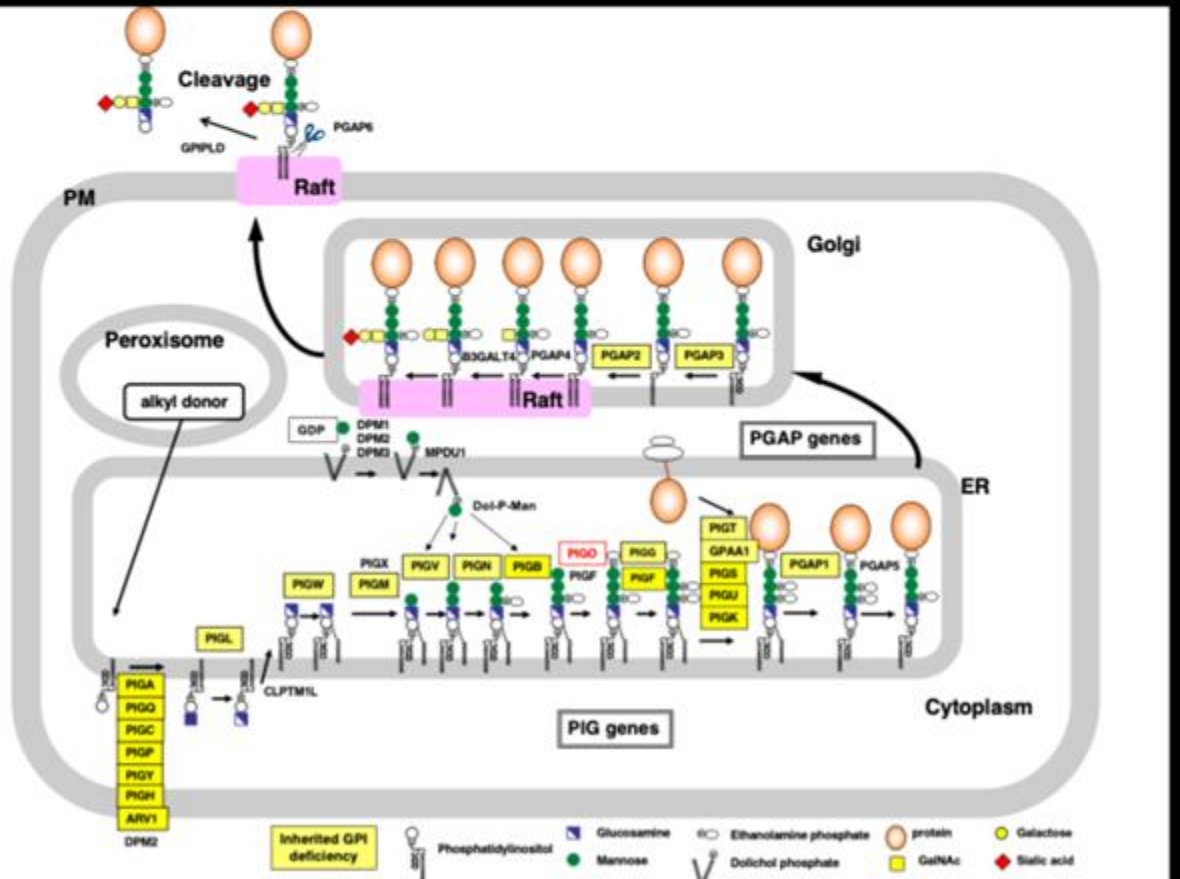
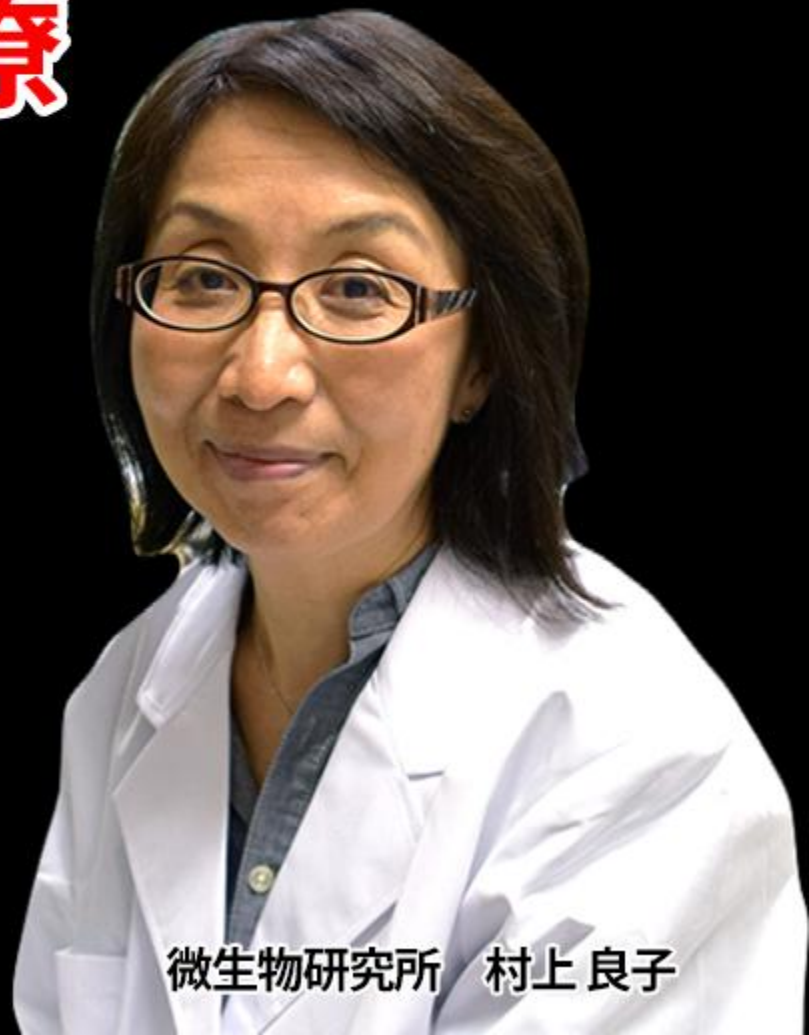
遺伝子治療

AAVベクターを用いた遺伝性GPI欠損症の根本治療





微生物研究所　村上 良子

大阪大学
THE UNIVERSITY OF OSAKA

Dec. 2025

The First Fundamental Treatment for Inherited Glycosylphosphatidylinositol Deficiency (IGD)

The University of Osaka

This Project is led by:

Dr. Yoshiko Murakami

Specially Appointed Professor

Division of Host Defense Laboratory of Immunoglycobiology

Research Institute for Microbial Diseases

The University of Osaka

IGD Caused by Inherited Gene Mutation

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Over 150 GPI anchored proteins(GPI-APs) are expressed on the surface of mammalian cells. GPI-APs have a variety of roles, including acting as hydrolytic enzymes, adhesion molecules, receptors, protease inhibitors, and complement regulatory proteins. At least 30 genes called PIG or PGAP genes are involved in the biosynthesis and transport of GPI-APs, and mutations in these genes cause inherited GPI deficiency (IGD).

IGD patient show various serious symptoms like mental retardation, refractory Epilepsy, hyperphosphatasia, brachytelephalangy, Hypoplastic nails etc. However, only symptomatic treatments are available, and no fundamental cure has been established.

http://igd.biken.osaka-u.ac.jp/en/

Reported Cases of Inherited Mutation of PIG Genes causing IGD:

736 (w.w.)

We Focus on PIGO/PIGA Gene Inherited Mutation:

As of Nov 2025
Counted by Prof. Murakami based on published papers and case reports

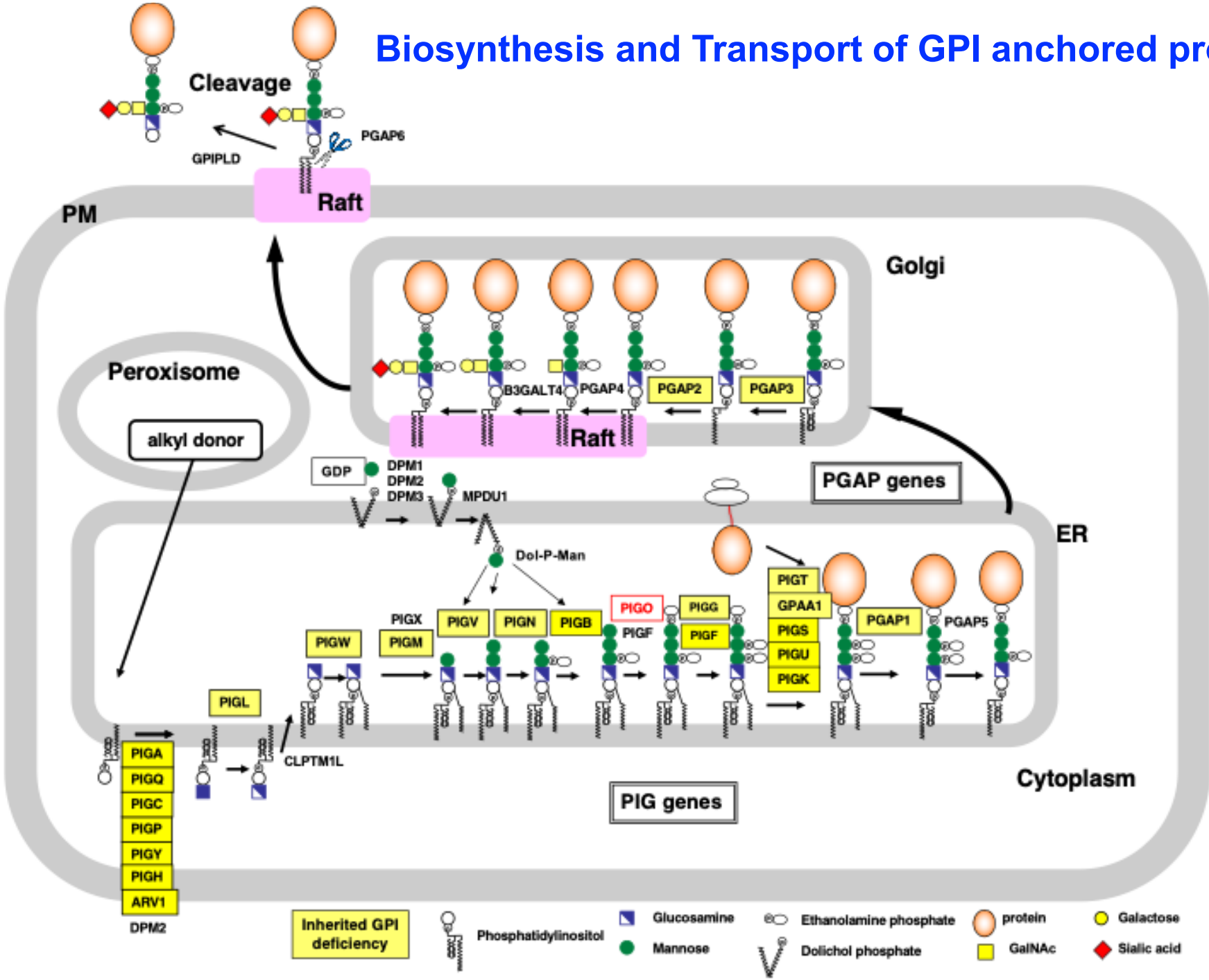
PIGO (27/17*)#

PIGA (109/16)#

: Pts. counts; (WW/JP)
* : Most pts. counts in JP among the mutations

- Current lower count of patients is caused due to the difficulty of diagnosis of IGD by the its broad range of symptoms similar to other diseases as well as shorter life span of patients
- Increase of patient no. is expected by popularization of IGD specific tests using patient's blood
  - CD16 expression test by FACS (already covered by health insurance in Japan)
  - PIG Gene panel test for definitive diagnosis is now available (already covered by health insurance in Japan)

Biosynthesis and Transport of GPI anchored protein



PIGO deficiency in Patient

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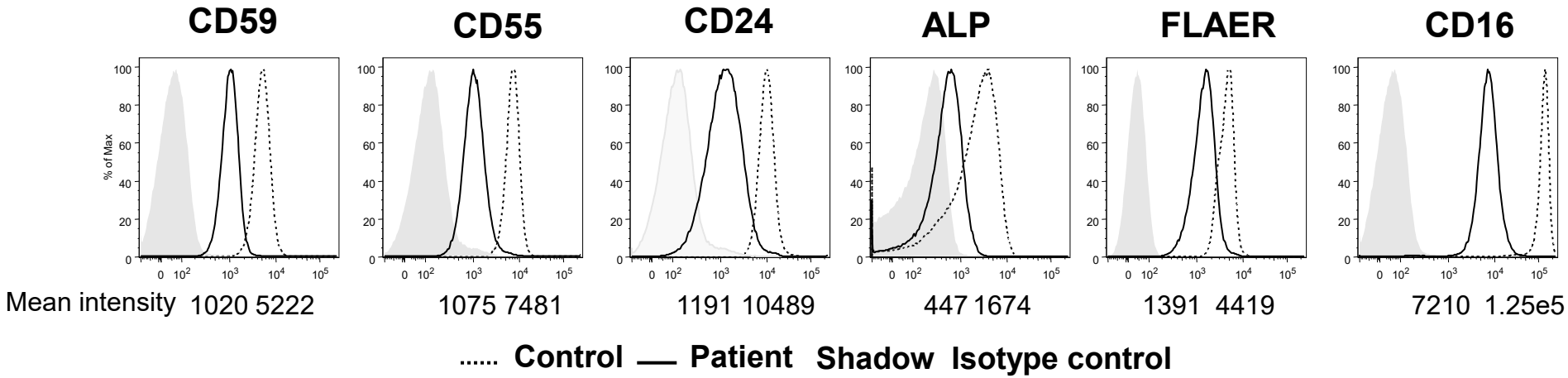
Symptoms:

Mental retardation, Refractory Epilepsy, Hyperphosphatasia, Brachytelephalangy, Hypoplastic nails, Hirschsprung's disease, Congenital heart disease

FACS analysis of the granulocytes from the patient*



*: PIGO Mutation in this patient: p.Arg119Trp/p.Ala834fs

Neurology. 2013 Oct 15;81(16):1467-9

Early Diagnosis For Early Start of Treatment

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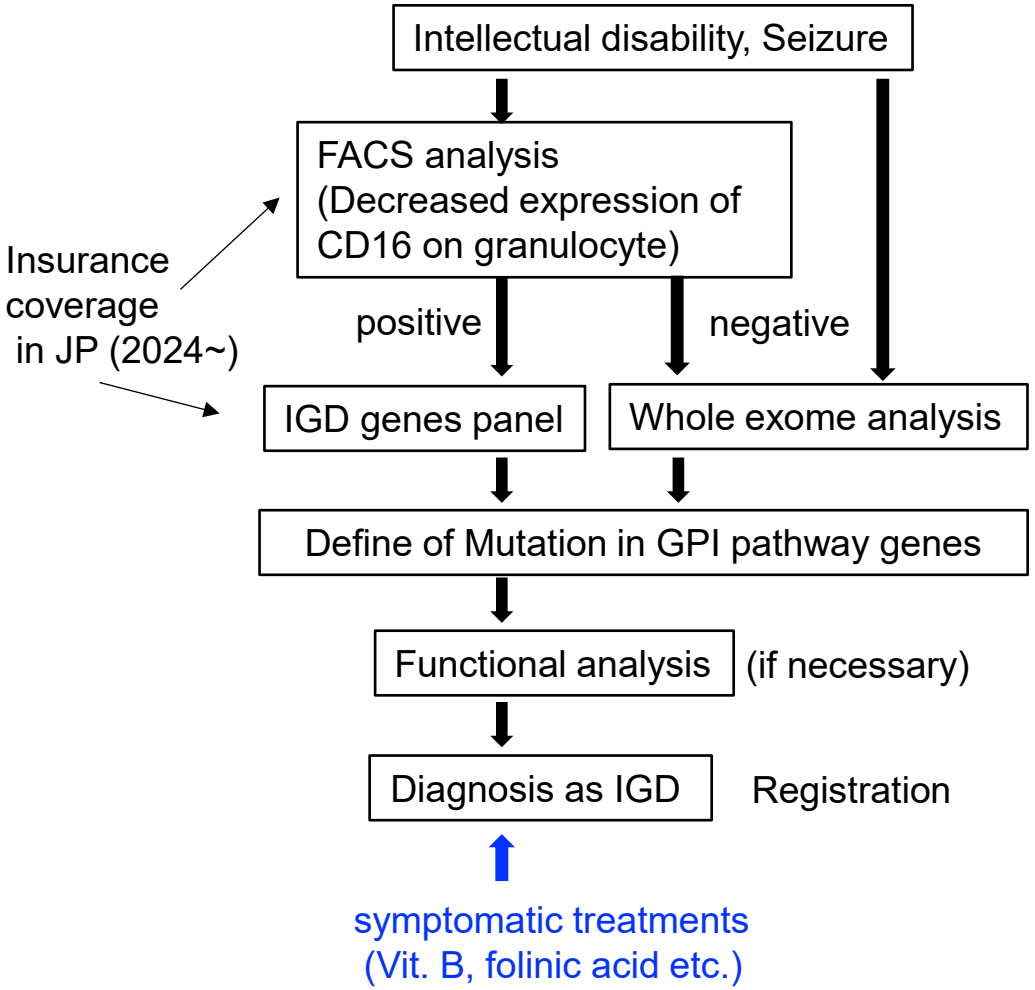
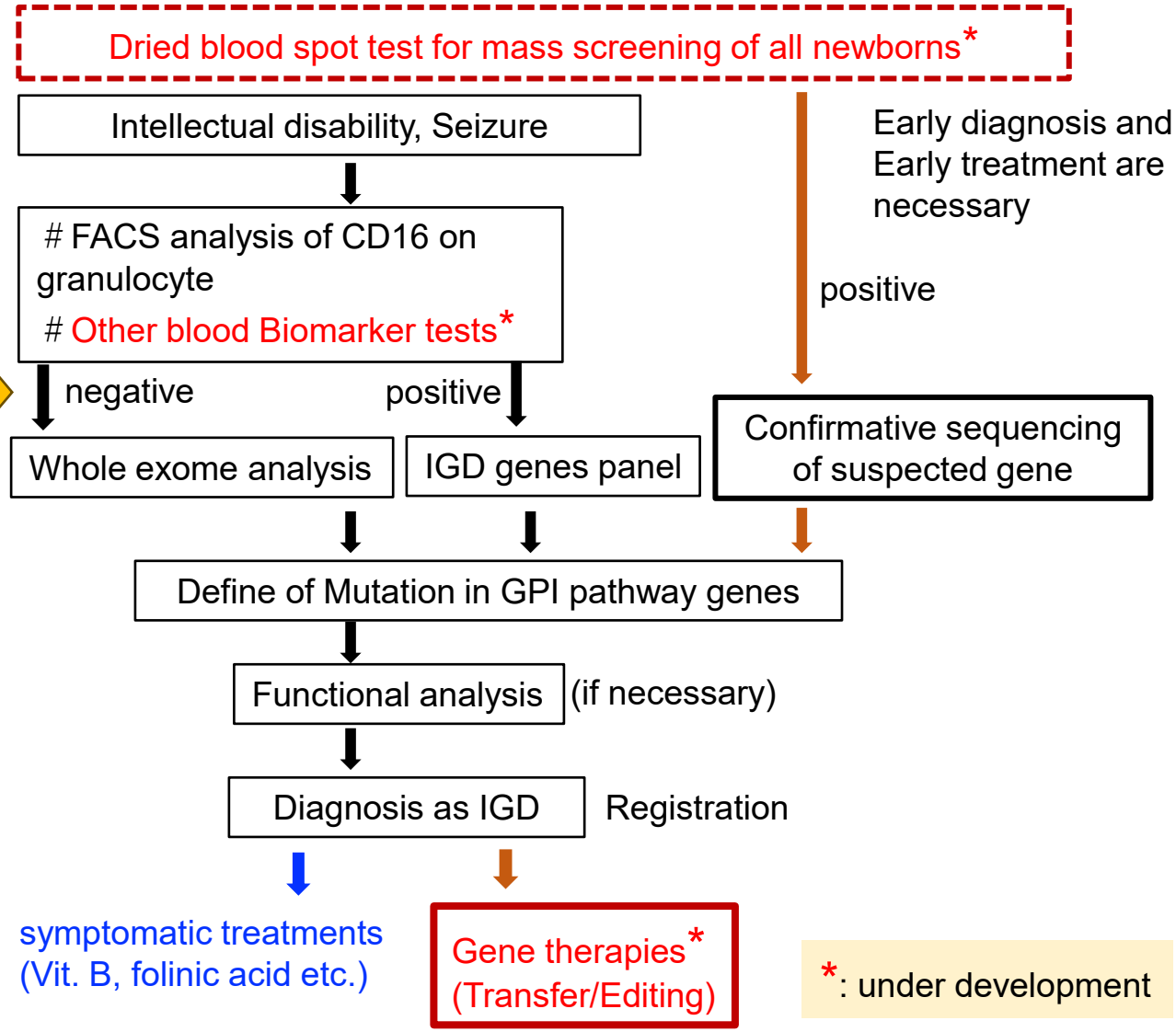
Current Diagnosis/Therapy Flow



Future Diagnosis/Therapy Flow



Executive Summary of Our IGD Project

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Gene Therapy for IGD

Targeted mutation in genes of IGD patients :

- PIGO gene (most frequent mutation in JP)
- PIGA gene (more frequent mutation in WW)

Development Phase:

- Intact PIGO expressing AAV9: nonclinical POC completed, DP for GLP tests in preparation
- Intact PIGA expressing AAV9: nonclinical POC in planning

Intellectual Property:

- pending(2024)

Access to Patients & Collaboration:

- IGD patient association in JP (https://gpi-igdjapan.org/, in Japanese)
- CDG* CARE in US (https://cdgcare.org/) and patient association in other countries
- Collaboration: Jichi Medical University in JP & Nationwide Children's Hospital in US

*: IGD is included in CDG, Congenital Disorders of Glycosylation

Development Plan:

- Manufacturing of AAV(PIGO) for GLP studies & fundraising (FY2025)
- Development of a novel AAV platform applicable to multiple genes involved in GPI proteins biosynthesis.

New Diagnosis Test of IGD

- New easy-to-implement blood biomarker test and dried blood spot test for mass screening are under development (patent pending)

History of Our Gene Therapy for IGD

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1. Selected PIGO deficiency (most in JP) as the model
2. Created PIGO deficiency model mice which showed similar symptoms as IGD patients caused by PIGO deficiency (P.7)
3. AAV expressing intact PIGO by CBA promotor* improved phenotypes of PIGO deficiency model mice (P.8)
4. Then, endogenous PIGO promotor was isolated to construct AAV expressing intact PIGO by the promotor (data not shown in this document)
5. AAV expressing intact PIGO by its endogenous promotor had enough potential to improve the phenotypes of PIGO deficiency model mice (P.9)
6. Treatment in 4-week-old IGD(PIGO) model mice with a higher dose also showed a Significant Effect (P.10)
7. In addition to the AAV expressing PIGO, construction of AAV expressing intact PIGA is on going. (not shown in this document)

*: hybrid CMV enhancer/Chicken β-actin promoter

The Mouse Model Closely Reflected The Symptoms of PIGO deficiency

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IGD(PIGO) Model Mice

Proprietary Information of The University of Osaka

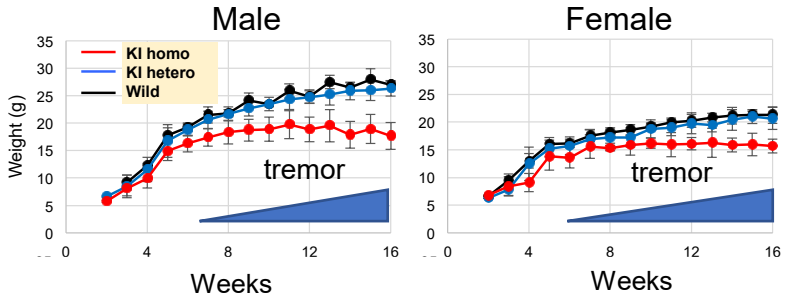
Nat Commun. 2022 Jun 3;13(1):3107

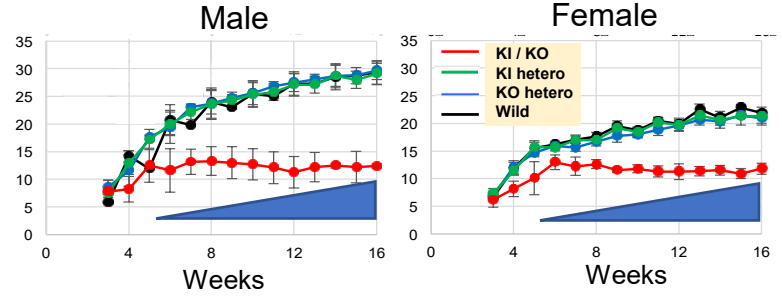
Combination of modified alleles

KI homo:
Mutation/ Mutation
KI hetero:
Mutation/Wild type
KI/KO:
Mutation/knock-out
KO hetero:
knock-out/ wild type

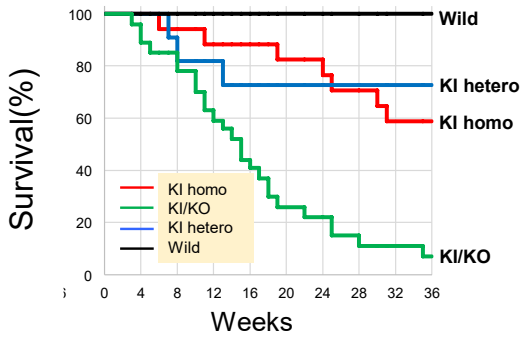
Mutation:
Thr130Asn in PIGO gene

Bodyweight
Low growth

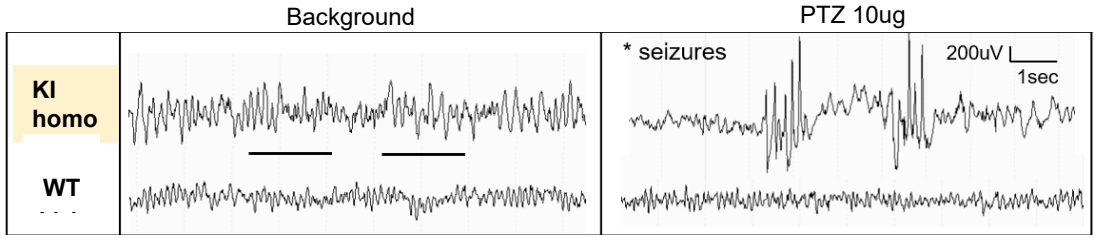




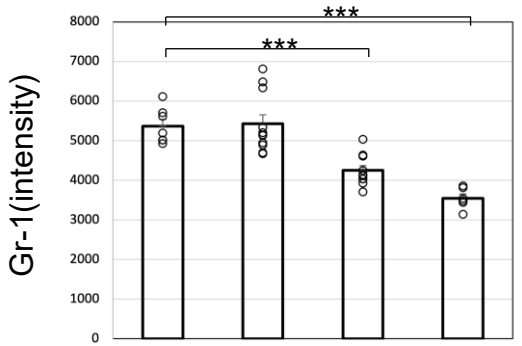
Survival
Low survival

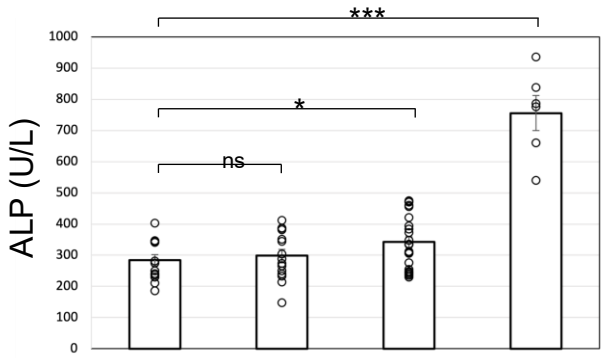


EEG
spontaneous seizures



GPI Protein expression
Low surface expression of Gr-1 and High ALP activity in blood





IGD(PIGO) model mice show similar symptoms as IGD patients caused by PIGO deficiency

- Tremor
- Seizures
- Shortened survival time
- Decreased expression of GPI-AP on granulocytes
- Hyperphosphatasia

KI/KO model mice were selected for the following gene therapy studies due to its severity

PIGO Expression by AAV Improved Phenotypes of Model Mice

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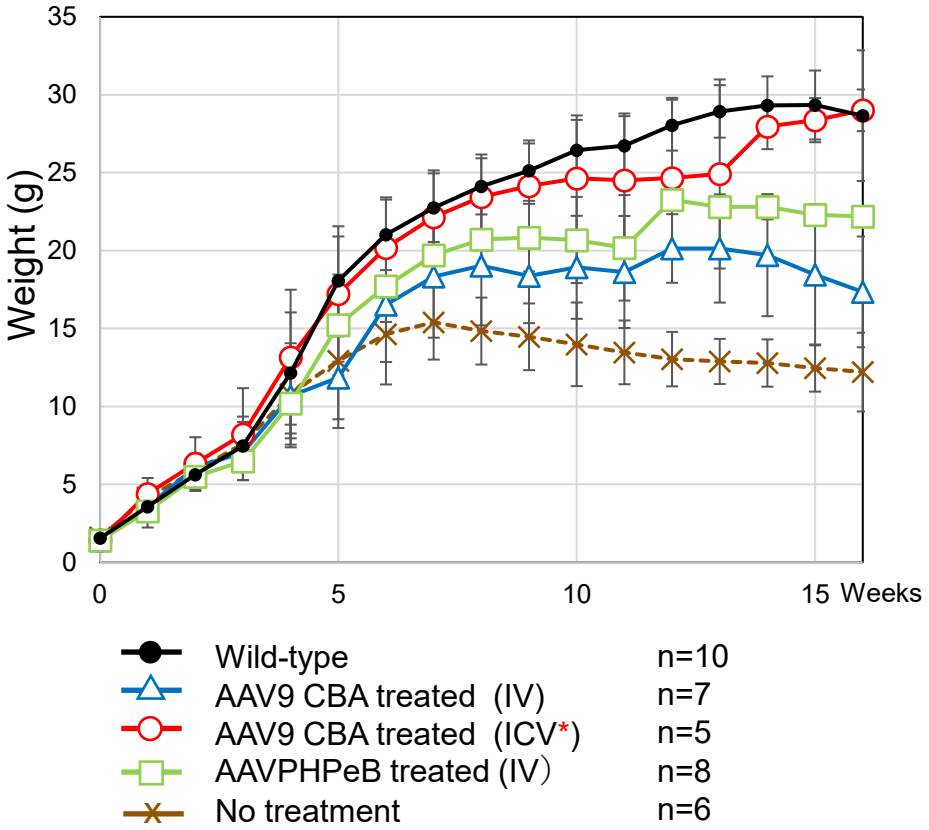
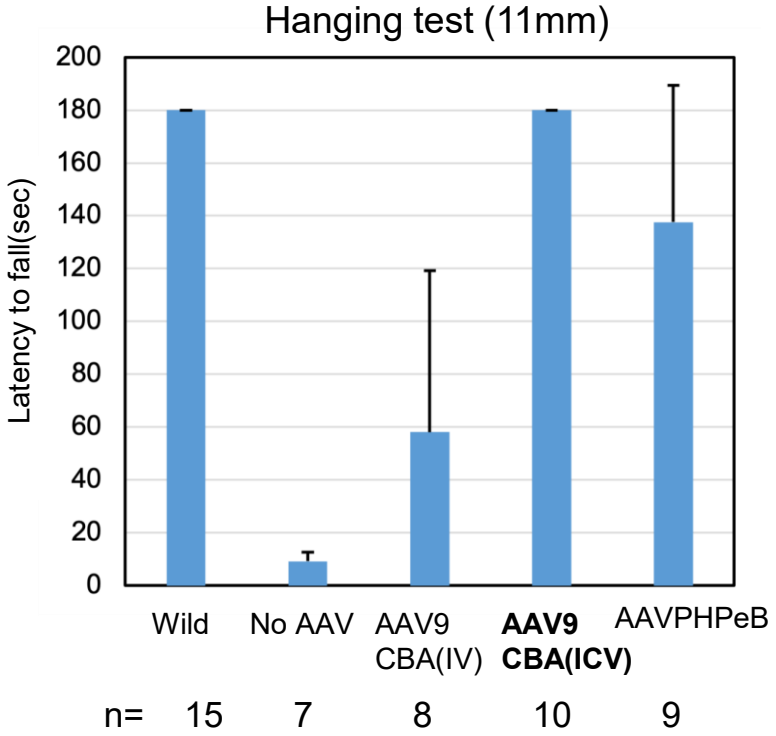
Bodyweight (male)

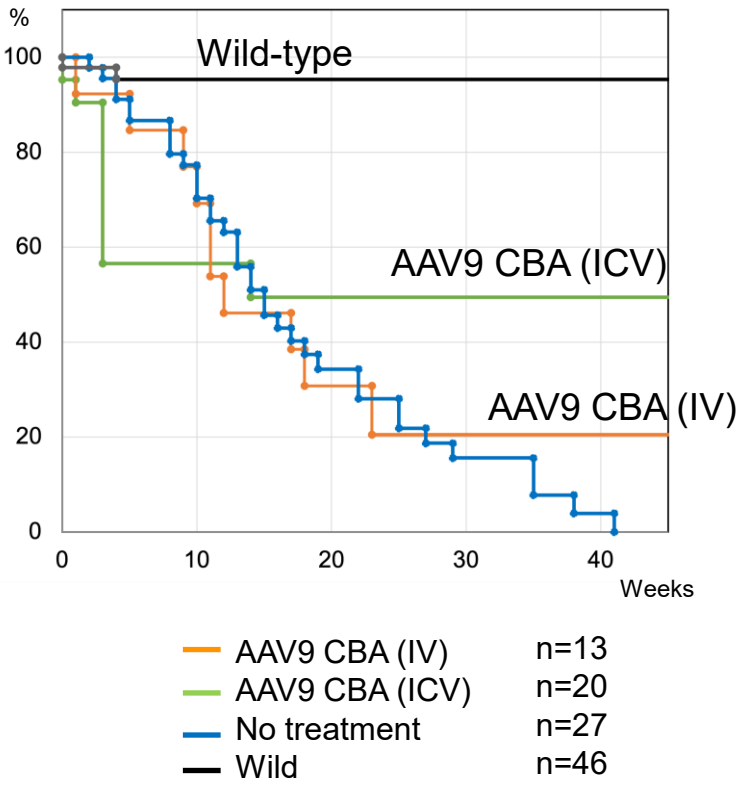


*: Intracerebroventricular administration

Coordination and muscle strength



Survival



PIGO expressing AAV9 with CBA promoter improved the phenotypes of Knock-in (Thr130Asn) / Knock-out IGD model mice

AAV9-endo-PIGO* Improved the Symptoms Comparable to AAV9-CBA-PIGO

*: AAV to express intact PIGO by its endogenous promotor

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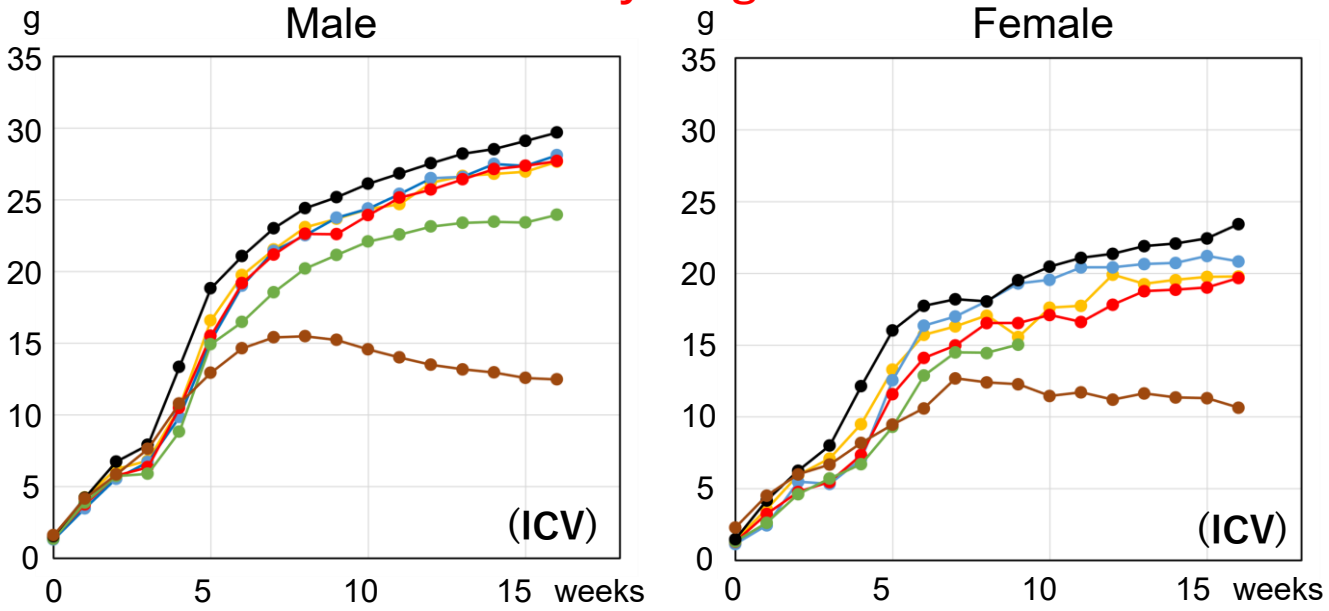
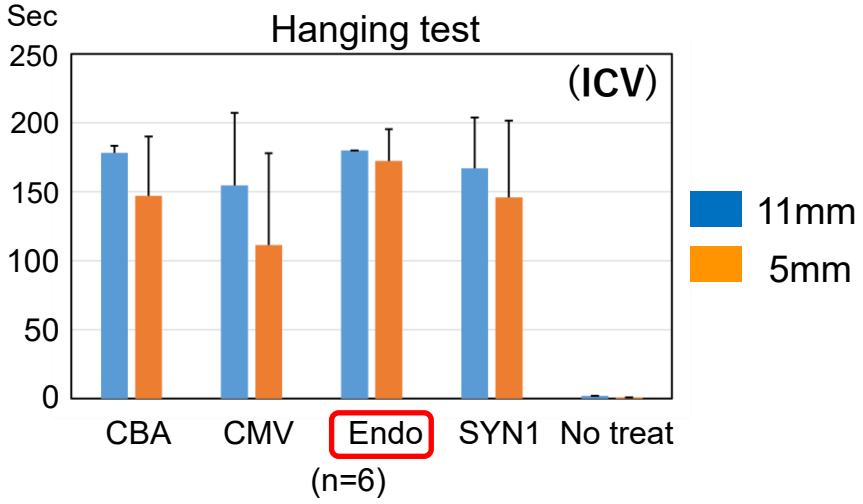
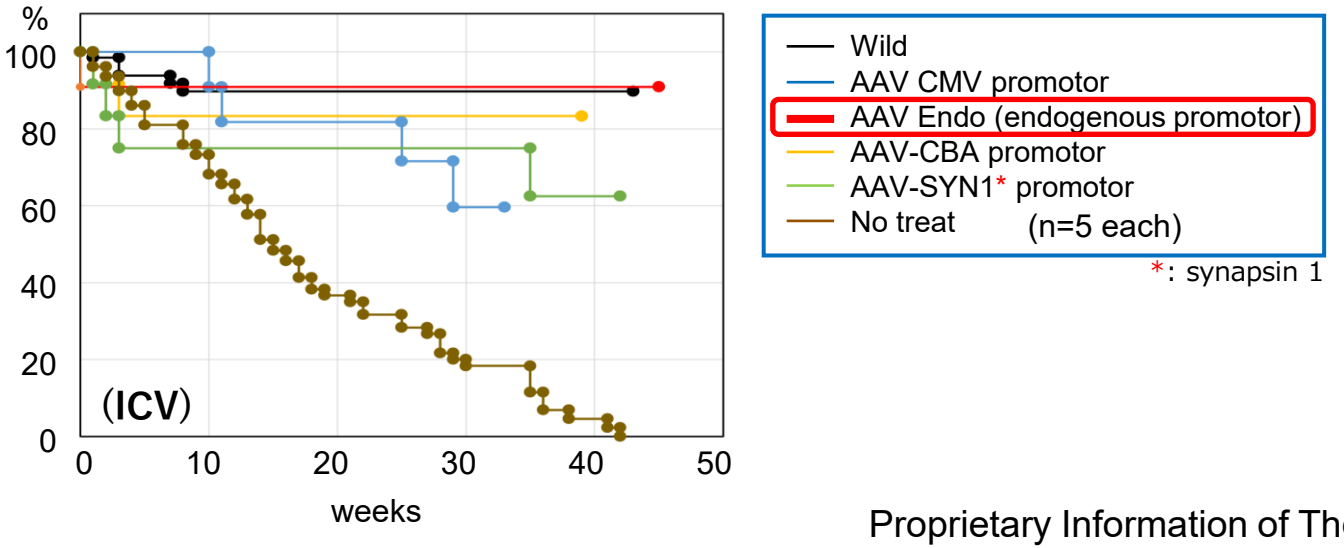
Body Weight



Coordination and Muscle Strength



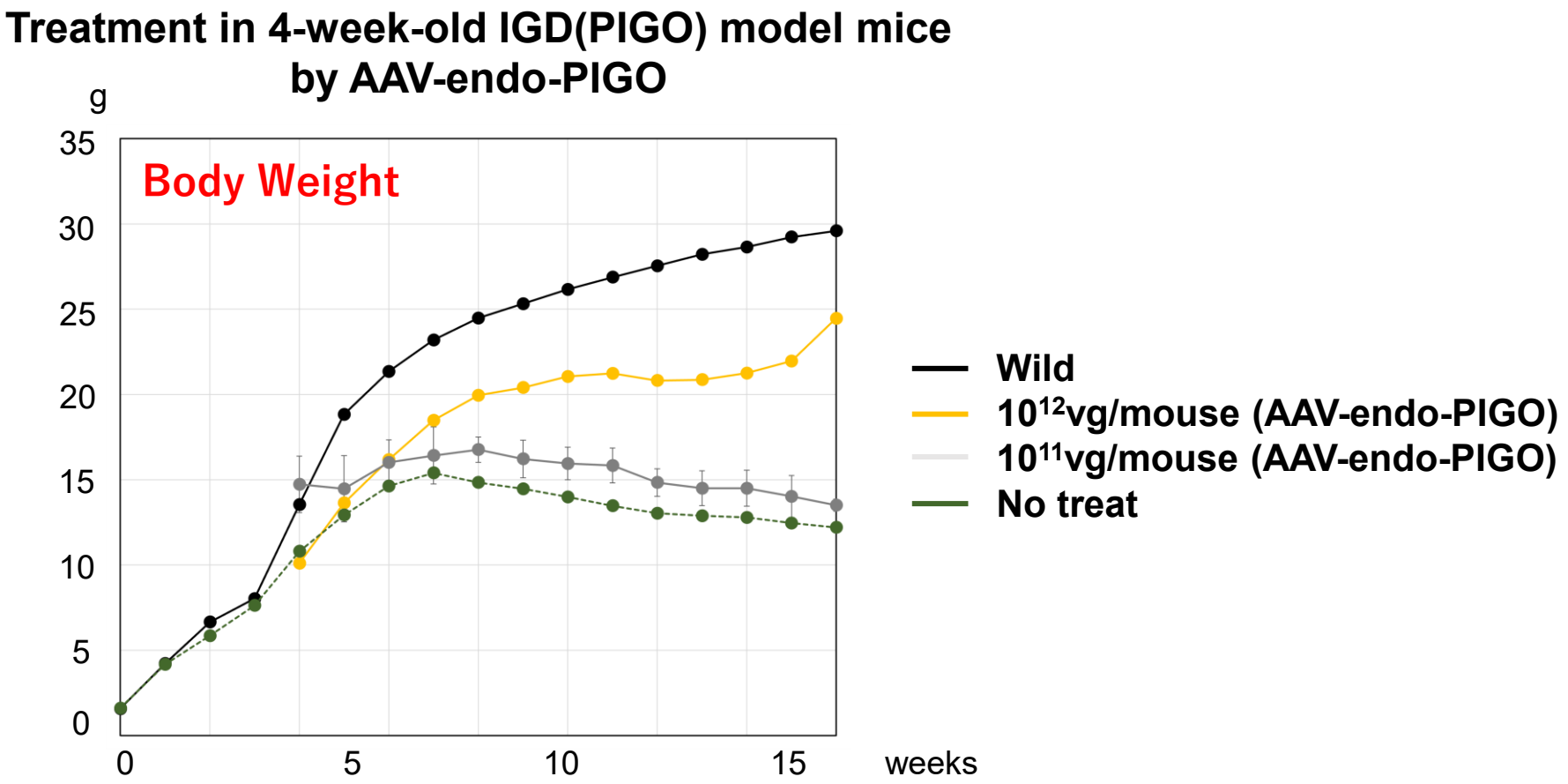
Survival



Expression PIGO by AAV with its endogenous promotor (AAV9-endo-PIGO) is enough to improve the key phenotypes of KI/KO(B mutation/knock-out) mice.

Intracisternal administration of AAV9-endo-PIGO was also effective, which suggest its efficacy by Intrathecal administration for patients.

Treatment in Older Mice with a 10-fold Higher Dose also Show Significant Effects



Older IGD child patients who are diagnosed after manifestation of the symptoms may also have benefit from this gene therapy.

Partnering Plan

- **AAV Gene Therapy:**
  We are looking for a partner who will work with us to develop the AAV expressing intact PIGO /PIGA and the novel AAV platform applicable to multiple genes involved in GPI proteins biosynthesis.

- **Diagnosis (1):**
  SRL, Inc.(diagnostic company in Japan) has obtained MHLW* approval for its CD16 FACS test to be listed in National Health Insurance Reimbursement List.
  We are also looking for a partner who will develop and commercialize the FACS test outside of Japan.

*: Ministry of Health, Labour and Welfare

- **Diagnosis (2):**
  Our researchers are developing another blood biomarker test & dried blood spot test which detect the defect in GPI-AP synthesis pathway to complement CD16 FACS test.
  We are also looking for a partner who will develop and commercialize these tests not only in Japan but also outside of Japan.

- **Patent application submitted (not published yet)**

- **Further data/information is available under CDA**

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