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Structural Impact of P-glycoprotein Mutations: Insights into Stability and Conformational Variability

Alexandra-Ioana NĂSTASIE ^{1*}, Ahmad ELBAHNSI ², Maria MITEVA², Adriana-Vetuța ISVORAN ¹

¹ West University of Timișoara, Faculty of Chemistry, Biology, Geography, Department of Biology

² University Paris Cite, France, MCTR Inserm U1268, CITCOM UMR 8038 CNRS

Abstract: This study investigated the effects of over 35 missense mutations in P-glycoprotein, an ATP-dependent efflux transporter encoded by the human ABCB1 gene, on its structural stability and conformational variability. Two structures, one experimentally determined and one AlphaFold-generated, were analyzed using DynaMut and Chimera. The results revealed both stabilizing and destabilizing effects, with destabilizing mutations predominating, and showed conformational alterations mainly in regions with multiple mutations, suggesting reduced stability and potential impairment of substrate binding and transport efficiency.

• Introduction

P-glycoprotein (P-gp) is an ATP-dependent efflux transporter essential for xenobiotic clearance and drug resistance. It is mainly expressed in barrier tissues, including the blood-brain barrier, intestine, liver, and kidneys, where it prevents intracellular accumulation of potentially harmful compounds. Figure 1 illustrates the structural organization of P-glycoprotein.

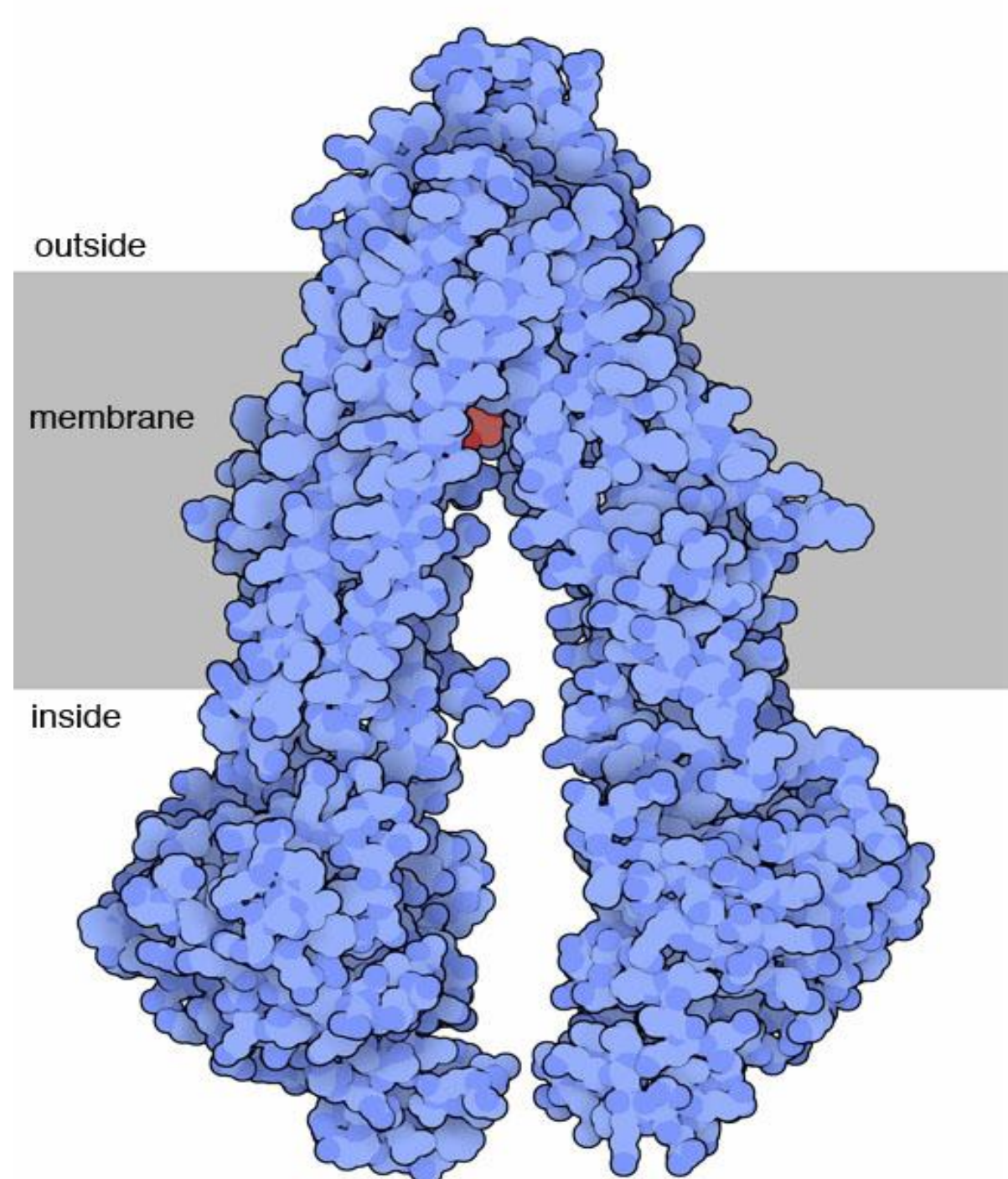


Fig. 1: Structural organization of P-gp

• Material and method

• **Crystallographic structures:** A experimentally determined structure retrieved from the Protein Data Bank (PDB)- 7A65 and a computationally generated structure predicted by AlphaFold- AF-P08183

• **Structural stability analysis:** Performed using the DynaMut server to evaluate the effects of missense mutations on protein stability

• **Conformational and structural comparison:** Conducted in UCSF Chimera by aligning the two models with the MatchMaker tool to assess residue alignment and domain orientation

• Results and discussions

Conformational variability

Chimera analysis revealed both local and global conformational changes between the allelic and native variants, with some regions showing notable alterations that may affect substrate binding. Local changes are shown in Figure 2.

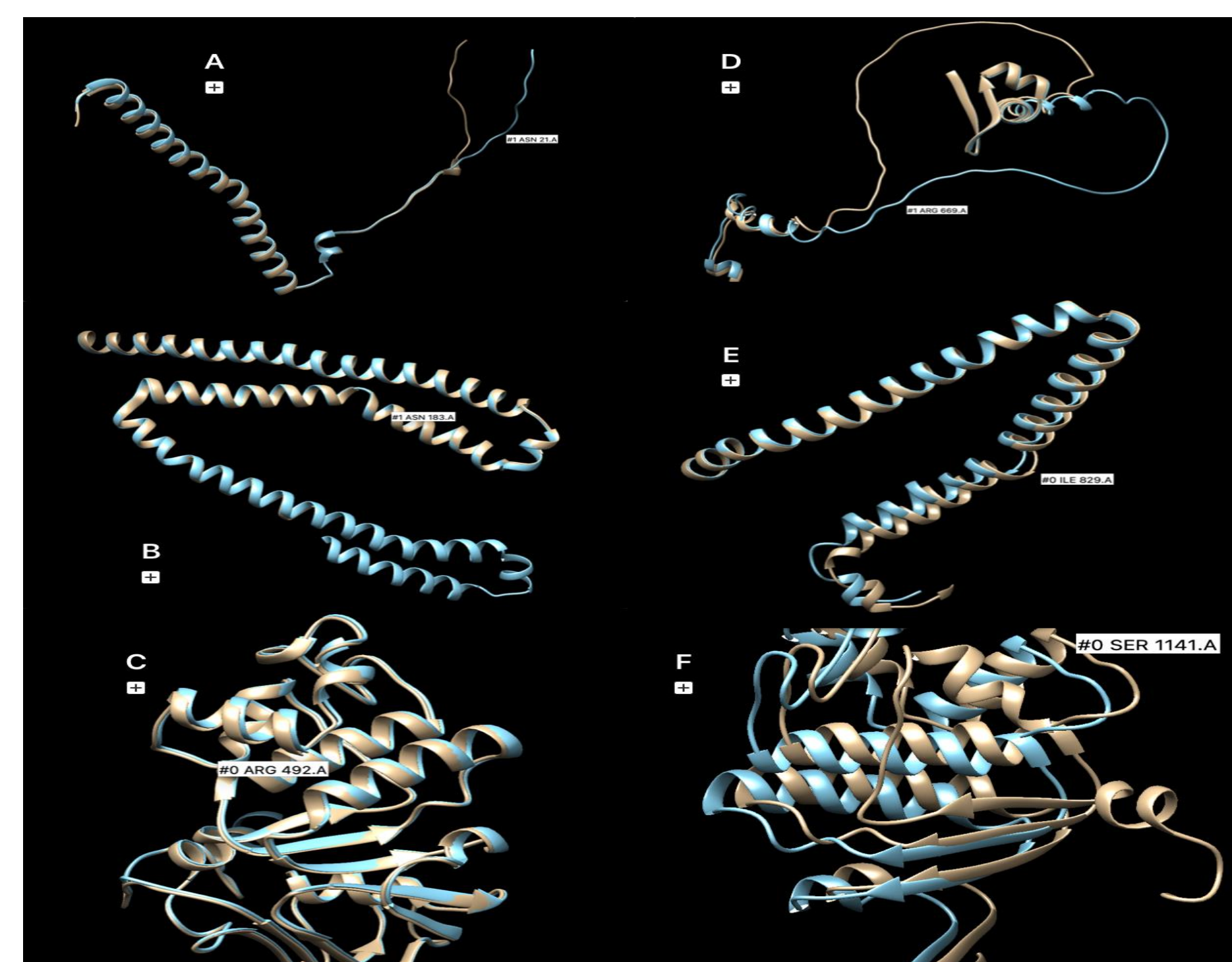


Fig. 2: Conformational variability of P-gp

Structural stability

DynaMut analysis showed both stabilizing and destabilizing effects, with destabilizing ones predominating. This indicates a general decrease in protein stability, as shown in Table 1.

Missense mutation	$\Delta\Delta G$ (kcal/mol)	
	Experimental structure 7A65	AlphaFold Model AF-P08183
N15D	unavailable	0,21
F17L	unavailable	-0,34
N21D	unavailable	0,07
N44S	0,08	0,33
A80G	-1,33	-1,51
M89T	unavailable	0,3
F103L	unavailable	-0,09
N183S	0,3	0,11
G369P	unavailable	unavailable
I261V	-0,76	-1,11
S400N	-0,56	-0,53
S400T	0,558	unavailable
R492C	0,55	-0,18
R593C	0,58	0,59
A599T	-0,88	-0,82
L662R	unavailable	0,37
R669C	unavailable	0,47
V801M	0,09	0,24
I829V	-1,07	-0,99
I836V	0,03	-0,52
I849M	0,03	-0,04
A893S	-0,379	-0,726
A893T	0,308	-0,867
M986V	-1,47	-0,42
A999T	-0,38	-0,66
P1051A	0,15	-0,3
Q1107P	-0,15	-0,13
W1108R	-0,33	-1,49
S1141T	-0,28	-0,62
V1251I	-0,45	-0,49
T1256K	-0,06	-0,28

Table 1: Changes of structural stability of P-gp

• Conclusions

The analysis of missense mutations revealed predominantly destabilizing effects on P-glycoprotein, leading to significant conformational differences, particularly in regions with multiple mutations. Together, these effects may compromise substrate binding and overall transport function. Further research is needed to explore their potential implications in diseases such as cancer.