2017年7月10日

医学部発生学(20)
DOHaD仮説と進化医学

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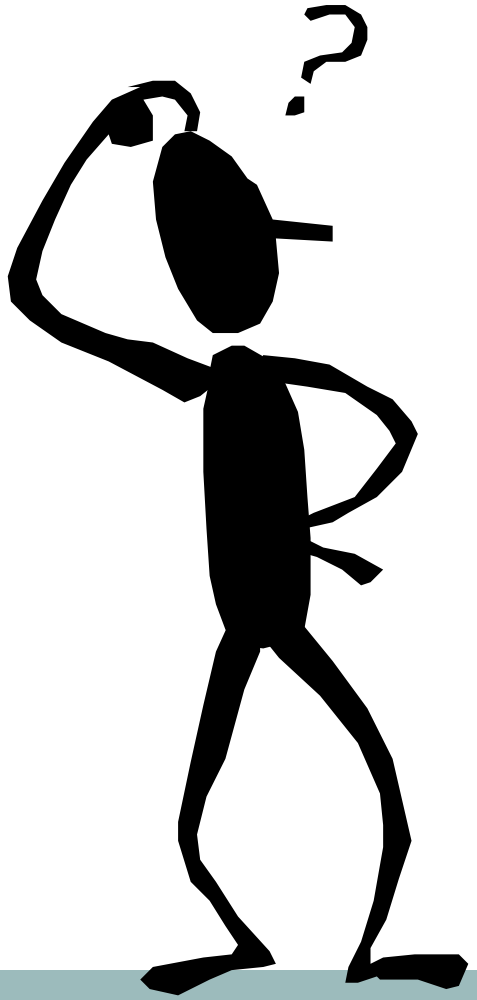
DOHaDって何？



David Barker (1938-2013)

THE LANCET, MAY 10, 1986

Epidemiology

INFANT MORTALITY, CHILDHOOD NUTRITION, AND ISCHAEMIC HEART DISEASE IN ENGLAND AND WALES

D. J. P. BARKER C. OSMOND

MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO9 4XY

Summary Although the rise in ischaemic heart disease in England and Wales has been associated with increasing prosperity, mortality rates are highest in the least affluent areas. On division of the country into two hundred and twelve local authority areas a strong geographical relation was found between ischaemic heart disease mortality rates in 1968–78 and infant mortality in 1921–25. Of the twenty-four other common causes of death only bronchitis, stomach cancer, and rheumatic heart disease were similarly related to infant mortality. These diseases are associated with poor living conditions and mortality from them is declining. Ischaemic heart disease is strongly correlated with both neonatal and postneonatal mortality. It is suggested that poor nutrition in early life increases susceptibility to the effects of an affluent diet.

死因と乳児死亡率の相関

TABLE I—CORRELATION OF CAUSE OF DEATH (SMRS*) AT AGES 35–74 YEARS IN BOTH SEXES AND INFANT MORTALITY RATES

Cause of death	ICD no, 8th revision	Correlation coefficient
Ischaemic heart disease	410–414	0·73
Bronchitis	490–492	0·82
Stomach cancer	151	0·79
Rheumatic heart disease	393–398	0·72
Stroke	431–438	0·54
Lung cancer	162	0·46

*Standardised mortality ratios.

虚血性心疾患による標準化死亡率と新生児死亡率の相関性

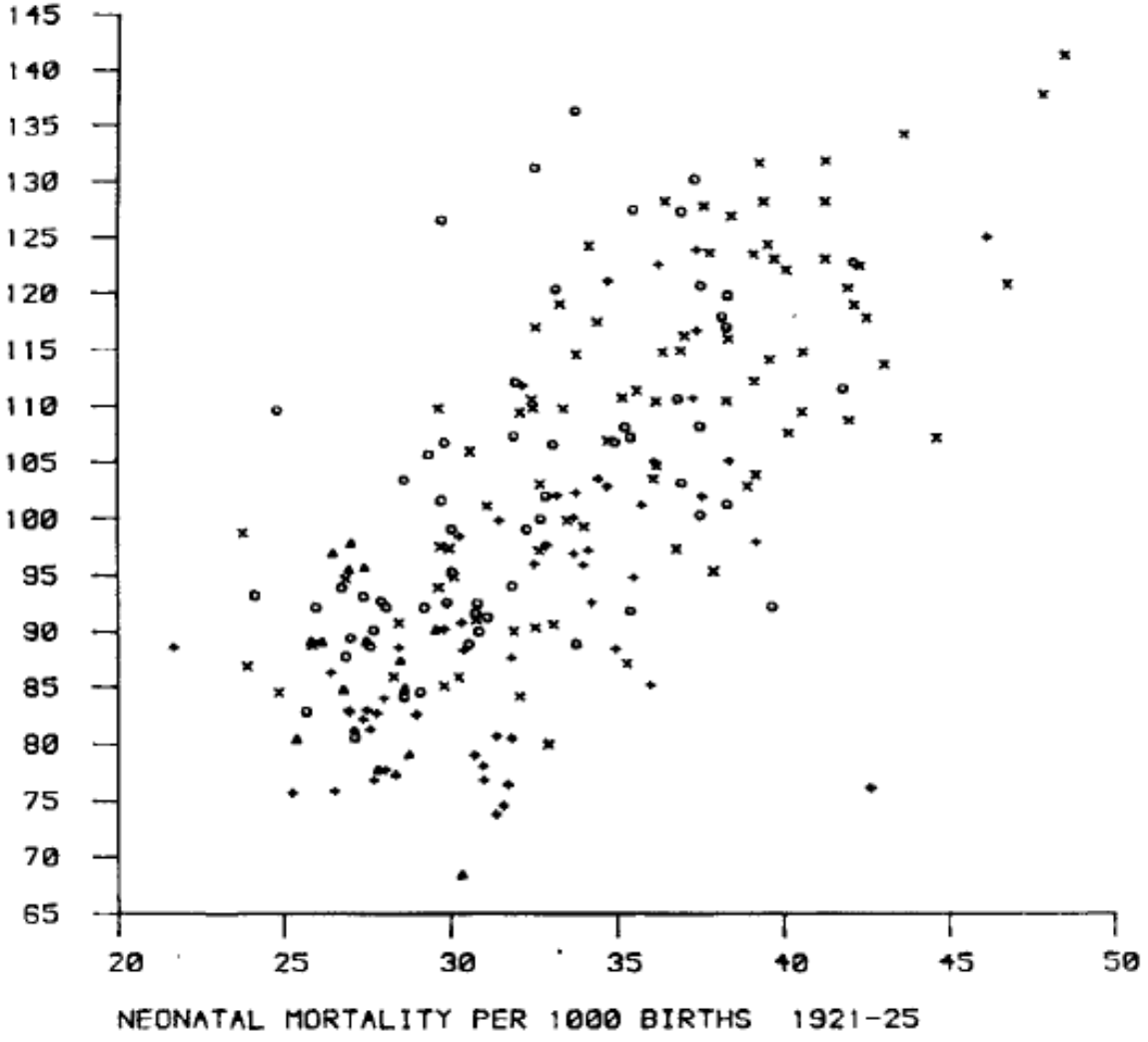


Fig 3—SMRs for ischaemic heart disease in both sexes and neonatal mortality.

WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

D. J. P. BARKER
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C. OSMOND
B. MARGETTS
S. J. SIMMONDS

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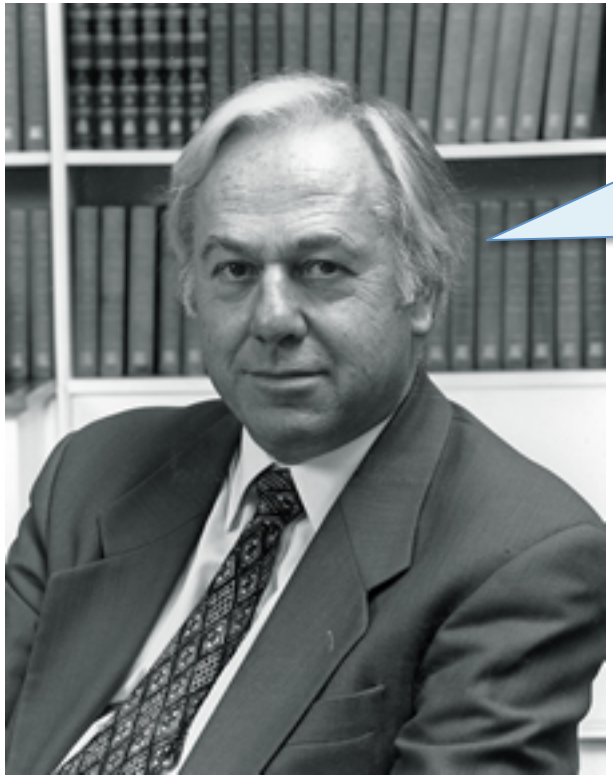
Summary Environmental influences that impair growth and development in early life may be risk factors for ischaemic heart disease. To test this hypothesis, 5654 men born during 1911–30 were traced. They were born in six districts of Hertfordshire, England, and their weights in infancy were recorded. 92·4% were breast fed. Men with the lowest weights at birth and at one year had the highest death rates from ischaemic heart disease. The standardised mortality ratios fell from 111 in men who weighed 18 pounds (8·2 kg) or less at one year to 42 in those who weighed 27 pounds (12·3 kg) or more. Measures that promote prenatal and postnatal growth may reduce deaths from ischaemic heart disease. Promotion of postnatal growth may be especially important in boys who weigh below 7·5 pounds (3·4 kg) at birth.

Lancet, 1989

TABLE I—SMRS ACCORDING TO WEIGHT AT ONE YEAR OF AGE AND BIRTHWEIGHT

Weight (pounds)	Cause of death			
	Ischaemic heart disease	Chronic obstructive lung disease	Lung cancer	All causes
One year old				
⩽18 (n = 324)	111 (37)*	129 (6)	98 (11)	89 (85)
19–20 (n = 971)	81 (76)	86 (11)	99 (31)	89 (238)
21–22 (n = 1850)	98 (163)	41 (9)	87 (48)	85 (405)
23–24 (n = 1464)	71 (98)	61 (11)	57 (26)	68 (265)
25–26 (n = 769)	68 (49)	52 (5)	97 (23)	73 (150)
⩾27 (n = 276)	42 (11)	29 (1)	70 (6)	58 (43)
Birthweight				
⩽5·5 (n = 251)	104 (25)	93 (3)	113 (9)	101 (69)
6–6·5 (n = 752)	77 (51)	59 (5)	101 (22)	69 (131)
7–7·5 (n = 1598)	90 (129)	75 (14)	68 (32)	83 (340)
8–8·5 (n = 1757)	85 (141)	50 (11)	85 (47)	80 (380)
9–9·5 (n = 868)	62 (53)	69 (8)	67 (19)	70 (170)
⩾10 (n = 428)	81 (35)	33 (2)	109 (16)	77 (96)
Total (n = 5654)	82 (434)	61 (43)	83 (145)	79 (1186)

*Number of deaths in parentheses. 2·2 pounds = 1 kg.



David Barker (1938-2013)

胎児期の発生が
成人期の疾患に
関係する！
（のではないか？）

別の研究

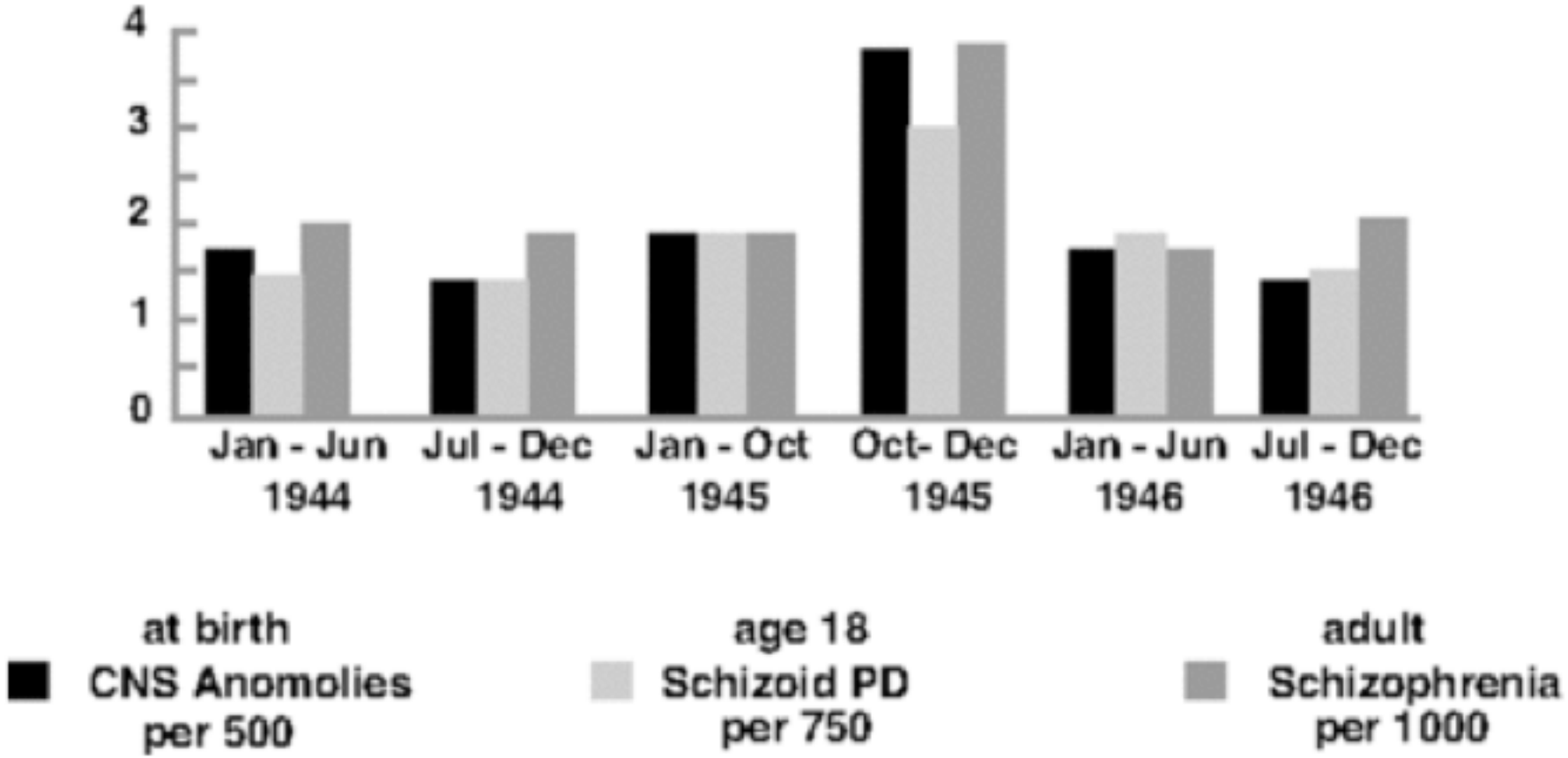
オランダの大飢饉
（1944）

Mervyn Susser (1921-2014)

オランダの大飢饉の時期に胎児だった集団

- 出生時の異常の増加
  - Stein & Susser, Pediatr Res, 1975
- 生殖能力の低下
  - Stein & Susser, Hum Biol, 1975
- 若い成人男性における肥満の増加
  - Obesity in young men after famine exposure in utero and early infancy (Ravelli et al., N Eng J Med, 1976)
- 統合失調症の増加
  - Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945 (Susser ES & Lin SP, Arch Gen Psychiatry, 1992
  - Schizophrenia after prenatal famine: further evidence (Susser et al., Arch Gen Psychiatry, 1996）
- 男性における依存症の増加
  - Brown et al., Br J Psychiatry, 1995

神経形成異常や統合失調症の増加



Susser E, *et al.* Arc Gen Psychiatry 1996

メカニズム？

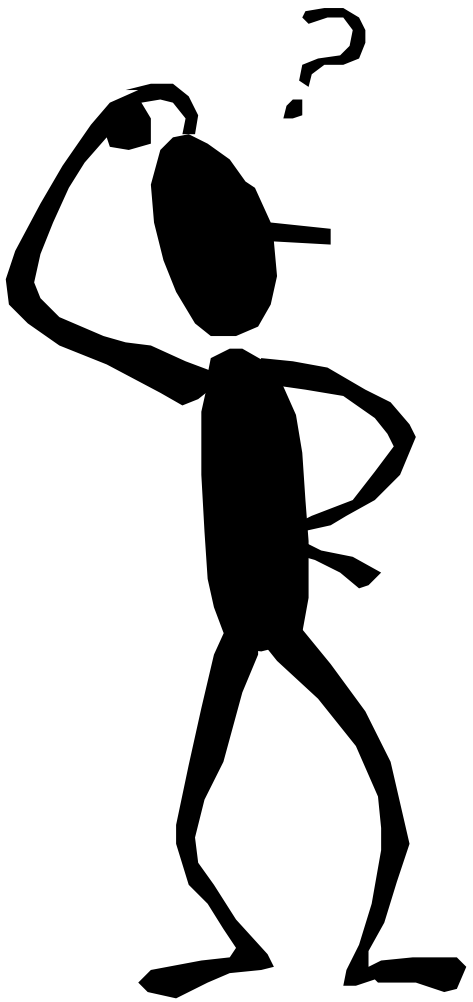
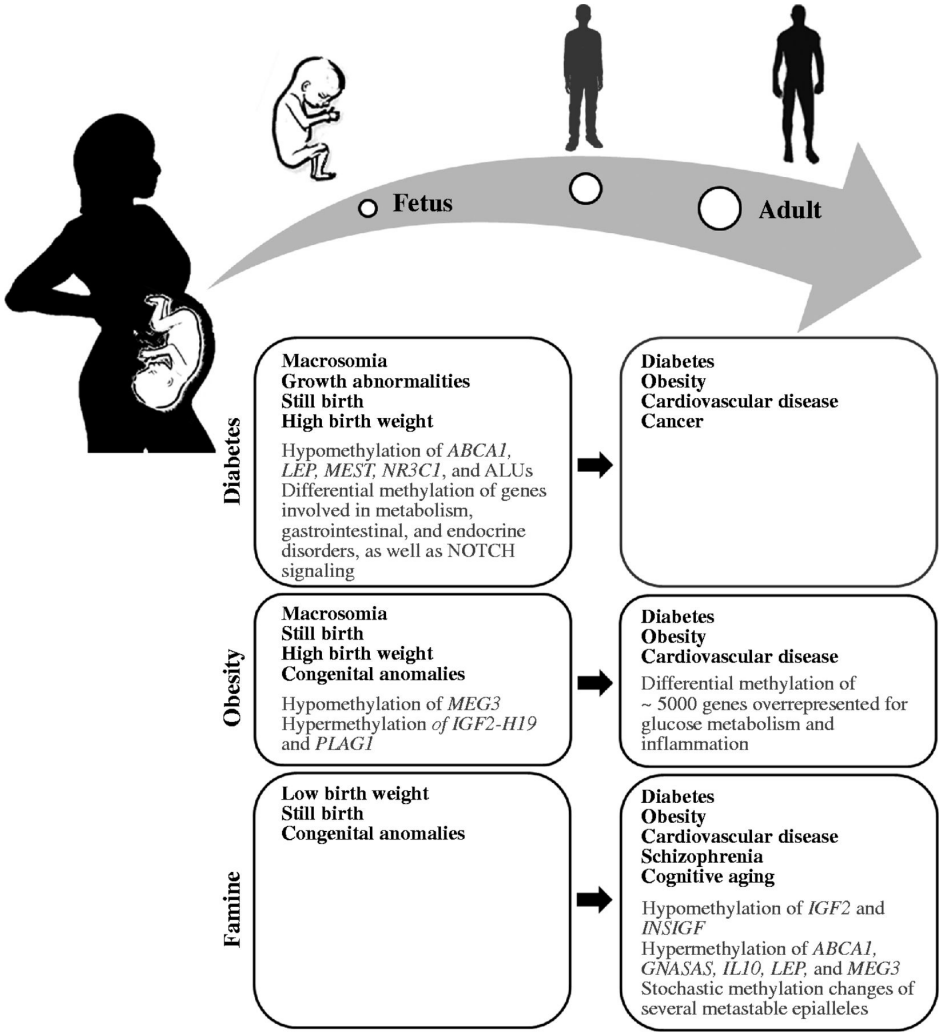


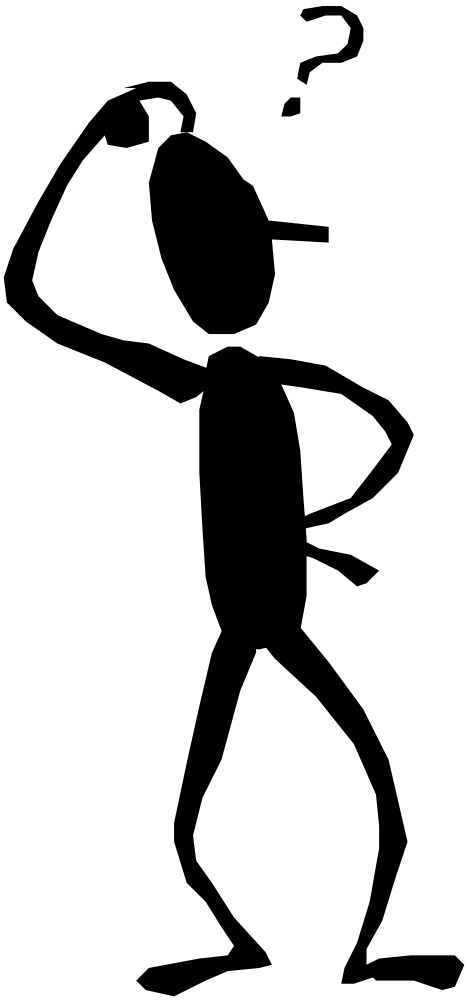
Figure 1 Medical problems and epigenetic changes (in placenta and blood) at birth and later in life, respectively, that have been associated with intrauterine exposure to diabetes mellitus, maternal obesity, and famine.



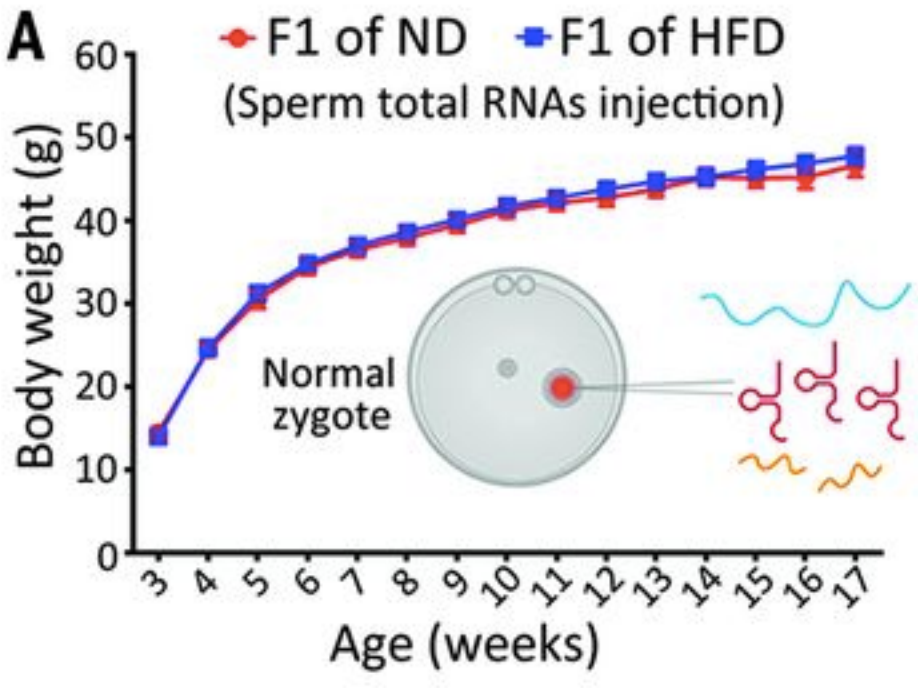
Nady El Hajj et al. Reproduction 2014;148:R111-R120

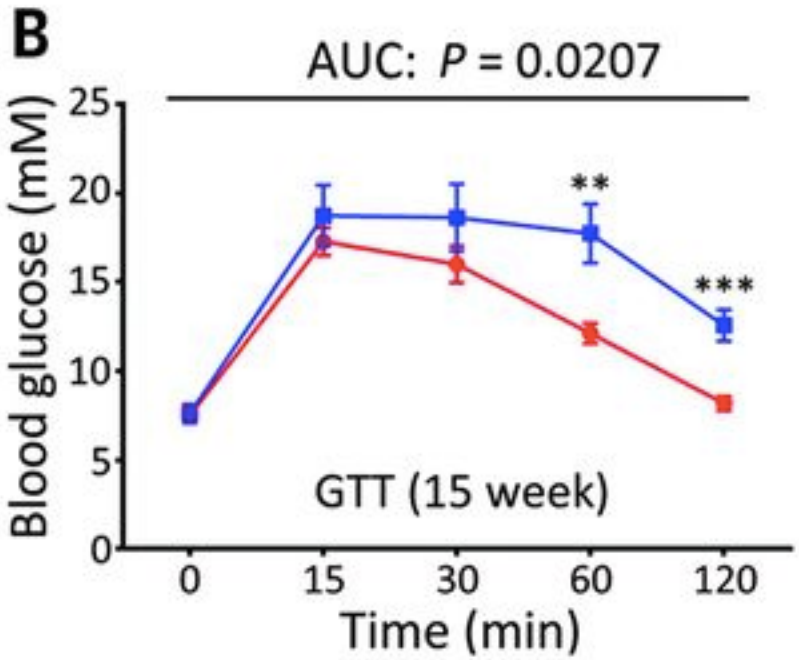
栄養過多

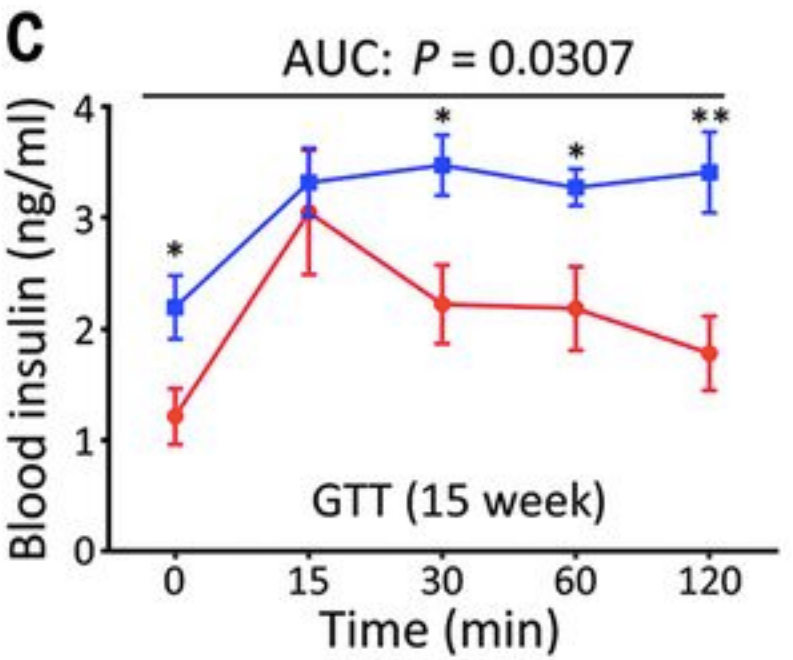
世代を超えた影響？



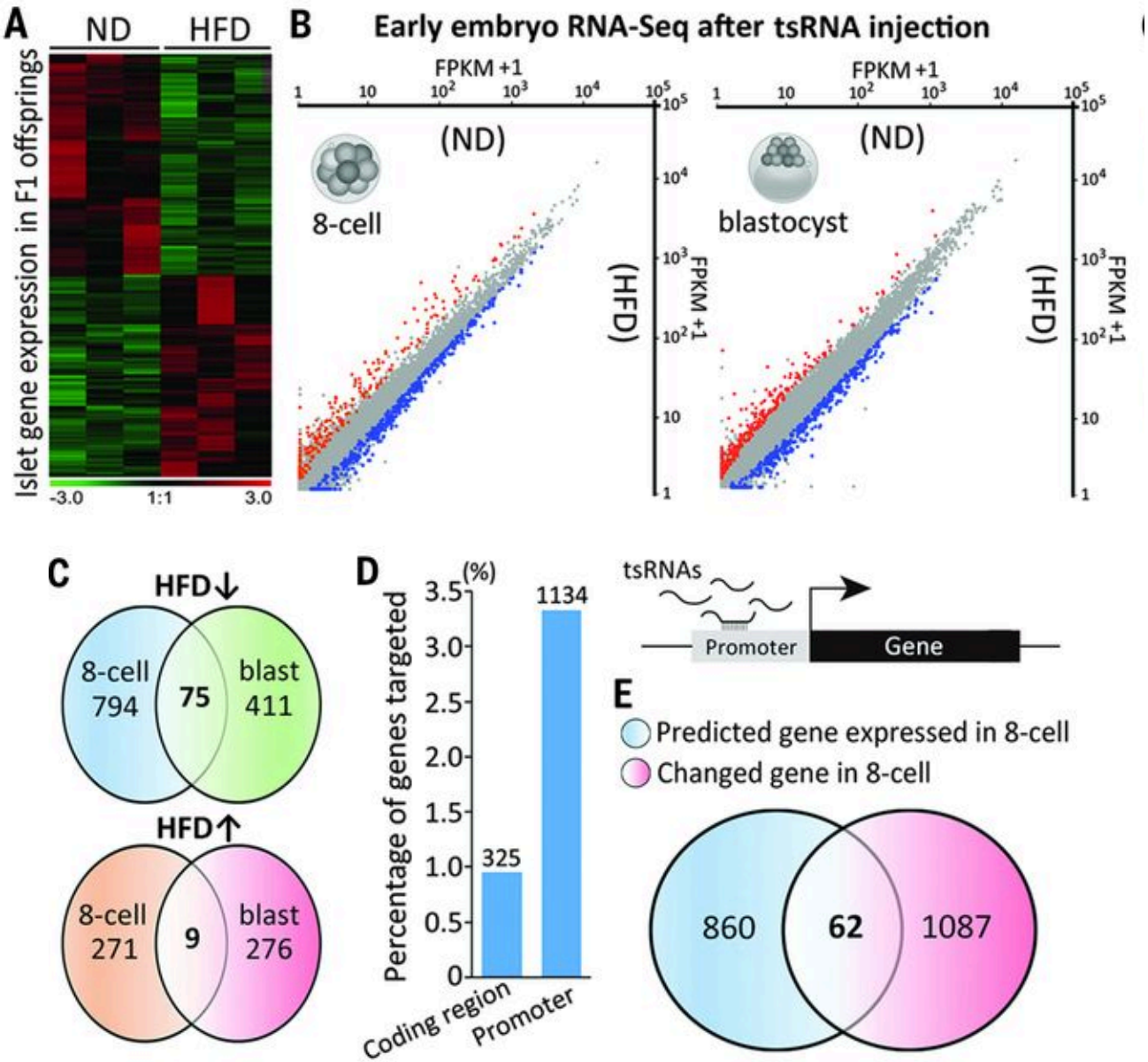
Qi Chen et al. Sperm tsRNAs contribute to internenerational inheritance of an acquired metabolic disorder. Science 2016;351:397-400



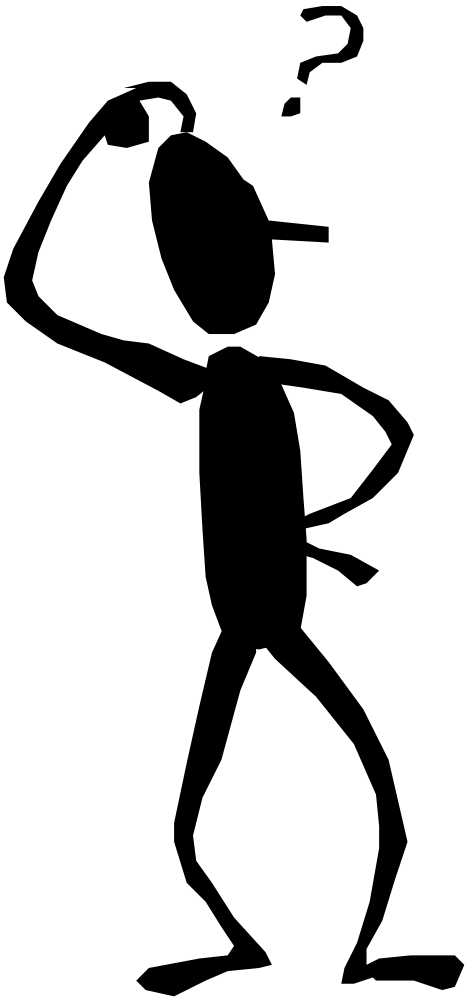




HFDにより仔マウスの遺伝子発現変化



父加齢の次世代への影響



自閉症

- 中核症状
  - 社会性の異常
    - コミュニケーションの異常
  - 興味の限定・常同行動
- その他の症状
  - 感覚統合異常
  - 軽微な運動異常
  - 消化器症状
  - てんかん
  - 睡眠障害
- 学習障害
  - 特殊学級、養護学校の増設
- 就業困難
  - 労働人口の更なる減少

- 頻度1/68-140
  - 男性：女性＝4:1
  - 近年先進国において増加

自閉症の原因？

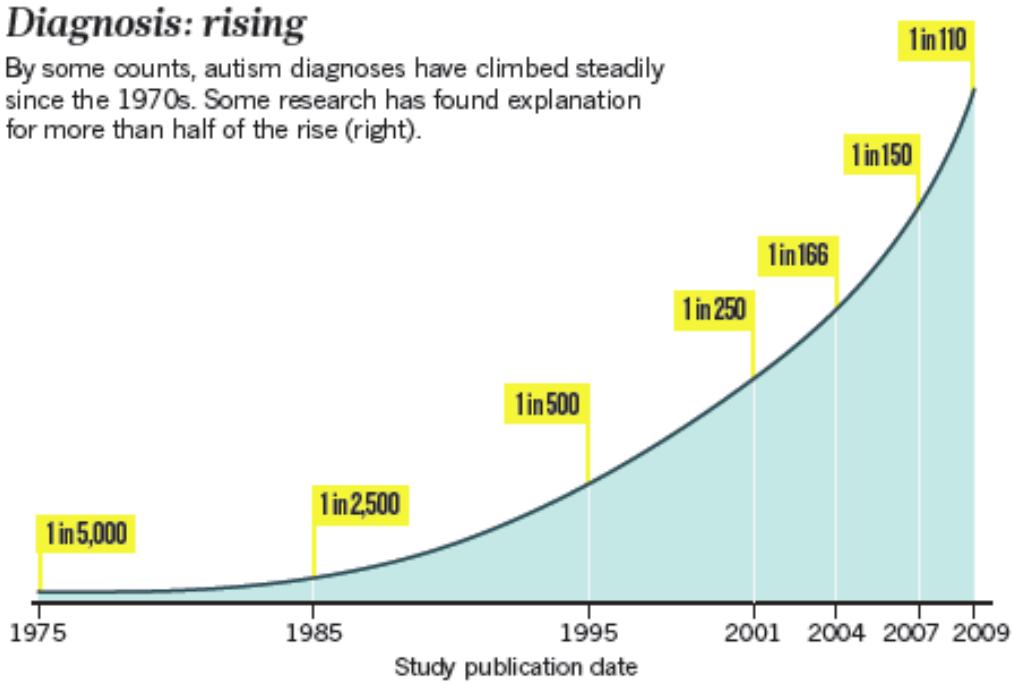
遺伝的要因

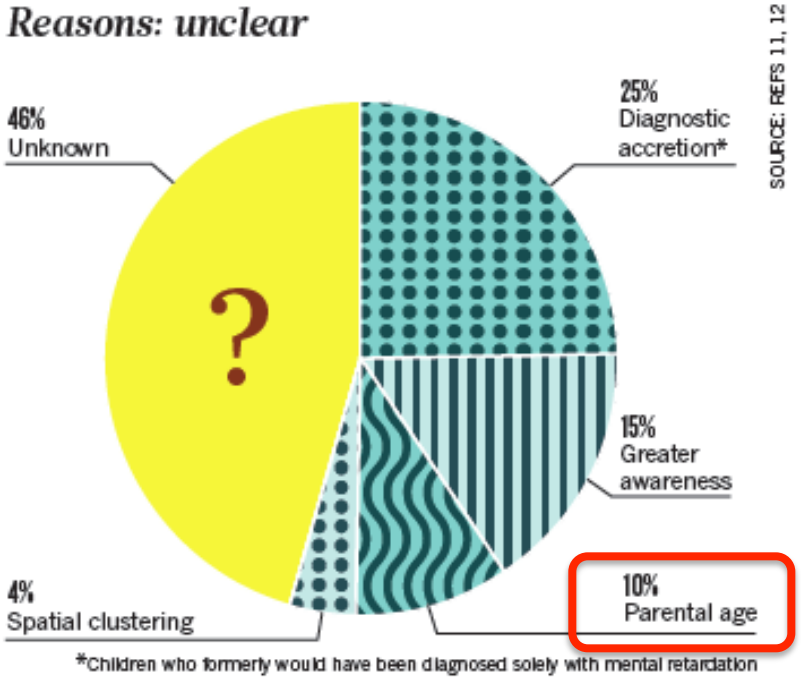
- 一卵性双生児において高い一致率（80-90%）
- 遺伝子・ゲノム解析から示唆される候補遺伝子
  - *FMR1*
  - *MeCP2*
  - *SHANK1/3*
  - *NLGN3/4*
  - *PHCD10*
  - *UBE3A*
  - *PTEN*
  - *PAX6*

環境要因

- 母体感染
- 母体の薬物暴露
  - バルプロ酸
  - サリドマイド
- 両親の加齢
  - 晩婚化
  - 生殖補助医療

自閉症の増加



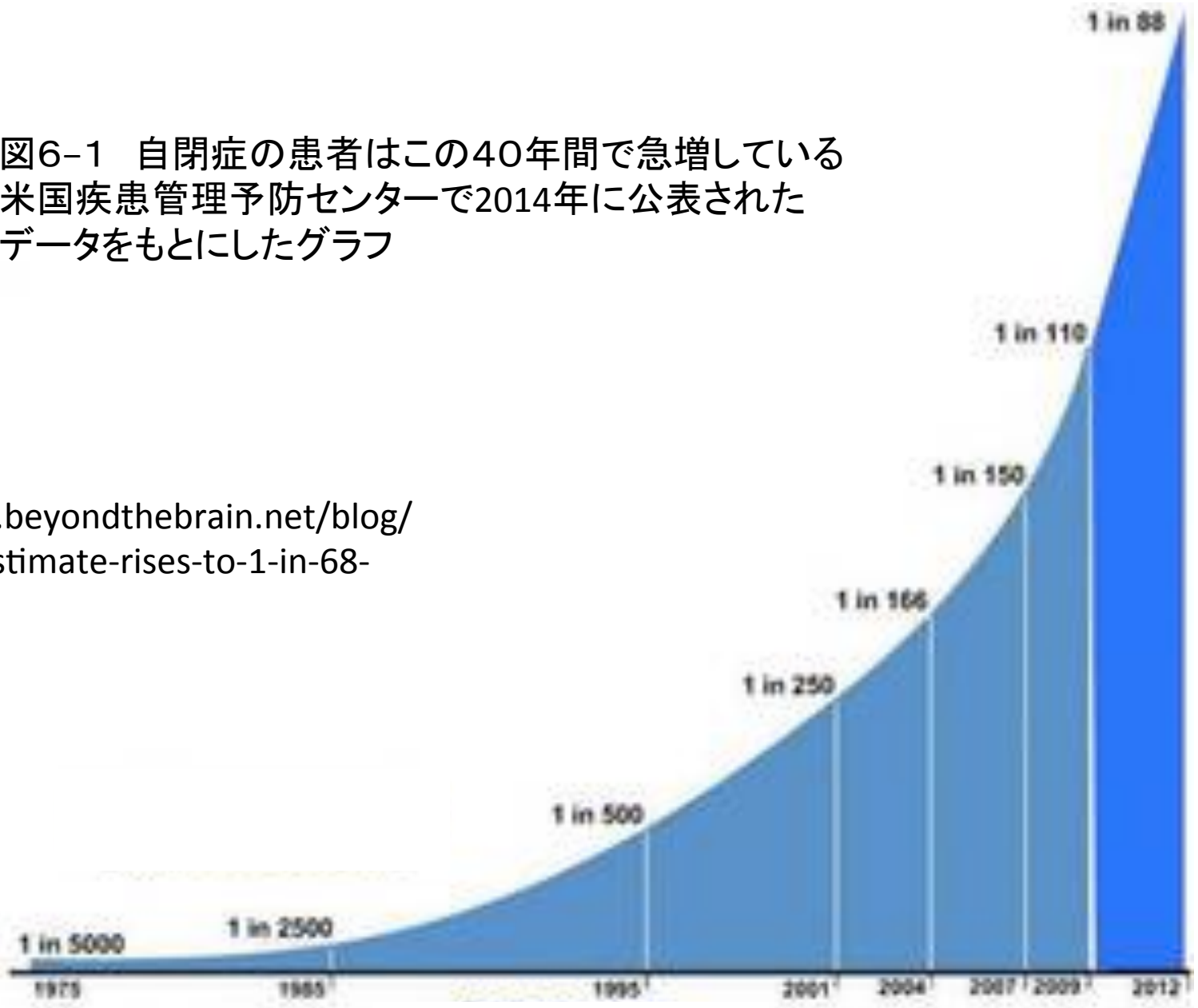


Weintraub, Autism counts, Nature, 2011

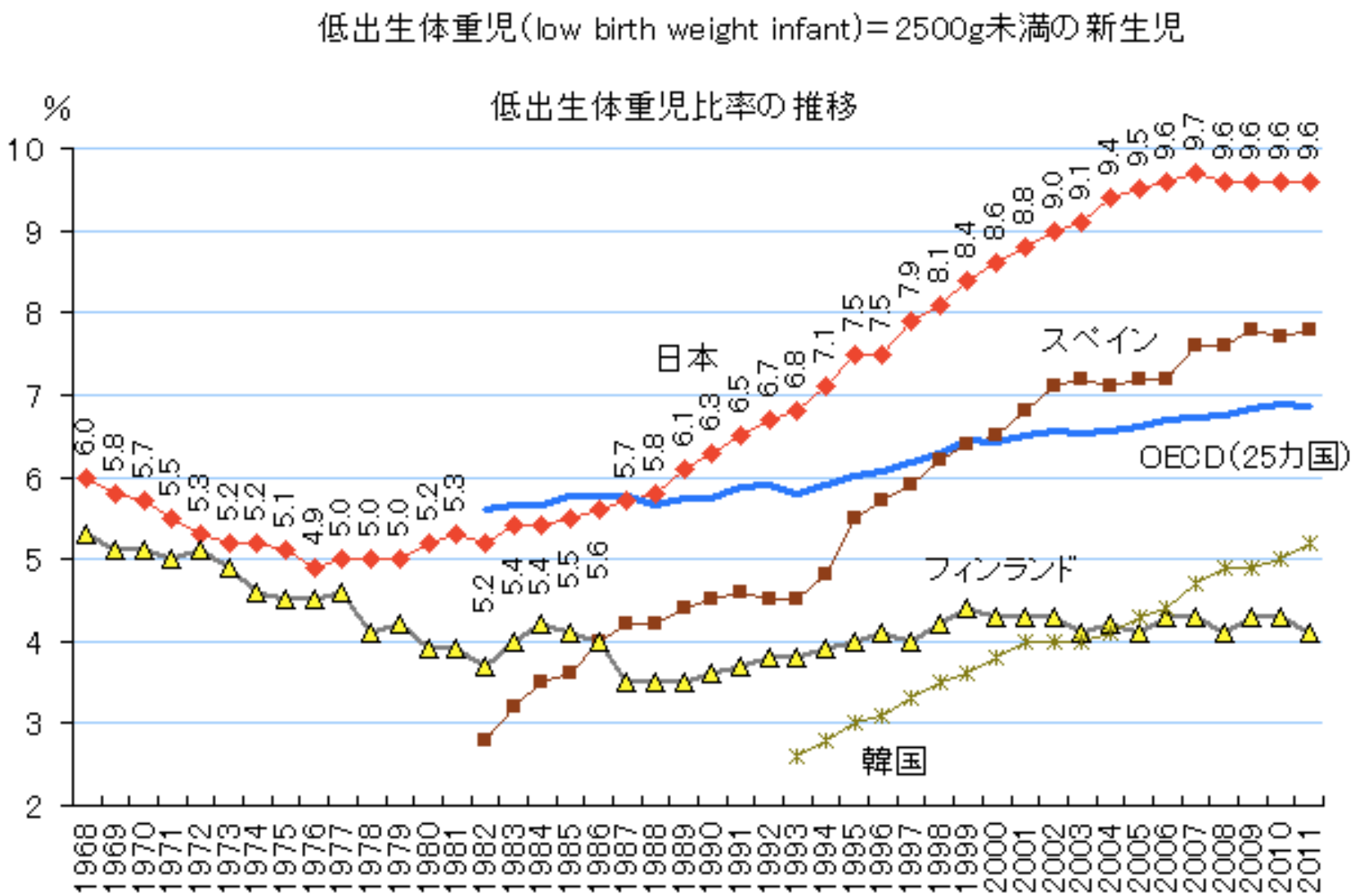
診断基準の変化等もあるが
それ以外の理由もある

図6-1　自閉症の患者はこの40年間で急増している
米国疾患管理予防センターで2014年に公表された
データをもとにしたグラフ

http://www.beyondthebrain.net/blog/us-autism-estimate-rises-to-1-in-68-children



OECD諸国の低体重出生児年次変化



http://www2.ttcn.ne.jp/honkawa/2246.html

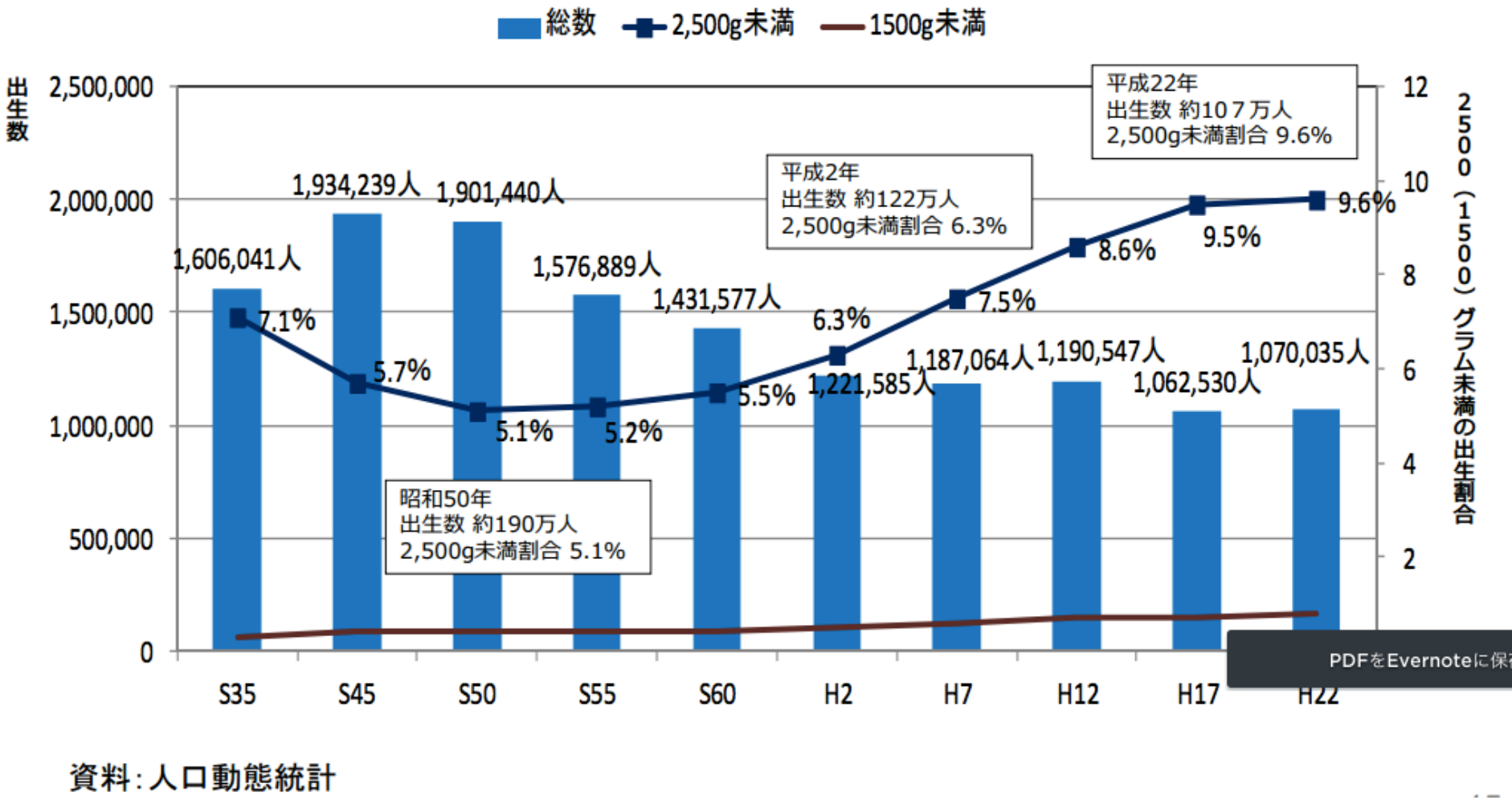
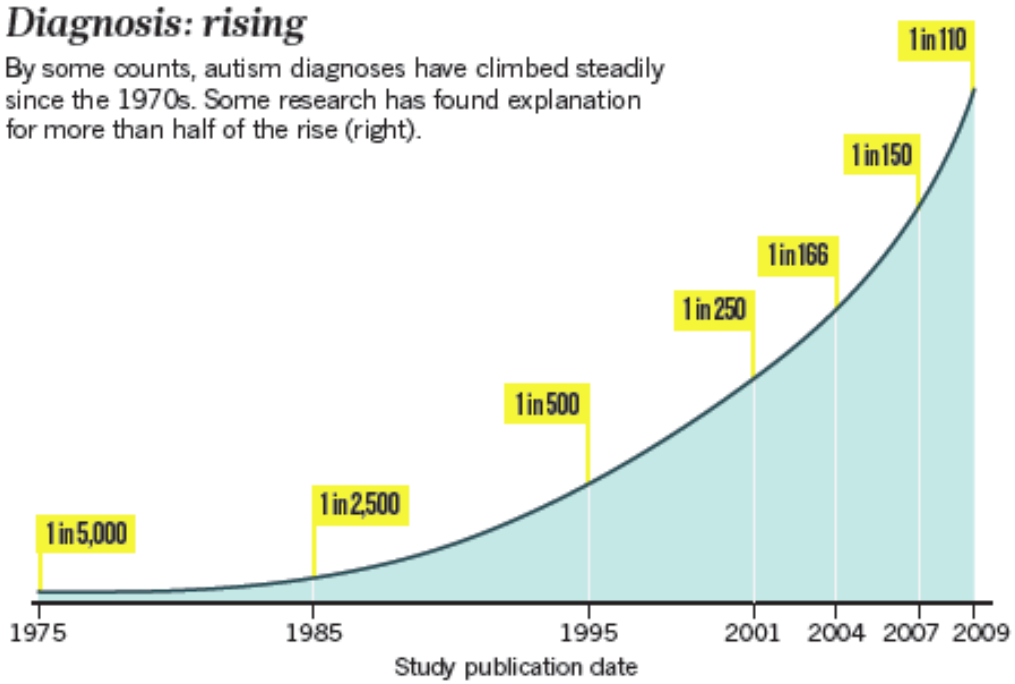
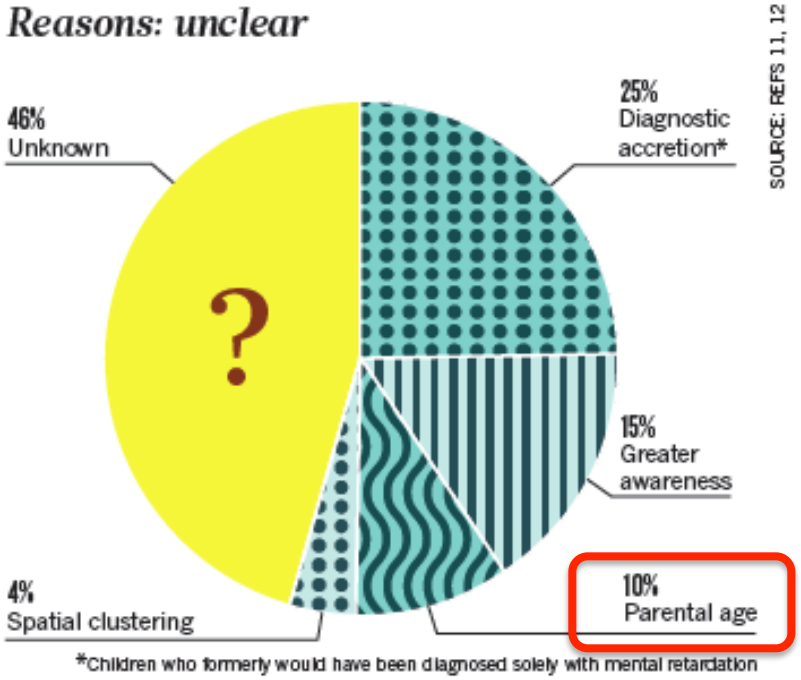


図6-1　わが国の低体重出生児の増加

自閉症の増加





Weintraub, Autism counts, Nature, 2011

診断基準の変化等もあるが
それ以外の理由もある

父加齢は子の自閉症発症のリスク

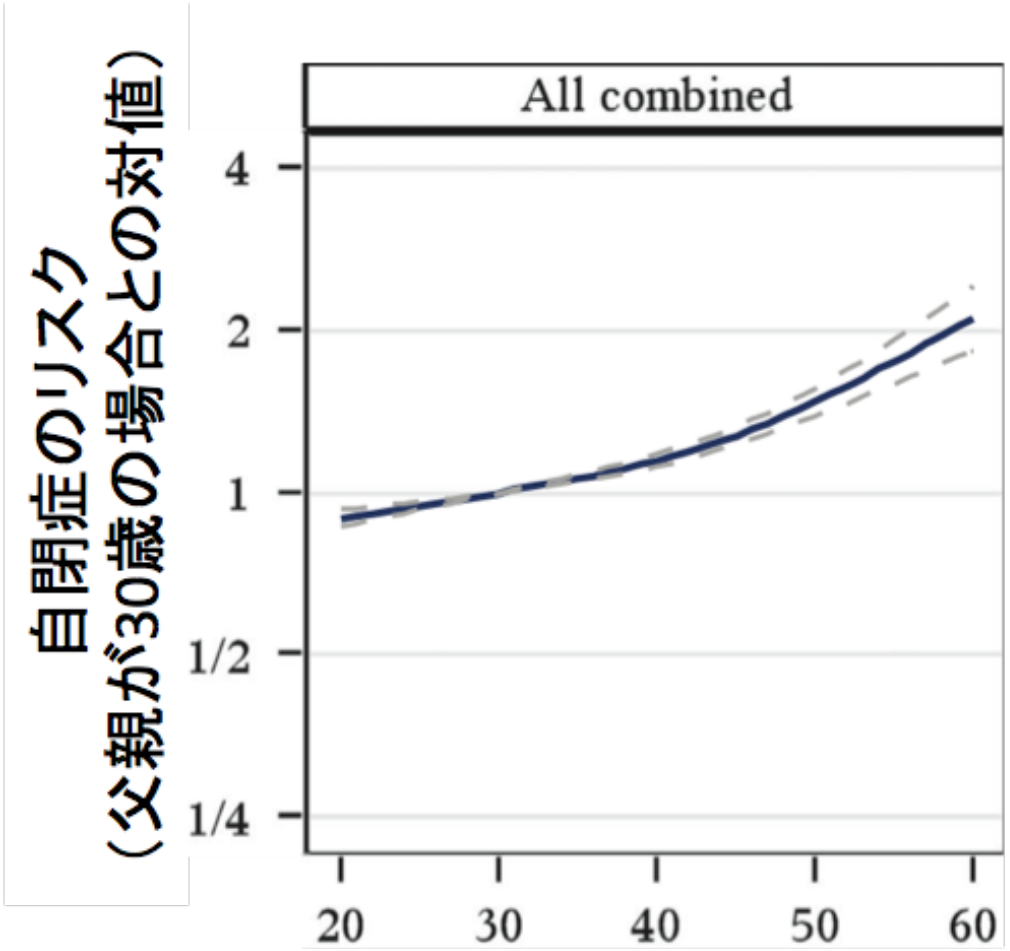
Table 1. Associations Between Paternal Age and Risk of Autism Spectrum Disorder (ASD) in the Smaller Subset With Data on Both Paternal and Maternal Age

Paternal Age Group, y	Non-ASD Cohort (n = 132 161)	ASD Cases (n = 110)	Risk	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
15-29†	60 654	34	6:10 000	1.00	. . .	1.00	. . .
30-39	67 211	62	9:10 000	1.64 (1.08-2.50)	.02	1.62 (0.99-2.65)	.06
40-49	4106	13	32:10 000	5.65 (2.98-10.71)	<.001	5.75 (2.65-12.46)‡	<.001
≥50	190	1	52:10 000	9.39 (1.28-68.94)	.03	. . .	. . .

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for year of birth, socioeconomic status, and maternal age.
†Reference group.
‡Includes oldest age group.

Based on data from Reichenberg et al.,
Arch Gen Psychiat, 2006

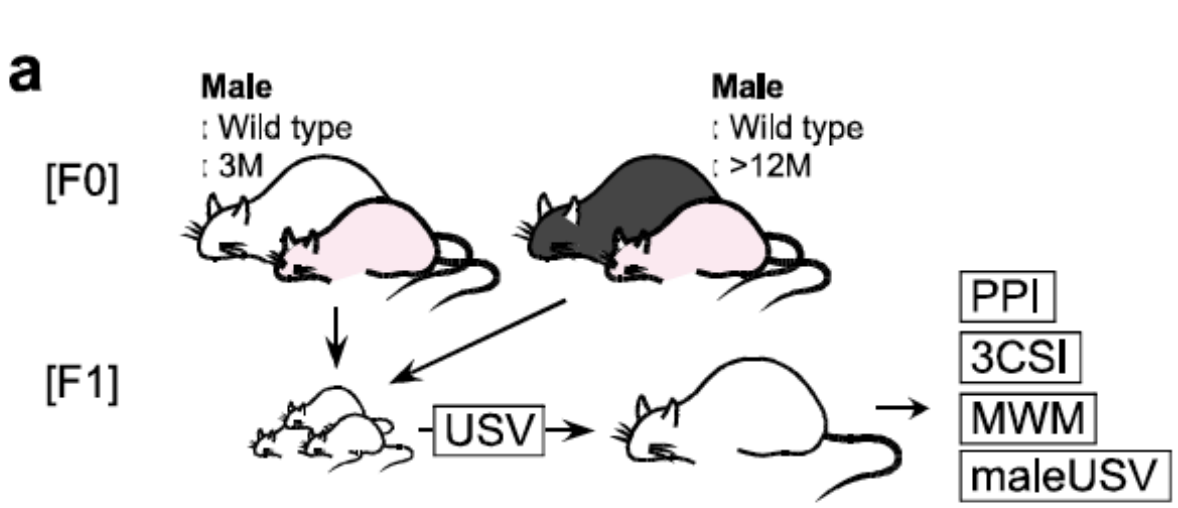
父加齢は子の自閉症発症のリスク

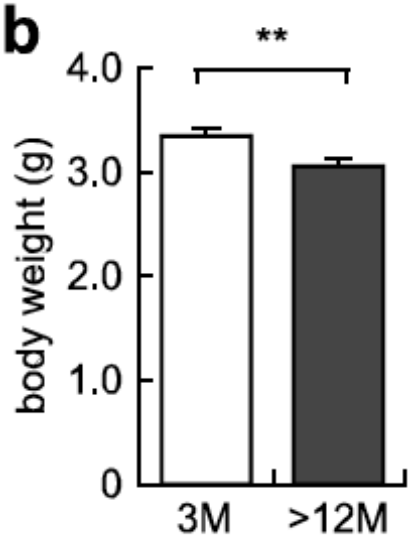


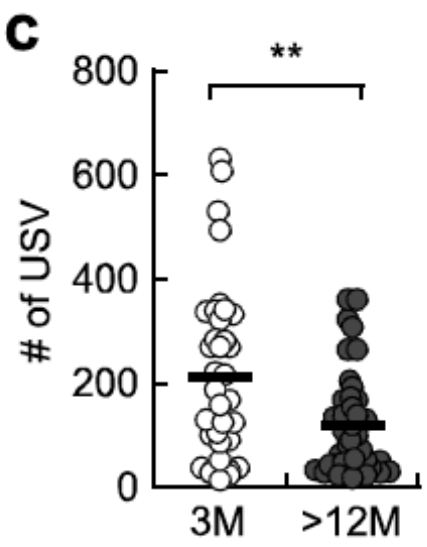
メタ解析

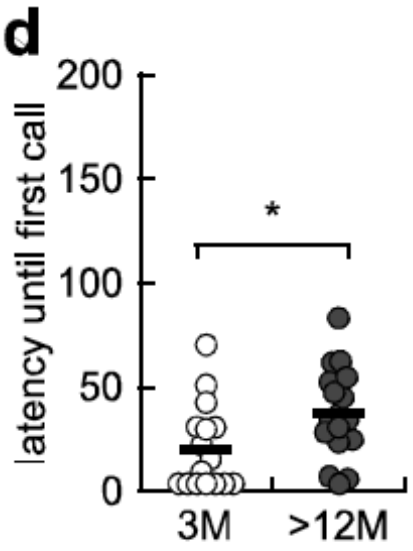
Sandin et al., 2015

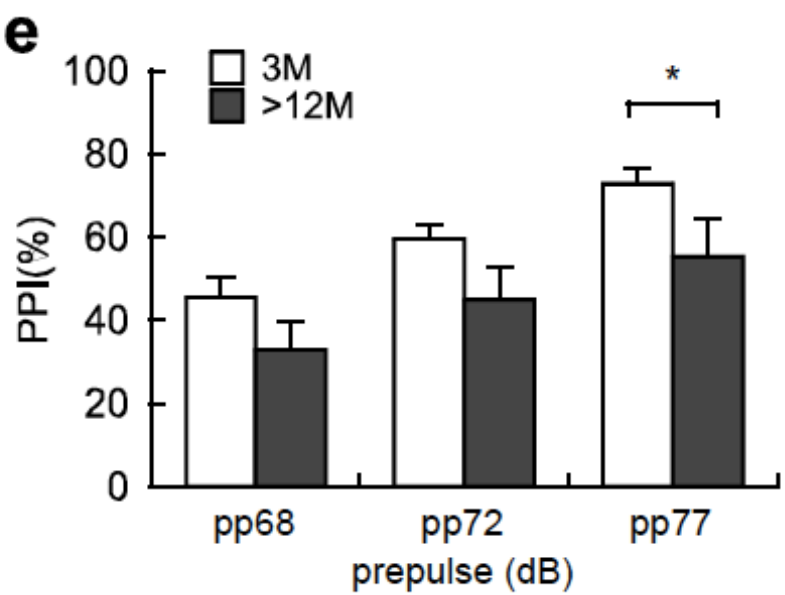
父加齢で仔マウス体重減少・行動変化





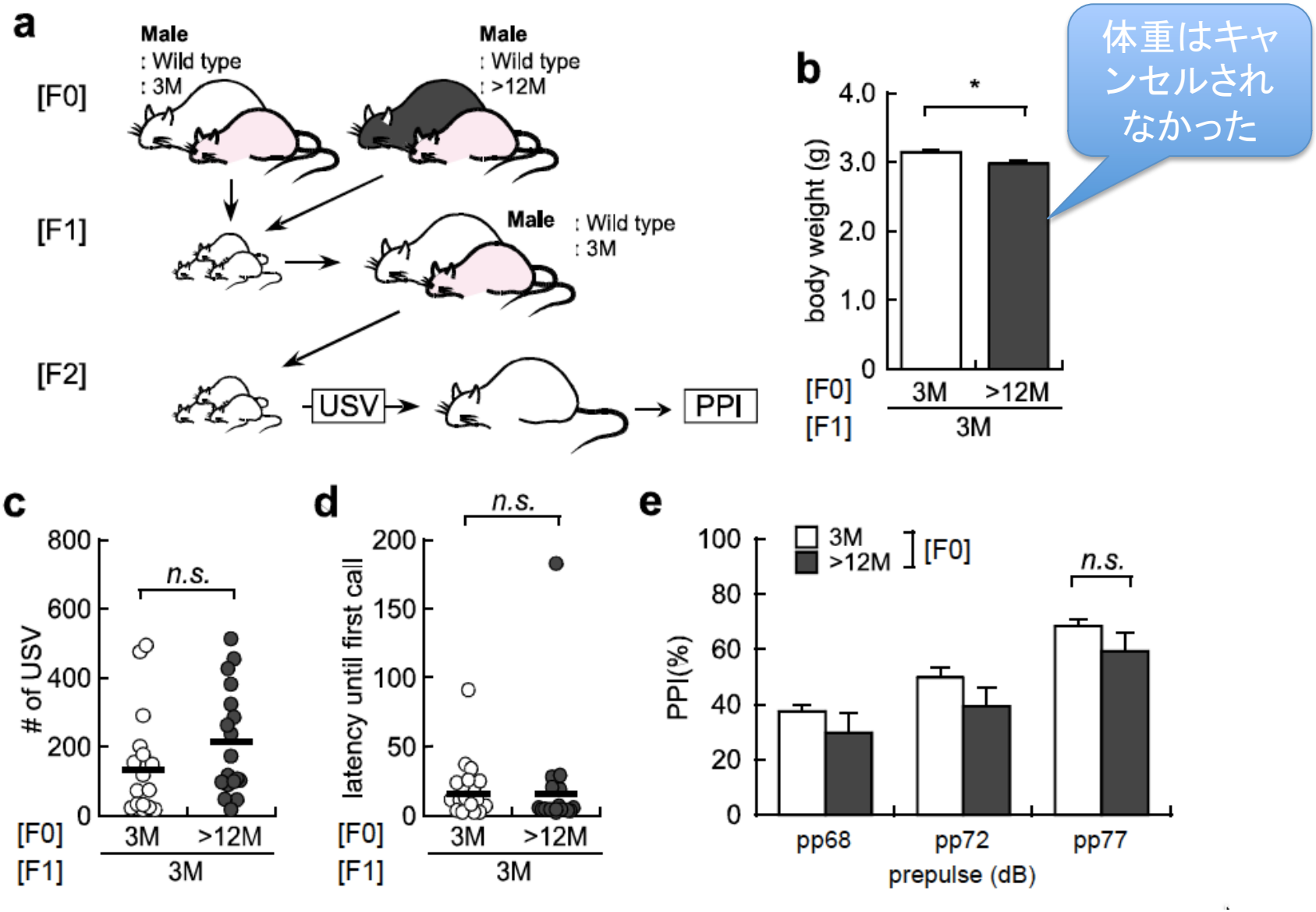




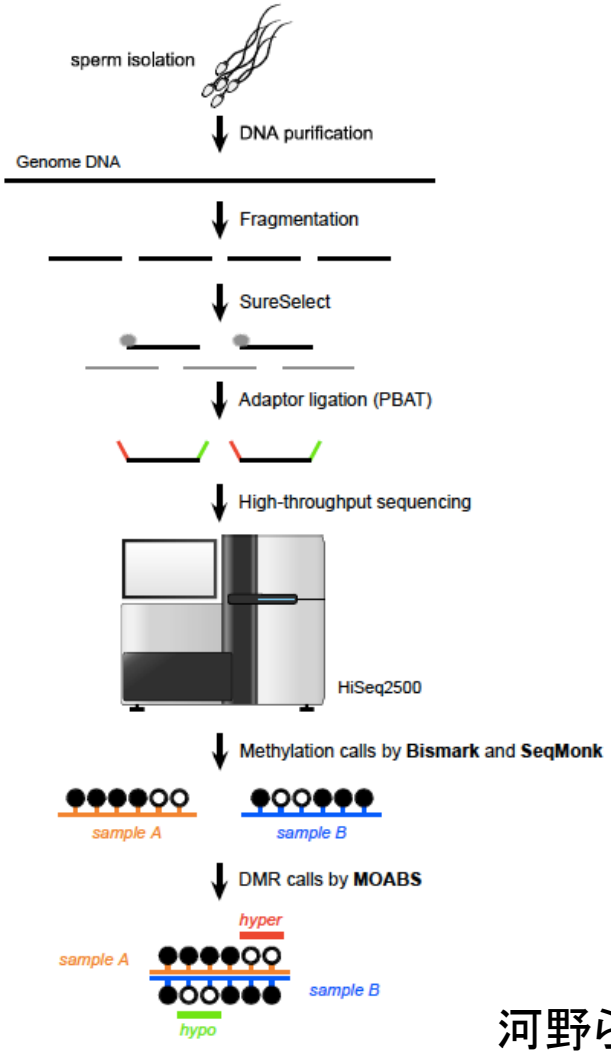


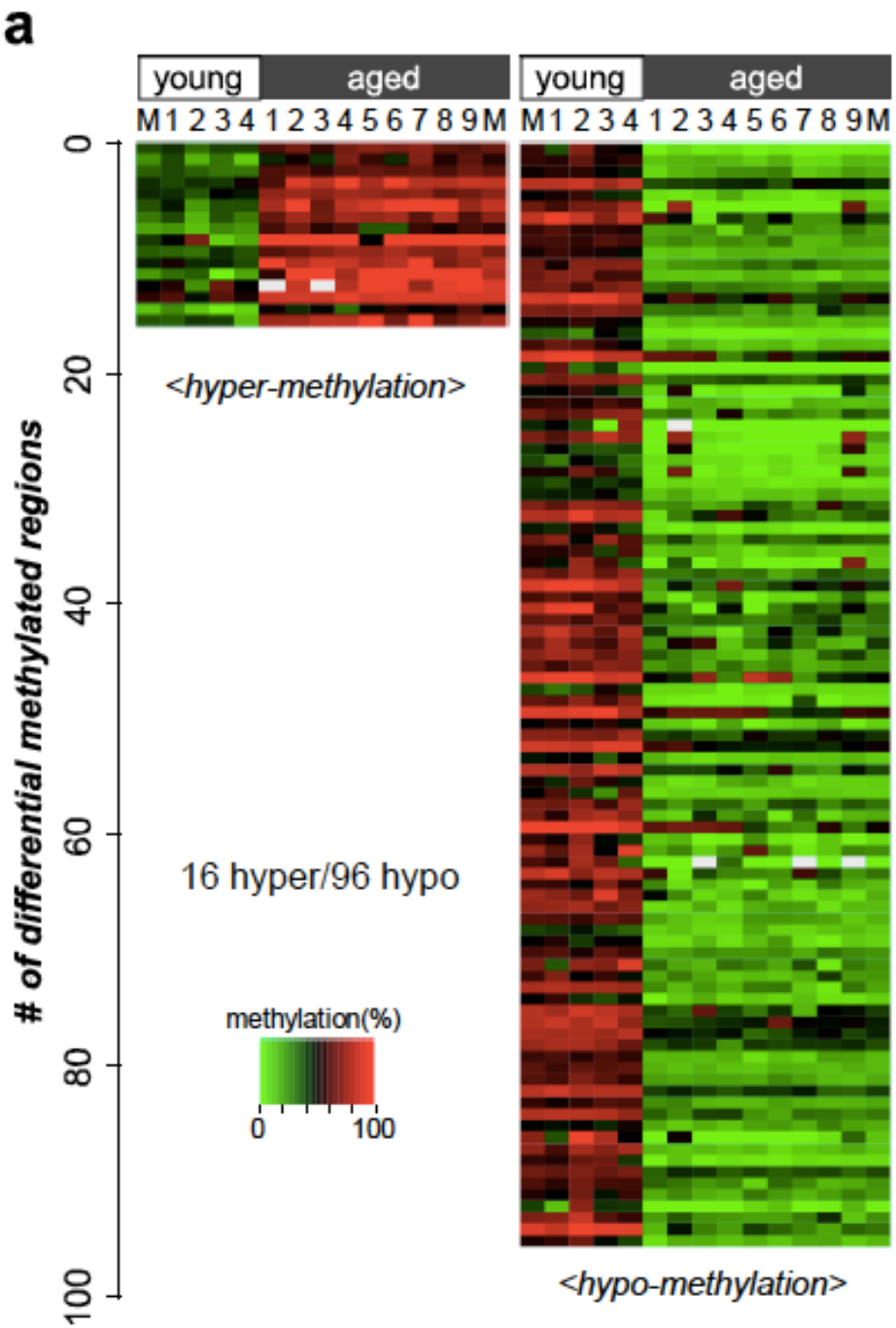
吉崎（未発表）

孫マウスでキャンセルされる



精子メチル化の変化

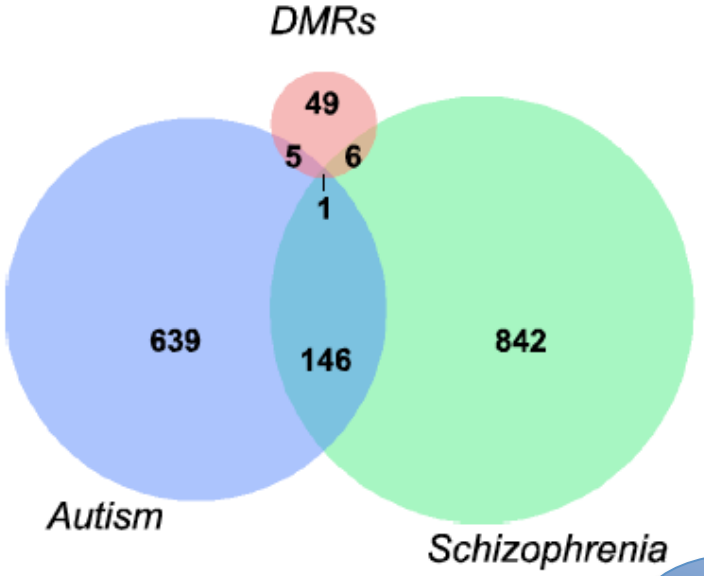




河野らとの共同研究

12/61個の遺伝子が統合失調症/自閉症に関連

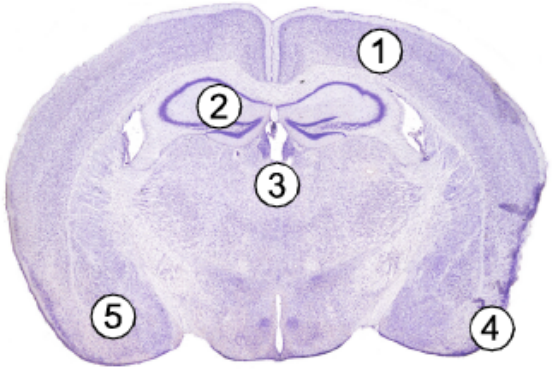
a



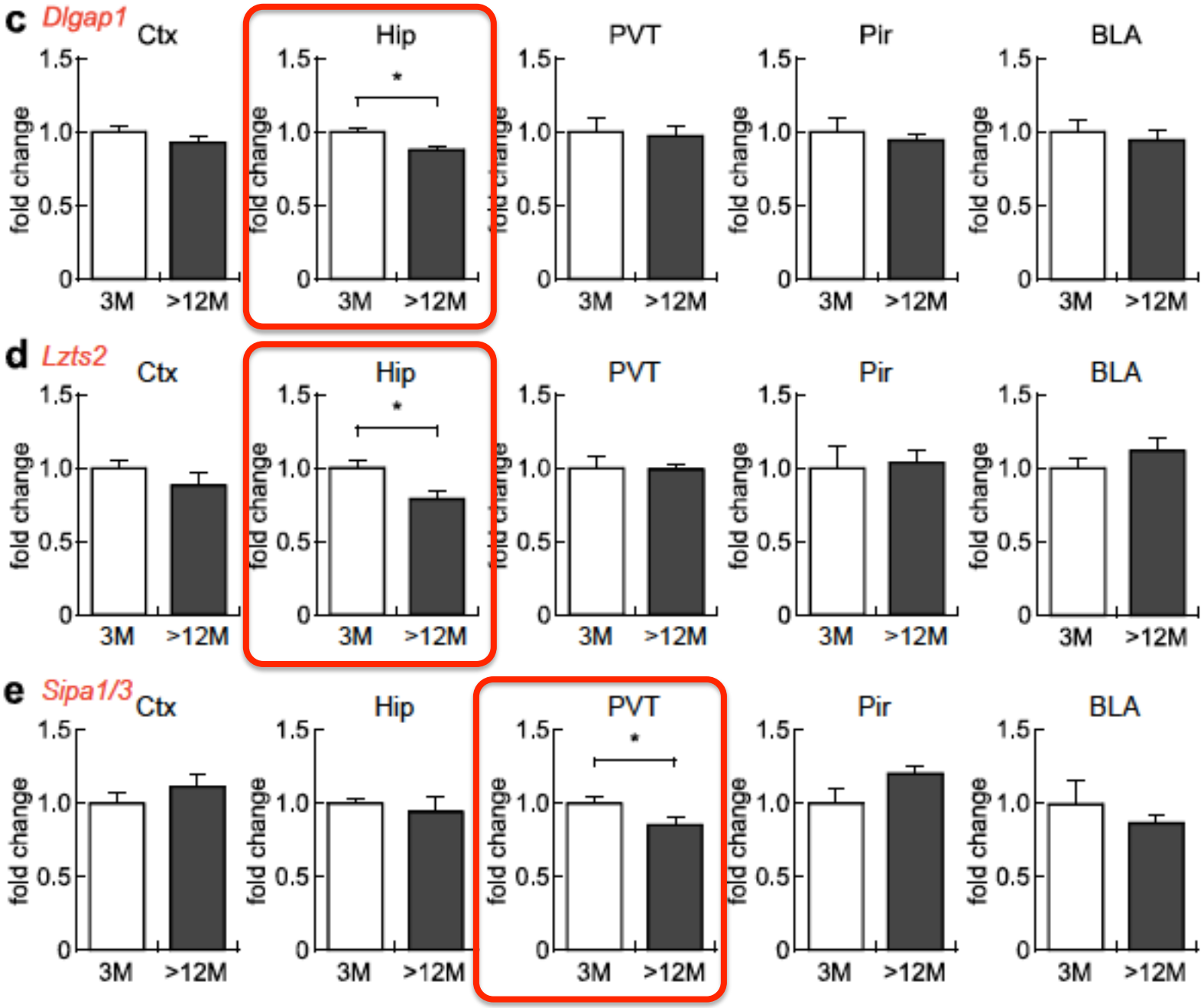
b

Gene	Fuction
Anks1b	interaction with amyloid beta protein precursor
Cacna1h	calcium channel alpha-1 subunits family
Lzts2	transcriptional modulation and cell cycle control
Reep3	receptor accessory protein 3
Shank2	postsynaptic scaffolding protein
Dlgap1	interaction with PSD95 members and clustering of NMDA receptor and potassium channels
Sipa1	GTPase activity
Ap3b2	neurotransmitter release
Celf5	contranscriptional and posttranscriptional RNA processing
Nfil3	pleiotropic transcriptional regulator on immunity
Mmp9	degradation of collagen of the extracellular matrix
Rbm24	RNA binding motif protein 24

仔マウス脳での遺伝子発現を調べた



① cerebral cortex (Ctx)
② hippocampus (Hip)
③ paraventricular nucleus of the thalamus (PVT)
④ piriform cortex (Pir)
⑤ basolateral amygdala (BLA)


c
Dlgap1
Ctx
Hip
PVT
Pir
BLA
fold change
1.5
1.0
0.5
0
*
3M
>12M
d
Lzts2
Ctx
Hip
PVT
Pir
BLA
fold change
1.5
1.0
0.5
0
*
3M
>12M
e
Sipa1/3
Ctx
Hip
PVT
Pir
BLA
fold change
1.5
1.0
0.5
0
*
3M
>12M

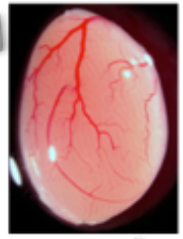
「個性」を明らかにするための
次世代継承エピゲノムプロジェクト

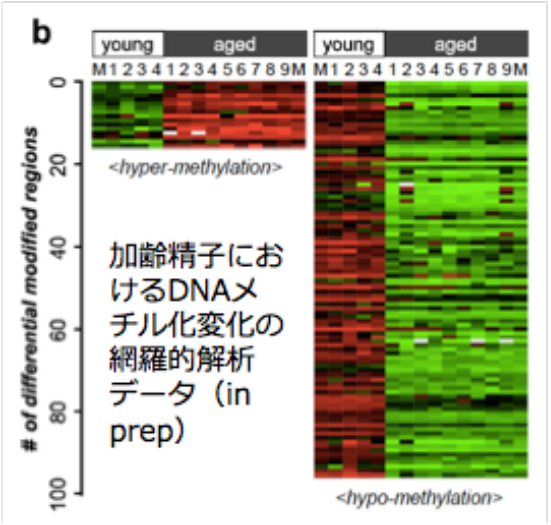
**父マウス加齢
過剰脂質等のゆらぎ**

**仔マウスの
「個性」発露への影響**

本研究のための予備的研究成果：
Sakayoriet al., Stem Cells, 2016
Kimura et al., J Anat, 2015

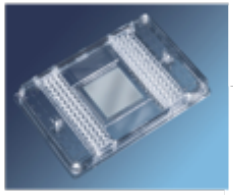
①マウス精巣ゲノム・
エピゲノム・遺伝子
発現網羅解析



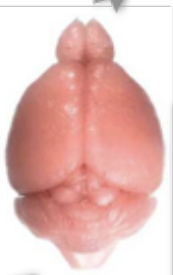


加齢精子におけるDNAメチル化変化の網羅的解析データ（in prep）

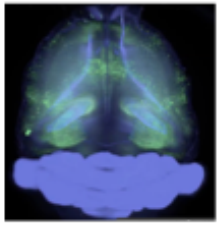
②マウス・ヒト
精子エピゲノム
遺伝子発現
網羅解析



ハイスループット
qPCRダイナミック
アレイの利用による
個別脳領域別
遺伝子発現解析

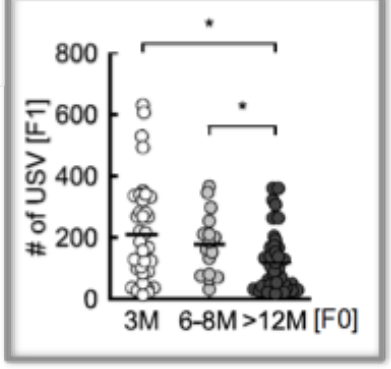


④仔マウス個別
多種行動・
脳生理機能解析



透明化脳による
cFos＋細胞全
脳計測

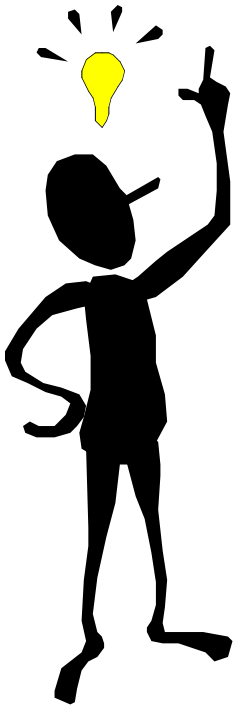
仔マウスの母子分離
超音波コール数測定



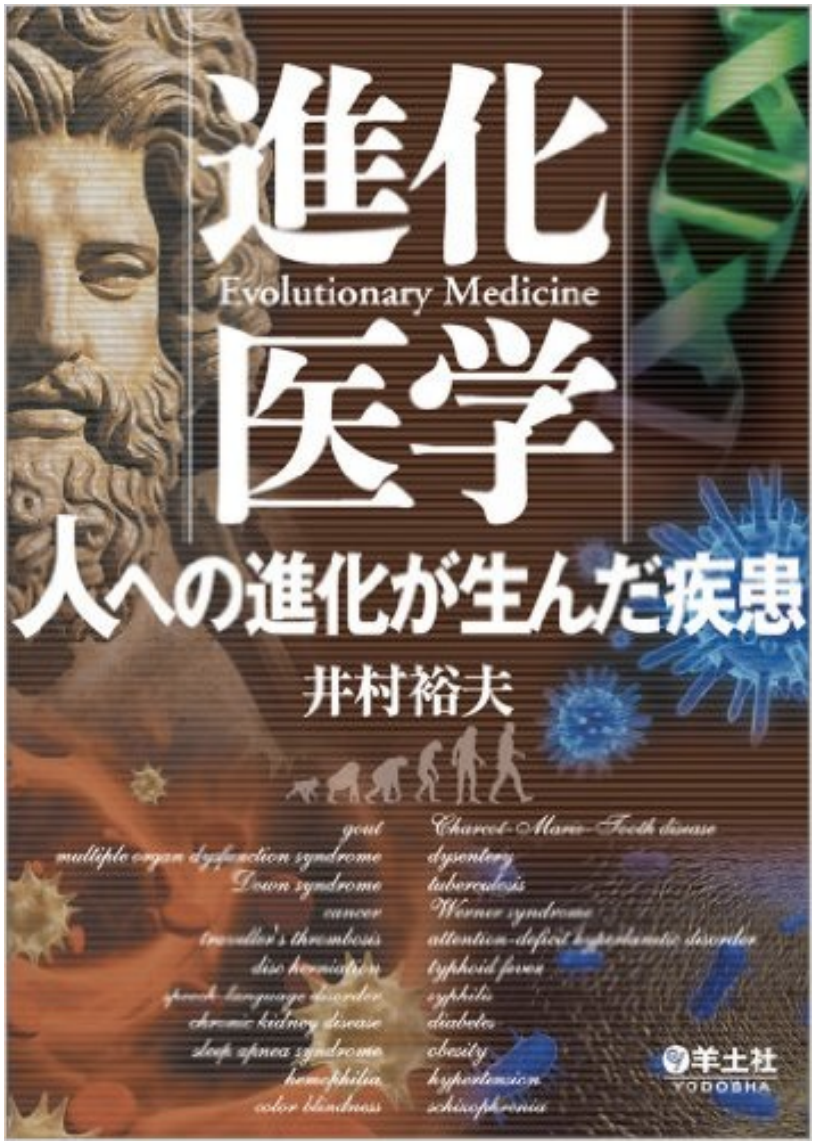
Yoshizaki et al., in preparation

・空間認知機能
・社会性行動
・常同行動
・感覚運動ゲート機構等
個体識別を行って各行動スコア間の多変量解析や遺伝子発現データ等との主成分解析を行う

多様な「個性」を創発する脳システムの統合的理解

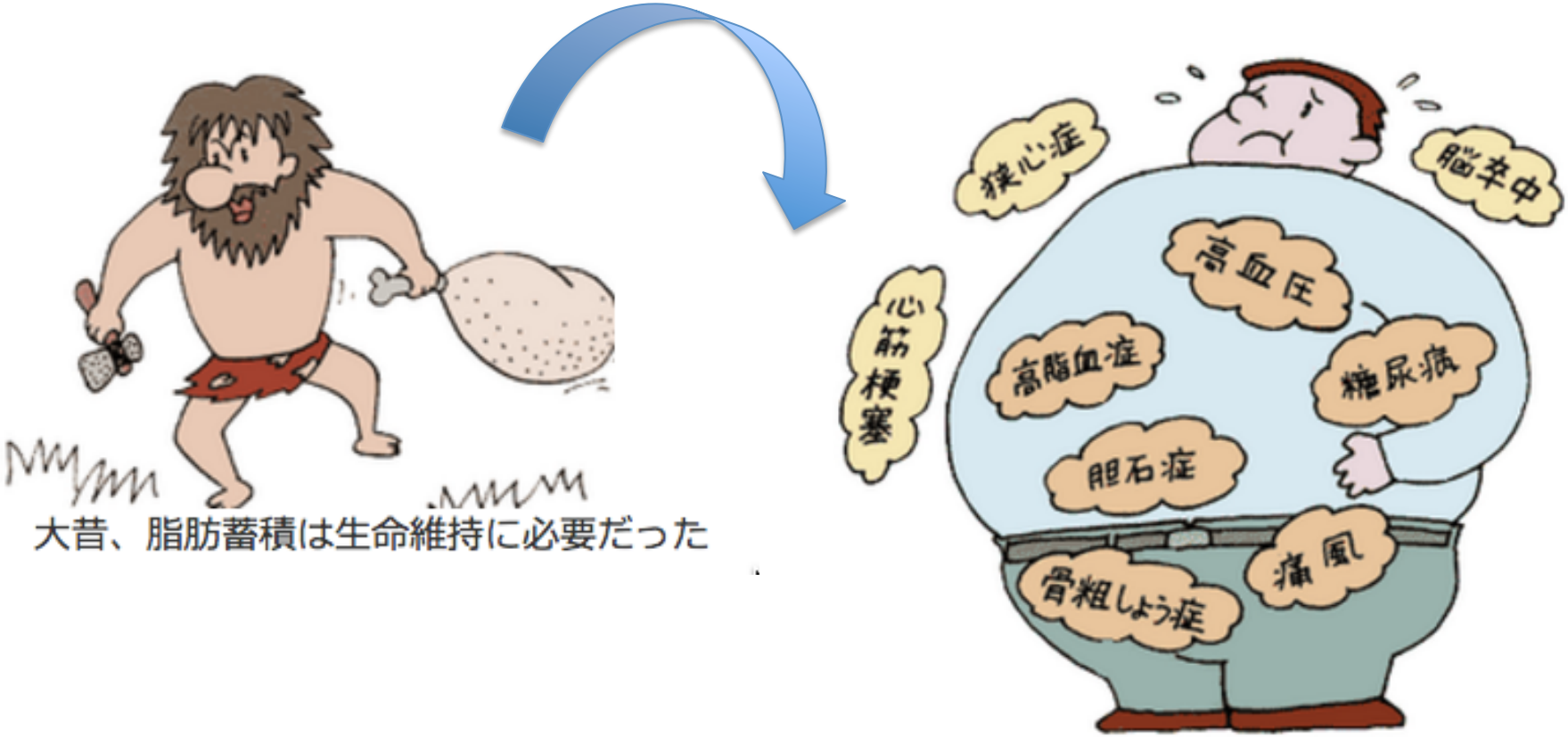


進化医学


進化医学
Evolutionary Medicine
人への進化が生んだ疾患
井村裕夫
羊土社
YODOSHA


お勧め！

進化的に有利だったはずが……

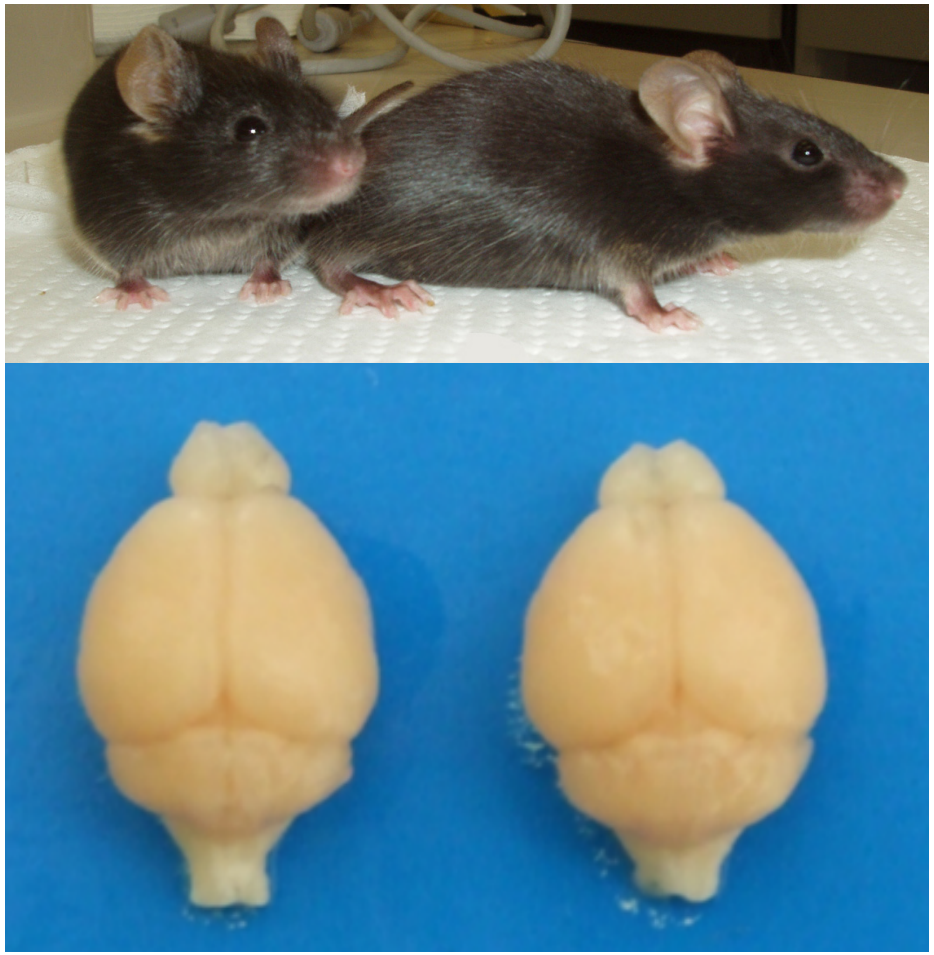


大昔、脂肪蓄積は生命維持に必要だった

肥満は万病のもと

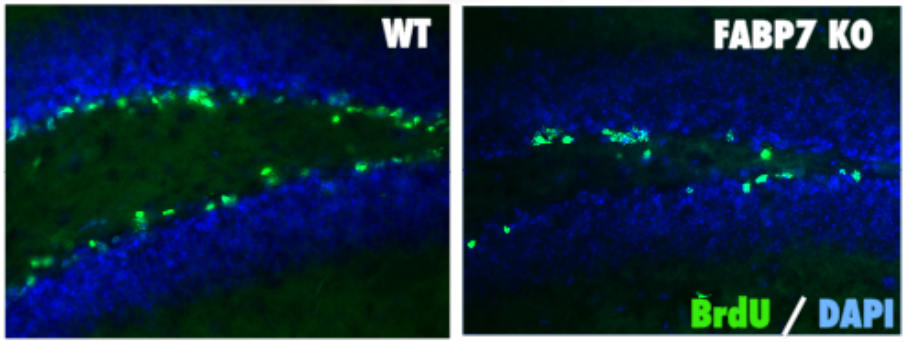
脂肪酸結合タンパク質Fabp7

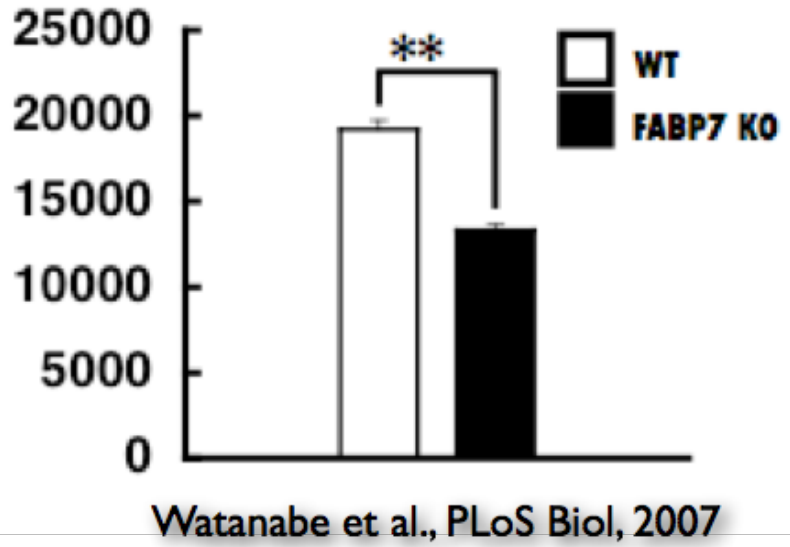
WT　　Fabp7 KO



Fabp7 KOマウス：統合失調症様行動異常

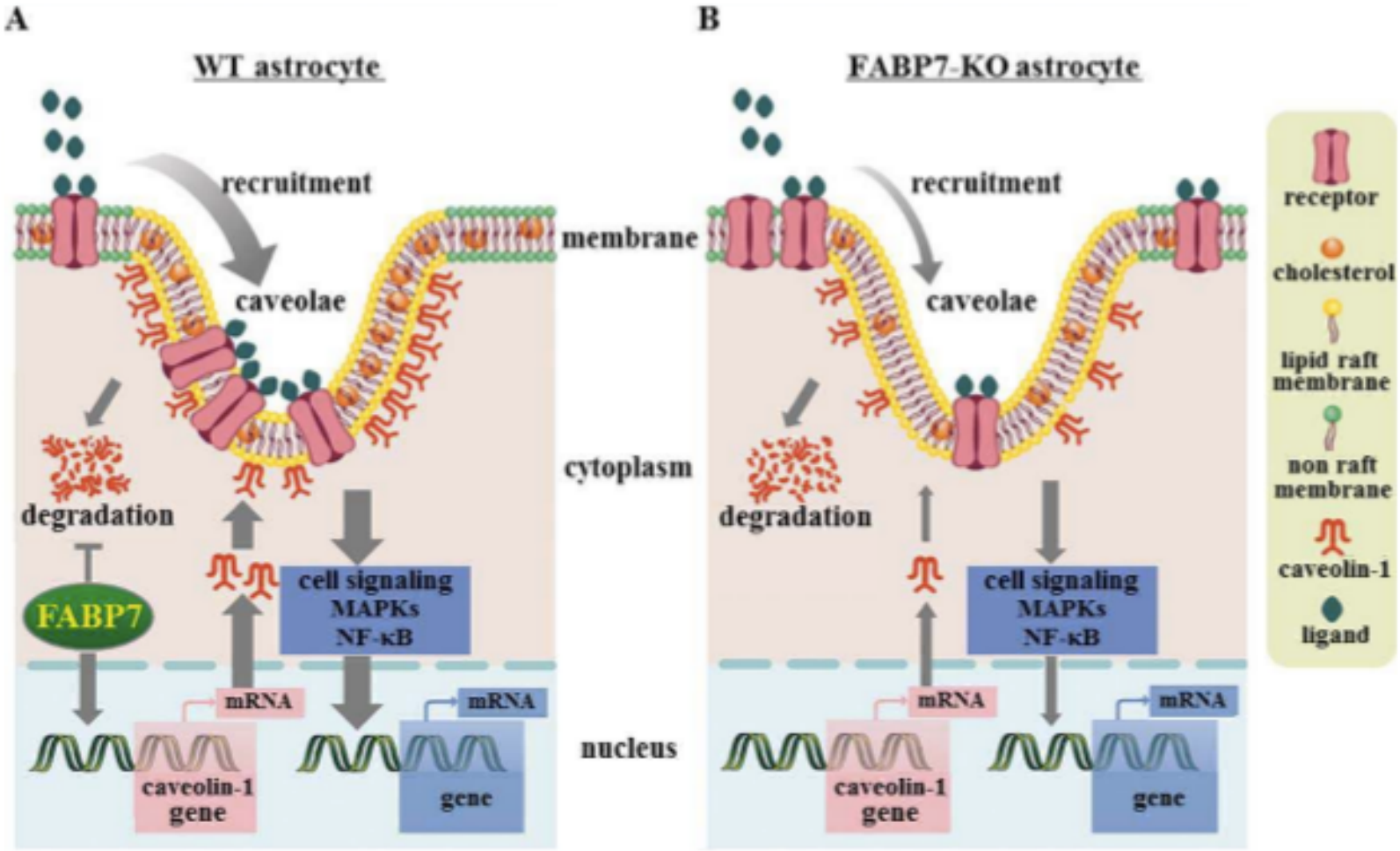
細胞増殖アッセイ





Watanabe et al., PLoS Biol, 2007

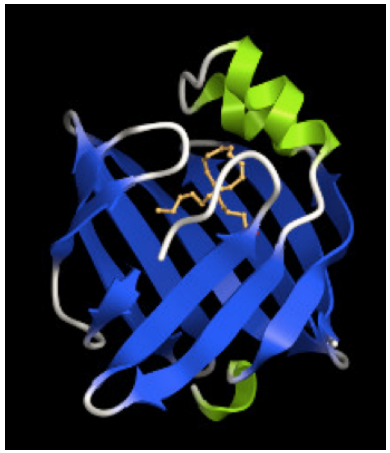
脂肪酸結合タンパク質Fabp7



Kagawa et al.: Fatty acid-binding protein 7 regulates function of caveolae in astrocytes through expression of caveolin-1 Glia, 2015

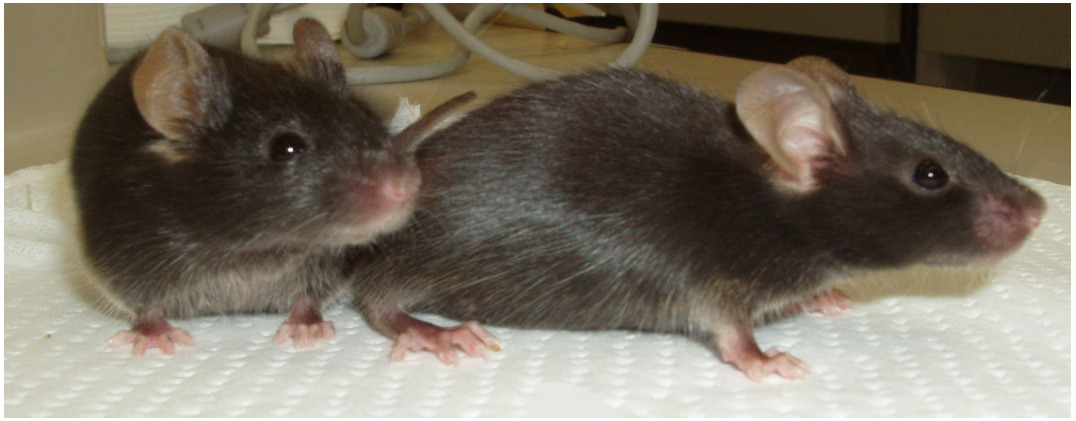
高度な神経機能

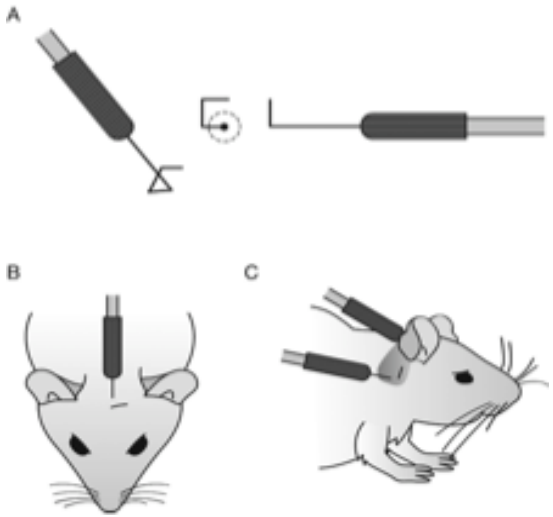
Fabp7

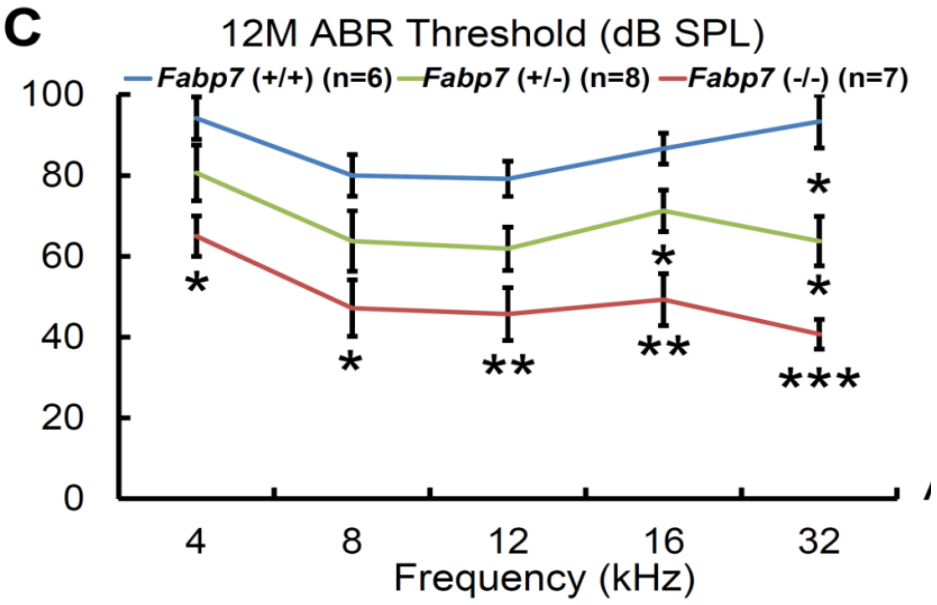


神経新生促進
神経伝達促進

加齢性難聴の進行とFabp7?



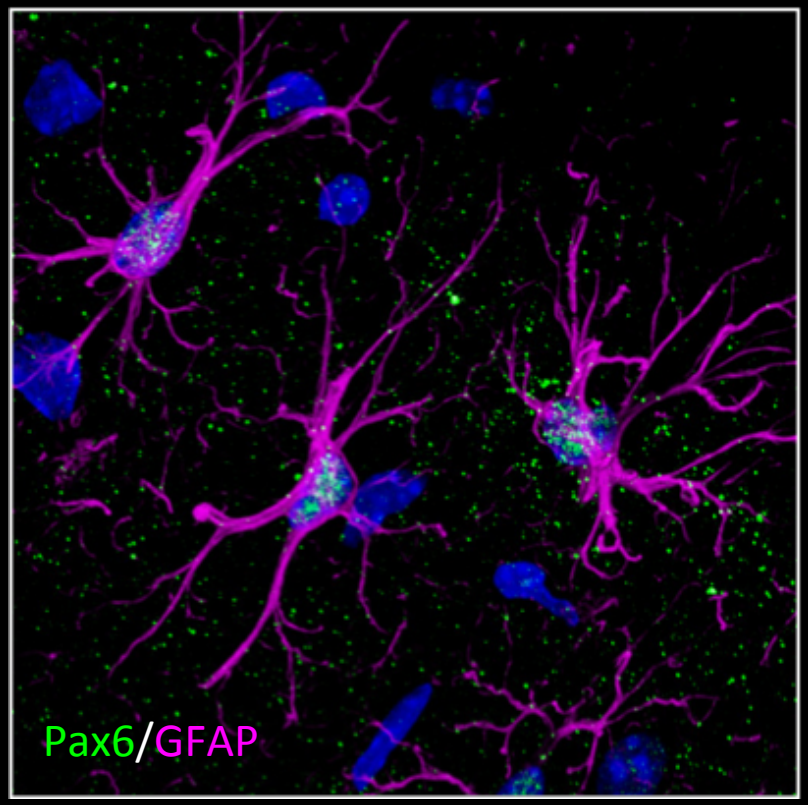


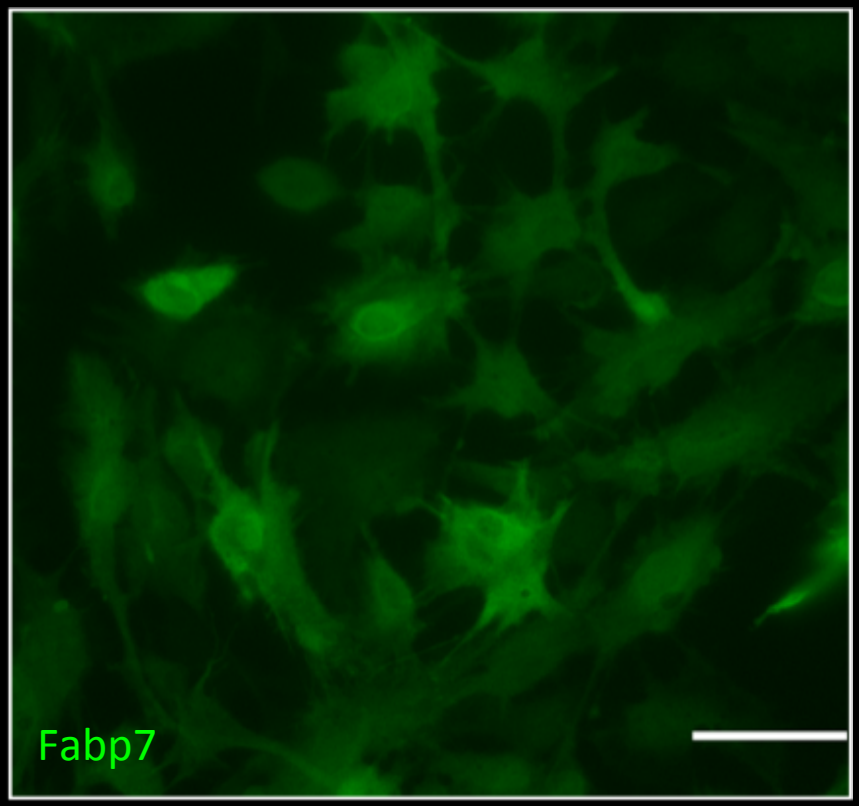


難聴の程度:
野生型＞ヘテロ＞ホモマウス

鈴木未発表

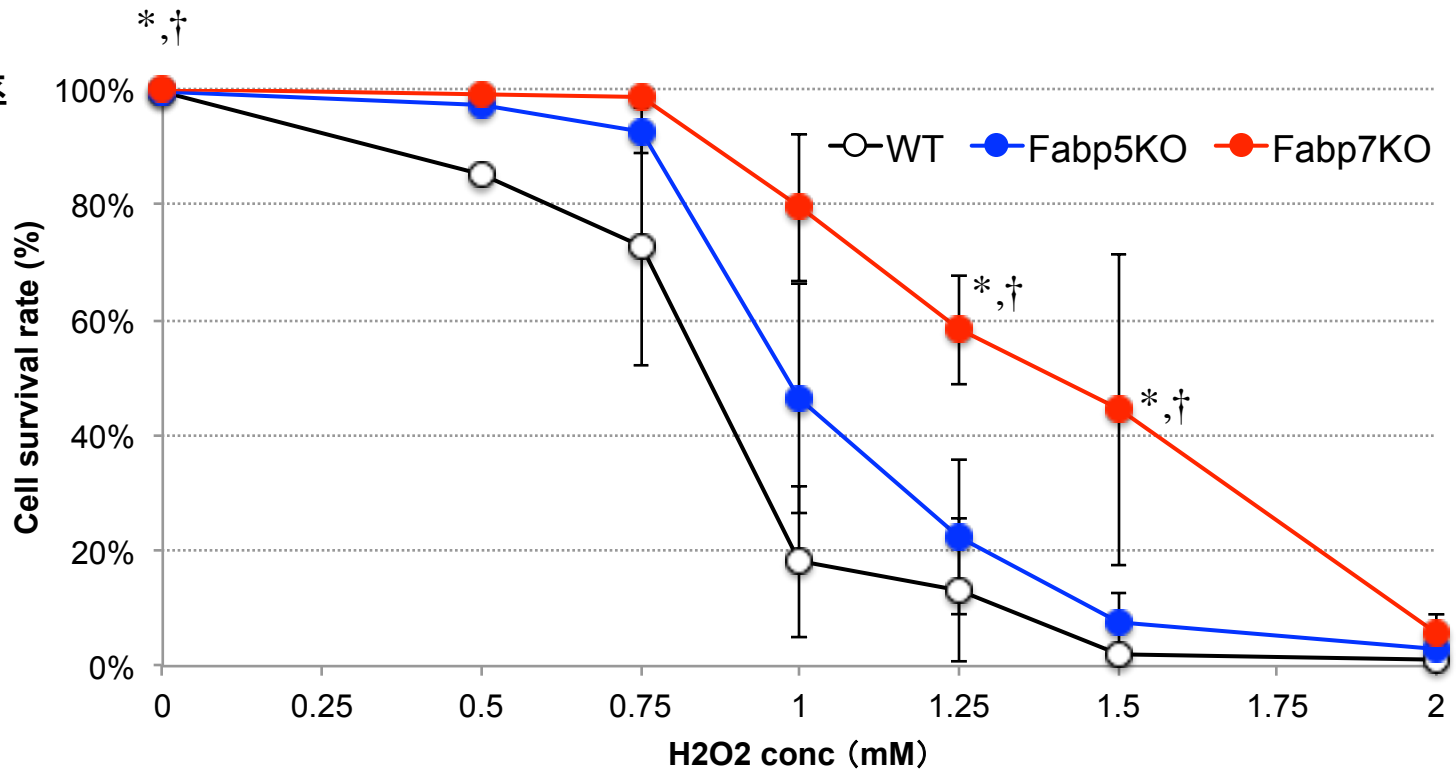
培養グリア細胞を用いた機能アッセイ





Fabp7 KO由来グリア細胞はストレス耐性

生存率

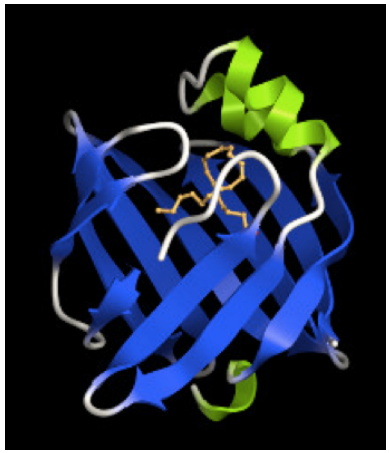


*, $p < 0.05$, WT vs Fabp7KO
†, $p < 0.05$, Fabp5KO vs Fabp7KO

柿沼、稲田未発表

高度な神経機能

Fabp7

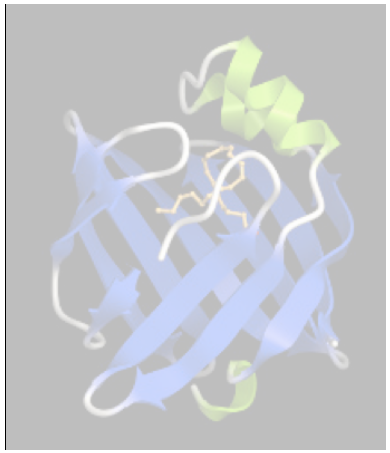


神経新生促進
神経伝達促進

酸化ストレス亢進

加齢性・騒音性
難聴易発症

Fabp7変異・発現低下・機能低下



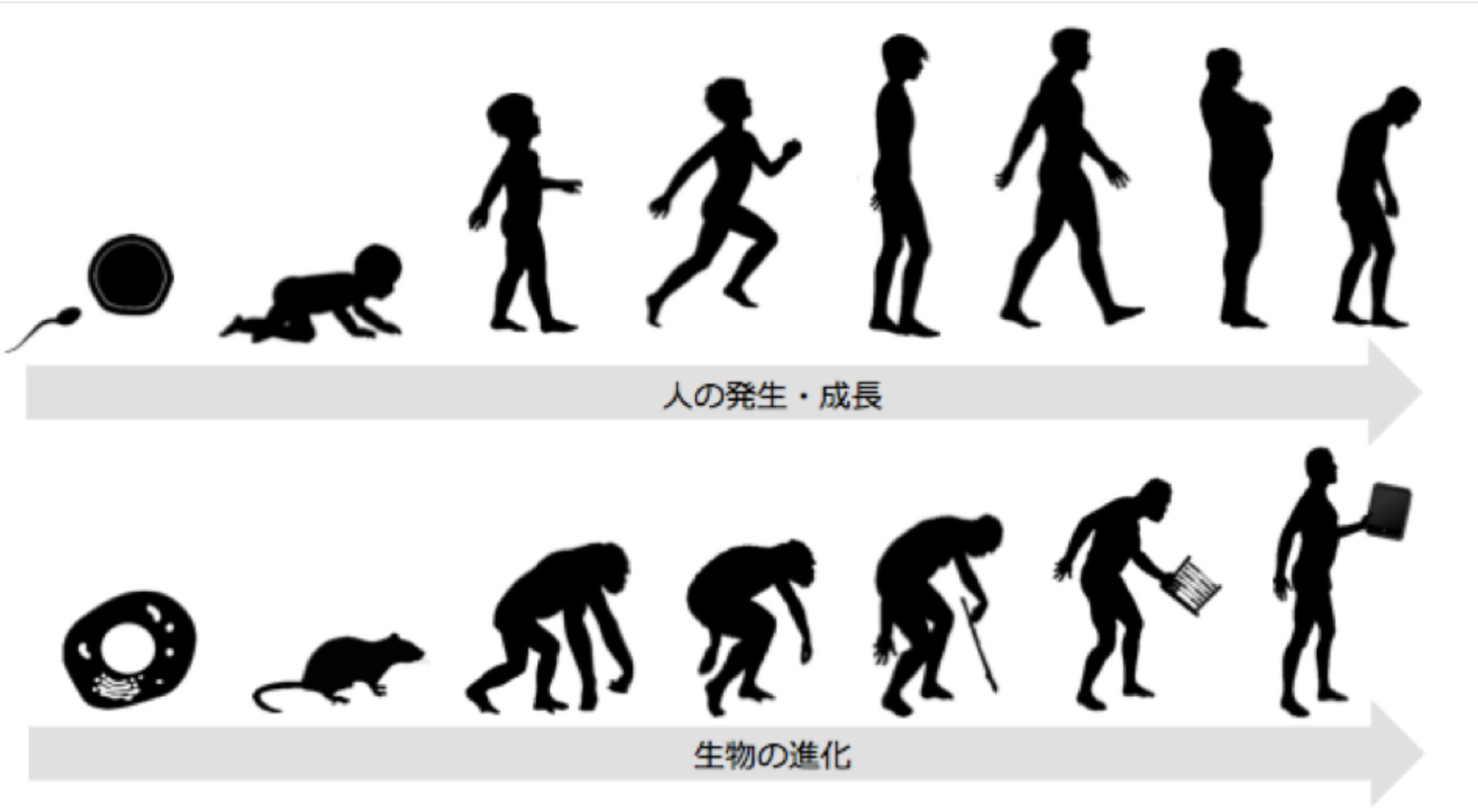
神経新生低下
神経伝達低下

精神疾患

酸化ストレス低下

加齢性難聴
発症遅延

ライフ・ステージに応じた脂質シグナル



進化医学的観点

視野を広く持とう！