様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

平成　３０　年　　６　月　１９　日現在

機関番号：　６３８０１
研究種目：　若手研究(B)
研究期間：　2015～2017
課題番号：　１５Ｋ１８６２２

研究課題名（和文）Identifying genetic loci related to the unique phenotypes and immune system of the Negrito populations in Southeast Asia

研究課題名（英文）Identifying genetic loci related to the unique phenotypes and immune system of the Negrito populations in Southeast Asia

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交付決定額（研究期間全体）：（直接経費）　　3,200,000円

研究成果の概要（和文）：およそ８０万個のゲノム規模ＳＮＰデータの解析を、特徴的な表現型を持つネグリト人を含んだいくつかの東南アジア人集団についておこなった。ネグリト間では共有しているが、他の集団とは分化している遺伝子のなかには、身長、顔面形態、マラリア対抗性に関連しているものがあった。旧人からの遺伝子移入が、フィリピン諸島のネグリトには相対的に高い頻度で見いだされた。またネグリト人を含むマレーシアの７人類集団において、免疫に関連したＨＬＡ遺伝子群の塩基配列を決定した。その結果、これら遺伝子の歴史性およびこの地域におけるさまざまな病原体に対する反応に関連するかもしれないＨＬＡ対立遺伝子頻度の差を見いだした。

研究成果の概要（英文）：I performed analysis of approximately 800,000 genome-wide SNPs in several Southeast Asian populations, including negritos who show unique phenotypes.
Some genes that are shared among negritos, but are differentiated in other groups are related to height, facial morphology and malarial resitance. The negritos also are phylogenetically basal to other SEA populations, but they also received substantial gene flow from these other groups. I also found relatively higher traces of archaic human ancestry in Philippine negritos, but not in Andamanese or Malaysian negritos. This results were published in Genome Biology and Evolution. I also performed sequencing of immune-related HLA genes in four Malaysian groups and found differences in HLA allele distribution that might reflect their ancestry and response to various pathogens in the region. Manuscript preparation for this result is ongoing.

研究分野：　Population genetics

キーワード：　population genetics　admixture　negrito　Southeast Asia

１．研究開始当初の背景

Human migration into Southeast Asia (SEA) dates back at least 50,000 years ago. Current day negrito populations found in Andaman islands, Malaysia and the Philippines are thought to have originated from this ancient migration. The negrito groups have unique phenotypes similar to African pygmies. They have also been living in the SEA region for a long time, and may have been exposed to endemic infectious diseases like malaria. Their adaptation history to such environments may be recorded in immune-related genes such as the HLA loci. A large scale genome-wide genetic analysis (Pan-Asian SNP Consortium, Science 2009) included some negrito groups, but only ~50,000 SNP markers were used.

２．研究の目的

The genetic loci that contributes to the 'negrito phenotype' has not been elucidated. Furthermore, the selection pressures that shape the diversity of immune-related genes in response to their environment is also unclear. We plan to answer those questions by analyzing genome-wide SNP markers and sequence data of the HLA region in the negritos.

３．研究の方法

Approximately 800,000 autosomal SNP data were generated in four Philippine negrito groups using Affymetrix 6.0 genechip. I combined that data with other population data, including Malaysian and Andamanese negritos, as well as other non-negrito groups. Various population genetics tests were conducted on this combined dataset.

The HLA region on chromosome 6 was sequenced in Malaysian populations, including a negrito group. Genes in the HLA region were enriched using SureSelect QXT target enrichment kit. These targeted fragments were sequenced using Illumina MiSeq. The resulting 350 bp paired-end reads were aligned to the human reference genome and the sequence data was used to identify HLA alleles.

４．研究成果

Using approximately 800,000 autosomal SNP, population genetics analysis was performed on various negrito groups. Phylogenetic tree analyses show that negritos are basal to other East and Southeast Asians, and that they diverged from West Eurasians approximately 40,000 years ago (Figure 1).

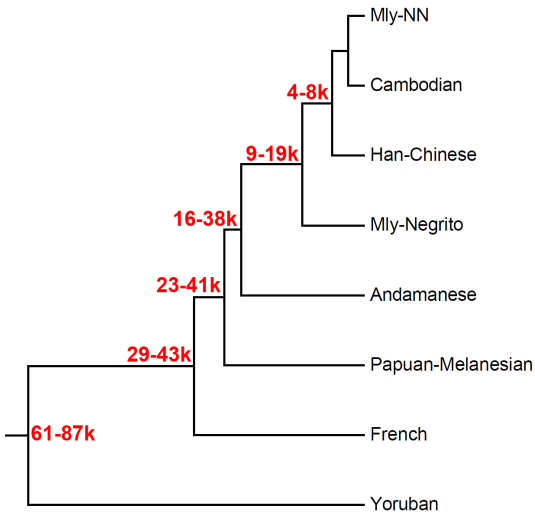

Fig 1: UPGMA tree showing estimated divergence times between populations.

PCA and admixture analysis showed a significant contribution from non-negrito groups to the genetic diversity of negritos.

Relatively high traces of archaic human (Denisovan) admixture was detected in the Philippine negritos (Aeta, Agta, Batak, Mamanwa), but not in the Malaysian and Andamanese groups, suggesting independent introgression and/or parallel losses involving Denisovan introgressed regions (Figure 2).

Fig.2: Denisovan introgression in Southeast Asian populations.

Shared genetic loci between all three Negrito groups were detected by filtering SNPs that have low differentiation between negrito groups, but are highly differentiated with non-negritos. These SNPs are located in genes that are related to skin pigmentation, height, facial morphology and malarial resistance (Table 1).

Phenotype	Gene	SNP	Between Negrito Fst	Negrito-CHB Fst
Skin pigmentation (Stokowski et al. 2007)	OCA2	rs1800414	0.041	0.588
	SLC45A2	rs6451050	0.001	0.071
Height variation (Wood et al. 2014)	ACAN	rs939587	0.013	0.327
		rs1042631	0.005	0.166
	ADAMTS17	rs11631646	0.002	0.018
Facial morphology (Adhikari et al. 2016)	PAX3	rs2276630	0.001	0.024
	PREP	rs1617445	0.007	0.112
	GRID1	rs3011704	0.000	0.169
Malarial resistance (Liu et al. 2015)	IL4	rs2243270	0.004	0.082
	CDH13	rs4783293	0.000	0.299

Table 1: Shared SNPs in negritos but highly differentiated in non-negritos are associated with some physical features.

These results were published in Genome Biology & Evolution journal in 2017.

In total, 192 individuals were sequenced for the HLA region. HLA allele calling from the DNA sequences was done for 3 HLA class I genes (HLA-A, -B, and –C) and five HLA class II genes (HLA-DRB1, -DQA1, -DQB1, -DPA1, and -DPB1). Allele frequencies for each of those HLA genes differ among the seven Malaysian groups studied. These differences reflect their ancestry and response to various pathogens in the region. Manuscript based on these data will be submitted for publication.

５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　1　件）

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（査読有り）

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