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学位論文題目 Studies on the Geographic Distribution of Human

Y Chromosome DNA Variation:

Inferences of the Human Dispersions from

the Phylogeographic Point of View

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## 論文内容の要旨

Many studies of genetic variation in human populations have revealed a recent common African origin of modern humans. According to this evolutionary history, modern human populations have dispersed into various parts of the world outside Africa for the past 150,000 years or so. Moreover, there have been many lines of molecular genetic evidence showing geographic variation of the human genome. These genetic differences must be a result of multiple evolutionary forces (such as mutation, genetic drift and selection) and evolutionary events (such as range expansion, migration and isolation by distance). However, there is incomplete understanding of how geographic patterns of variation have been shaped.

This thesis mainly dealt with questions in relation to human migrations into East and Southeast Asia, and the subsequent range expansions of modern humans. For this purpose, DNA variations on the non-recombining region of the human Y chromosome (NRY) were examined in 610 male samples from 14 global populations in North, East and Southeast Asia, and other regions of the world. Geographic distributions of the variations were analyzed at the level of Y-chromosome haplotypes, which were defined by allelic associations among polymorphisms. Moreover, a 12.6-kb region in the NRY was sequenced in eight males from East and Southeast Asia, Europe, and Africa. This comparative sequencing helped to find population-specific (or region-specific) polymorphisms for further Y-haplotype analysis. Overall, phylogeographic analysis with Y-haplotypes allowed to deduce the evolutionary history of modern Asian populations. The primary objectives of this thesis were (1) to set up a verifiable hypothesis on the peopling of East and Southeast Asia, and (2) to infer the formation process of modern Japanese populations.

This thesis consisted of five chapters including Introduction (Chapter 1), and Summary and Concluding Remarks (Chapter 5). Chapter 2 discussed early migration events of modern humans into East and Southeast Asia. First, eight haplotypes were observed by analyses of seven biallelic polymorphic markers (*DYS257*<sub>108</sub>, *DYS287*, *SRY*<sub>4064</sub>, *SRY*<sub>10831</sub>, *RPS4Y*<sub>711</sub>, M9, and M15), and were unevenly distributed among the populations. The maximum parsimony tree for the eight haplotypes had no ambiguity, indicating a robust phylogeny which is necessary for a phylogeographic analysis. Moreover, these haplotypes could be classified into four distinct haplotype lineages defined by three key mutations: an insertion of the Y *Alu* polymorphic (YAP) element at *DYS287*, a C-to-G transversion at M9, and a C-to-T transition at *RPS4Y*<sub>711</sub>. Coalescence analysis in the haplotype tree showed that estimated ages for three key mutations ranged from 53,000 to 95,000 years ago, suggesting that the three major lineages (defined by the allele of YAP<sup>+</sup>, M9-G, and *RPS4Y*<sub>711</sub>-T, respectively) were separated from one another during early stages of human evolutionary history.

Second, the three haplotype lineages (designated as YAP<sup>+</sup>, M9-G, and RPS4Y-T) accounted for 98.6% of the Asian populations studied, indicating that these three paternal lineages have contributed to the formation of modern Asian populations. Phylogenetic analysis revealed three monophyletic Asian clusters, which consisted of North Asian, Japanese, and Han

Chinese/Southeast Asian populations, respectively. In combination with the previous findings, extensive phylogenetic analysis in 20 Asian and Australo-Melanesian populations also showed the three distinct clusters which appear to correspond to geographic variations in the haplotype distributions.

Third, this chapter offered an important insight that human populations inhabiting the Asia-Pacific regions (a part of North and Central Asia, East and Southeast Asia, and Australo-Melanesia) may share common genetic backgrounds. Also, it hypothesized that three major groups with different paternal ancestries separately migrated to prehistoric East and Southeast Asia. This hypothesis is amenable to verifying by further phylogeographic studies with another haplotype systems.

Chapter 3 focused on the subject to find new single-nucleotide polymorphisms (SNPs) for an extensive phylogeographic Y-haplotype analysis. Two novel SNPs (named A46812 and A57316) were found by comparative sequencing in the 12.6-kb region in the NRY. For characterization of the two SNPs, they were analyzed on additional DNA samples from worldwide populations with newly developed PCR-RFLP (restriction fragment length polymorphism) methods. The A46812 polymorphism was effective in subdividing the ht4 haplotype (defined only by M9-G), while A57316 was shared by ht1 (defined only by YAP<sup>+</sup>) and ht2 (defined by YAP<sup>+</sup>/M15<sup>+</sup>). The results indicate that both are phylogeographically informative polymorphisms. Geographic distributions of the derived alleles (both C alleles inferred) at the two polymorphic sites revealed that these two SNPs may be specific to eastern Eurasian populations.

Chapter 4 mainly discussed the formation of modern Japanese populations from the paternal point of view. First, geographic distributions of Y-haplotypes in the 14 populations were analyzed with a total of 15 polymorphic sites, including the nine biallelic polymorphisms examined in Chapter 2 and 3. This analysis provided robust Y-phylogeny for 14 haplotypes which consisted of the 15 linked polymorphisms in the NRY. Also, the analysis revealed that the distributions of several haplotypes tended to be regionally specific. Taking account of estimated ages for three polymorphic markers (A57316, A46812, and *RPS4Y*<sub>711</sub>), the regional specificity may have been mostly due to evolutionary forces (such as mutation and isolation by distance) after human settlements in East and Southeast Asia. Therefore, these demonstrate the effectiveness of phylogeographic analysis with a set of the 14 haplotypes on deducing the evolutionary history of the Asian populations.

Second, several regional differences in paternal genetic characteristics were observed among modern Japanese populations. From the phylogeographic point of view in the Asia-Pacific regions, the Y-haplotype data suggest that the ancient Japanese populations in the late Pleistocene (or Jomon era) had diversified as evidenced by two paternal lineages (YAP<sup>+</sup> and RPS4Y-T), and regional differentiation within the RPS4Y-T lineage. Okinawan and the mainland Japanese populations might experience some extent of gene flow during the Holocene, implying Yayoi migrations to the Japanese archipelago. Therefore, the data support the hybridization theory that modern Japanese have resulted from distinct genetic contributions involving ancient

Jomon people and the Yayoi immigrants. To address the problem concerned with the geographic origin(s) of Jomon immigrants, it may be necessary to investigate sequence variation in the NRY in the ancient DNAs from Southeast and Northeast Asian populations in the late Pleistocene. This will also lead to a deeper understanding of human dispersal in the Asia-Pacific regions.

In conclusion, this thesis has shown that phylogeographic analysis with Y-chromosome haplotypes has a great ability to describe past human dispersion. This is mainly because the evolutionary relationships among geographic variants can be inferred without ambiguity. In general, evolutionary history of a single gene (such as Y-haplotype) should be cautiously interpreted as population history. Therefore, the present phylogeographic views need to be further integrated with much knowledge from other genetic systems, and many another disciplines such as paleoclimatology and archaeology. Nevertheless, the significance of the thesis is to present several insights in relation to the evolutionary history of modern human populations in the Asia-Pacific regions.

## 論文審査結果の要旨

本学位論文は、アジアを中心とした610人の男性からY染色体を抽出し、その変異の系統地理学的解析によってアジア人および日本人の起源を、性差を考慮しつつ明らかにすることが主眼である。第一の目的であるアジア人の起源を研究するため、既知の7つの多型座位を利用して610のY染色体をタイピングした。その結果、Y染色体は8つのハプロタイプに分類できるが、アジア人ではこのうちの3つのハプロタイプが主流であることが判明した。さらに論文では、ハプロタイプの地理的分布と生成時期に関する集団遺伝学的推定から、アジア人の起源は少なくとも由来の異なる3（男性）系統の移住者からなること、およびアジア周辺部には古い系統が偏在することが明らかにされた。第二の目的である日本人の起源に関しては、多型座位の数を増し精度の高い解析を行う目的で、まずY染色体の一部（約12 kb）の塩基配列を8個体について決定している。新しい多型座位を見つけるための塩基配列決定は、解析の精度をあげるための積極的な努力であり評価に値する。この成果を含めて、15の多型座位を用いたタイピングができるようになり、詳細な系統地理学的解析が期待された。実際、15の多型座位に対応して分類されたハプロタイプ数は14に増加している。このデータの系統地理学的解析から、日本人は縄文人と弥生人の混血である（混血説）ことを支持する結論が得られた。さらに、アイヌや沖縄人には弥生人からの寄与が少ないことが推定され、混血の程度は地域ごとに異なることが示唆された。

DNAマーカーを用いて人類集団の起源を探る研究—いわゆる分子人類学的研究—は国際的にも盛んに行われているが、これほど大規模にアジアの主民族のY染色体を網羅した研究はなかった。多くのサンプルはこれまでの調査研究で得られたものを活用しているが、自らタイ（クメール）の現地調査に赴き、サンプリングを行ったことは評価される。Y染色体の系統および地理的分布は男性の移住と対応しており、母性遺伝をするミトコンドリアDNAによるこれまでの研究結果と相補的な関係にある。そのため、本研究は人類のアジア地域における男性系統の移動分散に関して、新しい相補的な知見を得ている点に特色がある。

英語は全体的によく書けており、かなり正確な文章を書く能力を有している、と判断される。学位論文の一部は、国際誌に受理され発表済みである（Tajima et al. Hum. Genet. 110:80-88, 2002）。

以上のことから、学位論文の内容は十分な成果と基礎知識に裏付けられており、審査委員会は全員一致で学位授与に値するものと判断した。