（報告様式４）

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I.　基本情報

事　　業　　名：（日本語）難治性疾患実用化研究事業
（英　語）The Practical Research Project for Rare / Intractable Diseases

研究開発課題名：（日本語）福山型筋ジストロフィーの自然歴の把握と病状を反映するバイオマーカーの検索
（英　語）Grasping the natural history of Fukuyama type muscular dystrophy and searching for biomarkers reflecting the medical condition

研究開発担当者　（日本語）戸田　達史
所属 役職 氏名：（英　語）Tatsushi Toda

実　施　期　間：平成　26 年　6 月　2 日　～　平成　29 年　　3 月　31 日

分担研究　　（日本語）研究の総括および臨床評価・実験データ評価
開発課題名：（英　語）Research management and clinical and experiment data evaluation
研究開発分担者　（日本語）戸田　達史　神戸大学・大学院医学研究科・教授
所属 役職 氏名：（英　語）Tatsushi Toda, Professor, Kobe University Graduate School of Medicine

分担研究　　（日本語）臨床評価・遺伝子解析・検体の収集・分子生物学的実験・データ解析
開発課題名：（英　語）Investigating serum biomarkers in Fukuyama muscular dystrophy
研究開発分担者　（日本語）池田 真理子　神戸大学・大学院医学研究科・特命准教授
所属 役職 氏名：（英　語）Mariko Taniguchi-Ikeda, Associate Professor, Kobe University Graduate School of Medicine.

分担研究　　（日本語）(1) FCMD の自然歴の把握（２）FCMD の運動機能評価法の開発（３）FCMD 患者のインピーダンス法による筋量測定（４）FCMD における CT, MRI の経時的変化
開発課題名：（英　語）(2)(1) Natural history data of motor function in Fukuyama congenital muscular dystrophy patients （2）Developing reliable and valid motor function scales for Fukuyama congenital muscular dystrophy.(3) A new

index of muscle development and disease progression for patients with Fukuyama congenital muscular dystrophy, using bioelectrical impedance analysis; an Observation Study(4)Longitudinal study on skeletal muscle imaging in patients with FCMD Fukuyama congenital muscular dystrophy

研究開発分担者　（日本語）　石垣　景子　東京女子医科大学医学部・講師
所属 役職 氏名：（英　語）Keiko Ishigaki, Senior Lecturer, Department of Pediatrics, Tokyo Women's Medical University, School of Medicine.

分担研究　（日本語）福山型先天性筋ジストロフィーの臨床評価方の確立
開発課題名：（英　語）Development of functional assessment tools for Fukuyama congenital muscular dystrophy

研究開発分担者　（日本語）小牧　宏文　国立精神・神経医療研究センター病院・小児神経診療部医長
所属 役職 氏名：（英　語）Hirofumi Komaki MD, PhD. Head Physician, Department of Child Neurology, National Center of Neurology and Psychiatry

分担研究　（日本語）メタボローム解析
開発課題名：（英　語）Metabolome analysis

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II. 成果の概要（総括研究報告）

・ 研究開発代表者による報告の場合

福山型先天性筋ジストロフィー（FCMD）は不治の病であったため、患者の詳細な自然歴に関する研究はほとんどなく、病状把握や治療評価が困難である。またFCMD患者は歩行不能な例が多く、知的発達障害も必発なため、患者の適確な病状把握や治験における客観的な治療評価判定が難しい。したがって、FCMDの自然歴の把握を行い、適確な運動機能評価系を構築し、病状や治療評価を反映するバイオマーカーを同定することは必要不可欠である。そこで当研究では①運動機能評価・筋量測定・画像診断・発達機能評価を含めた自然歴の把握を後方視的・前方視的に行い、②遺伝子発現解析・メタボロミクスを用いて新規バイオマーカーの探索を行った。

FCMD特異的に上昇するマイクロRNA、血清中蛋白の同定の同定では、血清より特定のマイクロRNAについて、特にMiR206において、統計学的にも有意に、FCMD特異的な上昇がみられるという結果が出た（投稿準備中）。臨床試験副次評評価項目として用いうる。

FCMD患者の自然歴では、運動機能のピークと退行、骨格筋画像の変化に関しては、今後治験の基盤となるデータを得られた。FCMDの適切な運動機能評価尺度としての粗大運動評価尺度（Gross motor function measure：GMFM)、およびインピーダンスBIA法による筋量測定に関して妥当性を証

明し、治験の評価項目としての基準を作成した。また福山型先天性筋ジストロフィー患者の精神運動発達のマイルストンに関する情報を収集し、将来の運動機能の程度を予測する、予測式構築の可能性についての知見が得られた。最高到達運動能ごとに定頸、座位の平均時期に大きな差が認められ、定頸獲得時期により最高到達運動能の大よその予測は可能であった（Neuromuscul Disord, 2016)。粗大運動評価尺度（Gross motor function measure：GMFM）が臨床試験主要評評価項目として用いうると考えている。

またメタボローム解析により、福山型先天性筋ジストロフィーの病状を表現できる代謝物バイオマーカー候補を見出すことができた。

Since Fukuyama congenital muscular dystrophy (FCMD) was an incurable disease, there are few studies on detailed natural history of patients, so it is difficult to grasp the disease condition and evaluate the treatment. Also, many patients with FCMD are unable to walk and intellectual developmental delay is also accompanied, so it is difficult to grasp the patient's correct disease condition and objectively evaluate therapeutic evaluation in the clinical trial. Therefore, it is indispensable to grasp the natural history of FCMD, to construct an accurate motor function evaluation system, and to identify biomarkers that reflect disease condition and treatment evaluation. Therefore, in this research, we (1) grasped the natural history including motor function evaluation, muscle mass measurement, image diagnosis, and developmental function evaluation, retrospectively and prospectively and (2) searched new biomarkers using gene expression analysis and metabolomics.

We have investigated for finding circulating biomarkers which is specific for Fukuyama muscular dystrophy. We have identified that microRNA 206, 133, and 16 are especially high in patients serum compared to normal controls. We have also checked if there are such biomarkers to predict cardiac function in FCMD patients. We also identified that in FCMD, some microRNAs which are specific to cardiac muscle (i.e. miR377 and 22) have distinct expression profiles compared to those of normal control serum. These results might contribute to predict disease progression in Fukuyama muscular dystrophy patients.

Our study reevaluated the natural history of genetically diagnosed Fukuyama congenital muscular dystrophy patients, focusing on motor development and its deterioration. We retrospectively studied the medical records of 57 genetically diagnosed FCMD patients followed at our university from 1995. Age at which head control and sitting were achieved on average for each phenotype was delayed with severity of phenotype.

To confirm the validity of GMFM for the assessment of FCMD, 41 FCMD patients were recruited into the study. The GMFM scores correlated significantly with two previously used motor scales, and the time-dependent change in the GMFM scores was consistent with the natural course of the disease. The inter-rater reliability, which was assessed in four physiotherapists blinded to each other, was excellent. We concluded that GMFM was a useful and valid motor function measure for FCMD.

We evaluated whether it would be possible to assess growth and development in patients with FMCD using BIA The subjects were 21 FCMD patients who were being followed up on our

university. Our results showed that the qualitative index of the lower legs tended to decrease both before and after the age of eight, suggesting that replacement by fat in the lower legs may start from birth, which is characteristic of FCMD in which replacement by fat starts in the lower legs and extends up to the thighs. In addition, the upper arm qualitative index increased significantly until the age of eight, reflecting the usual clinical course of FCMD in which the upper limb function is better preserved than lower limb function.

We found high-intensity changes on skeletal muscle MRI in some young patients with FCMD patients without changes on T1-weighted imaging (T1WI). In this study, we evaluated the longitudinal changes on skeletal muscle MRI in FCMD patients focused on STIR and T1WI. Skeltal muscle MRI in 18 patients with FCMD (2 -13 years) were analyzed by two radiologists. We characterized the specific patterns of disease progression in FCMD patients. High intensity on STIR proceeded fatty replacement detected by T1WI at early stages, especially under 5 years.

Medical records of patients with FCMD were retrospectively reviewed. Patients with higher speech skill were able to attain better motor functions. Our study indicates that intellectual disability in FCMD patients potentially affect their motor developmental milestones.

First, the metabolome analysis system using gas chromatography/mass spectrometry was established, and then we performed the metabolome analysis for the plasma of the mice that were the animal model for Fukuyama type congenital muscular dystrophy. However, we could not find the effective biomarker candidates in the mouse plasma. Next, we performed the metabolome analysis for the plasma of the patients with Fukuyama type congenital muscular dystrophy. As a result, some metabolite biomarker candidates were discovered, and the relationship between metabolite biomarker candidates and pathological conditions of Fukuyama type congenital muscular dystrophy could be confirmed.

・ 研究開発分担者による報告の場合

III. 成果の外部への発表

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（３）「国民との科学・技術対話社会」に対する取り組み

（４）特許出願