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学位論文題目 The genetic diversity and population history of
indigenous peoples in Asia

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Asia is home to many diverse human populations and has been of much interest to anthropologists and geneticists alike. The focus of this thesis is the genetic diversity and migration histories of indigenous populations from Southeast Asia and the Japanese Archipelago. Based on archaeological and linguistic data, the origins of Southeast Asians can be traced back to two major migrations; the ancient 'Out of Africa' migration circa 50,000 years before present (YBP) and the relatively recent 'Out of Taiwan' expansion of agriculturalists who speak Austronesian languages, approximately 5,000 YBP. In Malaysia and the Philippines, there are indigenous groups called Negritos whose physical appearance is distinct from their neighboring populations and are thought to have originated from the 'Out of Africa' migration. The majority of other Southeast Asian groups are thought to have originated from the 'Out of Taiwan' migration. As for the peopling of the Japanese archipelago, it is characterized by two important periods: the Jomon period from 15,000 to 3,000 YBP; and the Yayoi period from 3,000 to 1,700 YBP. According to the dual-structure model, the current Japanese population was the result of admixture between Jomon populations who originated from Southeast Asia and the incoming Yayoi migrants from mainland Asia. Some minority groups in Hokkaido and the Ryukyu islands may be direct descendants of the Jomon peoples.

By analyzing approximately 50,000 genome-wide SNP data generated by me and other Pan-Asian SNP Consortium (PASNP) members, I investigated the genetic structure that may exist within indigenous groups of Malaysia and elucidated their relationship with other Southeast Asians. Using Principal Component Analysis (PCA) and STRUCTURE analysis, I found traces of recent and sustained admixture within the Negrito, Indian and Austronesian (Temuan, Bidayuh, Malay) groups. Comparisons with other Southeast Asians revealed that the Malaysian Negritos appeared to be distinct from the Philippine Negritos on the PCA plot. A closer look at the relationship between Austronesian populations revealed genetic substructure which mirrors geographical affinities, which may be explained by geographical isolation following the 'Out of Taiwan' expansion or alternatively there may be separate population movements involving other Austronesian groups. These observations demonstrate the impact of admixture on the genetic substructure of indigenous Southeast Asian groups and hints at a more complex migration history of the Negritos and Austronesians than the simple 'Out of Africa' and 'Out of Taiwan' models would suggest.

Next I conducted an analysis of complete mitochondrial DNA (mtDNA) sequences to test the plausibility, impact and timing of the migration models in indigenous Malaysian populations. I generated complete mtDNA sequences in 86 individuals from four indigenous Malaysian groups. In the Jehai (Negrito), one of the frequent haplogroups was R21 which is indigenous to West Malaysia and dates back to the

Pleistocene (~40,000 YBP). The three Austronesian groups (Bidayuh, Selatar and Temuan) showed high frequencies of haplogroups N9a6, N9a6a, F1a'c, N21 and N22 which have mainland Asian origins around 30,000 to 10,000 YBP. Haplogroups associated with the 'Out of Taiwan' expansion were either found at very low frequencies or not detected at all in those three Austronesian groups. Principal Component Analysis distinguishes the Malaysian Negritos from the Austronesians and also shows a dichotomy between Austronesians from Sumatra and Java and those from Taiwan and Philippines. As with the SNP analysis, results from mtDNA showed no apparent link between the Negritos of West Malaysia and those from Andaman and Philippines. Regarding the origin of Austronesians, our results show support for an 'early train' migration originating from Indochina or South China around 30,000 to 10,000 YBP which predates but does not rule out the subsequent 'Out of Taiwan' expansion.

Finally I conducted a study to find out the genetic structure in Japanese populations and to answer questions regarding which model of Japanese origins would be best supported by the genome-wide SNP data. I performed data analysis of close to 1 million genome-wide SNP genotypes generated using the Affymetrix 6.0 genechip in three Japanese populations: Hondo-Japanese, Ryukyuan and Ainu. Principal Component Analysis (PCA) plots showed that these three populations formed three distinct clusters, with greater genetic variation within individuals of the Ainu group, brought about by admixture with the mainland Japanese and possibly another population from Northeast Asia. Phylogenetic analysis revealed that the Ryukyuan and Ainu form a cluster with 100% bootstrap probability and comparisons with other global populations showed that all three Japanese populations cluster with other North East Asians. Current results appear to support the common ancestry of Ainu & Ryukyuan, which is compatible with the dual-structure model. However, the close affinity of all three Japanese populations with other North East Asians put the idea of Jomon origins from Southeast Asia in doubt although not entirely ruled out.

In summary, my results demonstrate the influence of surrounding populations to the genetic diversity in indigenous Malaysian and Japanese populations which also contributes to the genetic substructure in these indigenous groups. The presence of admixed individuals has to be considered when designing sampling strategies for future population genetic studies as well as when conducting and interpreting results of association studies. PCA analysis using SNP and mtDNA both showed the Malaysian and Philippine Negritos as distinct populations, which suggests they may originate from different migrations or alternatively the observed pattern was due to the enhanced effects of genetic drift due to their smaller population size. Regarding the Austronesians, results suggest an earlier movement originating from Indochina around 30,000 to 10,000 YBP which has more impact on the mtDNA diversity of indigenous Austronesians in West Malaysia and Borneo than the proposed 'Out of

Taiwan' expansion around 5,000 YBP. In the Japanese population, the Ainu and Ryukyuans have shared genetic ancestry and that the mainland Japanese may be the result of admixture between ancestral Yayoi and Jomon people, supporting some aspects of the dual-structure model. However, our data does not indicate a Southeast Asian origin of Jomon peoples but shows a closer affinity to Northeast Asians.

博士論文の審査結果の要旨

アジアには多様な集団が存在しており、それらの集団構造、移住などの集団遺伝学的研究は始まったばかりである。近年、全ゲノムを網羅する多型解析が可能となり、集団構造のわずかな違いを詳細に検討することが可能となった。本研究では、Pan-Asian SNP Project(申請者がタイピングに関与)、ミトコンドリア DNA データ(申請者がタイピング)、そして日本人 SNP データを用い、マレーシアおよび日本においてマイナー集団を含めた各集団の集団構造の特徴や歴史を、主に principal component analysis (PCA)を用いて検討している。

Pan-Asian SNP project ではグローバルにアジア集団の特徴が解析されている。Jinam 君はマレーシアのさまざまな集団の詳細な集団遺伝学的検討をおこなった。PCA によりそれぞれの集団の違いを示す事ができるとともに、ふたつの集団のハイブリッドと予想できる comet-like パターンを示す集団も観察された。また外見に類似した特徴のある Malaysia Negrito と Philippin Negrito は集団遺伝学的にはまったく異なる集団であることが確認できた。またこれらの結果はミトコンドリア配列からも追認できた。かつ、ミトコンドリア配列およびハプロタイプ決定により、分岐年数の推測ができ、集団移動の歴史の推察ができた。

最後に日本人において、沖縄の琉球集団と北海道のアイヌ集団の特徴をゲノム全域 SNP データを用い関東集団と比較しつつ解析、検討した。日本人において二重構造モデルが提唱されている、いわゆる縄文人と弥生人である。PCA にてアイヌ集団はばらついた分布を示し、admixture が進んでいる事が示唆された。PCA により、琉球集団とアイヌ集団にある程度の類似性はあったものの、琉球集団は関東集団とそれほど離れていなかった。無根近隣結合法による系統樹において、琉球集団とアイヌ集団は遺伝的に共有する部分を持つことが統計的に高い有意性で示され、日本人の2重モデルの根拠となる可能性が示された。

Jinam 君のアジア集団構造の解析は新たな知見を提供し、それぞれの集団の成り立ちを考察する上で重要なデータとなる。以上の理由から、Jinam 君の博士論文は本大学院における博士号授与の要件を満たすと審査委員全員一致で判断した。