学　位　論　文　内　容　の　要　旨

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学　位　論　文　題　名

A study of the genetic divergence of *Human mastadenovirus D* via comparative genomic analyses
（比較ゲノム解析によるヒトアデノウイルス D 種の遺伝的多様性に関する研究）

Human mastadenovirus D (HAdV-D) is an exceptionally type-rich human adenovirus species and causative agent of different diseases and neonatal fatalities, as well as an opportunistic pathogen in immune-compromised patients. A research group, including the author of this thesis, revealed that intertypic homologous recombination events between distant types have extensively diversified HAdV-D. This finding raised important questions, such as: (1) what mechanism has allowed frequent homologous recombination events between diverged types despite the fact that the homologous recombination rate is generally low between diverged sequences?; and (2) what has made it possible to produce functional recombinant genomes through homologous recombination events between distant genomes, even though it has been demonstrated that replacements of component proteins of a multiprotein system, such as the packaging system comprising several adenoviral proteins, with homologues from different types lead to malfunction? In order to address these questions concerning the mechanisms and processes that have generated functional recombinant HAdV-D forms via homologous recombination events, the author analyzed the evolutionary patterns of all available genome sequences of different HAdV-D types via three steps: i) identifying recombination events that have previously occurred in those genomes; ii) statistically analyzing the distribution of the recombination boundaries; and iii) detecting interregional coevolution conserved among different types. These analyses revealed that the recombination boundaries are concentrated in specific regions (referred to as hotspots), and these hotspots are located at genomic segments that are conserved over different genomes (referred to as universally conserved segments or UCSs), implying that these UCSs have participated in recombination initiation followed by the exchange of adjacent, highly diverged sections. In addition, the author developed a novel statistical method and showed the modularity of recombination, i.e., recombination events have exchanged specific blocks of the genome, thus allowing for the avoidance of the generation of nonfunctional chimeric proteins and chimeric combinations of physically interacting proteins. This evolutionary modularity was confirmed by the author's finding that the gene regions of physically interacting proteins have coevolved in different HAdV-D genomes in common, thereby suggesting strong purifying selection. It is therefore concluded that HAdV-D has diverged through frequent homologous recombination events initiated at UCSs and strong purifying selection against deleterious chimeric forms. The interregional coevolution analysis method that the author developed for this study provides a new means for predicting protein-protein and protein-DNA physical and functional interactions in other organisms.