学 位 論 文 の 要 旨

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〔題名〕

A Study of the Characterization New Hemoglobin Variant: Hb Hachioji (β62 E6 c.187C>T, alanine-valine), Coincidentally Found in a Japanese Subject with Hemolytic Anemia of Unknown Origin
（原因不明の日本人溶血性貧血患者において偶然発見された新規の異常ヘモグロビン：Hb Hachioji（β62 E6 c.187C→T、アラニン→バリン）の特性解析）

〔要旨〕

We report a new hemoglobin (Hb) variant, Hb Hachioji, which was detected in a 32-year-old male proband with hemolytic anemia. The proband had undergone splenectomy in his childhood after being diagnosed with hereditary spherocytosis with no clinical improvement. A recent study showed that Heinz bodies were frequently observed in his red cells, suggesting the presence of unstable abnormal hemoglobin; however, no abnormal band was separated in isoelectric focusing, and the isopropanol (instability) test was negative. These findings suggest that the Hb variant was no longer present in a soluble form in his red cells and that it may have been denatured and precipitated in his red cells. Therefore, the variant was thought to be “highly unstable hemoglobin.” Direct sequencing revealed that the proband was a heterozygote carrier of a novel mutation (GCT > GTT) at codon 62 of the *β-globin* gene, leading to an alanine-valine substitution. This variant was named Hb Hachioji. Characterization at the mRNA level by cDNA sequencing detected $\beta^{Hachioji}$ mRNA, as well as β^{normal} mRNA. Subsequently, the proband’s family study indicated that his father was a carrier of this Hb variant, although unexpectedly, the father was asymptomatic and clinically healthy. Oxygen affinity measurement of total Hb showed no alteration in the P_{50} and oxygen equilibrium curve. Thus, Hb Hachioji was, in fact, observed to be stable and functionally normal and to completely overlap with HbA in isoelectric focusing. The presence of Hb Hachioji was confirmed by mass spectrometry. Hb Hachioji comprises approximately 50% of the total Hb and is a stable variant. The phenotypic discrepancy between these two carriers suggests that Hb Hachioji may not be associated with the hemolytic involvement in the proband. We searched for the cause of hemolysis in the proband. Coombs’ test was negative. P4.2Nippon, which is the primary cause of most cases of Japanese hereditary spherocytosis, was absent in the proband’s parents. The coexistence of glucose 6 phosphate dehydrogenase deficiency was ruled out. Thus, the cause of hemolytic involvement in this patient remains unclear. Whole exome sequencing might further clarify the condition.

学位論文審査の結果の要旨

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学位論文題目名　（題目名が英文の場合は、行を変えて和訳を括弧書きで記載する。）

A Study of the Characterization New Hemoglobin Variant: Hb Hachioji (β2 E6 c.187C>T, alanine→valine), Coincidentally Found in a Japanese Subject with Hemolytic Anemia of Unknown Origin

（原因不明の日本人溶血性貧血患者において偶然発見された新規の異常ヘモグロビン：Hb Hachioji（β2 E6 c.187C→T, アラニン→バリン）の特性解析）

学位論文の関連論文題目名　（題目名が英文の場合は、行を変えて和訳を括弧書きで記載する。）

Coincidental discovery of a new stable Hb variant (Hb Hachioji) in a patient with chronic hemolytic anemia of unexplained origin

（原因不明の慢性溶血性貧血患者において偶然発見された新規の安定型異常Hb（Hb Hachioji））

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（論文審査の要旨）

論文本体に関して：

目的に対し十分に計画が練られ、実験が遂行されている。論旨が一貫しており、ディスカッションも十分行われている。溶血の原因解明を進めていく必要はあるが、現時点で使用可能なサンプル量が非常に少なく、少量の DNA サンプルで Genome wide に解析できる NGS (next-generation sequencer) の開発を待たなければ次の実験に着手するのは困難である。現時点で可能な解析は全て行われていると考えられ、研究の完成度は高く、内容について手直しの必要は無い。

フォーマットに関して：

一部の図に説明が不足しており、書き加えることが必要であった。また、数か所、フォントなどの訂正が必要であった。大きな訂正箇所は見当たらなかった。

以上、論文について、論文審査担当者全員一致で、博士を授与するのに十分なものであると判定した。

備考　審査の要旨は８００字以内とすること。