Form 3

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2022)

Date：2023/04/03

To Director of Institute for Molecular and Cellular Regulation, Gunma University

Principal Applicant	
Institution	Faculty of Medicine Siriraj Hospital, Mahidol University
Position	Instructor-Head of Cellular and Molecular Diabetes Research Group
Name	Prapaporn Thamtarana

We report on the results of joint research in fiscal 2022 as below.

（Program No. 2022-3-3 ）

1． Research Title	Characterization of Dnajc3, a candidate gene for autosomal dominant diabetes
2． Purpose and Significance of the research project	Functional characterization of novel autosomal dominant diabetes associated gene Dnajc3 in human pancreatic alpha cells and beta cells.
3． Period of The Program	April 1, 2022 ～ March 31, 2023

4． Project Members

Name	Age	Sex	Affiliation	Position	Role
(Principal Applicant) Prapaporn Thamtarana	41	F	Mahidol University/ Faculty of Medicine Siriraj Hospital/Research Department	Instructor	Project director
(Research Collaborators) Pa-thai Yenchitsomanus	69	M	Mahidol University/ Faculty of Medicine Siriraj Hospital/Research Department	Professor	Consultant
Nattachet Plengvidhya	58	M	Mahidol University/ Faculty of Medicine Siriraj Hospital/Department of Medicine	Associate Professor	Clinician/Subject recruitment
Chutima Chanprasert	41	F	Mahidol University/ Faculty of Medicine Siriraj Hospital/Research Department	Research Assistant	Genetic and Genomic analyses
Siriporn Riyajan	31	F	Mahidol University/ Faculty of Medicine Siriraj Hospital/Research Department	Research Assistant	Cell analysis

※If additional space is required, please attach a separate sheet.

5． Collaborating Researcher of IMCR	Name of Laboratory	Diabetes and Metabolic Disorders	Name	Jun Shirakawa

6． Research Plans

Monogenic diabetes is a heterogeneous group of distinct subtypes of diabetes characterized by different modes of inheritance and age of onset. Familial diabetes with autosomal dominant inheritance is more common and has more variable age of onset. Maturity-onset diabetes of the young (MODY) is a form of autosomal dominant diabetes that generally occurs during childhood and adolescence. Mutations in at least fourteen different genes (MODY1-MODY14) have been described to date as the cause of MODY in different families. However, in Asian populations, such as Chinese, Japanese, Korean, and Thai, up to 85% of MODY cases have unknown genetic causes.

We previously identified a missense mutation (c.T1424C:p.L475P) in ZYG11A identified by exome sequencing as segregating with hyperglycemia in a Thai family with autosomal dominant diabetes. ZYG11A functions as a target recruitment subunit of an E3 ubiquitin ligase complex that plays an important role in the regulation of cell cycle. We recently reported that ZYG11A as a cell cycle regulator required for beta-cell growth (Mol Cell Endocrinol. 2021) by this Joint/Usage Research Program for Endocrine/Metabolism in 2021.

We also identified a mutation in Dnajc3 identified by exome sequencing as segregating with hyperglycemia in a Thai family with autosomal dominant diabetes. Dnajc3 is a chaperon protein involved in protein folding and ER stress. In this study, the role of Dnajc3 in beta cells are evaluated.

7． Research results:
Please describe the details of the contribution of the joint research with IMCR in obtaining the results.

We analyzed the expression of Dnajc3 in islets under ER stress and found the time-dependent alteration of that expression.

Overexpression of WT and mutant Dnajc3 was performed by transducing adenoviral vectors. Protein translation by polysome profiling and gene expression by qPCR were conducted in those cells. The role of Dnsjc3 in the regulation of ER stress was estimated in terms of human mutation.

8． Present status of academic conference presentations and research papers associated with the results of the joint research, and exchange of information on the joint research with the collaborating researcher at IMCR.
(As much as possible, please state papers that include the names of the collaborating researcher at IMCR or papers stating that the research was supported by the Joint Research Program with IMCR.
Regarding papers, please send a PDF file together with the report to the email address of the general affairs section of the Institute.) Office of General Affairs: kk-msomu4@jimu.gunma-u.ac.jp

① Please list the publications that include the name of the collaborating researcher from IMCR and send a reprint of each publication to IMCR.
We are preparing the collaborative paper.

② Please list the publications that include a description that the research was supported by the Joint Research Program with IMCR and send a reprint of each publication to IMCR.
N/A

③ List up to 3 conferences (name of conference, date of conference, and title of the presentation).
N/A

④ Exchange of information exchange with collaborating researcher from IMCR (please list main points of communication).
We usually have web meetings monthly to share the experimental results.