Group project 2: Characterising the pathogenicity of amino acid change in ABCA1

Tangier disease (TD) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous variants in the ABCA1 gene, which encodes a cell plasma membrane cholesterol transporter.

Task

Ensembl

Download variants that fall within the ABCA1 gene with the criteria: clinical significance: Pathogenic .
Calculate the annotations using the Ensembl Variant Effect Predictor (Ensembl VEP).
Select: Protein, Uniprot, HGVS, Protein matches, Phenotype, AlphaMissense.
Filter the Ensembl VEP results:

1. AlphaMissense > 0.6

Do the AlphaMissense predictions of likely pathogenicity reflect the observed pathogenicity reported in ClinVar?

Click on the variant with the highest AlphaMissense score (rs137854494).
This will take you to the Variant tab
The Variant tab allows you to explore this variant further (You can view the variant in its genomic context, phenotype information and phylogenetic context).

2. Can you see if the reference allele is also present in other primates? Does it appear to be conserved?
3. The Ensembl VEP results show that the variant rs137854494 overlaps ENSP00000363868 (Uniprot match: O95477) at protein position 1477. Can you find out which protein domains this variant hits? (Hint: Check the AlphaFold model for this protein for visualisation of the structure).

G2P

1. Does G2P hold evidence for an association between Tangier disease and ABCA1?
2. How many publications provide evidence for this association? Are you confident the reported association is real?
3. What is the reported disease mechanism? What kind of variants would result in this?

Uniprot/ProtVar

Q. What genetic variants have been highlighted in the UniProt record as likely significant for Tangier disease (TD)?
Hint: look at the “variants and disease” section.

- Click on A>V at position 937 to go to ProtVar. Then look at the functional annotation button: 

Q. What is the likely role of this residue and how might varying the amino acid affect this role?

- Click the structural annotation button  and the second table, second row to see the variant position.

Q. Can you use the alphaFill structure to see which molecule it is interacting with?

PDB

PDB task 1:
Jupyter / Colab Notebook for this task:
01_structures_availability
(https://github.com/PDBeurope/pdbe-notebooks/blob/main/variants_embl-ebi_july2025/01_structures_availability.ipynb)

- Fill-in information on predicted and experimentally-determined structures availability. *HINT: Use UniProt ID to help find structures.*

Table 1: General Structure Availability	
No of predicted & exp-determined structures	
No of predicted structures	
No of exp-determined structures	
No of exp-determined structures from PDB	
No of exp-determined structures with resolution better than 3 Ångstrom	
PDB id(s) with best resolution	
PDB id(s) with most coverage	
PDB id(s) without any mutations	

PDB task 2:
Jupyter / Colab Notebook for this task:
01_structures_availability
(https://github.com/PDBeurope/pdbe-notebooks/blob/main/variants_embl-ebi_july2025/01_structures_availability.ipynb)
The following structures may help give insight into a genetic variant:

1. Experimentally-determined structure with an amino acid change at the position

2. Experimentally-determined structure with information at the variant position and no other mutations or variants
3. Experimentally-determined structure with information at the variant position but with additional mutations or variants
4. Predicted structure with information at the variant position

The usefulness of the structures for insight into genetic variants is as follows:
(1) is best, BUT if (1) does not exist, should consider (2), and if (2) does not exist should consider (3) or (4).

List 4-10 single amino acid changes from previous analysis (included 2 examples)	255 (Ala/Thr), 587 (Arg/Trp)

- Identify the corresponding data from predicted and experimentally-determined structures for a specific set of variants.
  HINT: Use UniProt numbering for variant position.

Table 2: Find PDB ids / AFDB ids potentially useful for understanding the variant		
Variant position	Best structure type available	PDB or AFDB id(s)
255	(2) Exp-det (no mut)	7tdt, 7roq, 5xjy
587	(2) Exp-det (no mut)	7tdt, 7roq, 5xjy

PDB task 3:
Jupyter / Colab Notebook for this task:

02_structural_visuallisation (https://github.com/PDBeurope/pdbe-notebooks/blob/main/variants_embl-ebi_july2025/02_structures_visuallisation.ipynb)

Visualising is a key part of understanding protein structures. We will use some of the structures previously identified for visualisation. Mutations that are clustered together spatially in a structure may be impacting in a similar manner. This visualisation will be useful for PDB task 5.

- Using the tool developed by PDBe and RSCB and partners called MolStar we can view where the variants are in a structure.

PDB task 4:

- Use the Ligand subpage of a PDBe-KB page to assess whether a ligand binding site is applicable for the variant or not. This analysis will be useful for PDB task 5.
  HINT1: Use UniProt ID to find the appropriate PDBe-KB page.
  HINT2: If no experimental structures are available, skip this task.

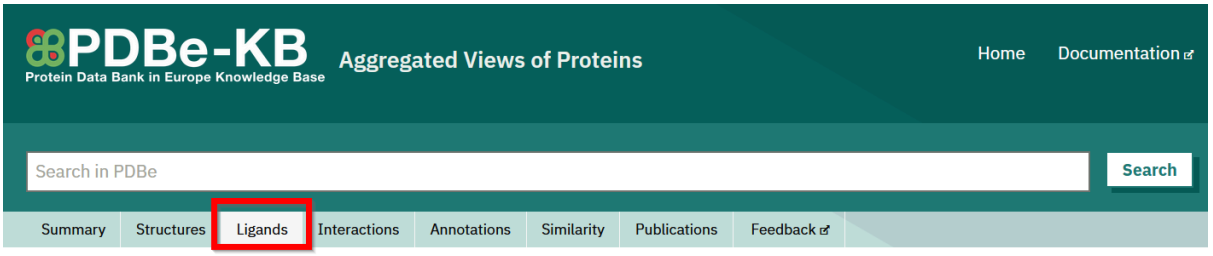

Table 3: Find PDB ids / AFDB ids if ligand is involved		
Variant position	Near ligand site? (CCD ID)	PDB id(s)
255	No	
587	No	

PDB task 5:

Jupyter / Colab Notebook for this task:
03_structural_assessment
(https://github.com/PDBeurope/pdbe-notebooks/blob/main/variants_embl-ebi_july2025/03_structural_assessment.ipynb)

- If possible, propose an interpretation of why the genetic variant may impact on the protein's function and thus cause disease.
  HINT: Use the tools from PDB task 3 & 4 to aid answering structural assessment questions.

Table 4: Propose why variant might impact on protein function	
Variant	**Variant interpretation (hypothesis based on structure)**
255 (Ala/Thr)	Unclear. May need further analysis or experimentation.
587 (Arg/Trp)	Structural fold may be broadly impacted by disruption in a linkage between two secondary structure elements.

Open Targets

- To know more about Tangier disease, go to the association page and see the most associated target. Are there any drugs in the clinic for this disease?
- As ABCA1 appears to be a promising target, we would like to know whether there are any specific precautions that should be taken when designing a drug for this target. Visit the ABCA1 target page to see if there is any pharmacogenetics information that could help us determine whether a patient stratification strategy would be useful.