最終試験の結果の要旨

報 告 番 号	総 研 第	３３Ｓ号	学位申請者	マンチョロ　エバ　マリア

審 査 委 員	主 査	堀内　正久	学 位	博士 （医学）・歯学・学術）
	副 査	秋葉　澄伯	副 査	乾　明夫
	副 査	橋口　照人	副 査	大石　充

　　主査および副査の５名は、平成２８年７月２５日、学位申請者　マンチョロ　エバ　マリア　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） Which site of Hcy levels act to increase arterial stiffness?
（回答）The major site for the effects is vascular intima.

質問２） What substantial role dose Hcy play in arterial stiffness in animal experiment?
（回答）The damage in vascular intima through various mechanisms was observed in animal model.

質問３）The proportion of longevity people aged more than 100 years in Amami is actually three times higher than average of Japanese population. Did you measure Hcy level among them?
（回答）No, we didn't. The age range of our subjects was 40-69 years.

質問４） CAVI is reliable index showing for arterial stiffness. Could you tell me the evidence or literature for supporting this CAVI actually related to arterial stiffness?
（回答）The validity and reproducibility have been evaluated using IMT and PWV in previous studies.

質問５） Did blood Hcy levels relate to MTHFR and MS polymorphisms? In the case of MTHFR polymorphism, how different are Hcy levels between three genotypes of CC, CT and TT?
（回答）Hcy levels were significantly different by MTHFR genotype, and the subjects with TT genotype showed the highest Hcy levels. Hcy levels were not different by MS genotype.

質問６） You examined the association between polymorphism and CAVI in Table 3 and 4. What's your hypothesis? Why did you suspect those polymorphism may be related to CAVI?
（回答）Previous studies reported significant association between Hcy levels and MTHFR polymorphism. We examined the association with MTHFR polymorphism as a representative host factor of Hcy levels.

質問７） In Supp. Table 1, Hcy is not related with IMT, in case of CAVI, you suspect it may be related to Hcy level. What is the difference between IMT and CAVI?
（回答）IMT is a measurement of the thickness of tunica intima and tunica media. CAVI and PWV are measurements of arterial stiffness of large artery. IMT, and CAVI and PWV are different measurements, but apparently related, in term of the evaluation for atherosclerosis. Listed previous studies showed inconsistent results between CAVI, and both PWV and IMT. The difference between IMT and CAVI was similarly observed between PWV and CAVI. It may be difference between studies, but not measurement difference.

質問８） In Table 1, LDL-cholesterol is usually higher in men than in women, but this population of LDL-C is higher in women, Why?
（回答）Total cholesterol levels were not different by sex among the present subjects aged 40's years, but its levels increased with age only in women, but not in men. Therefore, total cholesterol levels were higher in women than men among those aged 50's and 60's years. LDL- and HDL-cholesterol levels showed similar trend. These trends were similarly observed among total cohort subjects (n=7,640), and also by region of Amani and Kagoshima mainland.

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質問9）You enrolled 1,300 subjects in 2005, but the number of enrolled subjects were 856 in 2010. So, a lot of population is dropped out, why?

（回答）The enrolled 1,300 subjects in 2005 at the baseline are followed up for death, movement and disease incidence until 2024, and the second survey for the same subjects at routine health checkup examination was conducted in 2010. Therefore, CAVI examination was conducted only in 2005 and 2010. The eligible participants who attended in the second survey were 856, and the residual subjects were just followed up without CAVI examination.

質問10）CAVI change in 5 year , how do you calculate in 5 year change?

（回答）The individual difference in CAVI values between 2005 and 2010 was calculated. Most of CAVI values increased with age.

質問11）Was the distribution of MTHFR genotype similar to that of the previous report?

（回答）Yes, the present distribution was similar to those in previous studies among Asian population.

質問12）Can the obtained results in your study apply to general Japanese population? What kind of items should you consider about?

（回答）Yes, I think so. The association between conventional risk factors and CAVI was commonly observed, compared to other studies in Japan, and our results were also obtained after adjusted for these factors. Unknown genetic factors for atherosclerosis in Amami should be potentially taken into consideration to influence the results.

質問13）On limitation, 2nd paragraph, I still ambiguous about this limitation "MTHFR is thermolabile enzyme in this pathway" why this paragraph is limitation on your study?

（回答）Our meaning of the limitation on this paragraph is that of limited number of examined gene polymorphisms in folate metabolism pathway. The selection of MTHFR as the thermolabile enzyme is discussed as the most valuable one for reduced this limitation.

質問14）You measure Hcy levels, and Hcy levels are reduced in the blood. Did you measure its oxidative form?

（回答）No, I didn't measure Hcy oxidative form in this study.

質問15）In Table 1, the proportion of current drinking in women was 1.9% and very low rate. So, how do you think this is specific for this group? What is definition of current drink?

（回答）The definition of current drink is those who drank ≥35 gram alcohol/day, and should be described as "current heavy drink". It is reasonable that heavy drinkers were proportionally very small in women.

質問16）Is folate fortification is very useful to public people?

（回答）Yes. In 2006, WHO and the Food and Agricultural Organization of the United Nations published guidelines to help countries to set the Target Fortification Level of folic acid to be used to fortify flour with folic acid.

質問17）Which organ metabolize or excrete Hcy levels?

（回答）Hcy is an intermediate metabolite in methionine metabolism, and mainly exists in blood as compounds. Specific organ is not involved in its metabolism or excretion, but liver may play an important role.

質問18）In Table 5, you divided into 2 groups using logistic method models. CAVI is continuous variable, It's possible to evaluate or use a simple multiple regression analysis. So, how do you examine, or how the results?

（回答）CAVI value is continuous variable, and the definition of atherosclerosis is also proposed as ≥9.0. We analyzed non-parametric variable of CAVI using this definition as a kind of threshold model in Table 5. We also analyzed continuous variable of CAVI as dose-response model in Table 4. The concordat results were obtained in these two analyses.

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。