic, transcript, protein, pseudo-VCF
  - Positions: exon/intron, nearest splice site, MetaDome, WT and mutant sequences, pubmed IDs
  - Frequencies & db: gnomAD 2&3, dbSNP, clinvar, clingen criteria, classification ACMG, LOVD
  - Predictions: CADD, Eigen, MPA
  - Splicing: MaxEntScan, dbscSNV, SPiP, SpliceAI, SpliceAI-visual (radar chart), AbSplice
  - Missense: 10 predictors including 5 « meta » (radar chart)
  - uORFs: Morfeedb
  - miRNA target sites: dbMTS
  - Classification

MobiDetails: Missense predictions

Missense predictions: p.(Asp1692Tyr)

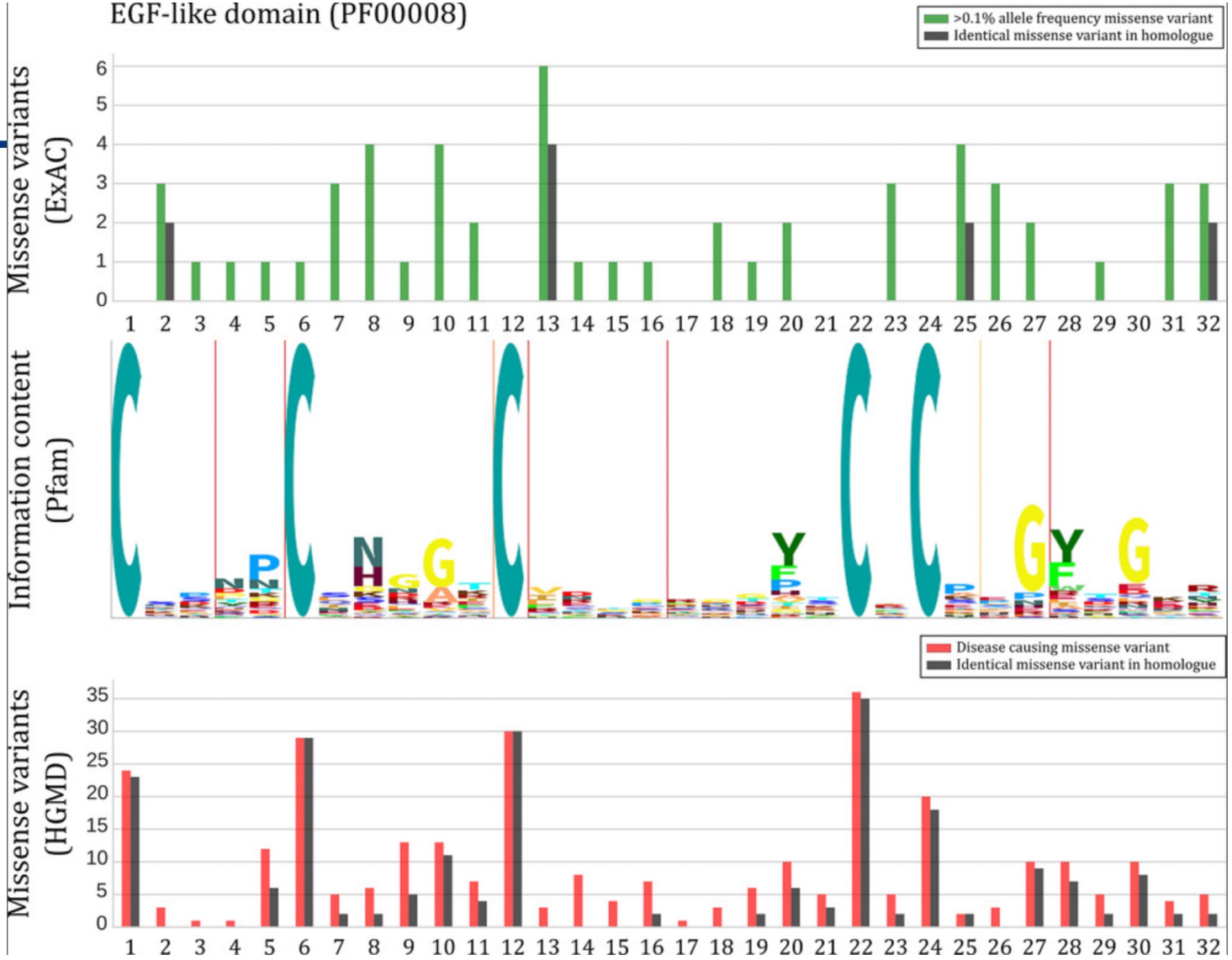
Features	Values	Prediction	Descriptions
SIFT:	0.0	Damaging	*Threshold < 0.05 for Damaging* - ***single score***
Polyphen 2 HumDiv:	0.958	Probably Damaging	*Thresholds ≥ 0.454|0.957 for Possibly and Probably Damaging* - ***single score***
Polyphen 2 HumVar:	0.311	Benign	*Thresholds ≥ 0.447|0.909 for Possibly and Probably Damaging* - ***single score***
Fathmm:	-1.25	Tolerated	*Threshold ≤ -1.5 for Damaging* - ***single score***
AlphaMissense:	0.831	Likely Pathogenic	*Thresholds 0.34|0.564 for Likely Benign, Ambiguous, Likely Pathogenic* - ***single score***
REVEL:	0.852	Damaging	*Thresholds 0.2|0.5 for Benign, Uncertain, Damaging* - ***meta score***
ClinPred:	0.990	Damaging	*Threshold ≥ 0.5 for Damaging* - ***meta score***
Meta SVM:	0.4280 (10)	Damaging	*Threshold ≥ 0 for Damaging (reliabilty index: 0-10), 10:high* - ***meta score***
Meta LR:	0.6531 (10)	Damaging	*Threshold ≥ 0.5 for Damaging (reliabilty index: 0-10), 10:high* - ***meta score***
Mistic:	0.76	Damaging	*Threshold ≥ 0.5 for Damaging* - ***meta score***

MobiDetails: Missense predictions



MetaDome

Wiel et al., 2017



MetaDome

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BRCA1 | Get transcripts

Please first retrieve the transcripts | Analyse Protein

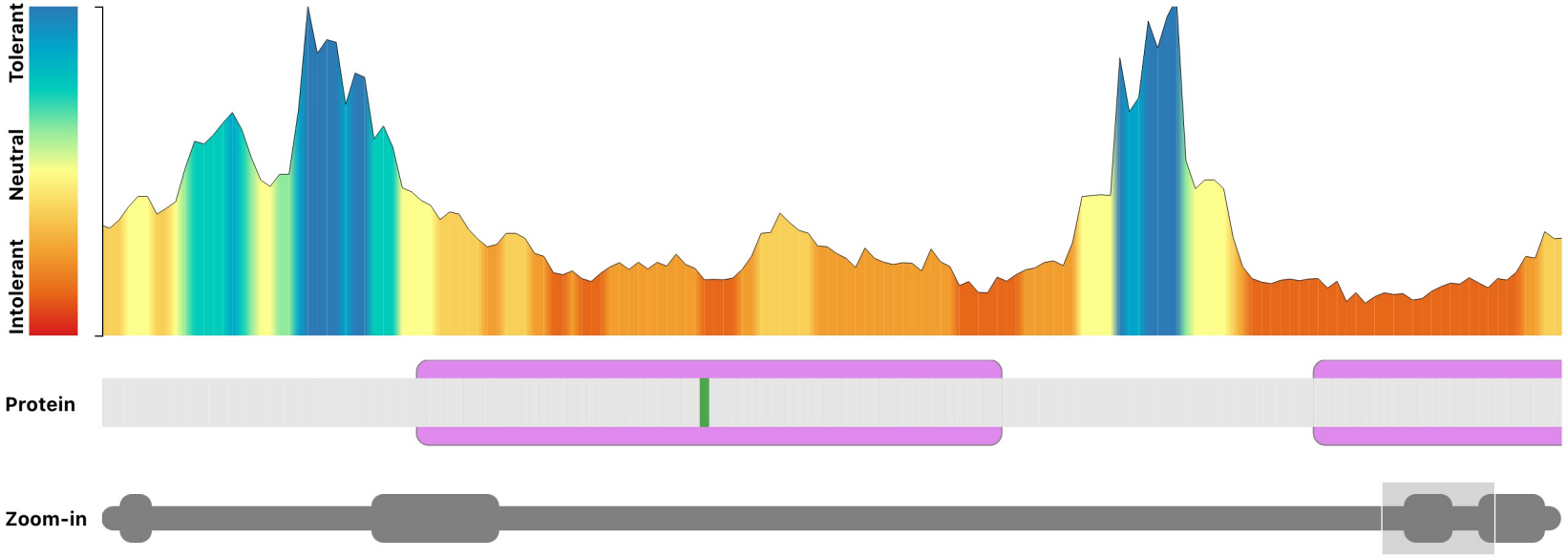
Graph control

Protein of BRCA1 (GENCODE: ENST00000357654.3, RefSeq: NM_007294.3, UniProt: P38398)

○ Show Meta-domain landscape ◉ Show Protein's Tolerance Landscape

Display ClinVar variants: ☐ in this protein ☐ in homologue protein domains

Download current visualization | Reset Zoom | Reset Page



MIZTLI : easy analysis of tertiary structure

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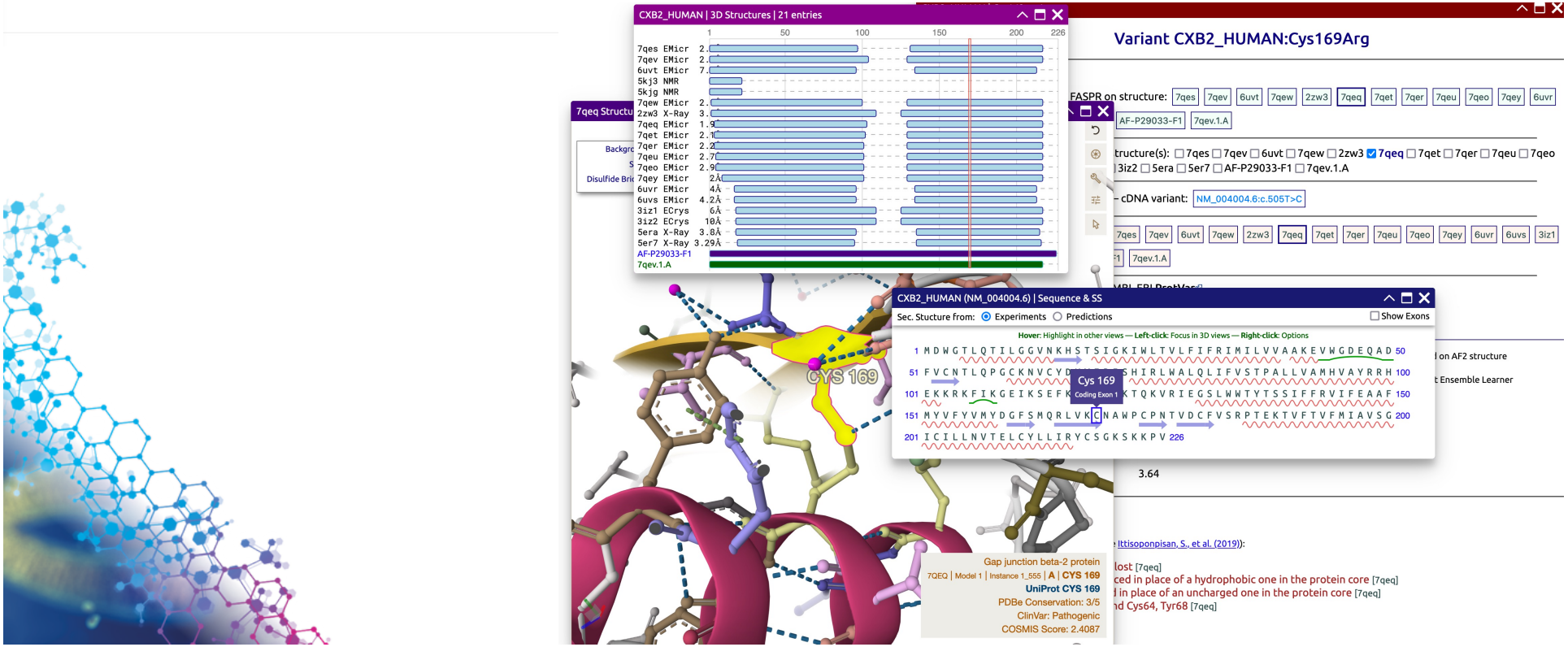
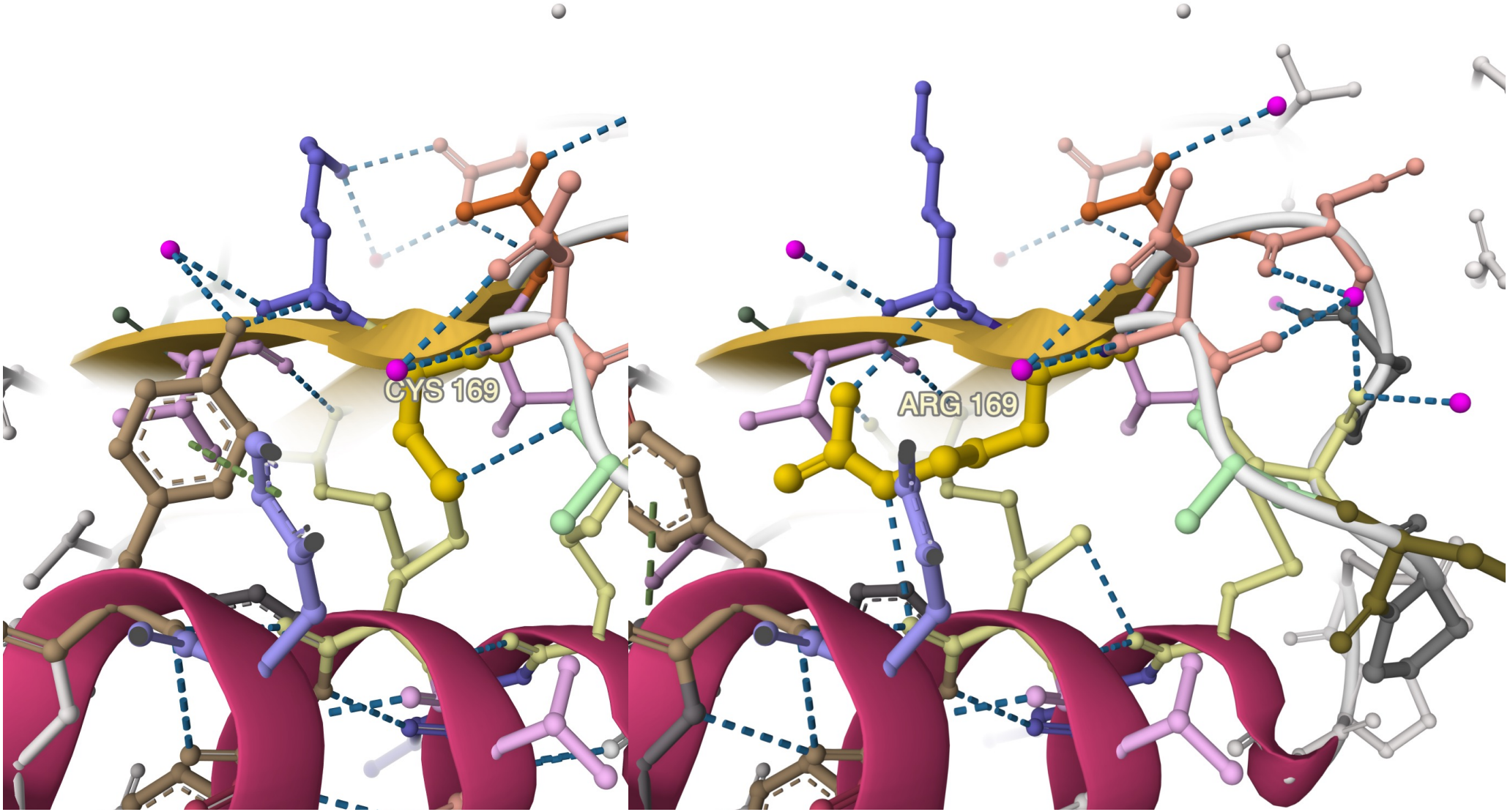
3D Modeling: p.(Cys169Arg)

Let's try this direct access to MIZTLI's 3D engine to compare the wild-type and mutant structure of your variant.




CYS 169
ARG 169

Cas d'étude

M. R, 43 ans

Pas d'antécédent, tabagisme actif 1 paquet par jour

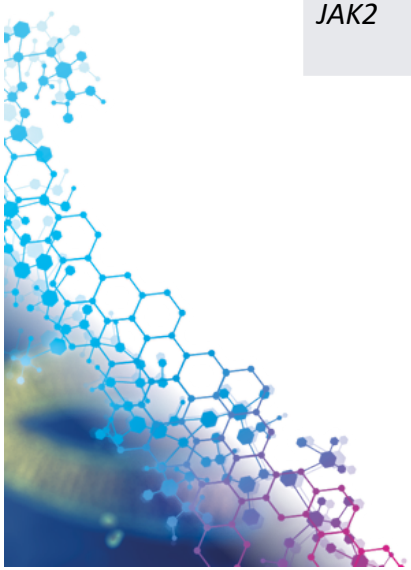
Hyperleucocytose (22G/L) avec PNN 15,6 G/L, lymphocytes 4,78 G/L, monocytes 1,25G/L
Hb 158 gr/L
Plaquettes 338 G/L

Caryotype 46, XY
BCR-ABL, JAK2, CALR, MPL négatifs

Différents immunophénotypages sur sang périphérique panel BT/NK étaient revenus négatifs. Sur le plan du panel monocytaire, il a été retenu une surexpression de la population MO1 en faveur d'un potentiel diagnostic de LMMC bien que tous les éléments nécessaires à ce diagnostic soient insuffisants pour le moment.

Cas d'étude

Gene ID	HGVS genomic	HGVS protein
DNMT3A	chr2(hg38):g.25247118C>T chr2(hg19):g.25469987C>T	p.Ser352Asn
JAK2	chr9(hg38):g.5050707G>A chr9(hg19):g.5050707G>A	p.Gly164Arg



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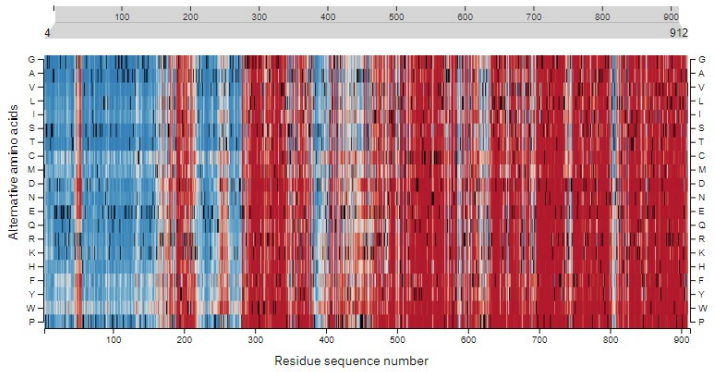
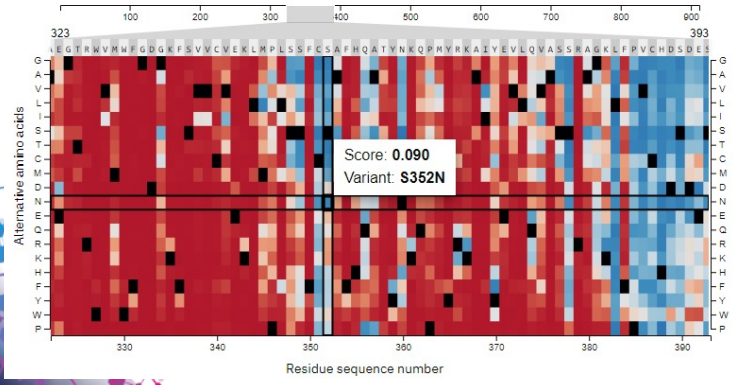
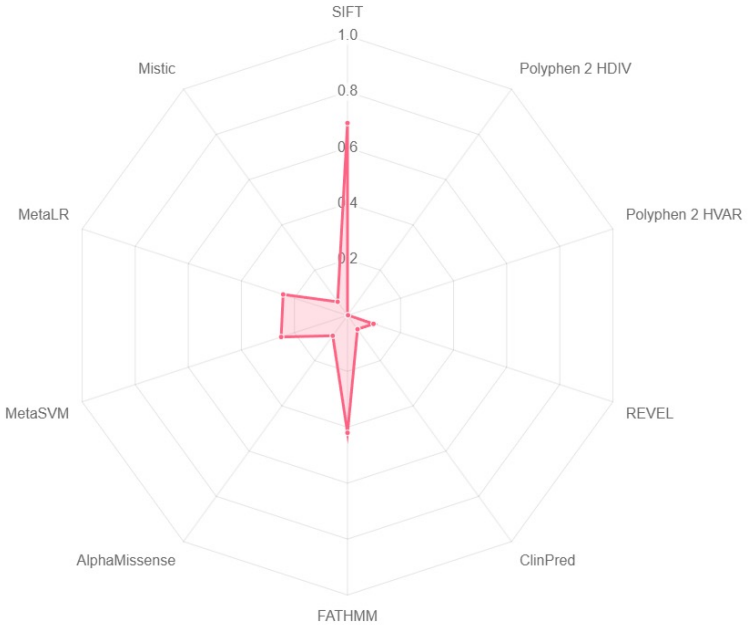
DNMT3A	chr2(hg38):g.25247118C>T chr2(hg19):g.25469987C>T	p.Ser352Asn

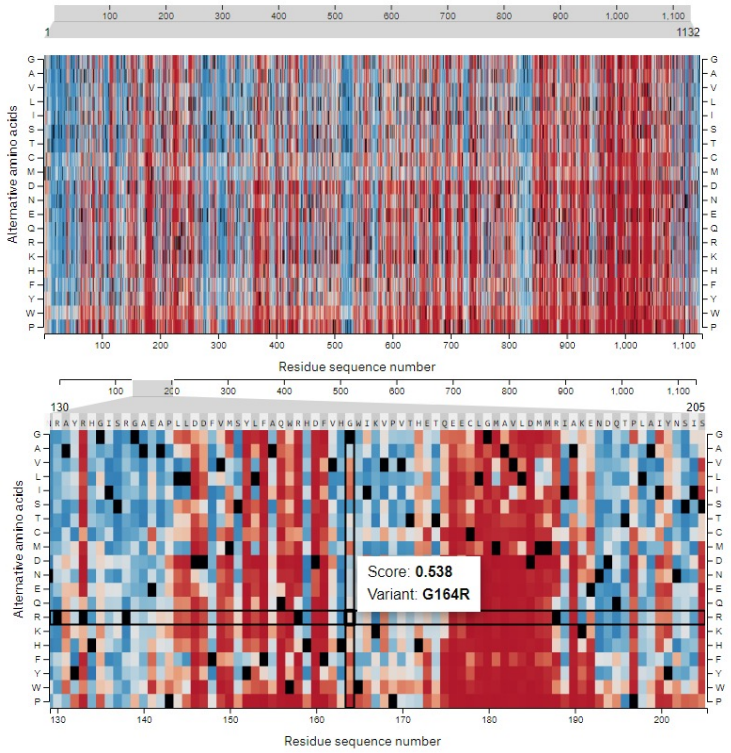


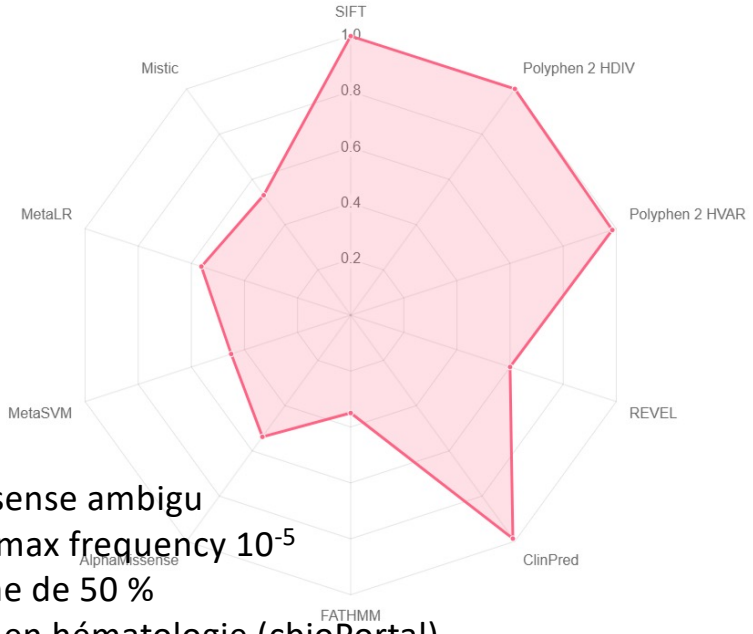




Alphamissense bénin
GnomAD max frequency 10^{-4}
VAF proche de 50 %
=> Ce n'est pas un variant somatique driver

Gene ID	HGVS genomic	HGVS protein
DNMT3A	chr2(hg38):g.25247118C>T chr2(hg19):g.25469987C>T	p.Ser352Asn
JAK2	chr9(hg38):g.5050707G>A chr9(hg19):g.5050707G>A	p.Gly164Arg





Alphamissense ambigu
GnomAD max frequency 10^{-5}
VAF proche de 50 %
Jamais vu en hématologie (cbioPortal)

=> Ce n'est pas un variant somatique driver

Conclusion: Absence de mutation somatique dans le panel de gènes testé

ABSTRACT

PURPOSE: This study aimed to characterize the white blood cell differential of tobacco smoking-induced leukocytosis and describe the longitudinal impact of smoking cessation on this peripheral blood abnormality.

METHODS: Medical records of patients undergoing evaluation by hematologists for persistent leukocytosis were reviewed. Patients in whom leukocytosis was determined to be secondary to tobacco use after exclusion of other causes were identified. Demographic and laboratory data were collected at time of diagnosis. Patients were longitudinally followed and information regarding smoking cessation and follow-up white blood cell values were recorded.

RESULTS: Forty patients were determined to have smoking-induced leukocytosis. The median age was 49.5 years (range: 28-75 years), 24 patients were female, and the mean body mass index (BMI) was 31.5 kg/m^2. The mean white blood cell count was 13.3 $\times$ 10^9/L (range: 9.8-20.9 $\times$ 10^9/L); 39 patients had absolute neutrophilia (98%), 21 had lymphocytosis (53%), 20 had monocytosis (50%), and 19 had basophilia (48%). During follow-up, 11 patients either quit (n = 9) or reduced (n = 2) tobacco use. Reduction in tobacco smoking led to a significant decrease in mean white blood cell count (13.2 $\times$ 10^9/L vs 11.1 $\times$ 10^9/L, $P = 0.02$). The median time to decrease in white blood cell count following reduction in tobacco use was 8 weeks (range: 2-49 weeks).

CONCLUSIONS: Tobacco-induced leukocytosis was characterized by a mild elevation in total white blood cell count and was most commonly associated with neutrophilia, lymphocytosis, monocytosis, and basophilia. Cessation of smoking led to improvement in leukocytosis. Tobacco history should be elicited from all patients presenting with leukocytosis to limit unnecessary diagnostic testing, and counseling regarding smoking cessation should be offered.

 • The American Journal of Medicine (2021) 134:e31–e35

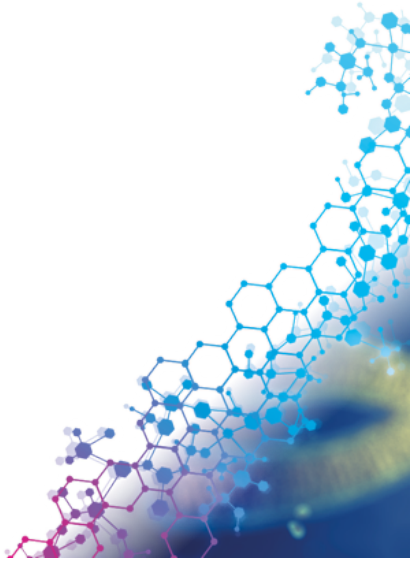
Smith, The American Journal of Medicine 2021

Cas d'étude

Mme D. , 70 ans

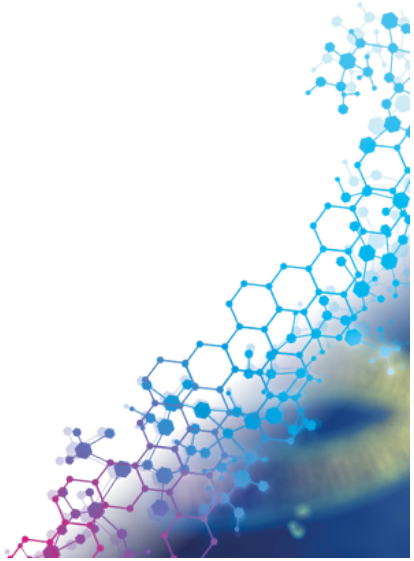
Pas d'antécédent

Thrombocytose isolée (750G/L)
Caryotype 46, XY
BCR-ABL, JAK2 V617F, CALR, MPL négatifs

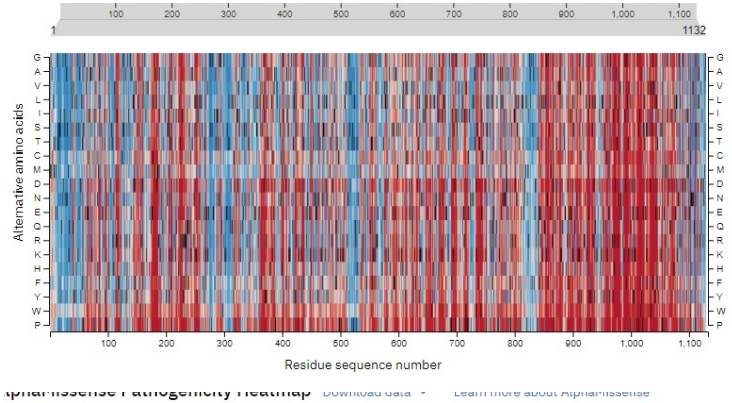


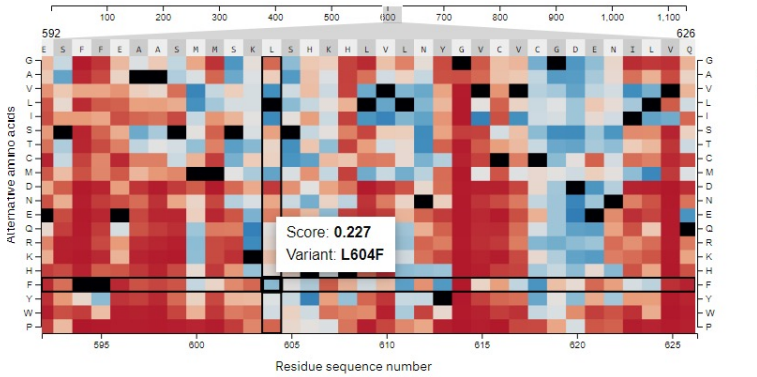
Cas d'étude

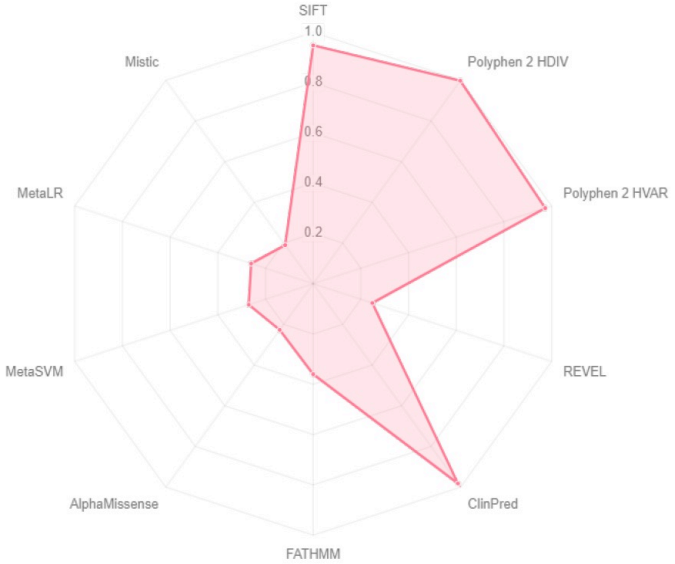
Gene ID	HGVS genomic	HGVS protein
JAK2	chr9(hg38):g.5073731C>T chr9(hg19):g.5073731C>T	p.Leu604Phe



Gene ID	HGVS genomic	HGVS protein
JAK2	chr9(hg38):g.5073731C>T chr9(hg19):g.5073731C>T	p.Leu604Phe







MIZTLI

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Variant JAK2_HUMAN:Leu604Phe

▼ Tools

- **Repack** Phe604 with FASPR on structure: 8ba3 8b8u 8b9e 8b9h 8ba2 8bab 8b99 8bak 8c0a 4fvq 5ut2 6m9h 7f7w 8ex0 8ex2 4fvr 8b8n 4fvp 5wij 7t0p 7t1t 8ba4 5wil 5win 5wim 5wik 6d2i 5ut3 8ex1 5i4n 6bs0 6g3c 5ut6 6obf 7jyq 5ut5 6obb 7szw 6oav 5ut1 5ut4 6brw 6occ 6obl 5usz 5ut0 6bss 8c08 8c09 6xjk 7jyo AF-O60674-F1
- **Analyze** Leu604Phe on structure(s): ☐ 8ba3 ☐ 8b8u ☐ 8b9e ☐ 8b9h ☐ 8ba2 ☐ 8bab ☐ 8b99 ☐ 8bak ☐ 8c0a ☐ 4fvq ☐ 5ut2 ☐ 6m9h ☐ 7f7w ☐ 8ex0 ☐ 8ex2 ☐ 4fvr ☐ 8b8n ☐ 4fvp ☐ 5wij ☐ 7t0p ☐ 7t1t ☐ 8ba4 ☐ 5wil ☐ 5win ☐ 5wim ☐ 5wik ☐ 6d2i ☐ 5ut3 ☐ 8ex1 ☐ 5i4n ☐ 6bs0 ☐ 6g3c ☐ 5ut6 ☐ 6obf ☐ 7jyq ☐ 5ut5 ☐ 6obb ☐ 7szw ☐ 6oav ☐ 5ut1 ☐ 5ut4 ☐ 6brw ☐ 6occ ☐ 6obl ☐ 5usz ☐ 5ut0 ☐ 6bss ☐ 8c08 ☐ 8c09 ☐ 6xjk ☐ 7jyo ☑ AF-O60674-F1
- Investigate with **MobiDetails** – cDNA variant: NM_004972.4:c.1810C>T
- Run **DynaMut2** on structure: 8ba3 8b8u 8b9e 8b9h 8ba2 8bab 8b99 8bak 8c0a 4fvq 5ut2 6m9h 7f7w 8ex0 8ex2 4fvr 8b8n 4fvp 5wij 7t0p 7t1t 8ba4 5wil 5win 5wim 5wik 6d2i 5ut3 8ex1 5i4n 6bs0 6g3c 5ut6 6obf 7jyq 5ut5 6obb 7szw 6oav 5ut1 5ut4 6brw 6occ 6obl 5usz 5ut0 6bss 8c08 8c09 6xjk 7jyo AF-O60674-F1
- Investigate this variant with EMBL-EBI **ProtVar**

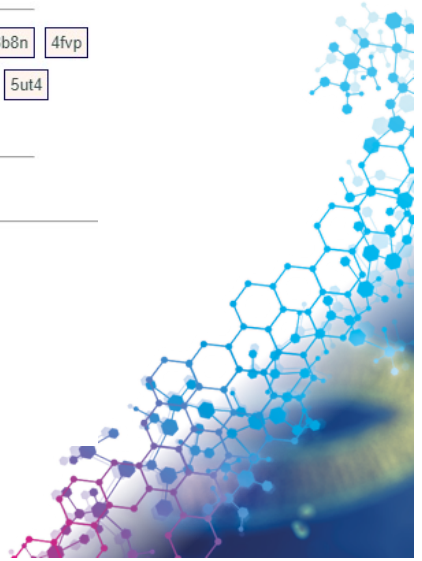
▼ Structural Effects

Potentially damaging structural effects (see Ittisoponpisan, S., et al. (2019)):

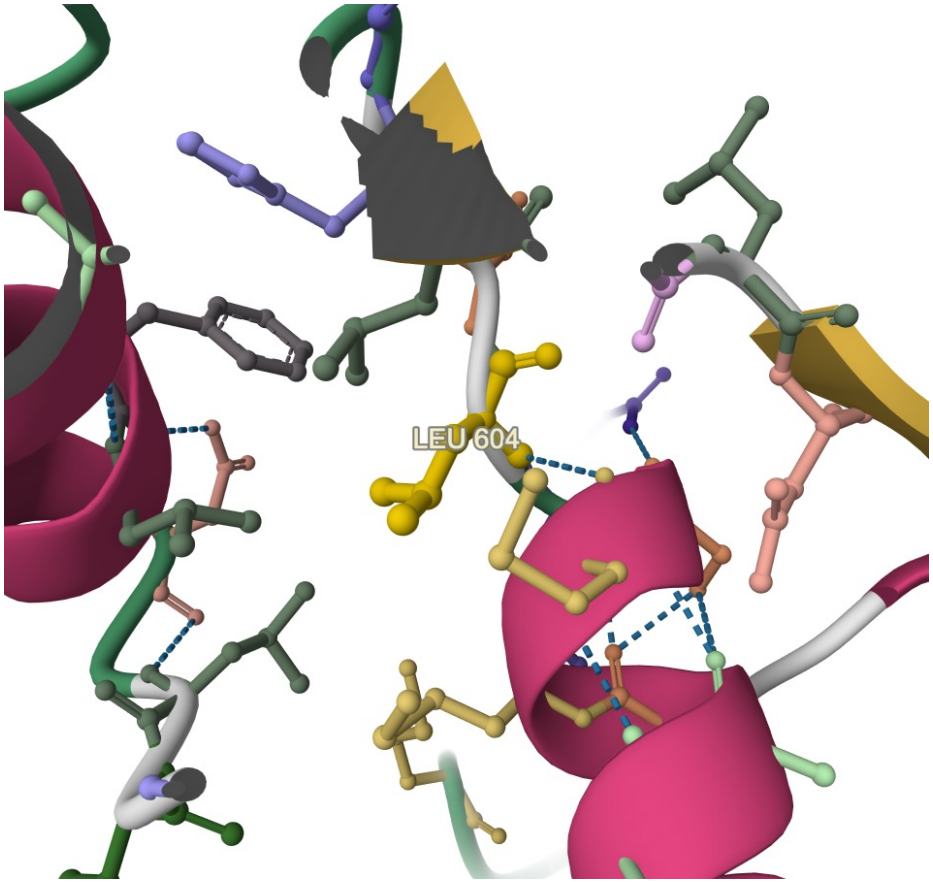
- Steric clash between Phe604 and Met600, Leu669 [AF-O60674-F1]

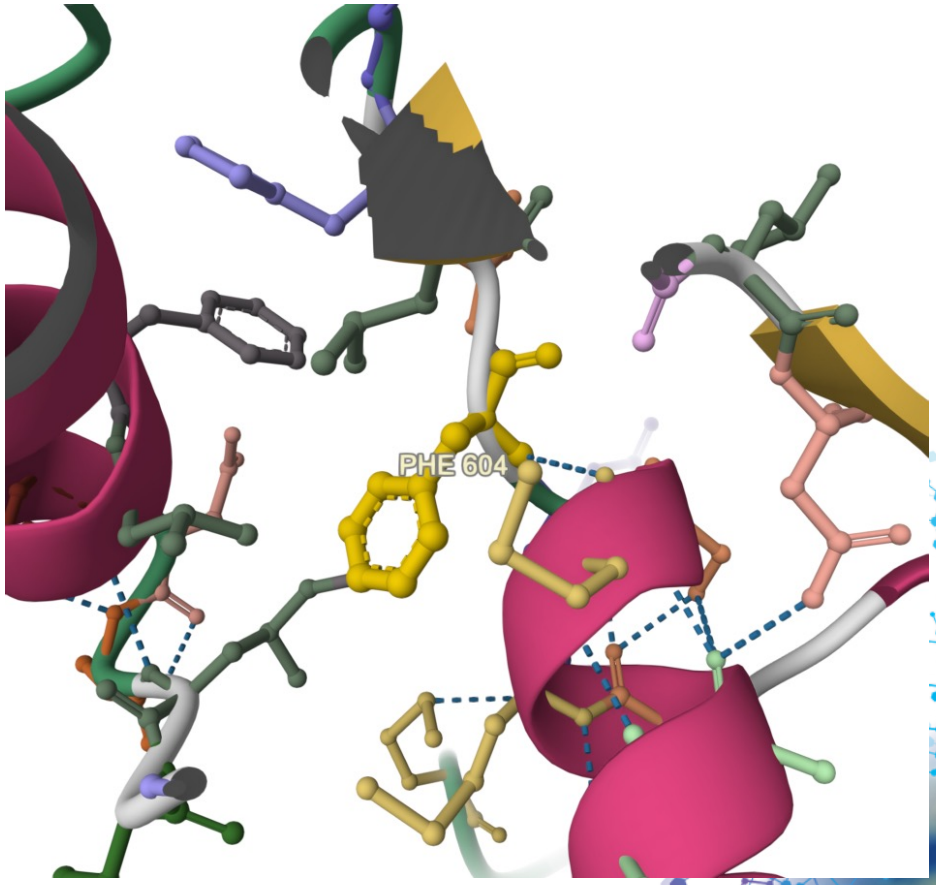
Relative Solvent Accessibility (RSA) of Leu604 / Phe604:
- In AF-O60674-F1: 0.14 / 0.13

Buried/Exposed threshold used: 0.36 (see Rost, B. and C. Sander (1994))

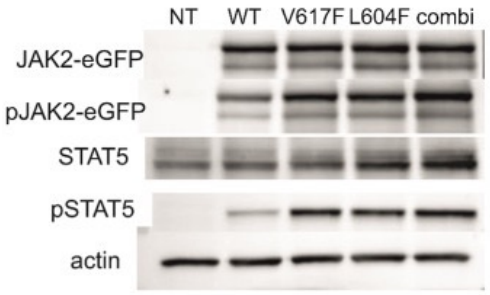


MIZTLI

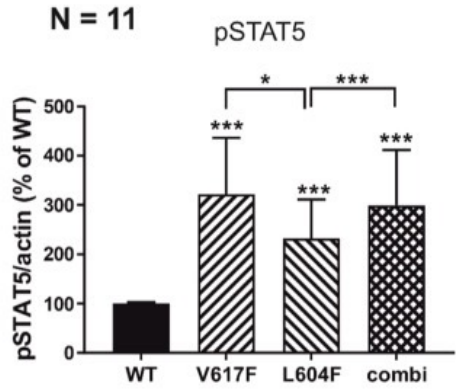




Gene ID	HGVS genomic	HGVS protein
JAK2	chr9(hg38):g.5073731C>T chr9(hg19):g.5073731C>T	p.Leu604Phe



Alphamissense bénin
GnomAD unknown
VAF 23 %
Données fonctionnelles
=> C'est un variant driver



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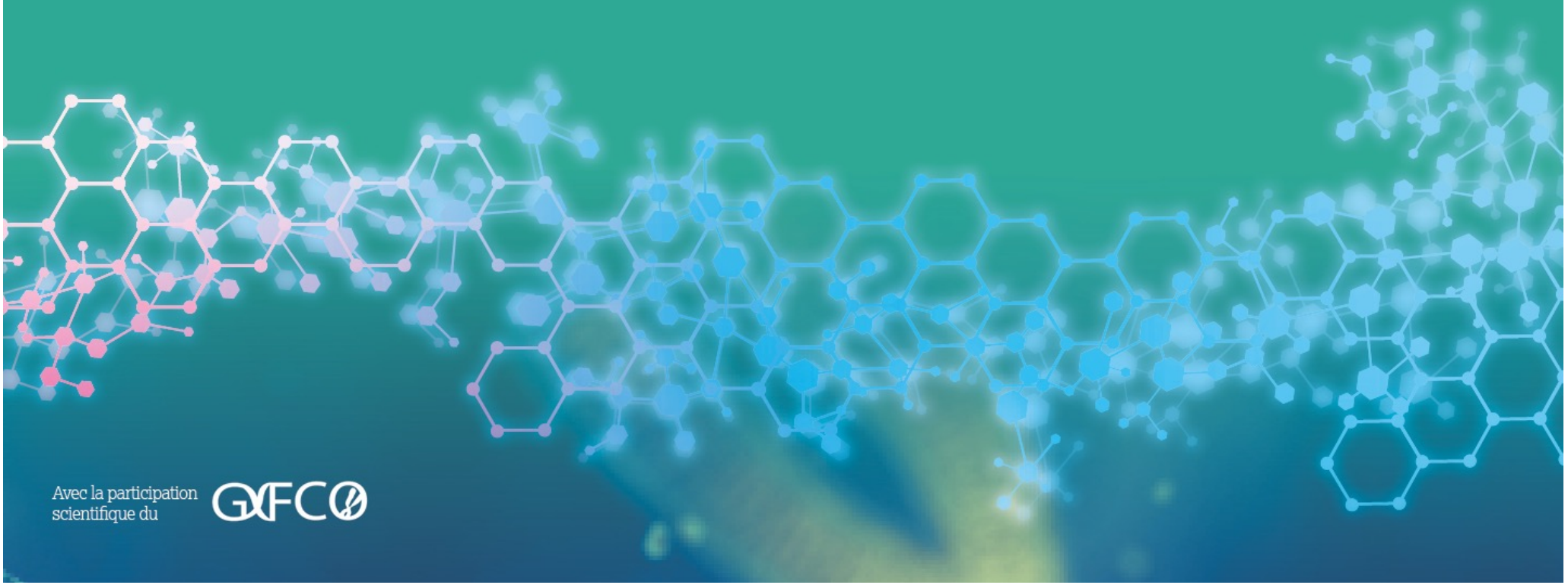

Avec la participation scientifique du GIFCO