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学位論文題目 Analyses of genomic changes associated with rodent
evolution

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論文内容の要旨
Summary of thesis contents

Rodents are the mammalian order generally characterized by continuously growing pair of incisors. They have the highest number of species and an unrivalled ecological success among mammals. Rodents are found in many habitats and have huge phenotypic diversity across body size, longevity, physiology, morphology, litter size and so on. Despite the phenotypic diversity among rodent species, limited number of genome sequences constrains extensive investigation of genomic changes associated with rodent phenotypic diversity.

Extensive comparative genomics requires the availability of genome sequences. Therefore, I set to sequence the whole genomes of two strategically located species in rodent phylogeny. The first species sequenced is capybara, the largest living rodent species. The second species is Japanese giant flying squirrel. These two species, in addition to mouse, are representatives of the three major rodent lineages. The main aim of this study is to investigate the genomic changes that have accompanied rodent evolution. Based on the long standing hypothesis that regulatory evolution might have contributed to morphological evolution, I decided to investigate the role of conserved noncoding sequence (CNS) evolution in rodent phenotypic diversity. In this study, I found that CNSs often have regulatory signals and that CNSs are probably involved in more conserved expression of the flanking protein-coding genes. In addition, I found that the physical distance between CNS and the closest protein-coding gene tend to be evolutionarily conserved. Furthermore, I found that CNS-associated genes tend to be enriched in transcription, development and nervous system, but underrepresented in genes associated with defense and immunity. As expected from gene ontology enrichment, CNS-associated genes are highly expressed in embryonic brain and poorly expressed in testis. These observations suggest the importance of CNS evolution in phenotypic diversity as the major players of morphological evolution should be active during developmental stage.

The evolutionary dynamics of CNS across four mammalian orders and evolutionary ages revealed interesting features of rodents. I found that CNS loss is highest in rodents but lowest in primates. On the contrary, CNS gain is highest in primates but lowest in rodents. Carnivores and cetartiodactyls have intermediate values. These observations highlight the high turnover rate of rodent CNSs, and by extension, regulatory elements. Focusing on primate CNSs due to limited rodent data; I found that more ancestral CNSs tend to have stronger constraints than the recently evolved ones. These results suggest that rodent phenotypic diversity might be connected to the high regulatory turnover in rodents. Even among rodents, CNS

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evolution was found to be heterogeneous with the highest loss in mouse-related lineage and the lowest in squirrel-related lineage.

To further investigate these observations, I asked how quickly regulatory turnover happen in rodents. For this analysis, I focus on *Muridae*, the largest rodent and mammalian family in terms of the number of species. The transcriptome data of mouse and rat are already available. In addition, I sequenced the transcriptome of 3-, 5- and 7-day postnatal wild large Japanese wood mouse species for the retrieval of large number of transcripts. Liver transcriptome analyses reveal that expression dynamics highlight phylogenetic relationships, and that CNSs seem to be less active in liver.

Mutation-driven hypothesis of evolution suggests that species with relatively high mutation rate would have higher ecological success rate because they would have abundant “raw materials” upon which evolutionary forces can act. Interestingly, previous studies and my own analyses show that rodents have higher evolutionary rates. I then asked if the high evolutionary rates in rodents have contributed to their phenotypic diversity and ecological success. If this is true, I hypothesized that rodent clades with higher number of species would have higher evolutionary rate. Using the published rodent genome data, I first show that though primates’ evolutionary rates are lower than rodents’, there is heterogeneity among rodents. Of particular interest is the observation that murids with the highest number of species indeed have the highest evolutionary rates. Unlike the previous reports however, I found limited evidence supporting the correlation between body size and evolutionary rate.

In conclusion, my study suggests that higher regulatory evolution in rodents might have contributed to rodent phenotypic diversity. This higher regulatory evolution is brought about by the high evolutionary rates among rodents. These results support mutation-driven hypothesis of evolution. The whole genome sequences of Japanese giant flying squirrel and capybara, with the transcriptome data of large Japanese wood mouse will be invaluable resources for future rodent evolutionary studies. The next line of analyses would be trait- and region- targeted to establish the genomic regions responsible for some interesting rodent phenotypes.

博士論文の審査結果の要旨

Summary of the results of the doctoral thesis screening

げっ歯目は、含まれる種の数や生息域の広さにおいて、哺乳類の中で最も成功した分類群である。Babarindeさんは、この分類群の特徴である形態などの表現型多様性がどのようなゲノム進化によってもたらされたかに興味を持って研究を行った。特に、形態の多様性が、タンパク質をコードする翻訳配列の置換よりも非翻訳配列であるシス制御配列の置換によって生じているという仮説に着目し、進化的に保存された非翻訳配列 (Conserved noncoding sequence: CNS) の解析を行った。

げっ歯目を代表する三つの科の中では、ネズミ科に属するマウスとラットのゲノム配列が最も良く解析が進んでいる。一方、他の二つの科のゲノム解析は遅れていた。そこで、Babarindeさんは、まず、げっ歯目の中で最大の体重を持つカピバラとリス科に属するムササビのゲノム解読と、ネズミ科に属するアカネズミのトランスクリプトーム解析を行った。次に、得られたデータや公開されている霊長類、哺乳類、鳥類等のゲノム関連データを用いて情報解析・進化学的解析を行い、以下の事実を見出した。

- ・ 一般に、CNSは遺伝子発現の進化的保存性と関連しており、近傍にCNSの数が多い遺伝子ほど、ヒトとマウス間での遺伝子発現レベルの相関率が高い。また、CNSを持つ遺伝子は、神経系、発生、転写などに関与し、組織・時期特異的な発現を示すものが多い。
- ・ CNSと近傍遺伝子の物理的距離は、隣接する二つの遺伝子のそれより進化的保存性が高く、また、遺伝子に対するCNSの物理的距離が保存されている遺伝子ほど、ヒトとマウス間での遺伝子発現レベルもよく保存されている。このことから、遺伝子発現制御におけるCNSと標的遺伝子の位置関係の重要性が示された。
- ・ 哺乳類の4つの代表的な目である霊長目、齧歯目、食肉目、偶蹄目で比較すると、げっ歯目の系譜で最もCNSの頻度が少ない。特に、系譜内での欠失数が多く、新規獲得数が小さいことが明らかになった。それに基づき、げっ歯目内のCNSの高い喪失率と表現型多様性が関連している仮説が提唱された。
- ・ アカネズミのトランスクリプトーム解析から、遺伝子発現パターンが系統関係を反映し、近縁種の中でもダイナミックに変化し得ること、肝臓の発現制御にCNSの関与が少ないことが明らかになった。
- ・ カピバラを含むゲノム配列データを対象とした比較ゲノム解析の結果は、げっ歯類のゲノム配列の進化速度が速いことを支持したが、系譜の中でも違いがあり、ネズミ科が最速であった。一方、進化速度と体サイズが逆相関するという従来の仮説は、カピバラを含むゲノムデータを用いた検証では支持されなかった。

これらの結果は、げっ歯目の表現型多様性とCNS進化速度との関連性を示しており、今後のげっ歯目のみならず哺乳類の表現型とゲノム進化の研究に貴重な情報を与えるものである。また、本研究では、独自のゲノム関連データを生産しており、それらも今後の関連分野の発展に寄与するものと評価できる。以上から、本論文は学位を授与する水準を超えていると判断した。