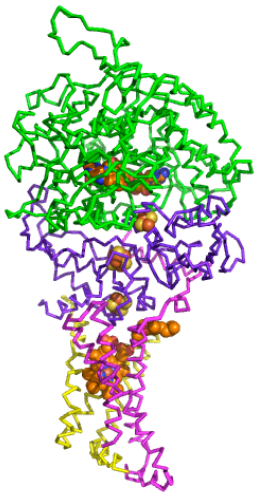
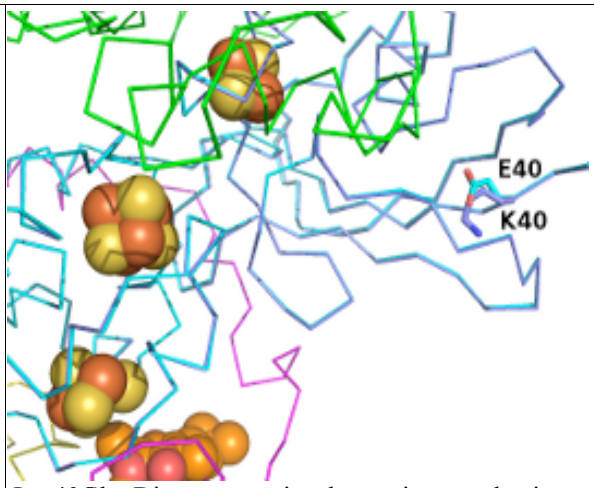
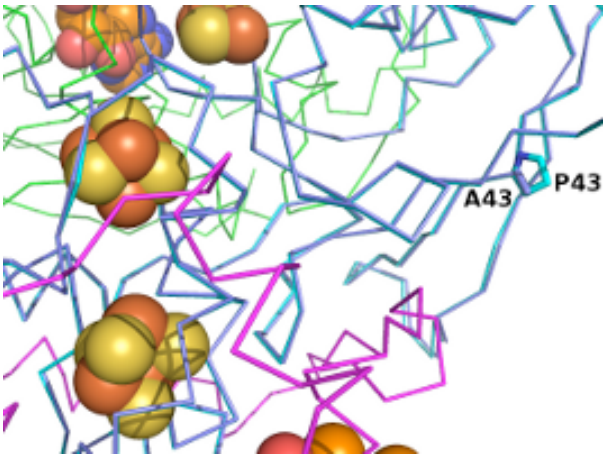


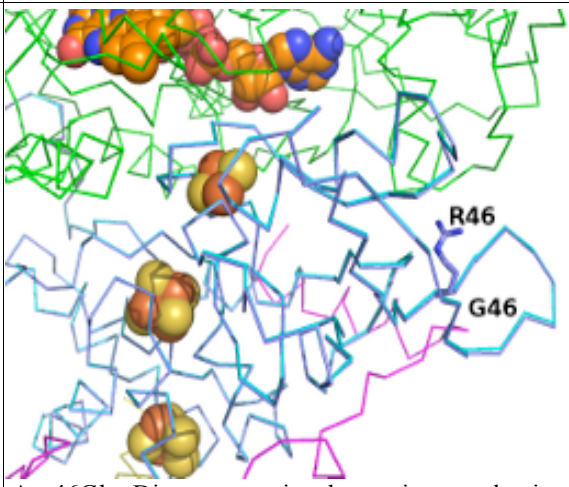
Arg27X. Purple represents wild-type protein is missing in the mutant.



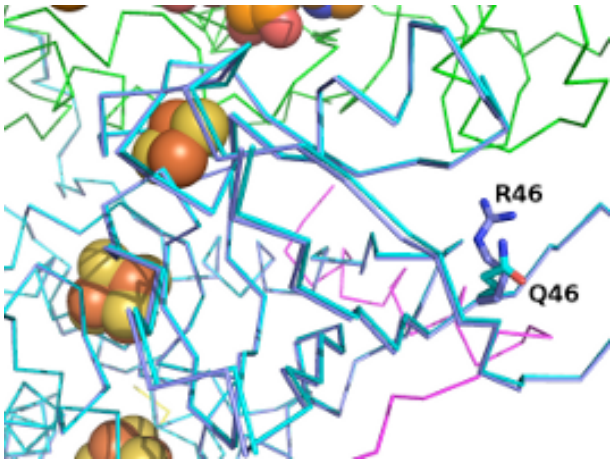
Lys40Glu. Disease-associated mutations not having an obvious structurally deleterious effect.



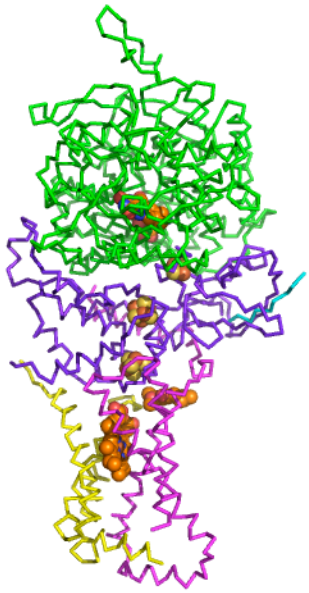
Ala43Pro. Disease-associated mutations not having an obvious structurally deleterious effect.



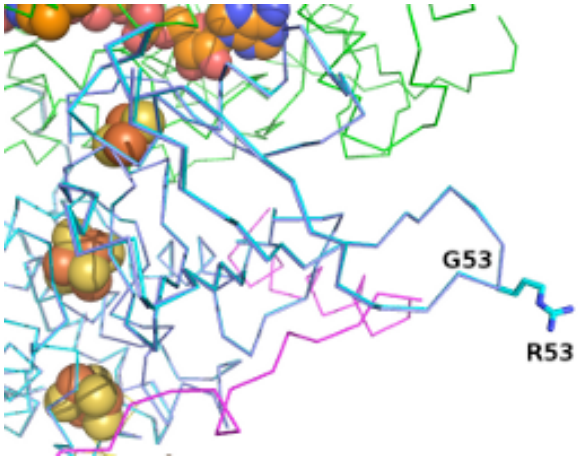
Arg46Gly. Disease-associated mutations not having an obvious structurally deleterious effect.



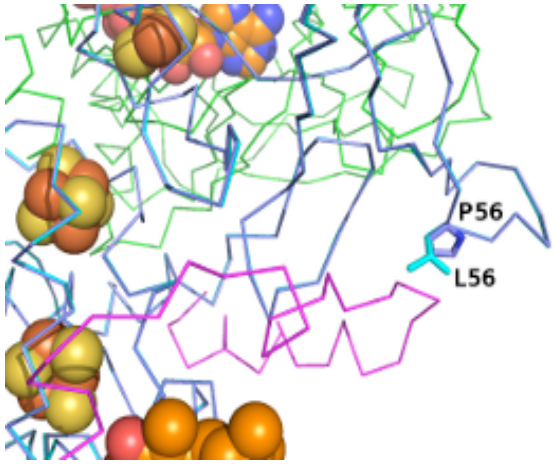
Arg46Gln. Disease-associated mutations not having an obvious structurally deleterious effect.



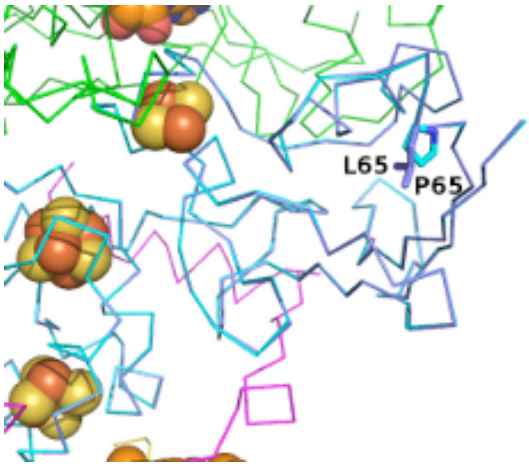
Arg46X. Purple represents wild-type protein is missing in the mutant. Cyan represents the rest of subunit B that is present in the mutant.



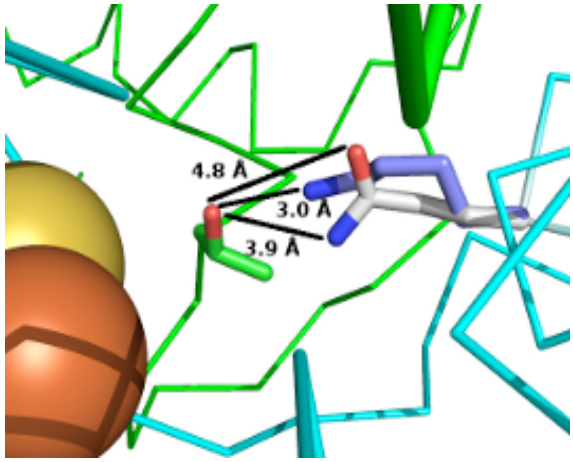
Gly53Arg. Disease-associated mutations not having an obvious structurally deleterious effect.



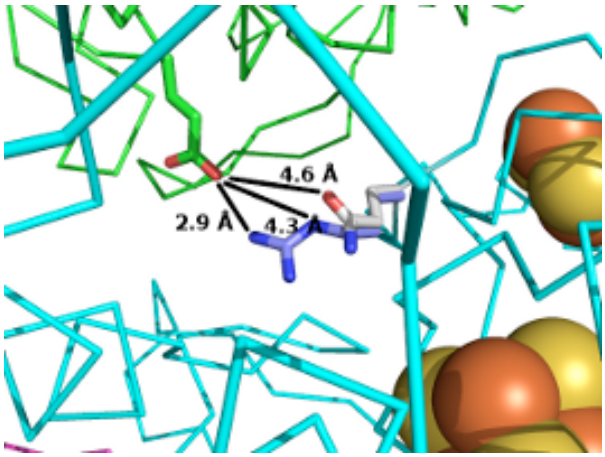
Pro56Leu. Disease-associated mutations not having an obvious structurally deleterious effect.



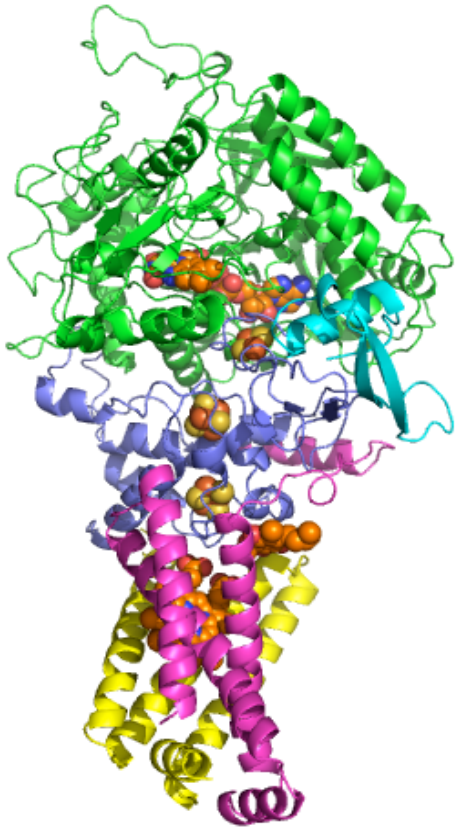
Leu65Pro. Disease-associated mutations not having an obvious structurally deleterious effect.



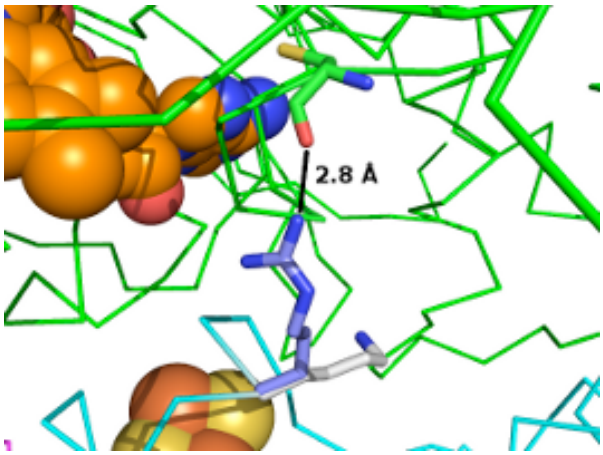
Lys80Gln. Wild-type K80 side chain is purple sticks. Mutant Q80 side chain is white sticks. Subunit A T560 is green sticks. Distances between atoms are shown by black lines. Wild-type B:K80:NZ is involved in a hydrogen bond with A:T560:OG1, and this bond between subunit A and B is lost in the disease-associated mutant, possibly destabilising the SDH macromolecular assembly.



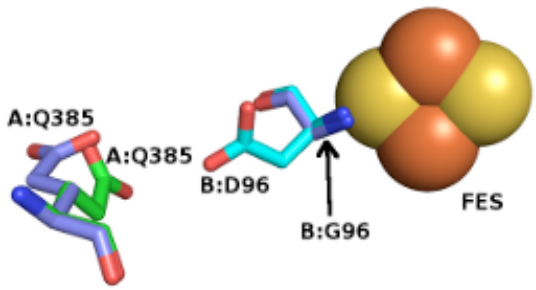
Arg90Gln. Wild-type R90 side chain is purple sticks. Mutant Q90 side chain is grey sticks. Subunit A E218 is green sticks. Distances between atoms are shown by black lines. The hydrogen bond between wild-type SDHB:R90 and SDHA:E218 is missing in the mutant. In its place, the negatively charged mutant SDHB:E90 may be repulsing the negatively charged SDHA:E218.



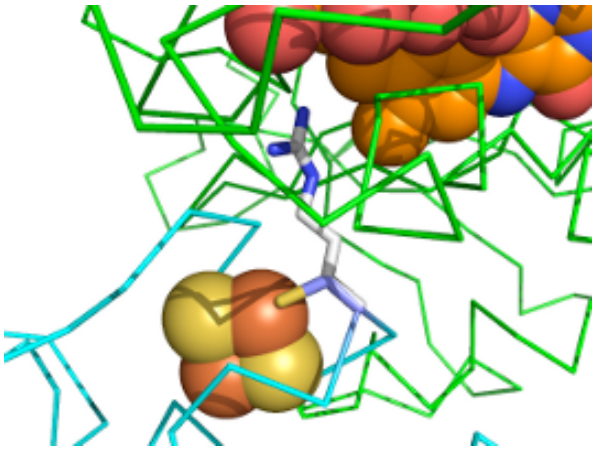
Arg90X. Purple represents wild-type protein is missing in the mutant. Cyan represents the rest of subunit B that is present in the mutant.



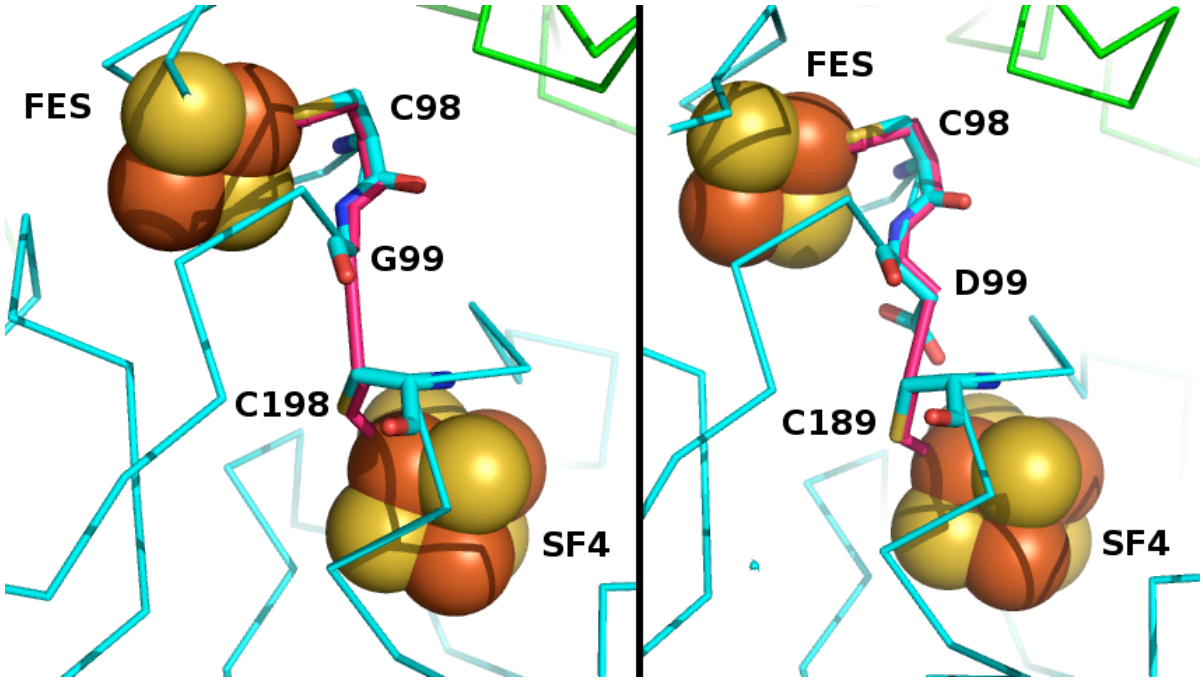
Arg94Lys. Wild-type R94 side chain is purple sticks. Mutant K94 side chain is grey sticks. Subunit A C266 is green sticks. Distances between atoms are shown by black lines. Wild-type B:R94:NH4 is involved in a hydrogen bond with A:C266:O, and this bond between subunit A and B is lost in the disease-associated mutant, possibly destabilising the SDH macromolecular assembly.



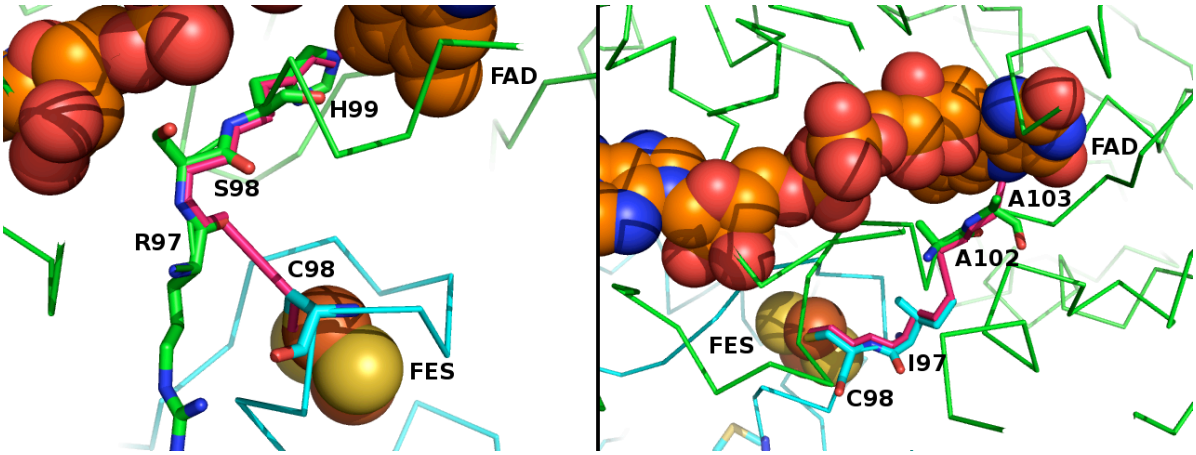
Gly96Asp. The wild-type residues are shown in purple. The mutant subunit B is shown in cyan and mutant subunit A is shown in green. The wild-type SDHB:G96 is calculated to contain a hydrogen bond between the backbone of subunit B residue 96 and FES that is not present in the mutant SDHB:G96D. This may indicate that there is a loss of bonding in the mutant that would affect the FES redox potential difference by reducing the potential difference, which would abolish the rate of electron transfer to FES.



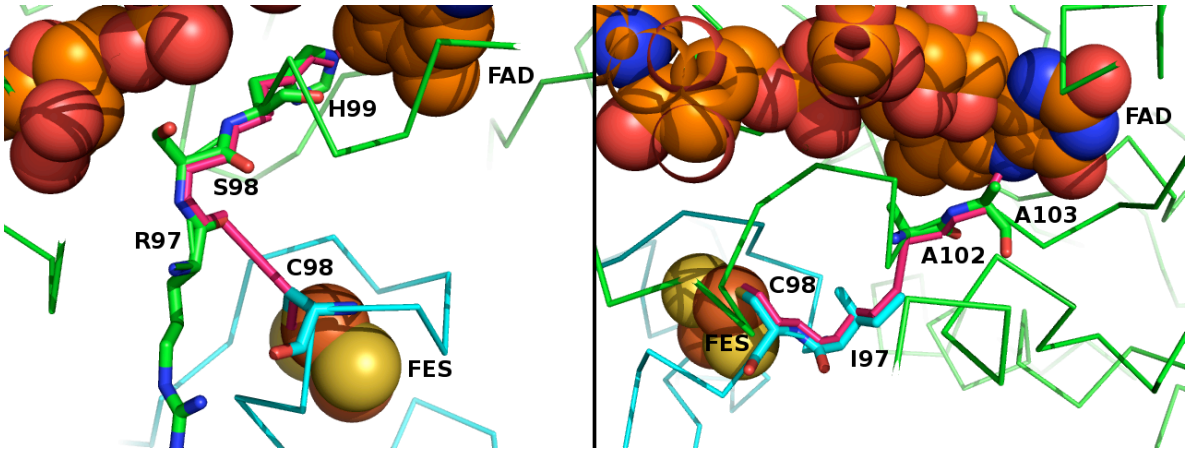
Cys98Arg. Wild-type C98 side chain is purple sticks and is bound to the iron-sulfur centre. Mutant R98 side chain is white sticks and does not bind the iron-sulfur centre.



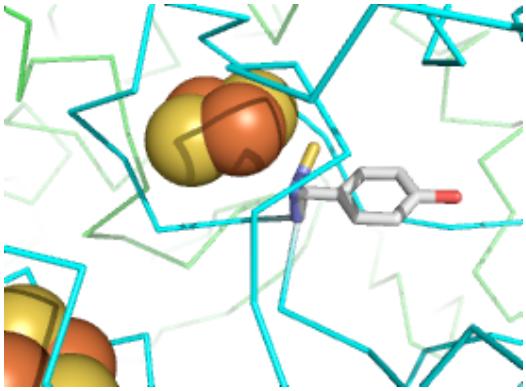
Gly99Asp. Homology model for SDH subunit B wild-type (left) and mutant G99D (right), showing close-ups of the calculated electron transfer paths between iron-sulfur clusters FES and SF4. The mutant is calculated to pass through more chemical bonds than the wild-type. This suggests that electrons will tunnel faster in the mutant than in the wild-type because electron transfer is better through covalent bonds than through space, and electrons may be lost and cause formation of reactive oxygen species. The electron path segments are shown in pink. Subunit B backbone is coloured cyan and subunit A backbone is coloured green. The iron-sulfur clusters are shown in gold and brown balls.

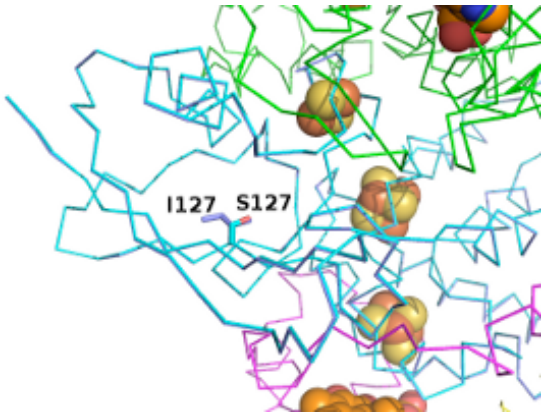


Ser100Phe. Homology model for SDH subunit B wild-type (left) and mutant S100F (right), showing close-ups of the calculated electron transfer paths between FAD and iron-sulfur cluster FES. The electron path of the mutant is calculated to pass through more chemical bonds than the wild-type. This suggests that electrons will tunnel faster in the mutant than in the wild-type because electron transfer is better through covalent bonds than through space, and electrons may be lost and cause formation of reactive oxygen species. The electron path segments are shown in pink. Subunit B backbone is coloured cyan and subunit A backbone is coloured green. The iron-sulfur cluster is shown in gold and brown balls. FAD is shown in orange, red and blue balls.

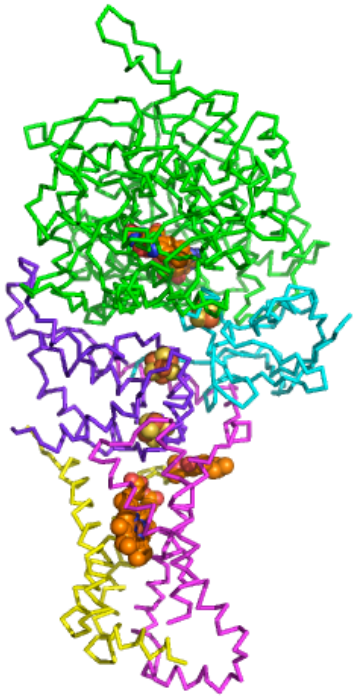
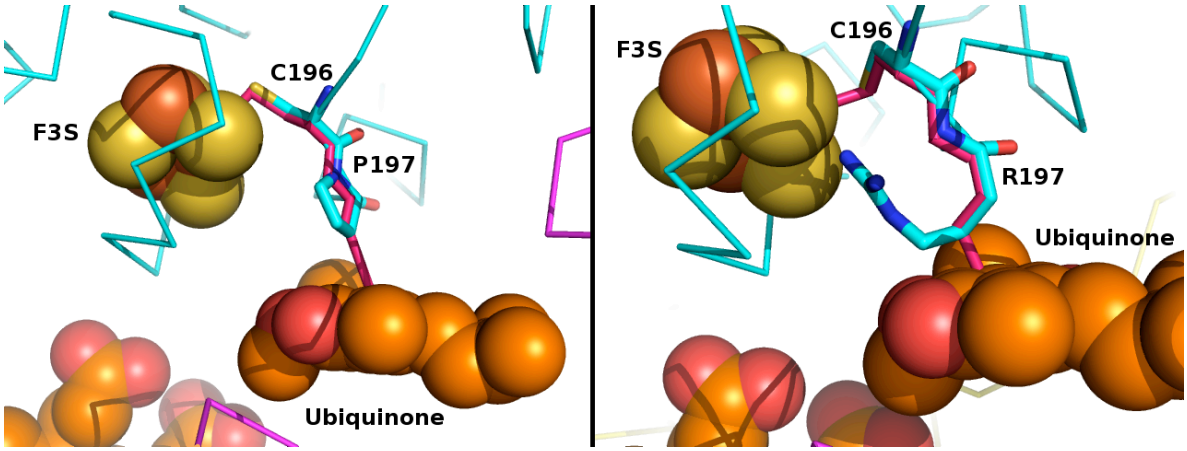


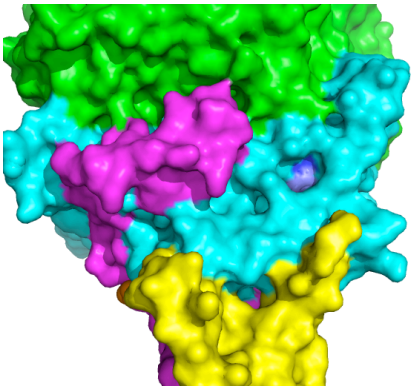
Ser100Pro. Homology model for SDH subunit B wild-type (left) and mutant S100P (right), showing close-ups of the calculated electron transfer paths between FAD and iron-sulfur cluster FES. The electron path of the mutant is calculated to pass through more chemical bonds than the wild-type. This suggests that electrons will tunnel faster in the mutant than in the wild-type because electron transfer is better through covalent bonds than through space, and electrons may be lost and cause formation of reactive oxygen species. The electron path segments are shown in pink. Subunit B backbone is coloured cyan and subunit A backbone is coloured green. The iron-sulfur cluster is shown in gold and brown balls. FAD is shown in orange, red and blue balls.

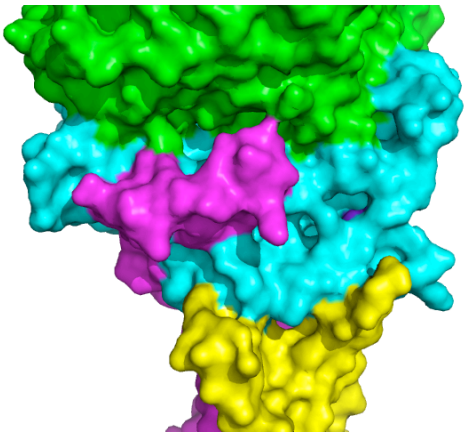




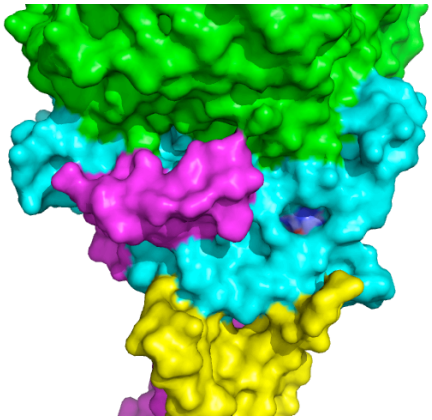
Cys101Tyr. Homology model for SDH subunit B mutant

C101Y, showing close-up of subunit B residue 101. Wild-type C101 side chain is purple sticks and is bound to the iron-sulfur centre. Mutant Y101 side chain is white sticks and does not bind the iron-sulfur centre.	Ile127Ser. Disease-associated mutations not having an obvious structurally deleterious effect.
 Tyr150X. Purple represents wild-type protein is missing in the mutant. Cyan represents the rest of subunit B that is present in the mutant.	
 Pro197Arg. Homology model for SDH subunit B wild-type (A) and mutant P197R (B), showing close-ups of the calculated electron transfer paths between iron-sulfur cluster F3S and ubiquinone. The electron path of the mutant is calculated to pass through more chemical bonds than the wild-type. This suggests that electrons will tunnel faster in the mutant than in the wild-type because electron transfer is better through covalent bonds than through space, and electrons may be lost and cause formation of reactive oxygen species. The electron path segments are shown in pink. Subunit B backbone is coloured cyan and subunit C backbone is coloured magenta. The iron-sulfur cluster is shown in gold and brown balls. Ubiquinone and heme are shown in orange and red balls.	

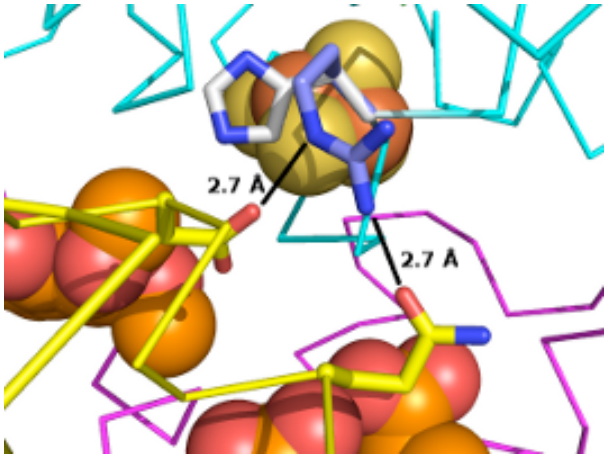




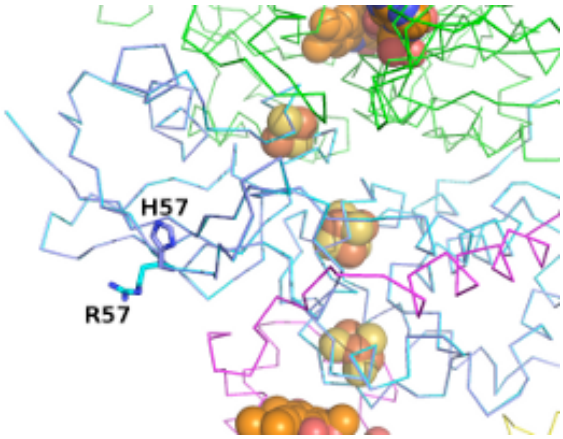
Arg230Gly. Homology models for mutant SDHB:R230G (above) and wild-type human SDH (above the mutant). Residue 230 is coloured purple for carbon atoms, blue for nitrogen atoms and red for oxygen atoms. Residue 230 is located in a solvent-exposed pocket whose surface is changed in the mutant when compared to wild-type.



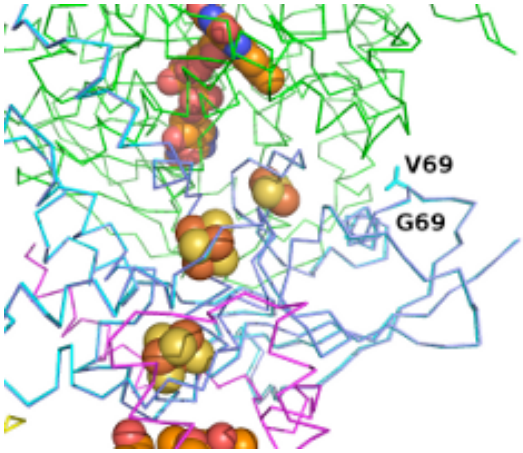
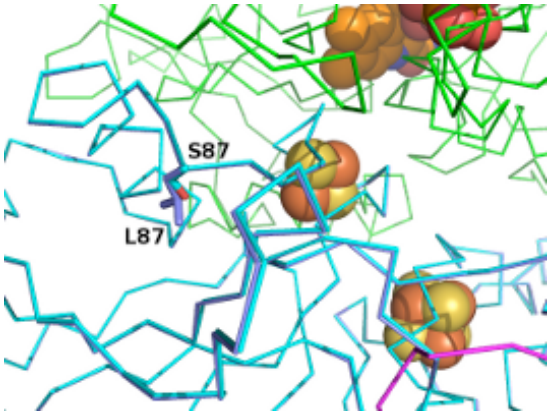
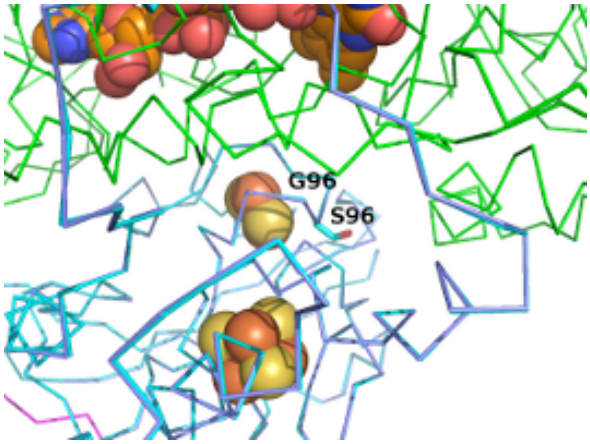
Arg230His. Homology models for mutant SDHB:R230H (above) and wild-type human SDH (above the mutant). Residue 230 is coloured purple for carbon atoms, blue for nitrogen atoms and red for oxygen atoms. Residue 230 is located in a solvent-exposed pocket whose surface is changed in the mutant when compared to wild-type.



Arg242His. Homology model for SDH subunit B mutant R242H, showing close-up of subunit B residue 242. Wild-type R242 side chain is purple sticks. Mutant H242 side chain is grey sticks. Subunit D Q109 and D113 are green sticks. Distances between atoms are shown by black lines. Wild-type B:R242:NE is involved in a hydrogen bond with D:D113:OD1. Wild-type B:R242:NH2 is involved in a hydrogen bond with D:Q109:OE1. These bonds between subunit B and D are lost in the disease-associated mutant (Figure D.8.3), possibly destabilising the SDH



His57Arg. A non-disease-associated control mutation.

macromolecular assembly.	
 Gly69Val. A non-disease-associated control mutation.	 Leu87Ser. A non-disease-associated control mutation.
 Gly96Ser. A non-disease-associated control mutation.	

Supplementary Figure 2. In silico analysis results. Subunits are coloured green, cyan, magenta, and yellow for subunits A, B, C, and D respectively. Cofactors are shown in orange and brown. Except where otherwise stated, mutated residues are shown in purple. Images created using PyMOL (DeLano 2009). Sticks show the side chain of mutated residues.