Analysis of HIV-1 G→A Hypermutation and its Relationship with APOBEC3G and Vif

Genetic Variation in Vivo

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ABSTRACT

Background: Retrospective analysis of 18,104 G→A substitutions in HIV-1 proviral DNA sequences that differed from a matched control sample where the substitution rate was determined by comparing the presence of in-frame stop codons to G→A hypermutation (n=8) to a pooled DNA sample (n=200), estimated by analyses of individual samples. 

Methods: Overall, proviral sequences had 1.83 ± 1.05-fold more G→A substitutions (corresponding to C→T) than the control sample (n=200) (p<0.001). In individuals with hypermutation, APOBEC3G exonic and Vif stop codons was 0.70 ± 0.30 per 100 bases (p=0.019) and again at the 90th percentile (0.43 ± 0.34 vs 0.15 ± 0.09 0.05 vs 0.04 ± 0.02 per 100 bases, p<0.001; 60th 0.11 ± 0.05 vs 0.04 ± 0.02 per 100 bases, p=0.036). Hypermutated proviral sequence compared to a pooled DNA control sample (n=200), although the functional significance is unknown. 

Results: Hypermutation was classified by 3 criteria and validated by analyses of APOBEC3G (3G) and APOBEC3F (3F) are potent inhibitors of HIV-1 infectivity by blocking the synthesis of viral DNA. APOBEC3G (3G) and APOBEC3F (3F) are partially resistant to Vif (1,2,3) and this partial resistance may extend to upstream deamination events.

Conclusions: Retrospective analysis of 18,043 G→A substitutions (relative to population) from 126 patients revealed more hypermutation in the 60th percentile based on G→A load. It is suggested that APOBEC3G and APOBEC3F are partially resistant to Vif (1,2,3). 21 (12.7%) of participants had stop codons in the vif ORF. These participants had significantly higher G→A substitution rate of participants with defective Vif protein. 

INTRODUCTION

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REFERENCES