



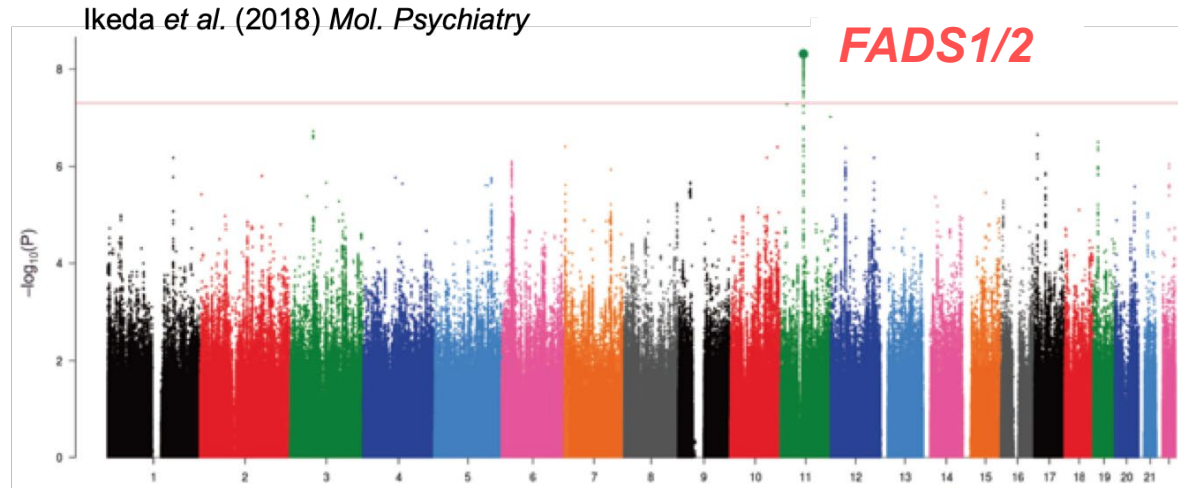
GWAS-identified bipolar disorder risk allele in the *FADS1/2* gene region links mood episodes and unsaturated fatty acid metabolism in mutant mice

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Hirona Yamamoto (PhD student)

Bipolar Disorder (BD) and GWAS

Japanese population (2,964 cases and 61,887 controls)

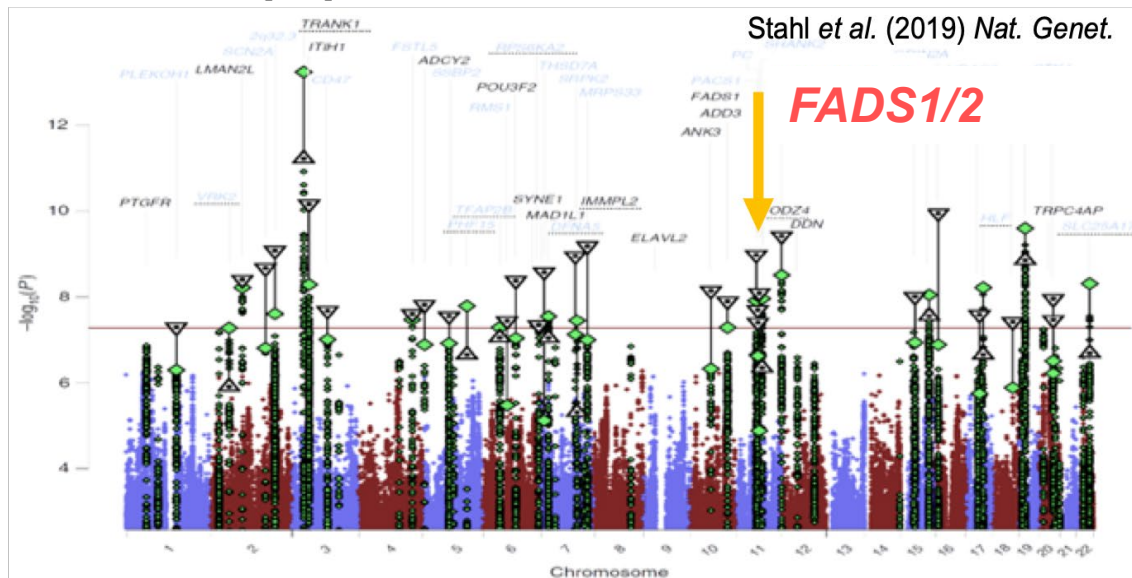


Carrying this risk allele makes

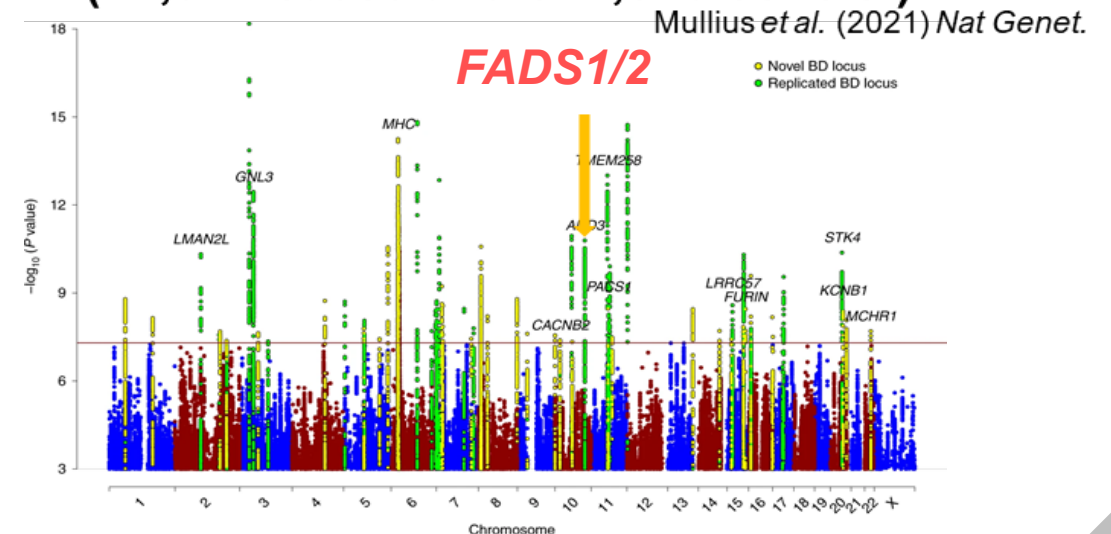
1.18 times more likely to have BD

- Reported as a risk gene in several populations
 - *FADS1/2* are functionally established gene
- It has been focused on as a risk gene for BD.

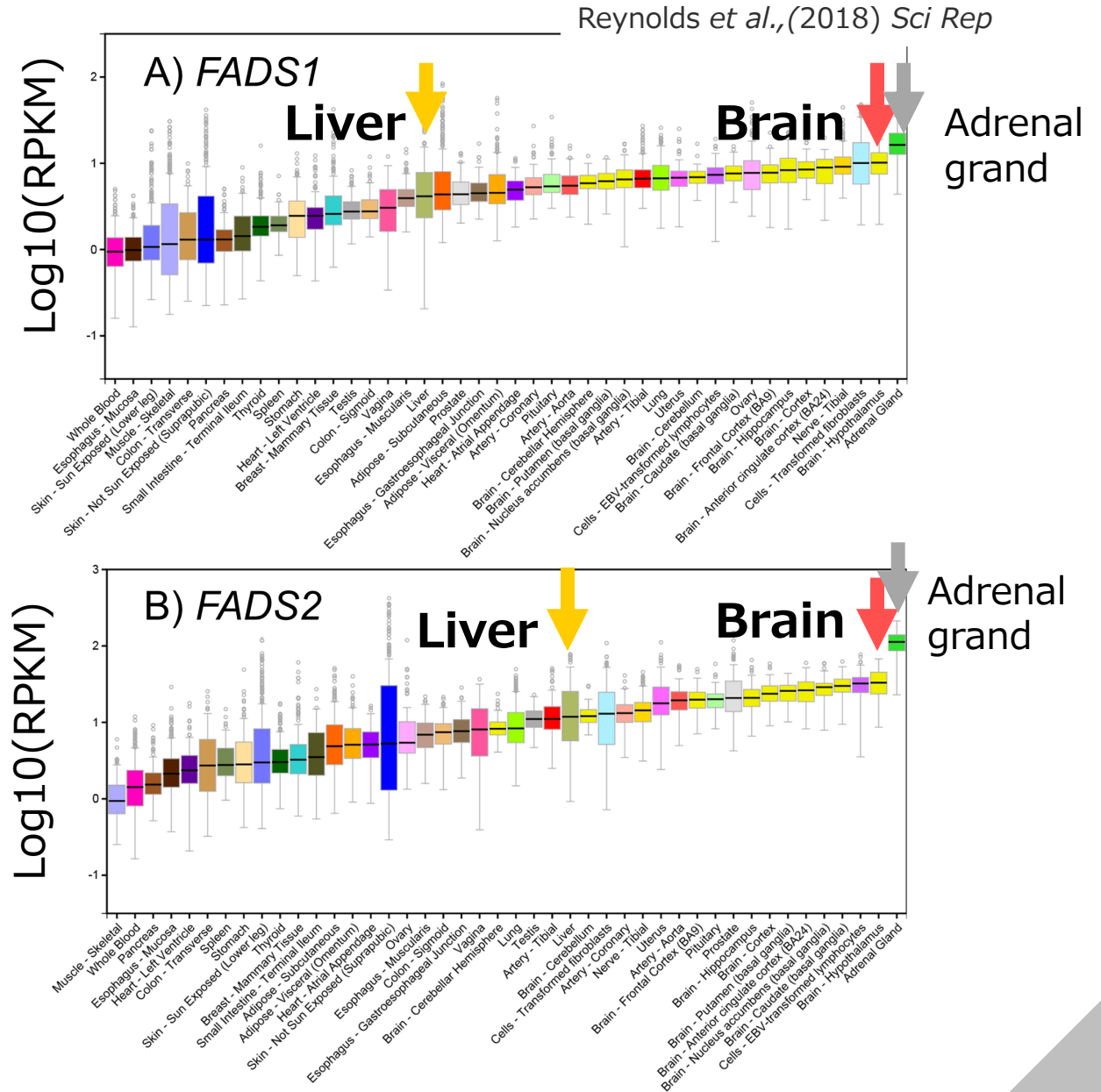
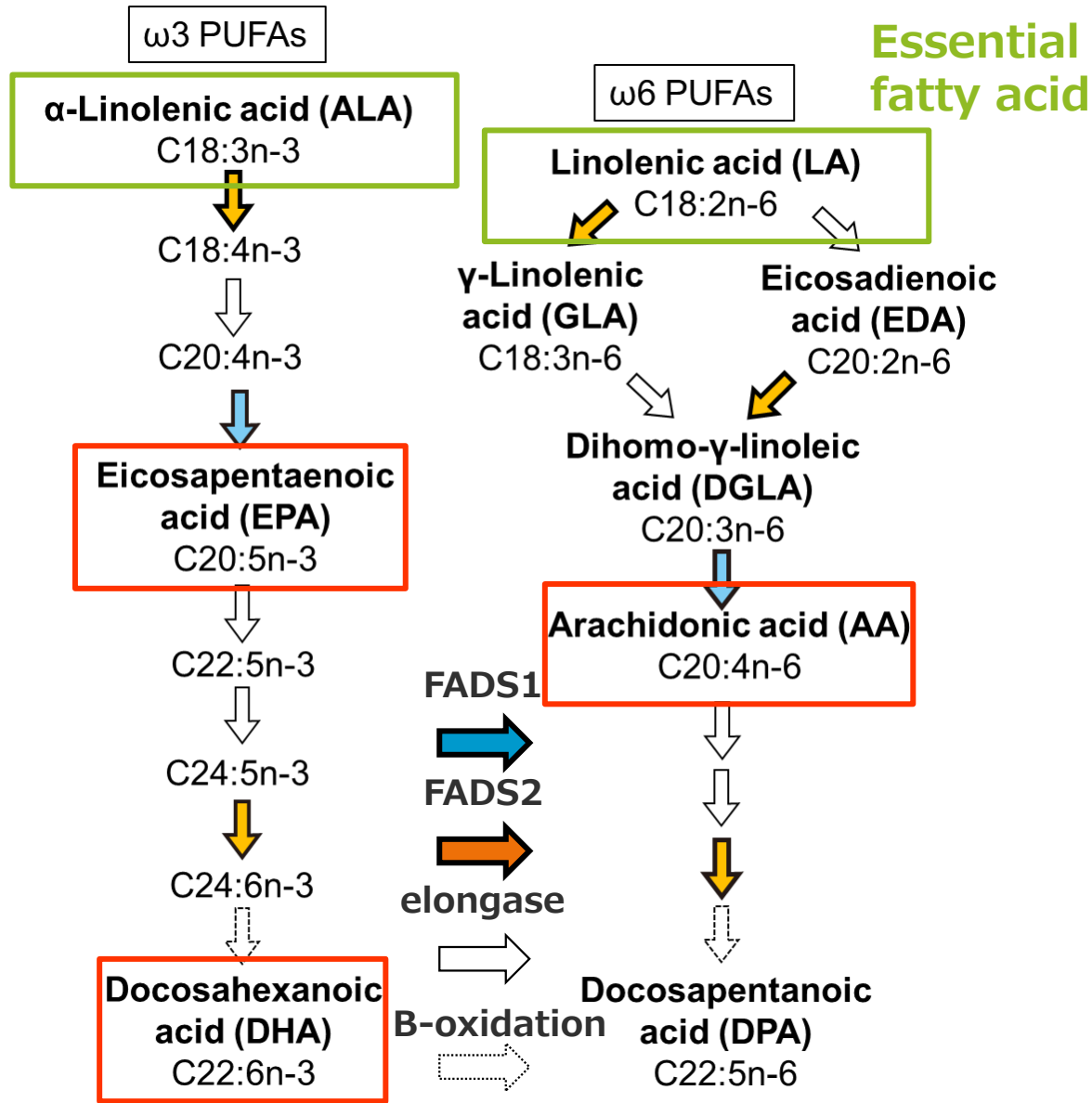
Caucasian population (20,352 cases and 31,358 controls)



Caucasian population (41,917 cases and 371,549 control)



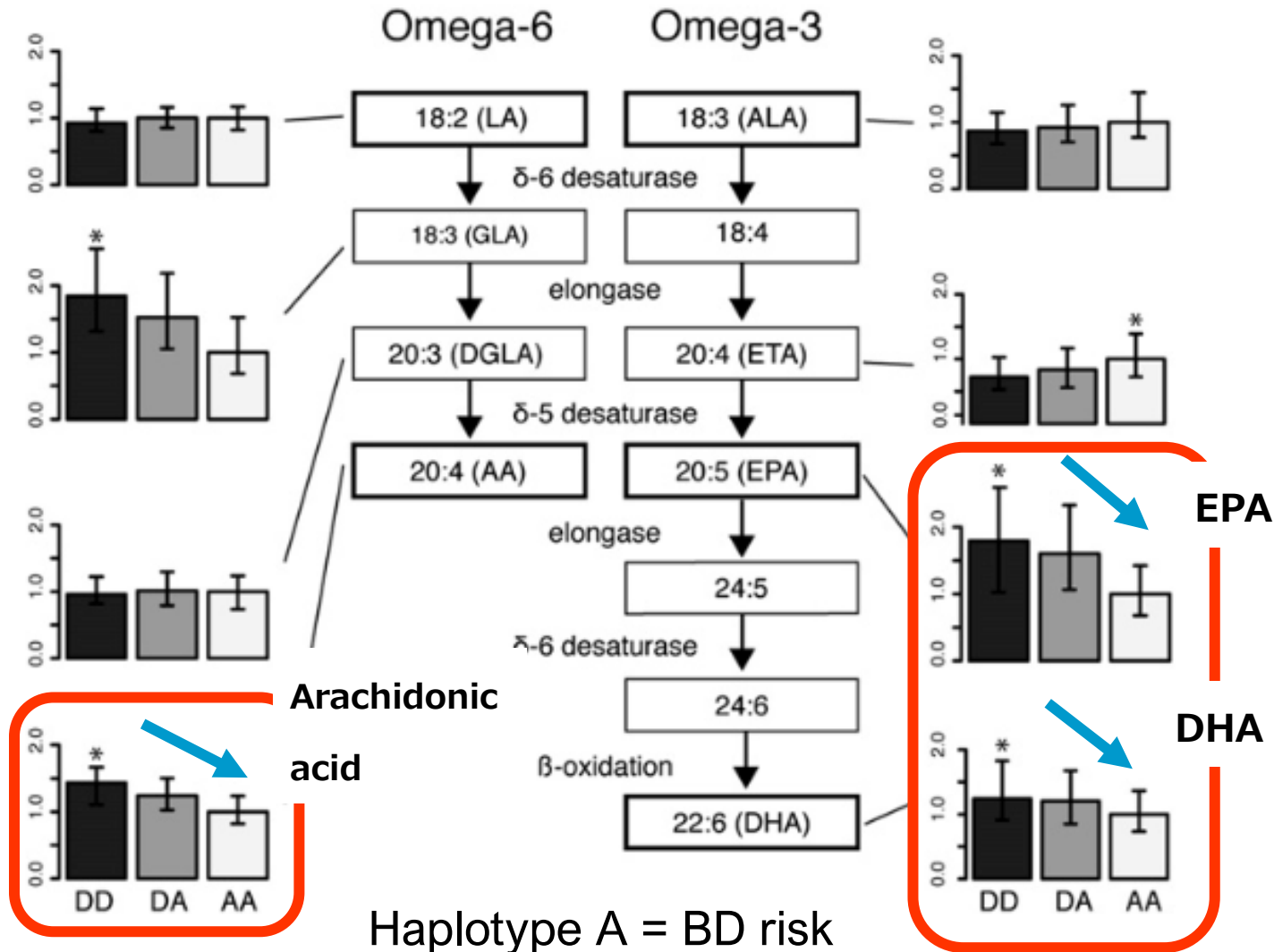
***FADS1/2* and PUFA(Polyunsaturated fatty acid)**



BD risk allele and fatty acid metabolism

Haplotypes and PUFA synthesis in *FADS1/2*

Ameur A et al., (2012) Am J Hum Genet



Haplotype **A**

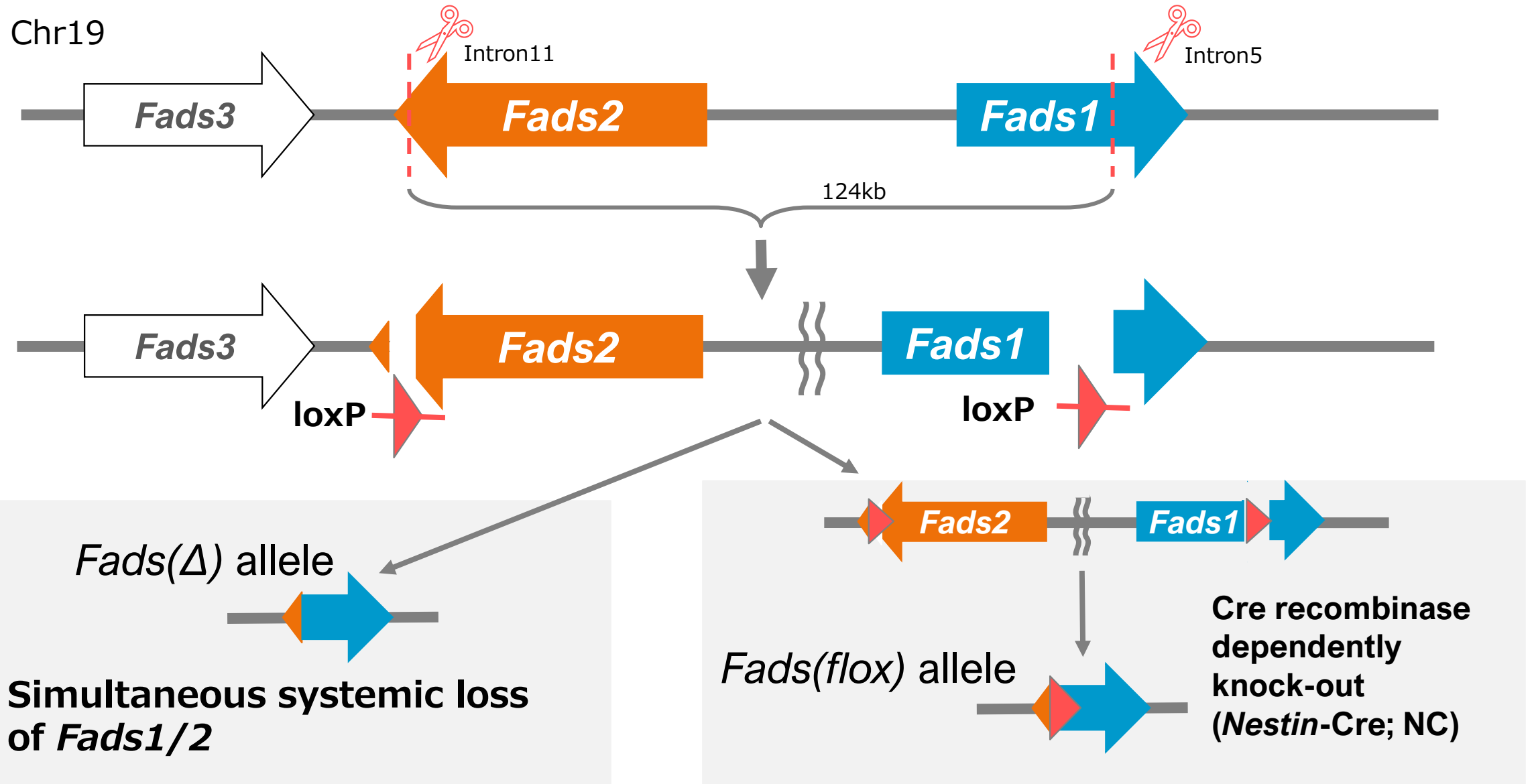
= **BD risk** haplotype

= **EPA, DHA, AA(decrease ↓)**

= Decreased activity of *FADS1/2*

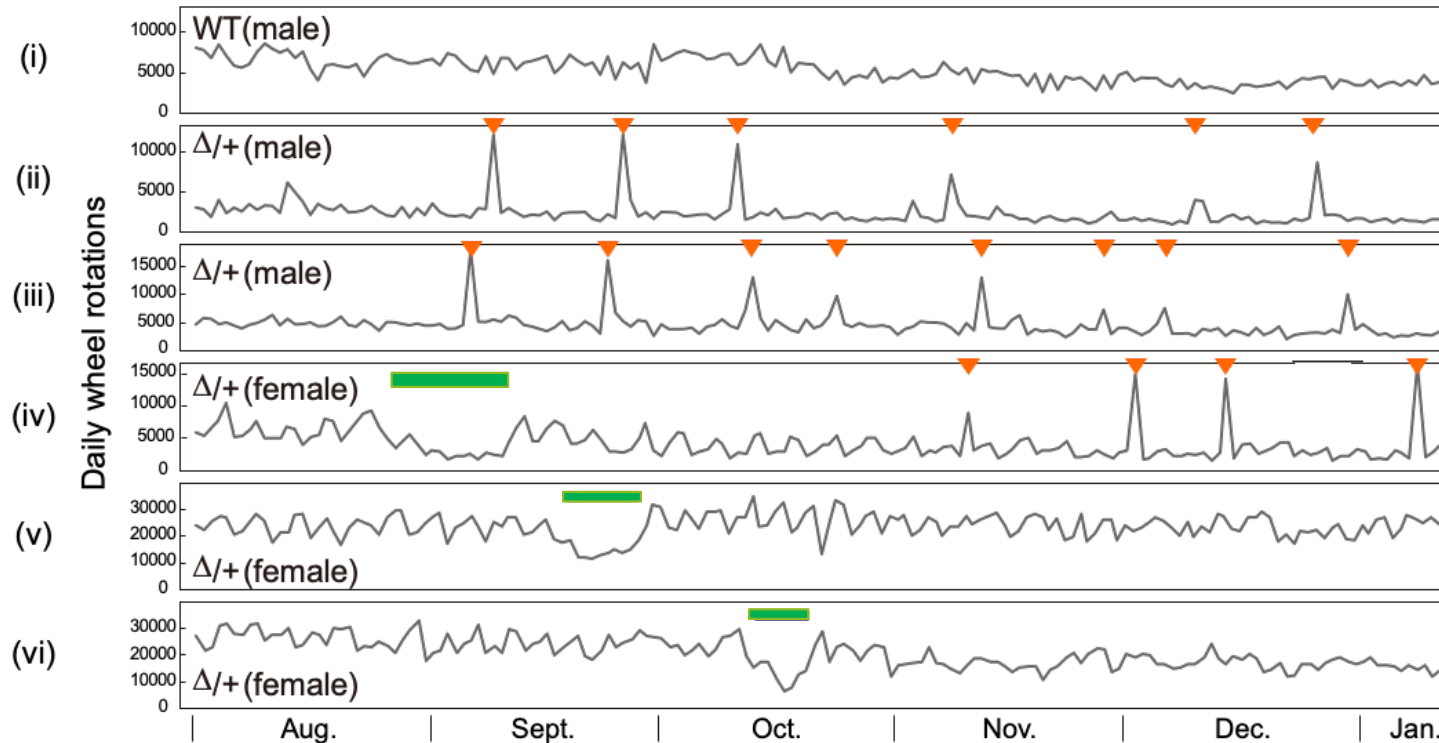
In BD risk haplotypes
decreased *FADS1/2* activity
is expected

Fads1/2 KO mice (originally generated by Dr. Kasahara)



Long-term wheel running analysis of *Fads*(Δ /+) mice

Days with a significant increase in activity compared to the days before and after **Hyperactive bouts (HABs)**

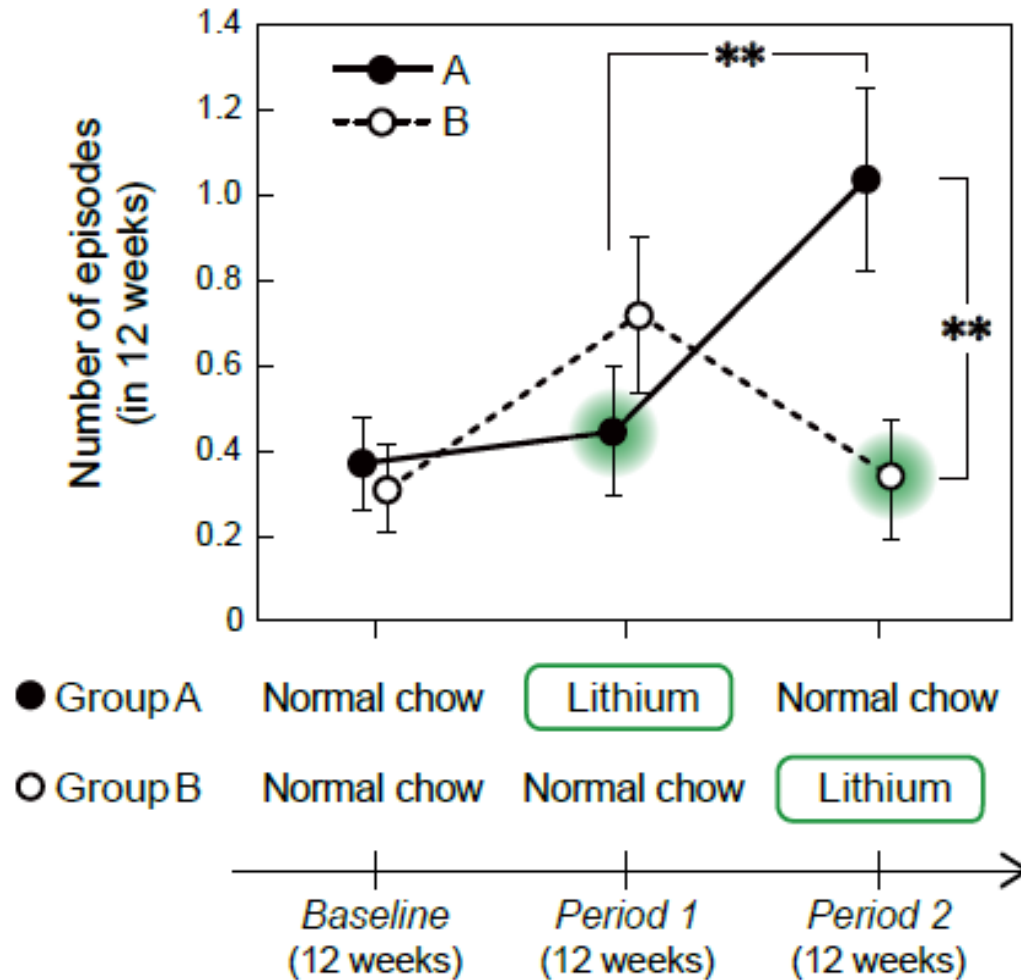


Sex	Genotype	n	HABs (per half year)
Male	<i>Fads</i> (Δ /+)	7	2.43
	WT	13	0.15
Female	<i>Fads</i> (Δ /+)	15	0.67
	WT	6	0.17

Sex	Genotype	n	DEs (per half year)
Male	<i>Fads</i> (Δ /+)	7	0
	WT	13	0
Female	<i>Fads</i> (Δ /+)	15	1.33
	WT	6	0

Days with a significant decrease in activity compared to the days before and after **Depressive-like episodes (DEs)**

Preventive effect of lithium administration



Depressive-like episodes in females were suppressed by lithium
(Period2 GroupA vs GroupB $p < 0.01$, medium effect size)

Fads($\Delta/+$) mice are
BD animal model that **satisfies**
three validities

Preventive effect of PUFA supplementation

In humans, several dosing patterns (DHA, EPA, DHA+EPA) have been studied for prophylactic effects however, no consistent results have been obtained for these effects. Bozzatello et al.,(2019) Int J Mol Sci

The preventive effect against **depressive-like episodes** was examined by multiple administration methods.

Diet	n	DEs (per half year)	
AIN-93G	20	1	* # P<0.1
AIN+EPA	10	1.3	
AIN+DHA	18	0.28	
AIN+EPA+DHA	12	0.34	



Depressive-like episodes frequency was suppressed in female mice supplemented with **DHA**

Long-term wheel running analysis of *Fads cKO* mice

Hyperactive bouts → none

Sex	Genotype	n	HABs (per half year)
Male	<i>Fads</i> (flox/+);NC/+	20	0
	<i>Fads</i> (+/+);NC/+	17	0.06
Female	<i>Fads</i> (flox/+);NC/+	11	0
	<i>Fads</i> (+/+);NC/+	10	0

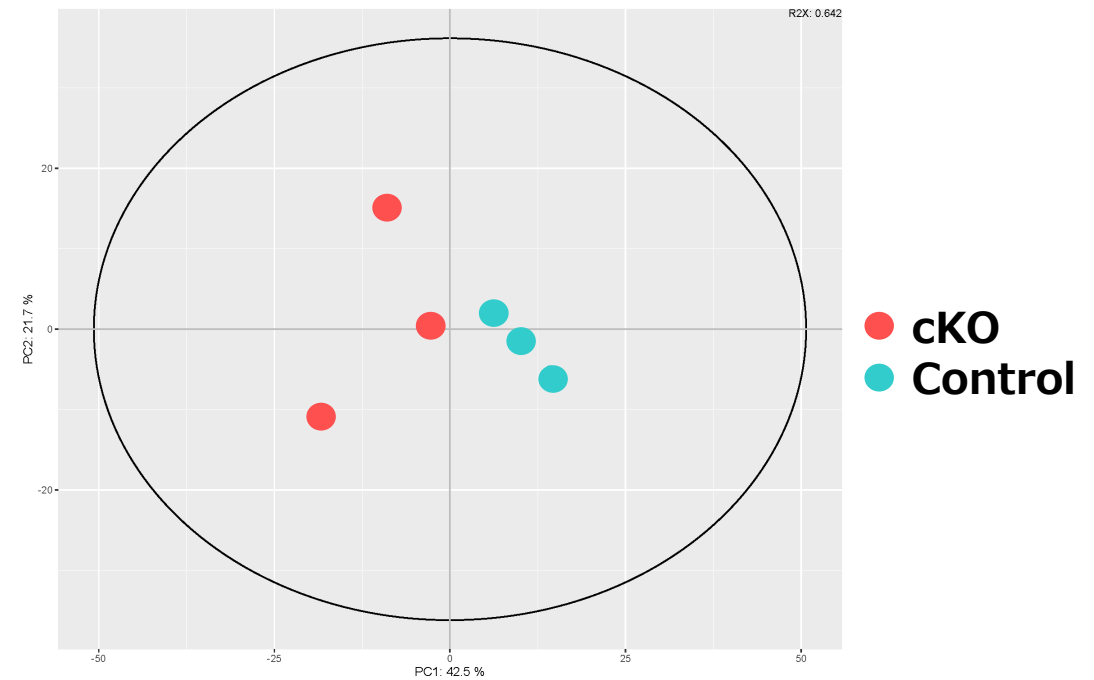
Depressive-like episodes → none

Sex	Genotype	n	DEs (per half year)
Male	<i>Fads</i> (flox/+);NC/+	20	0
	<i>Fads</i> (+/+);NC/+	17	0
Female	<i>Fads</i> (flox/+);NC/+	11	0
	<i>Fads</i> (+/+);NC/+	10	0

Behavior and **plasma lipids** were unchanged in cKO mice
Lipid composition in the brain may be altered

Plasma fatty acid → no changes
Brain lipids

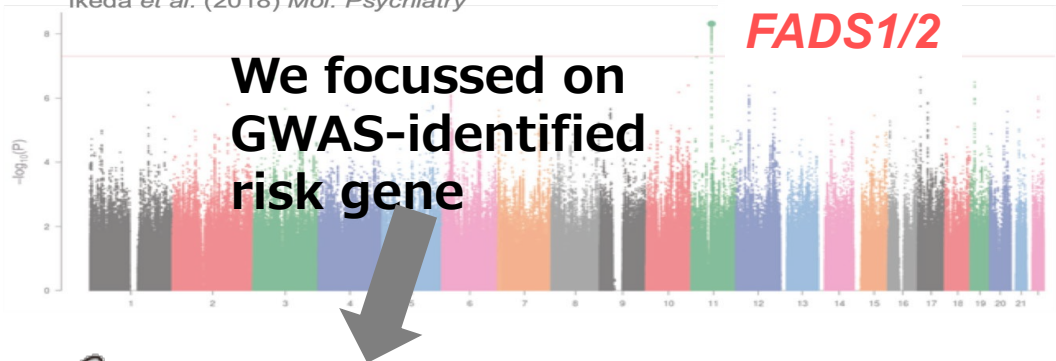
→ **Separated by genotype**



Summary

Japanese population (2,964 cases and 61,887 controls)

Ikeda et al. (2018) Mol. Psychiatry



Fads(Δ/+)

Three validity

- Construct validity

Decreased function of *Fads1/2*

- Face validity

Mood Swing Episodes

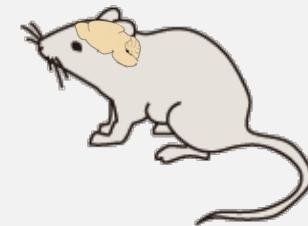
- Predictive validity

Effects of lithium administration

Diet	n	DEs (per half year)	
AIN-93G	20	1	* $P < 0.05$ # $P < 0.1$
AIN+EPA	10	1.3	
AIN+DHA	18	0.28	
AIN+EPA+DHA	12	0.34	

Effect of **DHA** supplementation

Brain-specific cKO
showed any episodic
behavior



Fads(flox/+);*Nestin-Cre*

Utilization of BD model mice generated based on GWAS findings is expected to improve our understanding of the relationship between BD and PUFAs