最終試験の結果の要旨

報告番号	総研第 264 号		学位申請者	袁 軍輝
審査委員	主査	橋口 照人	学位	博士（医学・歯学・学術）
	副査	佐野 輝	副査	武田 泰生
	副査	久保田 龍二	副査	矢沢 和人

主査および副査の５名は、平成25年12月2日、学位申請者袁 軍輝君に面接し、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） In your result, why 2% of the target region was covered less than 10 reads, and need Sanger sequencing.

（回答） Two main reasons: 1) high GC content; 2) second structure of the fragment.

質問2） Have you done the expression study in the biopsied sural nerve sample, like the immunohistochemical study?

（回答） We did not do it.

質問3） Have you detect the mRNA or cDNA to check the sequence?

（回答） It might help us to understand the mechanism. But we need more blood sample from the patients, we didn't perform it.

質問4） In your country, what is the situation of leprosy sensory neuropathy, another kind of sensory neuropathy?

（回答） We met a leprosy patient in our department only once. It is not so common.

質問5） There are gain-of-functions in the same gene, but what are the molecular feature of these mutations.

（回答） The previous studies have identified the dysfunction of the sodium channel, and they were not exactly the same, including lowering the threshold of action potential, or impairing the inactivity phase.

質問6） In three patients with a same mutation, what do you think is the molecular reason of the phenotypic variants.

（回答） We are also curious about the mechanism between the genotype and phenotype. I think several factors should be considered, such as the modifier genes, related proteins, gender difference, and environmental factors.

質問7） Many mutations have been found in SCN9A, Did other mutations also related with the HSAN phenotype?

（回答） No, our study is the first report. All the previous loss-of-function mutations were related with the CIP phenotype. This might be the first report for a short insertion.

質問8） What will happen due to the gain-of-function? For example, the threshold of gate will be prolonged, and the potential changes.

（回答） The function of sodium channel was changed. Such as in inherited erythromelalgia, the threshold was lower than normal.

質問9） You showed us that the myelinated fibers were reduced, but what are these myelinated fibers? Sensory nerve fiber or motor nerve fiber?

（回答） Sural nerve is a sensory nerve, so sensory nerve fiber only.

質問10） The three patients, harboring the same mutation, but variable phenotypes. Any other mutations in the 16 genes?

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（回答）No other pathogenic mutation in 16 genes. Besides these genes, there might have another phenotype-related mutation.

質問 11）Before your study, SCN9A is not causative gene for HSAN, why you study this gene and the other four genes?

（回答）We planned to select all of the genes related with the sensory and autonomic dysfunctions, and these five genes including SCN9A could generate sensory and autonomic dysfunctions. So we enrolled these genes in our study.

質問 12）The patients are insensitivity of temperature and pain, why the sensation of position, vibration are not affected?

（回答）Nav1.7 mainly expressed on the A δ and C fibers, but the position sensation and other sensations were carried by the other kinds of nerve fibers. So they were not affected.

質問 13）Patient 3 showed muscle weakness, why did this happen?

（回答）This might be related with the surgeries, joint contracture, and long-period bed-bound due to the recurrent fractures.

質問 14）Why does the rash and pigmentation in patient 2 associated with the disruption of autonomic innervation?

（回答）This is the comment from the reviewer. I am not sure about the detail.

質問 15）Patient 1 had asymptomatic sensorineural hearing loss with an increase in the 4,000-Hz threshold in the left year, but can you rule out the possibility of the noisy difference?

（回答）I got this information from the patient's record.

質問 16）Due to the gain-of-function, what was changed of the sodium channel, expression level or the function?

（回答）I think I can say that the function of the sodium channel was changed, but I am not sure about the expression level.

質問 17）In hearing loss, sometimes calcium channel (in HeLa cell) is modulated, and it is very hard to hear.

（回答）I can 't exclude this possibility. But in genetic study, we always try to explain all the symptoms by one reason.

質問 18）Did anyone explain the mechanism of anhidrosis? Is it caused by a gland problem or nerve problem?

（回答）It is a nerve problem in our field.

質問 19）Why your patients show many bone symptoms, such as fracture or bone dysplasia?

（回答）We do not know the exact reason. The repetitive fracture was also observed in other patients with CIP. The bone development is related with autonomic nervous system, so there might have some interaction.

質問 20）I concerned that the patients might have more autonomic disorders, like temperature sensation, the corneal reflex?

（回答）We do not check all the autonomic dysfunctions.

質問 21）About the heterozygous carrier, do they have any subclinical symptom?

（回答）No, not yet.

質問 22）For concluding as a homozygous mutation, did you check that there might have a large deletion on another allele.

（回答）In genetics, the possibility of one case harboring two mutations is quite low. The haplotype study is necessary to check.

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。