Nonsynonymous Amino Acid Mutations in gp120 Binding Sites are Related to Progression of HIV-1

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BIOL 368: Bioinformatics Laboratory
Loyola Marymount University
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Outline

1. Nonsynonymous mutations in binding sites affects gp120 and CD4 binding.
2. Variability of four subjects' clones were analyzed across two visits to determine structural and functional differences.
3. Rapid progressors showed major mutations across all clones, but few highly variable amino acids appeared.
4. Moderate progressors showed multiple major mutations at amino acids that interact with binding sites.
5. Other studies identified position 317 in gp120 essential for antibody recognition.

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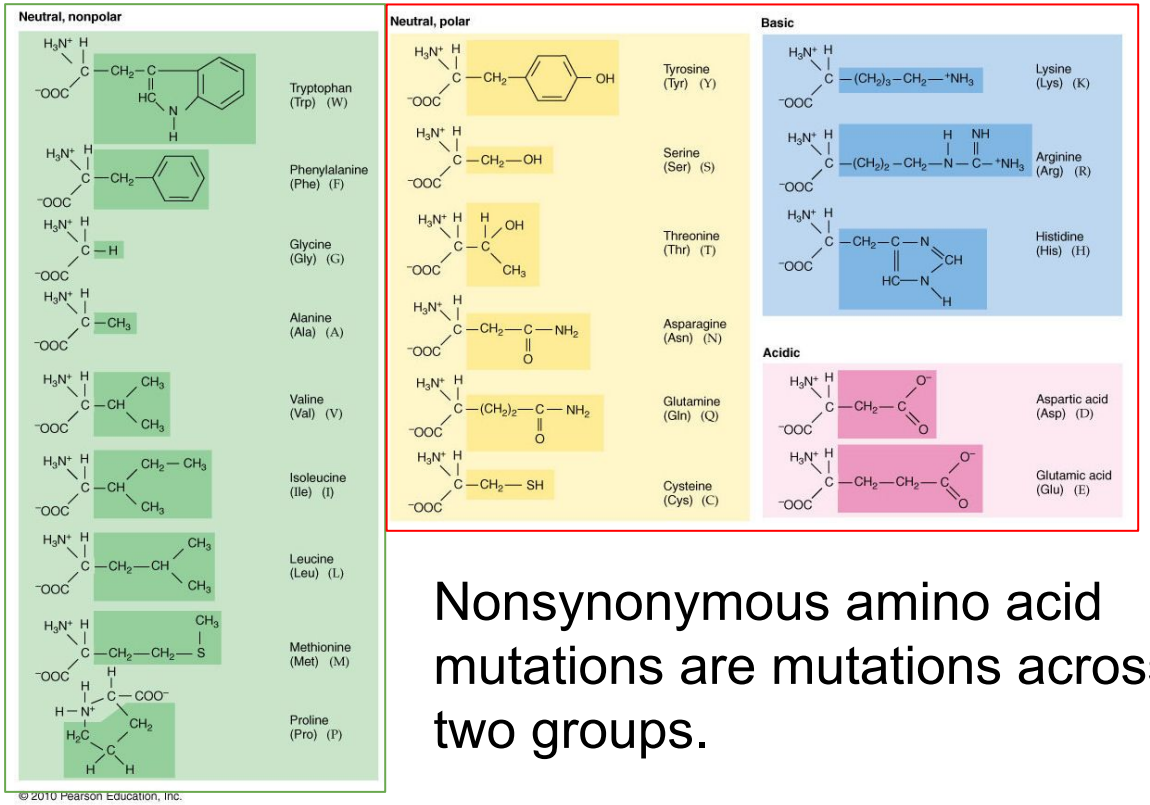
Amino Acids are Categorized According to R Groups

Hydrophobic



Hydrophilic

Nonsynonymous amino acid mutations are mutations across these two groups.

https://www.mun.ca/biology/scarr/iGen3_06-02.html

Amino Acids in Binding Sites Must be Highly Specific for Proteins to Successfully Bind With Ligands

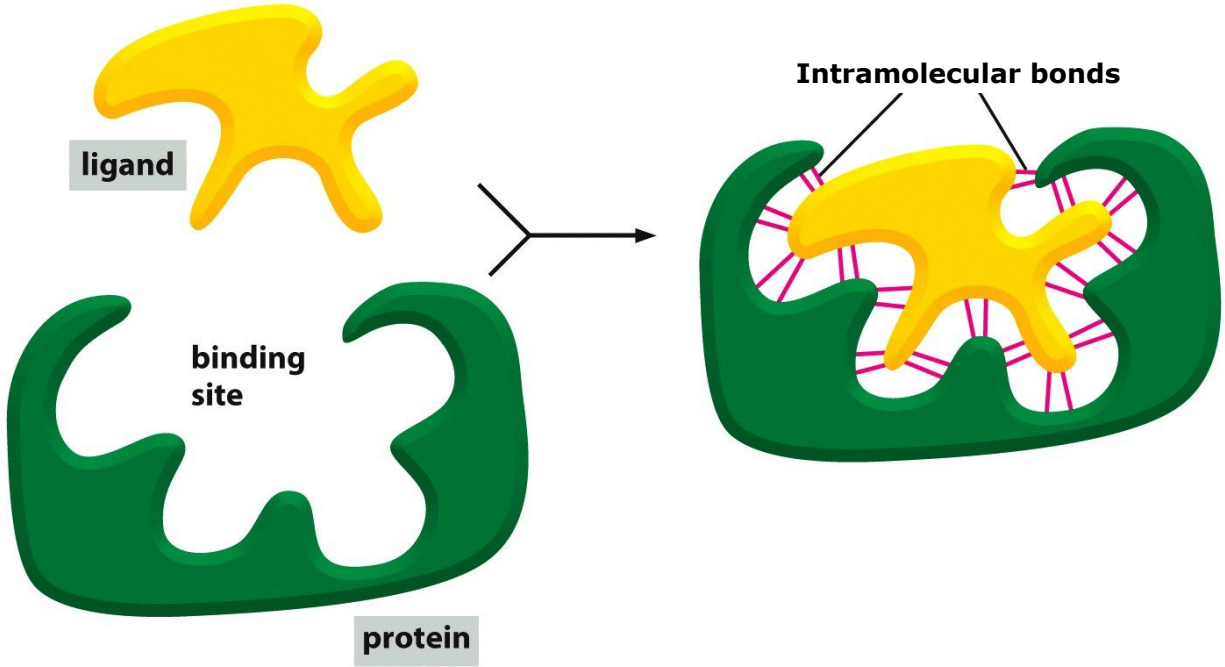
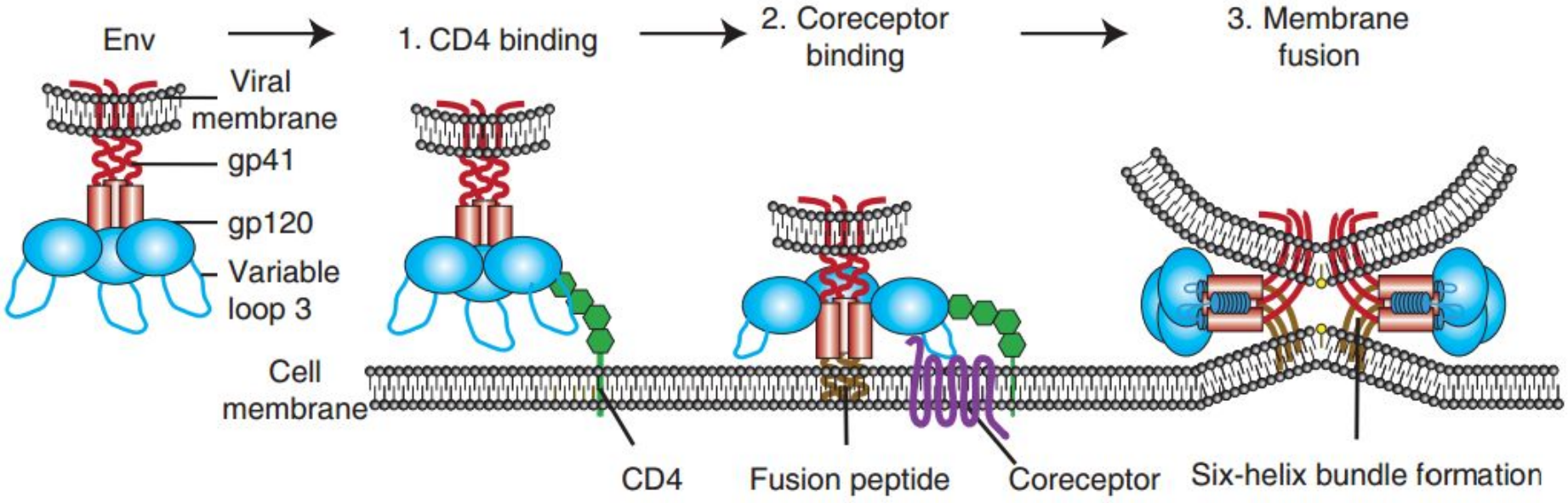


Figure 4-27 Essential Cell Biology 3/e (© Garland Science 2010)

http://oregonstate.edu/instruction/bi314/fall11/cellchemistrycontd.html

Interactions Between gp120 and CD4 cells Impact Progression of HIV-1



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3405824/

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Mutations in Four Subjects' Protein Sequences Were Analyzed to Determine Functional Differences

Question: How do mutations in gp120 affect function of the protein?
Hypothesis: Nonsynonymous mutations in gp120 in key locations will most greatly affect protein function.

- Subjects 4(RP), 9(MP), 11(RP), and 14(MP)
  - Different progressor groups, but same dS/dN values
- Clones collected from Visit 1 and Visit 4
  - Compare extent of change in structure over time
- Amino acids 269 - 363 in gp120 analyzed

Subjects Have Identical dS/dN Values in Different Progressor Groups

Table 1. Summary data on 15 seroconverters

Subject	No. of observations	Baseline			Annual rate of CD4 T cell decline	Slope of change in intravisit nucleotide differences per clone per year	Slope of divergence (% nucleotides mutated from baseline consensus sequence per year)	Median dS/dN
		CD4	Median intravisit nucleotide differences among clones	Virus copy number ($\times 10^3$)				
Rapid Progressor								
Subject 4	4	1,028	0.90	6.8	−593	4.64	2.09	0.0
Subject 10	5	833	1.71	99.3	−363	3.16	1.00	0.2
Subject 11	4	753	2.27	62.2	−363	1.11	0.32	0.0
Subject 15	4	707	15.16	171.0	−362	−2.94	0.68	0.7
Subject 3	5	819	1.82	302.5	−294	0.53	0.74	1.0
Subject 1	3	464	5.64	307.6	−117	5.10	1.55	0.3
Moderate Progressor								
Subject 7	5	1,072	2.27	317.6	−392	−0.79	1.35	1.3
Subject 8	7	538	1.24	209.0	−92	1.68	1.16	0.5
Subject 14	9	523	1.00	50.9	−51	1.69	0.60	0.0
Subject 5	5	749	2.50	260.6	−41	0.06	0.50	1.4
Subject 9	8	489	9.49	265.0	−11	1.58	1.21	0.0
Subject 6	7	405	2.82	321.4	52	1.92	0.82	0.4
Nonprogressor								
Subject 2	5	715	1.64	21.6	30	1.32	0.49	1.8
Subject 12	6	772	2.80	5.1	44	0.62	0.13	0.9
Subject 13	5	671	0.87	1.7	53	0.53	0.28	3.5

Major Mutations in Protein Sequences were Measured According to the Number and Importance of Substitutions

- We measured the number of positions with:
  - Any amino acid substitutions
  - Major substitutions (hydrophobic to hydrophilic or vice versa)
  - Multiple major substitutions across clones

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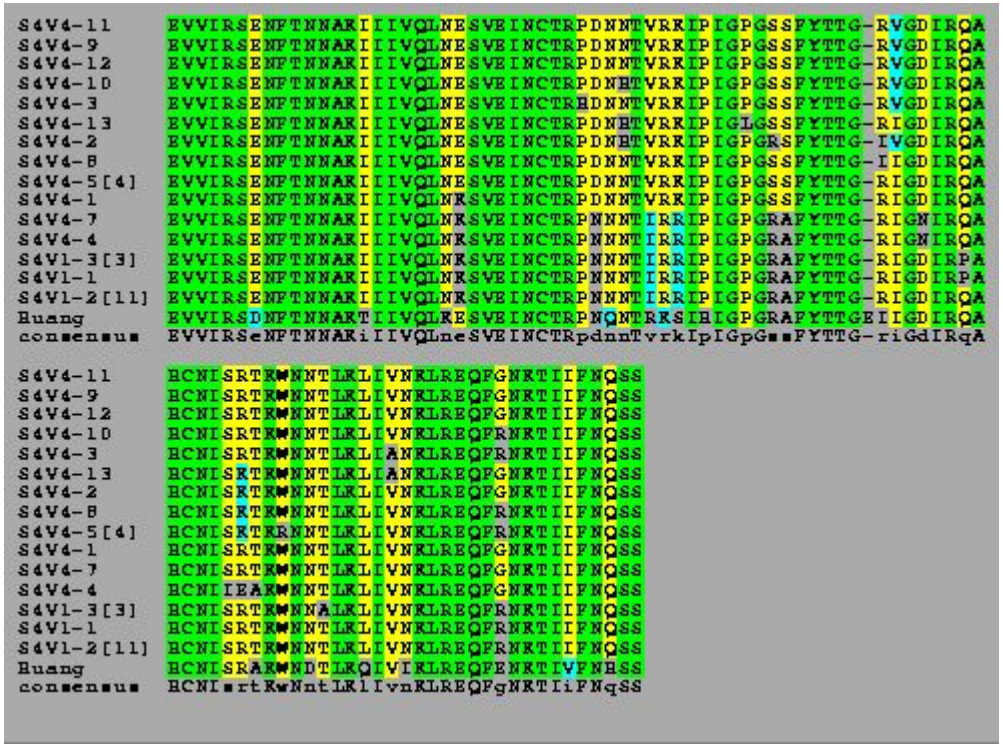
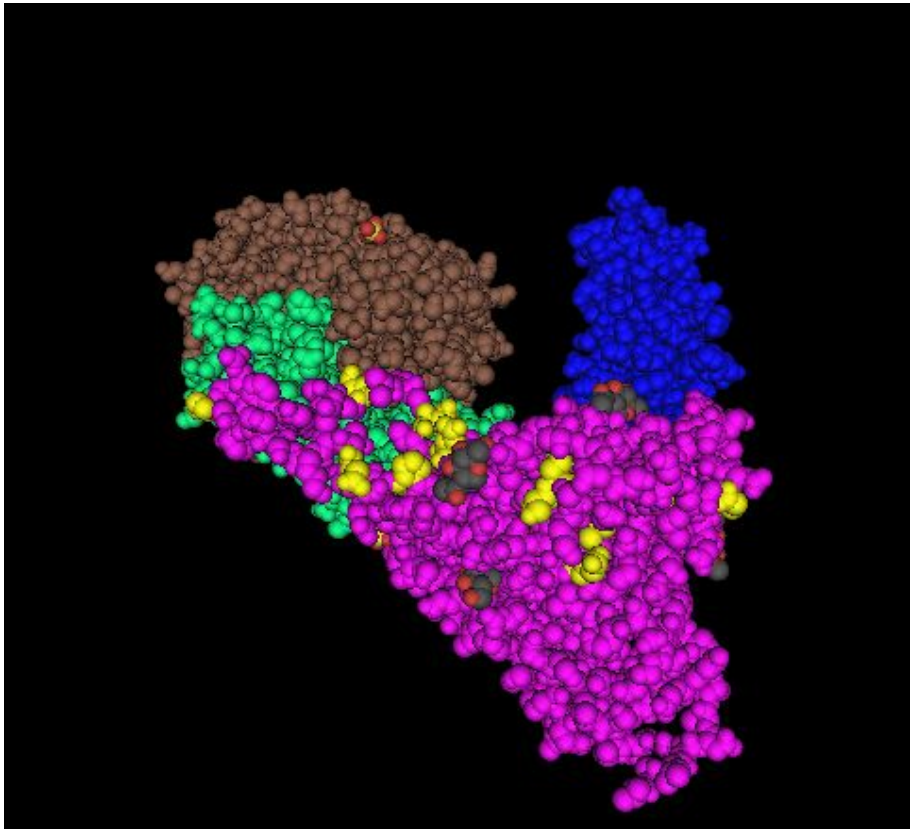
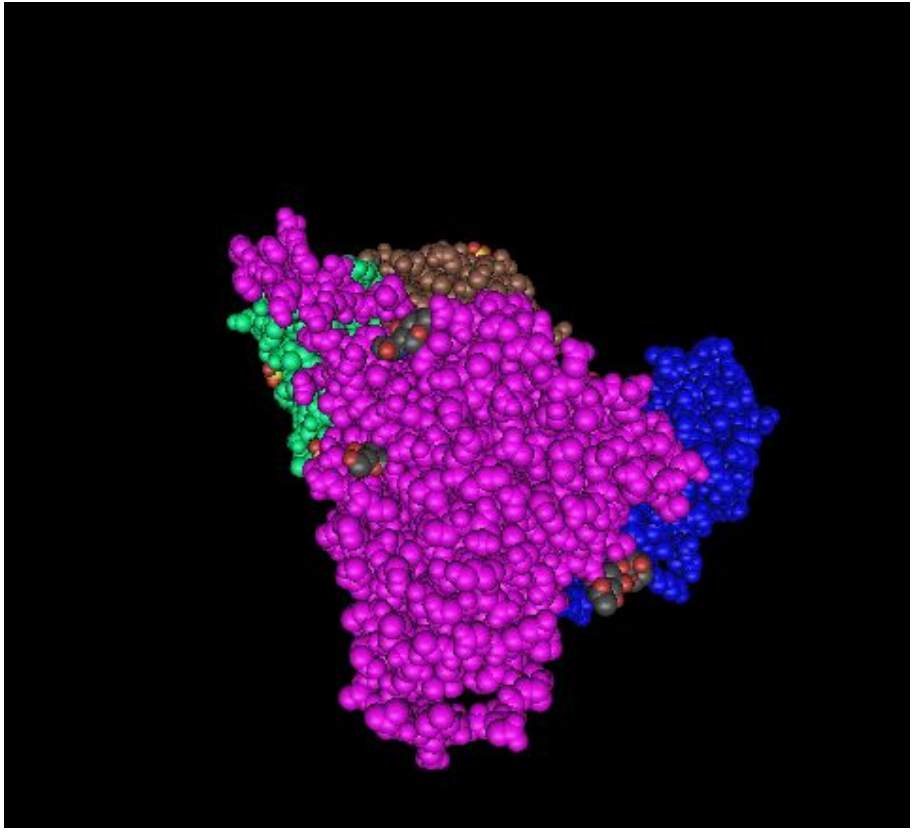
Subject 4 (RP) Has Major Mutations at More Positions with Less Variability



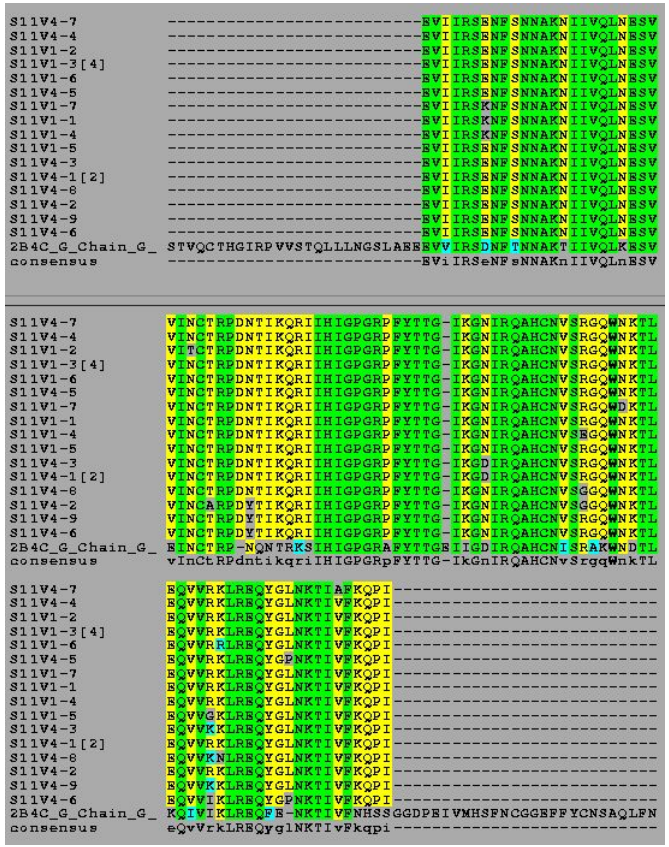
Subject 4 (RP) Had Major Mutations at 19 Positions



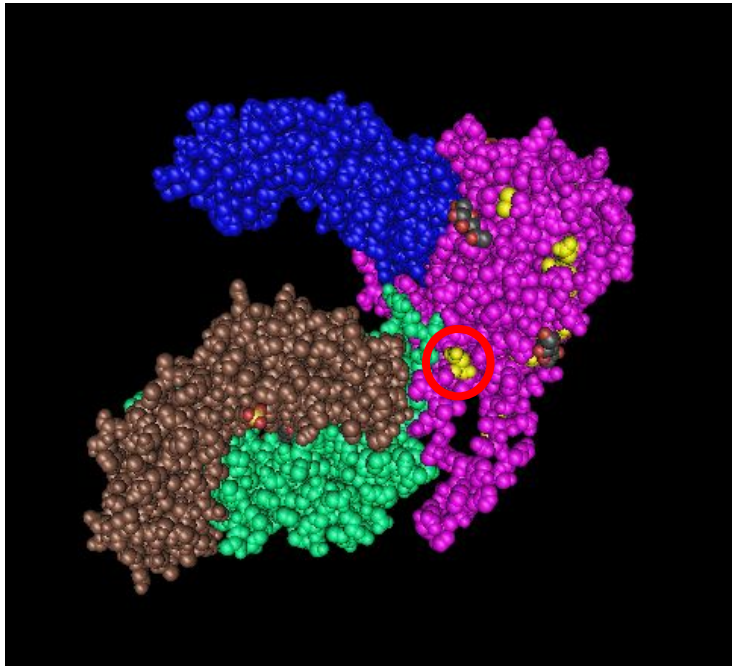
Subject 4 (RP) Lacks Positions with Multiple Major Mutations

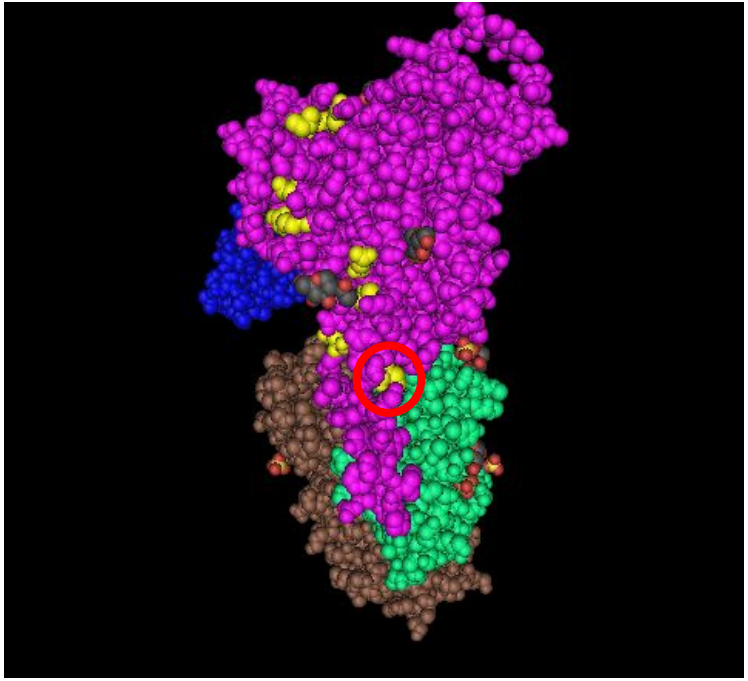


Subject 11 (RP) Indicates Several Locations With Major Amino Acid Mutations



Subject 11 (RP) Has Mutations on gp120 Near Antibody Interaction Sites





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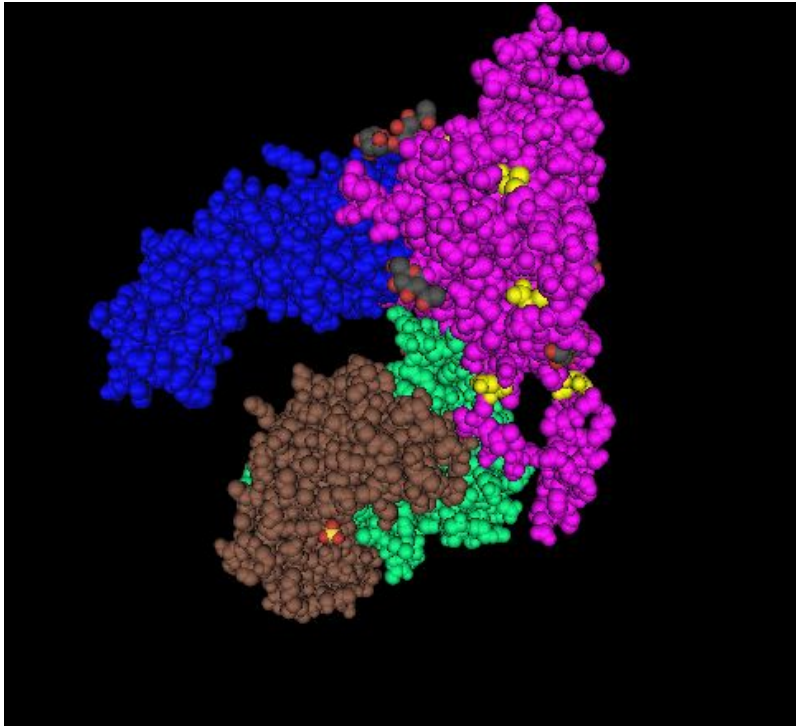

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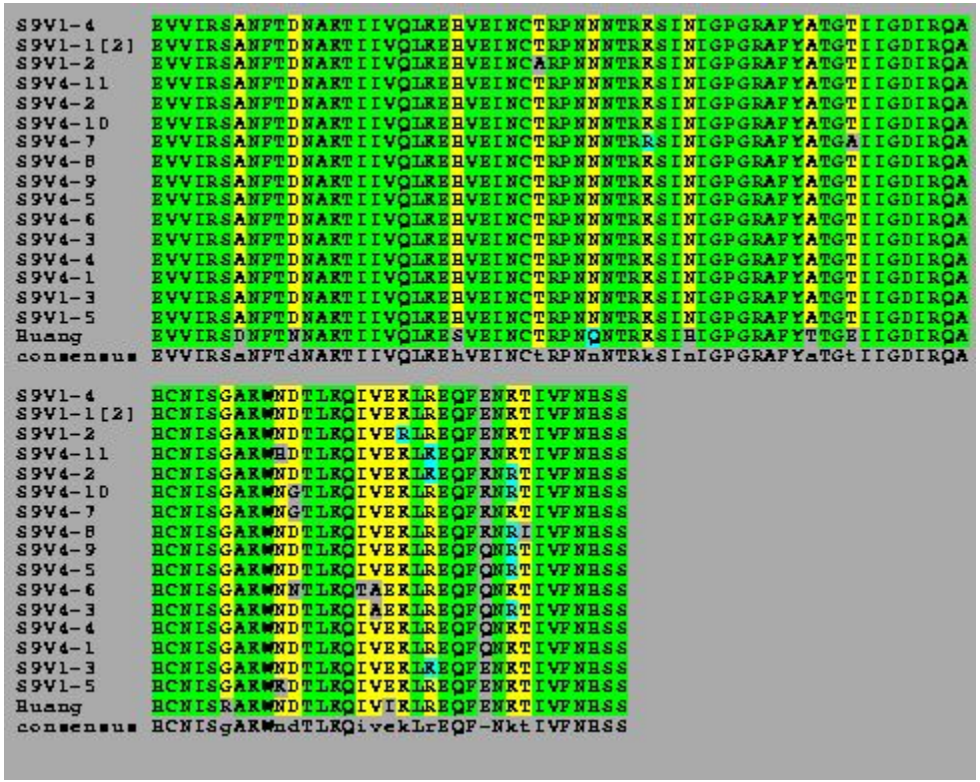
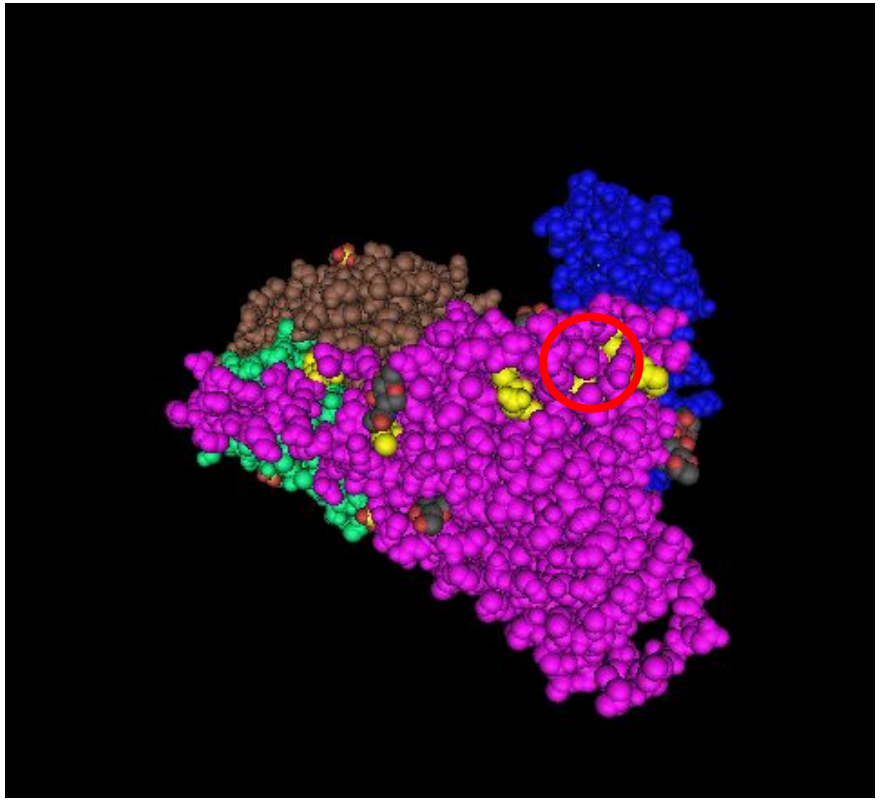
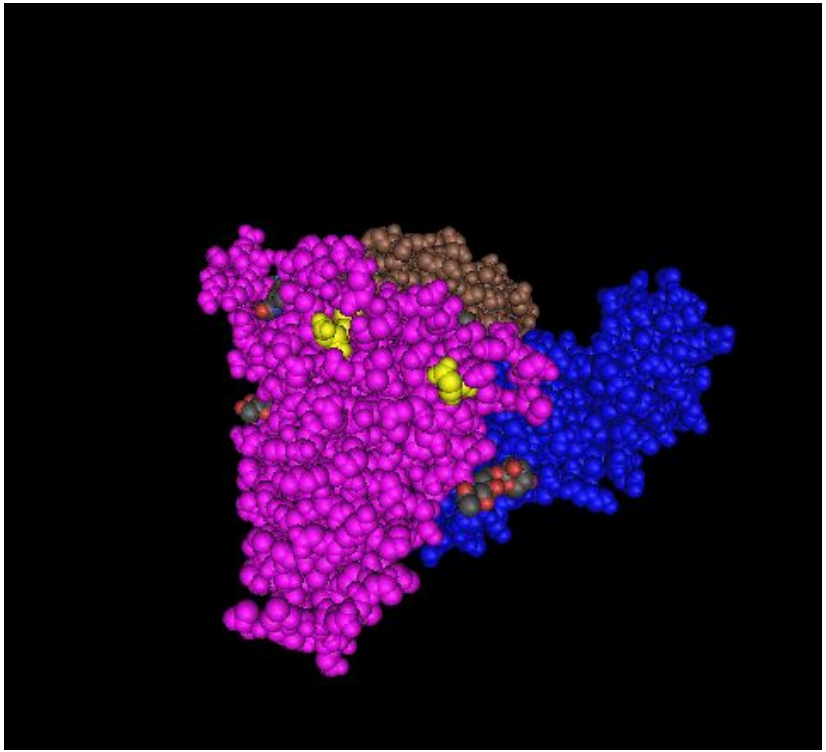
Subject 9 (MP) Indicates Several Positions with Major Mutations



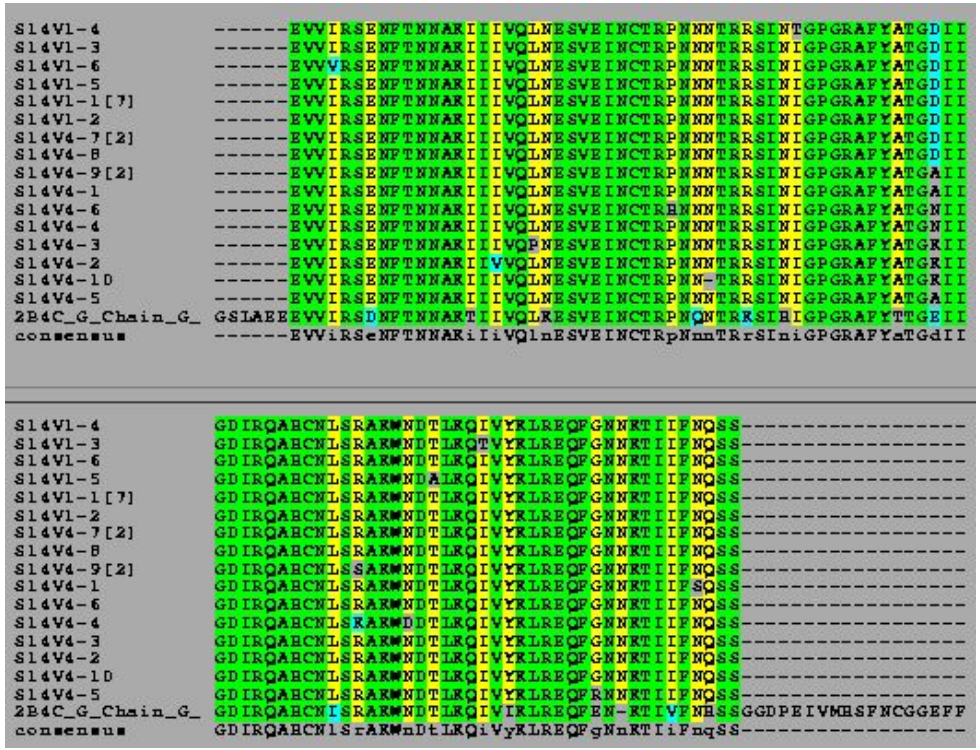
Subject 9 (MP) Has Non-Surface Mutations



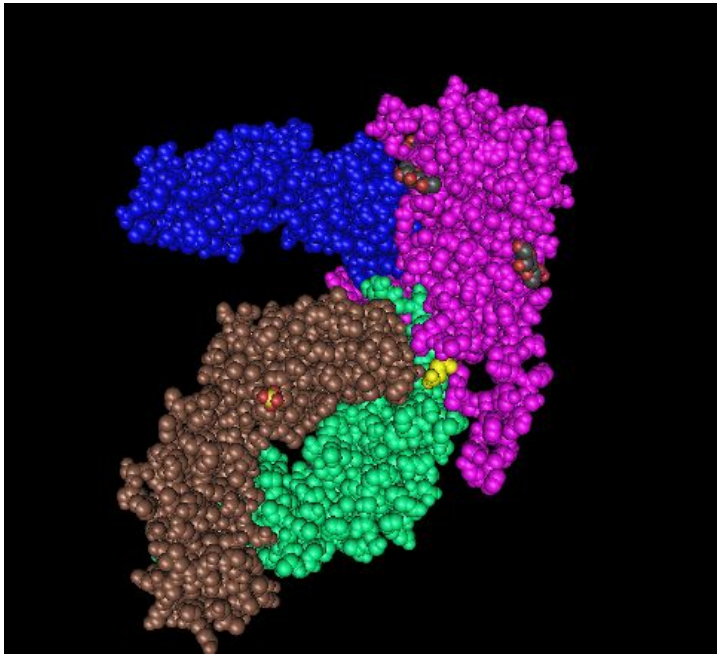
Subject 9 (MP) Has Multiple Major Mutations on Its Surface

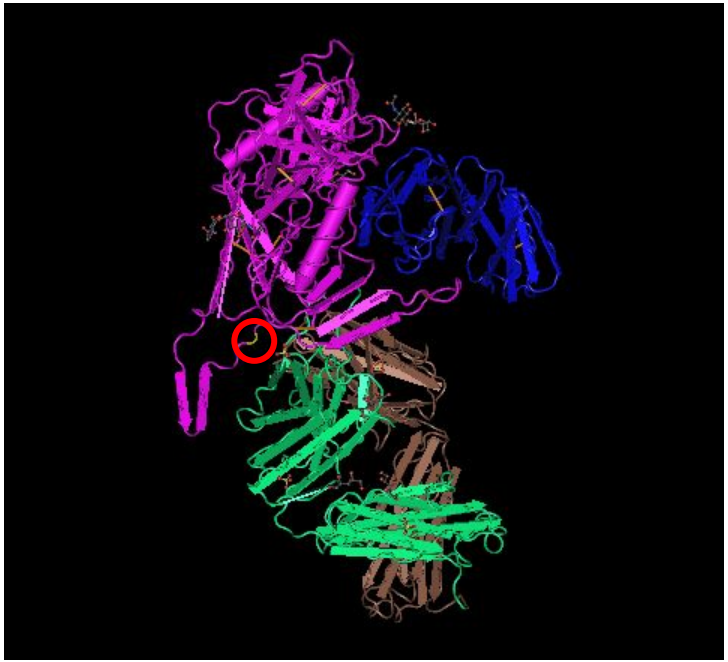


Subject 14 (MP) Indicates Multiple Major Mutations Between Clones at an Interaction Site



Subject 14 (MP) Indicates Multiple Major Mutations Between Clones at an Interaction Site





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Subject 9 and 14 Carry Mutations at an Antibody Recognition Site

- “HIV-1 Env-gp120 include sites in the antibody binding regions at the crowns of the V2 (Sites 169, 181) and V3 (Site 317) variable loops”
  - Edlefsen et al. (2015)
- Both are moderate progressors with identical mutations at this position
- Mutations at this site may increase ability of antibodies to neutralize virus

Future Work

- See if mutations at site 317 persist in other subjects in each progressor group
- Human serum could be used to test neutralization susceptibility of each subject to antibody responses similar to Kirchherr et al. (2011)

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Acknowledgements

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