学力確認の結果の要旨

報告番号	総論第 44 号		学位申請者	ヨラ ニンディタ
審査委員	主査	堀内 正久	学位	博士（(医学)・歯学・学術）
	副査	郡山 千早	副査	大脇 哲洋
	副査	橋口 照人	副査	西尾 善彦

主査および副査の５名は、平成４年２月２日、学位申請者 ヨラ ニンディタ 君に面接し、学位申請論文の内容について説明を求めると共に、関連事項について試問を行った。具体的には、以下のような質疑応答がなされ、いずれについても満足すべき回答を得ることができた。

質問１）Is there a difference in HDL-C levels by ethnicity?
（回答）Yes, Japanese have higher HDL-C levels than those in western countries, including the USA.
質問２）How were the triglyceride levels in your population, and did you measure it?
（回答）The triglyceride levels were also measured in this J-MICC study population. We focused on HDL-C in our GWAS analysis.
質問３）Were there any patients in your study who have taken medicines that affect cholesterol levels?
（回答）Yes, there were 1,064 (9.4%) subjects taking cholesterol lowering drugs.
質問４）What medicine affect HDL-C levels?
（回答）Niacin, fibrates, and CETP inhibitors raised HDL-C levels. Niacin increases HDL-C levels more safely and effectively than fibrates and statins, reducing the cumulative CHD risk in a previous study.
質問５）According to your thesis, what kind of categories did you use to divide selected genes in Table A1?
（回答）We divided the SNPs based on the protein-coding gene and cytoBand (chromosome).
質問６）In your thesis, Table 1, page 5, you mention about major HDL subclasses. Were increased HDL-C levels with alcohol intake different by each HDL-C subclass?
（回答）One of our study limitations is that we didn't analyze HDL-C levels by subclass; but a previous study showed that alcohol consumption was associated with increased HDL-C levels in large and medium HDL sizes.
質問７）You didn't mention about liver disease in your exclusion criteria. Liver disease will decrease HDL-C levels. How do you think about it?
（回答）The prevalence of liver cirrhosis history was 0.18% in our subjects, and they did not show decreased HDL-C levels.
質問８）Why did you take plasma in your study? What did you use plasma for?
（回答）The study protocol of the J-MICC study required plasma collection and storage for future another studies.
質問９）Please explain more details about identity-by-descent method implemented in the PLINK 1.9 software that was used to identify close relationship pairs.
（回答）PLINK focus on the estimation and use of identity-by-state and segments of identity by descent (IBD) information in the context of population-based whole-genome studies. This information can identify extended chromosomal segments that are shared IBD between very distantly related individuals.
質問 10）Table 3 mentioned that BMI was also closely related with HDL-C. How do you think about it?
（回答）Obesity profoundly affects HDL metabolism and leads to changes in HDL composition and a shift towards small HDL3 particles.
質問 11）In 7 selected major SNPs, APOA5 was included, but APOA1 was not. Why is APOA1 not included in GWAS catalog?
（回答）As APOA1 in the previous reports didn't meet the genome-wide significance, it was not listed in the catalog.
質問 12）Please explain in simple term that PAF formula represent the population-based impact.
（回答）Population attributable fraction (PAF) was calculated using both impact and prevalence of the exposure to take account their combined effect. The PAF has been used to quantify the proportion of disease burden in the population level.

学力確認の結果の要旨

質問 13) Why was the HDL-C data lack in Chiba and Aichi Cancer Centers? Didn't they use the same protocol?

(回答) They used the same protocol, except examining atherosclerosis-related items, because the first main purpose of the J-MICC study was for cancer prevention. The present study was a part of the J-MICC study.

質問 14) The subjects for whom sex information was inconsistent between the questionnaire and the genotyping results were excluded. Why did such event occur? How many cases were excluded?

(回答) Although some participants wrote wrong answer on sex in the questionnaire, and its information was revised after corrected by the information on consent form and other items of the questionnaire, some unclear cases may be residual. The information on another possibility, such as LGBT, was not collected. The number of those with inconsistent data was 26, whose data were excluded.

質問 15) How many pairs identified as close relationship pairs (pi-hat > 0.1875) were excluded?

(回答) The number of close relationship pairs was 388, and they were excluded.

質問 16) In Amami, relative high prevalence on related relative in conjugal relation is suspected, and the pi-hat may probably be higher than that in other parts of Japan. Didn't you mention the limited regional differences of the phi-hat data? Have you looked the data of Amami islands?

(回答) The pi-hat was not analyzed by study region, because this regional difference includes some naïve part.

質問 17) SCARB1 rs921919 was not listed in the GWAS catalog. Do you think this is a new SNP and will be listed in the catalog?

(回答) As the listing in the catalog from the published report is decided by some committees, I have no idea at the moment.

質問 18) Why was BMI divided into 2 categories with cutoff point 23?

(回答) BMI was divided with similar number in combined both sexes and comparable number of respective subjects in each.

質問 19) Why was age divided into 2 categories with cutoff point 57?

(回答) Age was also divided with similar number in combined both sexes and comparable number of respective subjects in each.

質問 20) How did you decide the cutoff point for daily activities and habitual exercise?

(回答) The cutoff point was decided at the median value. The subjects with lower daily activity were relatively shifted to the lower values and different between sexes.

質問 21) Why were the groups in table 4 (RR + RA and AA) and table 5 (RR and RA + AA) divided differently?

(回答) As the direction of the coefficients of rs2575876 and rs429358 was negative, their opposite genotypes with the positive coefficient side and their prevalence was used for PAF calculation in Table 5, because comparative PAF estimation requires the same direction.

質問 22) Did you estimate the PAF for men and woman separately? Especially regarding smoking and drinking habits, the impact might be different between these two groups.

(回答) The PAF on smoking and drinking was not estimated by sex, because the limited number of the subjects and the ORs by sex for estimating PAF were not always significant.

質問 23) Why do heavy drinkers have high HDL-C levels?

(回答) Alcohol is partially involved in an increase in transport rate of apoA-I and apoA-II and cholesterol esterification by stimulating the efflux of cholesterol from peripheral cell. The whole mechanism is still unclear.

質問 24) Did you check the association between green tea and cholesterol level including HDL-C in your study?

(回答) We didn't analyze the association between them, because our previous study did not find this association.

質問 25) Why did GWAS analysis exclude XY chromosome?

(回答) Males are hemizygous for the X chromosome and so have only two distinct genotypes. Females have three possible genotypes for X loci. Thus, simply, association testing in males is akin to allele-based testing, whereas association testing in females generally requires a genetic model to be specified.

質問 26) Are HDL-C levels influenced by epigenetic regulation?

(回答) Yes, the cholesterol homeostasis is also under the control of epigenetic mechanisms such as histone acetylation, DNA methylation; and miRNAs also act as a novel class of epigenetic regulators of HDL-C from synthesis to clearance.

質問 27) After doing the research, how do you think the result of your study will be applied in the population health?

(回答) We can improve our health and prevent diseases after changing environment factors of lifestyles. Genetic factors represent some susceptible person for disease burden with lifestyle. Taylor-made prevention and health promotion are expected according to their susceptibility.

以上の結果から、５名の審査委員は申請者が大学院博士課程修了者と同等あるいはそれ以上の学力・識見を有しているものと認め、博士（医学）の学位を与えるに足る資格を有するものと認定した。