

Title	Late-onset Krabbe disease is predominant in Japan and its mutant precursor protein undergoes more effective processing than the infantile-onset form
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論 文 内 容 の 要 旨  
Synopsis of Thesis

氏 名 Name	Hossain Mohammad Arif
論文題名 Title	Late-onset Krabbe disease is predominant in Japan and its mutant precursor protein undergoes more effective processing than the infantile-onset form (日本におけるクラッベ病は若年型が最も多く、この若年型変異の前駆体は乳児型変異に比べてプロセッシングの効率が高い)
論文内容の要旨	
<p>〔目的(Purpose)〕 Krabbe disease is an autosomal recessive leukodystrophy caused by the deficiency of lysosomal enzyme galactocerebrosidase. Typical infantile form is known to share more than 90% of all Krabbe disease patients. We summarized the clinical information of Japanese patients to compare with the Caucasian patients' characters. We detected <i>GALC</i> mutations to see the genotype-phenotype correlations. We also analyzed the enzyme processing to elucidate the molecular pathology of Krabbe disease.</p> <p>〔方法ならびに成績(Methods/Results)〕 51 Japanese patients were summarized with the phenotype. Mutation analysis was performed and the expression vectors for common mutations were constructed with pSVL by PCR based mutagenesis. Transient expression was performed in COS1 cells. Measurement of enzyme activities was done with several substrates including HM-gal, 3H-galactocerebroside and 3H-psychosine. Western blotting was performed with transfected COS1 cells. 3D structure analysis was done for novel mutations.</p> <p>90 mutant alleles were detected and we found that 59% of all patients are late-onset and 61% of all Krabbe disease patients can be diagnosed by the seven most frequent mutations including c.635_646delinsCTC, p.T652P, p.R204X, p.P302A, p.[I66M+I289V], p.L618S and p.G270D. Among them first four were infantile and others were late-onset mutations. We found that the early onset mutants had no activity, late onset mutations showed 4-20% of normal activity for all the three substrates. When we checked the protein expression, we found the 80kDa band for precursor <i>GALC</i> protein for all the missense mutations, and deletion, however 30kDa band for the processed protein were detected only for late-onset mutations.</p> <p>〔総括(Conclusion)〕 We summarize Japanese patients with Krabbe disease and report the most common phenotype in Japan is the late-onset phenotype and not the infantile phenotype. We analyzed the common mutations in a transient enzyme expression system and found that enzyme activity using three substrates was correlated with that for the natural substrate and could be used to estimate clinical phenotype. Higher residual activity for late-onset mutations resulted from the higher processing rate of the mature enzymes.</p>	

## 論文審査の結果の要旨及び担当者

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<b>論文審査の結果の要旨</b>	
<p>ライソソーム病の一つであるクラッペ病の病態解明のために、まず日本人患者51名について臨床的なまとめを行ない、欧米で90%と言われていた乳児型が日本人では41%にすぎないことを明らかにした。更に遺伝子型を明らかにするために新たに22例の新規患者の変異解析を行ない、51例の変異をまとめて、7つの高頻度変異を同定した。特に3つの若年型に寄与する変異は一つ持つことにより、遅発型になることを示し、乳児型の変異4つと合わせて解析することにより、61%の患者の病型が推定できることを報告した。</p> <p>次に、高頻度変異と新規変異に関して発現ベクターを作成し、COS1細胞で発現させ、天然基質、サイコシン、蛍光基質を用いてその活性を測定した。その結果は高頻度変異7つに関しては、臨床病型から推定される変異の重症度と酵素活性に相関関係が見いだされた。そして発現細胞を用いてWestern法により、酵素の前駆体から成熟蛋白へのプロセッシングの高率を解析し、若年型の変異においてはこのプロセスの効率が乳児型に比べて高いことをしめした。</p> <p>また、高頻度変異の立体構造への変化を調べるために、コンピューターシミュレーションを行ない、乳児型で平均的に構造変化が大きく、若年型での変化は小さい傾向を認めた。</p> <p>以上の報告を行い、学位の授与に値すると考えられる。</p>	