

最終試験の結果の要旨

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主査および副査の5名は、平成25年8月27日、学位申請者 モタヘラ カルデマンド 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) Did you check the combined effect of SNPs?

(回答) We analyzed the accumulation effect of SNPs, but their association was not apparent, although the number of subjects in each stratum was small.

質問2) What do you think about the postmenopausal effect for atherosclerosis development in women?

(回答) The association of conventional risk factors and SNPs was not different between premenopausal and postmenopausal period. Its effect was not observed in the present study.

質問3) How many times does the CD14 C-260 T increase the transcriptional activity of CD14?

(回答) The study using cell lines have shown that T allele increased the transcriptional activity by 32%.

質問4) Did you check the association between the green tea intake and atherosclerosis?

(回答) Yes, we did, but we did not observe any association between green tea intake and CAVI values.

質問5) What is the role of CD14 in atherosclerosis development?

(回答) CD14 plays a key role in innate immunity, as it is the receptor of LPS, a component of gram negative bacteria, and it is expressed mainly by mature monocytes and macrophages.

質問6) How do you explain the association between smoking status and CAVI in women since the number of female smokers is very small?

(回答) It is most probably due to random error.

質問7) Which question did you ask in order to collect information about the green vegetable intake?

(回答) We collected its information using the combined intake of various green-leaf vegetables with intake frequency.

質問8) How did you measure habitual exercise?

(回答) We asked each frequency of mild, moderate and hard exercise habits, and then we combined the answers to three categories.

質問9) Is insertion deletion polymorphism in NF- κ B located in the promoter region?

(回答) Yes, it is located in the promoter region of NF- κ B.

質問10) Does CAVI values change at different time of a day?

(回答) The previous study reported that the average coefficient of the CAVI value variation in a day is 3.8%, which is small enough for clinical usage, indicating CAVI has good reproducibility.

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質問 11) Why did you select these 7 SNPs?

(回答) Since our study subjects were selected from general population and we used CAVI as a surrogate marker of pre-atherosclerotic diseases, we selected our candidate gene from those affecting the initial stages of atherosclerosis. In addition, we referred literature, particularly in Japanese population.

質問 12) Since CAVI is related to arterial stiffness, not atherosclerosis, how do you explain no association of CAVI and these SNPs which were associated with atherosclerosis?

(回答) Previous studies reported a positive association of SNPs with indices measuring atherosclerosis, and arterial stiffness is a part of atherosclerosis process. Other studies had shown that CAVI was related with atherosclerotic diseases. No association may be due to small effect of SNPs and wide variation of CAVI values.

質問 13) Did you check the association of pulse pressure and selected SNPs?

(回答) No, we did not.

質問 14) Why your response rate in follow up study is low?

(回答) Most of the subjects who did not participate in the second survey were those who did not undergo a routine health checkup because of changes in the health checkup system or for their own reasons. We compared the baseline characteristics, and we did not observe any significant differences between the study and residual subjects.

質問 15) Does inflammatory polymorphism measured by PCR affect the function of molecules?

(回答) We did not measure the function of molecules but previous studies reported that the selected SNPs can either increase or decrease the activity of transcriptional factors or cytokines.

質問 16) Are there any indices which show an association between arterial stiffness and gene polymorphism other than CAVI?

(回答) Yes, significant association was reported on baPWV.

質問 17) What was your contribution in this study?

(回答) I involved in measuring CAVI and laboratory work in these three islands, and DNA extraction, its genotyping and analyzing data.

質問 18) Did you examine mRNA using real time PCR?

(回答) No, we did not.

質問 19) Do you think that deviation of HWE might be because of migration which happened long time ago?

(回答) The deviation of HWE was observed in one island, but not in other two islands. Other study actually reported different distribution of SNPs between Amami and other regions, but it was very small.

質問 20) How do you explain the negative association between smoking and CAVI in women?

(回答) Small number of female smokers may lead to random error.

質問 21) Which has stronger effect on CAVI values between the number of cigarette smoked per day and the duration of smoking?

(回答) No study investigated the effect on CAVI between them in long term observation, but the smoking cessation study showed the stronger effect on the duration of smoking.

質問 22) How does smoking effect the atherosclerosis process?

(回答) Various toxic substances of cigarettes can reduce prostacyclin synthesis which leads to artery shrinkage and decrease vasomotor activity, and decrease anticoagulative action. In addition, large amounts of free radicals in cigarette lower the activation of nitrogen monoxide, which may obstruct the vasodilation reaction in vascular wall.

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しての学力・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。