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２８年１０月２４日、学位申請者 タラ セファニャ カイルパン君に面接し、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） What were the reasons for the out-migrations in your study population?
（回答） As we collected the information of the migration from the official resident card of the local government, we have no information on their reasons.

質問 2） In your baseline study, did you include the people with medical histories of CHD and stroke? If so, why individual histories of CHD and stroke were not adjusted in your Cox proportional hazard analysis?
（回答） Yes, we included CHD cases in our baseline study. However, we did not perform adjustments for CHD and stroke as the proportions of these diseases, because the number was relatively small and their distribution was not different between HTLV-I seropositive and seronegative groups in our preliminary analysis.

質問 3） Did you performed multiple comparisons for Table 3 and Table 4? If not, why?
（回答） No, we did not, because the number of the subjects was limited in terms of statistical power.

質問 4） Regarding your sub-cohort matching rule, is there any specific reason why "*+1 year of age*" was applied before "*-1 year of age*"? Also, what is the meaning of "*adding age for the candidates respectively*"?
（回答） There was no specific reason. The age criteria were chosen only for consistency in matching subject selection in our study. The latter means the subjects with "+2 od -2 year of age" were selected, when the subjects with "+1 od -1 year of age" were limited.

質問 5） In your thesis (page 11), you mentioned that *"The virus predominantly infects CD4+T-cells but can also infect CD8+ T-cells, dendritic cells, very rarely B-lymphocytes, monocytes, and fibroblasts"*. Are these findings still coherent with recent consensus update?
（回答）We admit that the references for this statement were not recently published studies. Based on newer *in vivo* studies, HTLV-I predominantly infects CD4+ T-cells and also small fraction of CD8+ T-cells (Melamed *et al,* 2015). However, we could not find any newer findings of dendritic cells, B-lymphocytes, monocytes, and fibroblast involvements. Thus, we will correct the content of thesis accordingly.

質問 6） How many times does the TNF-α 1031T/C polymorphism increased the serum level of TNF-α?
（回答） C allele increased the TNF-α serum level 1.79 times higher than T allele. The transcriptional promoter activity of C allele was 2 times higher than its T allele (Higuchi *et al,* 1998).

質問 7） Did IL-10 819T/C and NF-κB 94ATTG ins/del induce amino acid substitution?
（回答） We could not find any supporting evidence for this.

質問 8） In Table 5, TNF-α TT polymorphism, HR for total death was 1.90 (above 1.00), on the other hand, the HR for cancer incidence and for atherosclerosis related disease incidence were 0.46 and 0.33 (below 1.00). What do you think causing this difference?
（回答）This discrepancy was similarly observed in the case of other two SNPs. As the person years and number of events of incident subjects were limited, further follow-up study is warrant to explain it.

質問 9）What causes the discrepancy between high HR in Amami island subjects and low HR in mainland subjects?
（回答） 1) Follow-up duration was relatively lesser with smaller statistical power in mainland subjects (2.8 years); 2) the distributions of HTLV-I by sex between Amami island and mainland was different, thus the different mode of transmission might influence the impact for deaths with HTLV-I.

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質問 10）Why did you used 4 time matched controls instead of using the whole HTLV-I seronegative subjects?
（回答）Age distributions were different between HTLV-I seropositive and seronegative subjects. HTLV-I seropositive subjects were apparently shifted to the older population and the adjustment was not enough, in term of different immunological background by age. The number of subjects has the limitation of the 1:4 matching.

質問 11）NF-κB1 94ATTG ins/del was not within HWE in the sub-cohort population? How about in the total cohort population?
（回答）NF-κB1 94ATTG ins/del was within the Hardy Weinberg Equilibrium (p=0.052) after adding more subjects of the total cohort. However, because more than half of total cohort subjects had not examined SNP, this result also cannot represent general population.

質問 12）Did you do combined analysis for the three polymorphisms?
（回答）We did not analyzed the combined effect of SNPs because of the limited number of subjects.

質問 13）In the TT genotype of the TNF-α, what type of atherosclerosis related disease is increased?
（回答）The TT proportion of stroke was significantly higher (10/11 for stroke, 11/20 for AMI and aneurysm), but TT and HTLV-I (1/11, 0/20) was very low. Further study on stroke may be warrant.

質問 14）Do you think the interview method to obtain incidence information is sufficient?
（回答）We tested the positive predictive values among selected subjects, comparing the information with medical records, which values were sufficiently high (95.6%, cancer; 93.8%, atherosclerosis related diseases).

質問 15）Did you exclude ATL patients? I recommend excluding ATL patients because ATL is caused by HTLV-I.
（回答）One case of ATL deaths was included. Its impact may be very small, but it may be better to be excluded.

質問 16）Your study reported that HTLV-I seropositivity was higher in main island compared to Amami island. Is this consistent with previous reports?
（回答）There is no paper, but previous Kakenhi report on the seropositivity among pregnant women in 1980' showed the positive rates in Amami was not high compare with other regions of Kagoshima.

質問 17）In Table 1a, you showed total HTLV-I seropositivity of HTLV-I in men and women were 5.6% and 7.0%, respectively. However, in Table 1b, the total seropositivity were both 100%, and I think they should be 20%. This means the mean age of this sub-cohort study group is higher than the total cohort study group, am I right?
（回答）Yes, the seropositivity rates were 20% in men and women in the sub-cohort population due to age matching to HTLV-I seropositive subjects, thus the mean age was higher compared to the total cohort.

質問 18）Why did you choose these 3 SNPs? Are there any other inflammatory genes related to HTLV-I, cancer, and atherosclerosis?
（回答）We chose 3 immune groups to play the most important roles in chronic inflammation in HTLV-I, which are also related to cancer and atherosclerosis pathogenesis. Then, we selected one representative SNP from each group based on previous studies.

質問 19）Do you include deceased subject in the incident cases?
（回答）Yes, death cases were also included if the deceased subjects develop cancer or atherosclerosis-related diseases, prior to and/or as the cause of their death.

質問 20）Please calculate the sample size required for your study based on power calculation.
（回答）Sample size calculation was difficult, because this is the first study to estimate the risk for death and incidence with HTLV-I according to SNPs, and no information on the impact of RRs was shown.

質問 21）Based on your experience and your research, what is your future plan when you go back to your country?
（回答）I will use my statistical knowledge and experience to conduct epidemiological studies about common diseases in Indonesia.

質問 22）Why did you conduct your PCR differently to the standard PCR protocol?
（回答）We basically followed the PCR experiment setting according to the standard protocol, and had small arrangement due to previous our study experience (Kheradmand *et al*, 2013; Mantjoro *et al*, 2016).

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。