Common mutations in HIV-1 env sequences between rapid progressor and non-progressor groups

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Outline

● Experiment designed to compare strains of fringe behaviors

● Aligned sequences of clones show no location along env gene that defines rapid progression

● Phylogenetic tree shows that no mutation is favored among rapid progressors
Experiment based off the results found by Markham et al.

- Studied the evolution of HIV-1 env sequences in 15 subjects
  - Subjects were injection drug users
  - Looked for differences in CD4 T Cell decline after seroconversion

- Subjects in original study split into three different groups
  - Rapid Progressors
  - Moderate Progressors
  - Non-Progressors

- Rapid progression and nonprogression dS/dN medians differed
Is there any way to differentiate rapid progressor subjects from non-progressor subjects, solely based on characteristics of their HIV-1 env sequences?
Subjects selected based on dS/dN values

- Subjects 2 and 13 showed the highest median dS/dN
- Subjects 1 and 10 showed the lowest non-zero median dS/dN
- Subject 3 had a median dS/dN of 1.0
Comparison of invariants in set windows would show if a location on the env gene is favored for mutation

- Sequences of all clones from selected subjects were aligned with others from their respective visits
- S values calculated and compared between first and last visits
- There was increased diversity seen in the last visits as compared with the first visits of the rapid progressor subjects
Comparison of $S$ values from first and last visits show no window favored by HIV-1 for mutation.

Graph comparing the $S$ values for the first and last visits of rapid progressors.
Graph comparing the S values for the first and last visits of nonprogressors
Phylogenetic tree would show if a certain mutation is favored by HIV-1

- If a specific mutation is favored by HIV-1, rapid progressors would be more related to each other at their last visit than at the first
- Strains in subjects generally clustered together in tree generated for first visit
- Tree generated between all strains in the study to track evolutionary progression
Generated phylogenetic tree suggests that there is no “rapid progression mutation”

- Most subjects cluster individually
- Subjects 1 and 2 cluster together
  - 1 is a rapid progressor, 2 is a nonprogressor
- Tree organized primarily by subject rather than progression
  - The exception (subjects 1 and 2) exhibited different progression states
Summary

- Experiment designed to compare strains of fringe behaviors
  - Strains from those with highest and lowest $dS/dN$ values compared
- Aligned sequences of clones show no location along $env$ gene that defines rapid progression
  - Mutations dispersed throughout gene, no window was favored
- Phylogenetic tree shows that no mutation is favored among rapid progressors
  - Clustering of subjects regardless of visit
Future Directions

● Look at Window 11 in depth
  ○ Induce mutations in window and track CD4 cell decline

● Analysis of windows throughout all visits from the study
  ○ Do locally concentrated mutations shortly after seroconversion trigger rapid, random mutations

● Does HIV-1 preferentially mutate specific nucleotides?
  ○ Is the nucleotide that is mutated important, rather than the mutation itself
Acknowledgements

Kam D. Dahlquist, PhD

Markham et al.

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References