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Genetic variations of fyn-tyrosine kinase in Psychiatric disorders

Hattori K, Iljima Y, Uchiyama H, Yamamoto N, Fujii T, Hori H, Teraishi T, Tatsumi M, Omori M, Okamoto N, Arima K, Higuchi T, Kunugi H

Dept Mental Disorder Research, National Inst Neurosci, Nat Center Neurol & Psychiatry, Japan

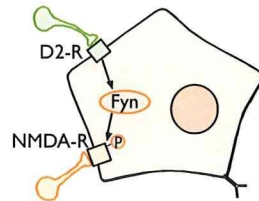
Summary

Fyn kinase regulates NMDA-R function, and participates in learning, emotion and sensitivity to antipsychotics. Recently, we found Fyn's expressions are altered in schizophrenic platelets.

To find a possible association of fyn gene and psychiatric disorders, we genotyped 8 SNPs in total 2000 of Japanese subjects. Although no association with schizophrenia or depression was detected, a significant association with bipolar disorder was found with several SNPs. Associations with scores of WCST in control subjects was also detected.

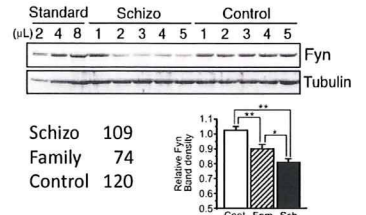
Introduction

Fyn kinase is a key mediator of the crosstalk between D2-R and NMDA-R



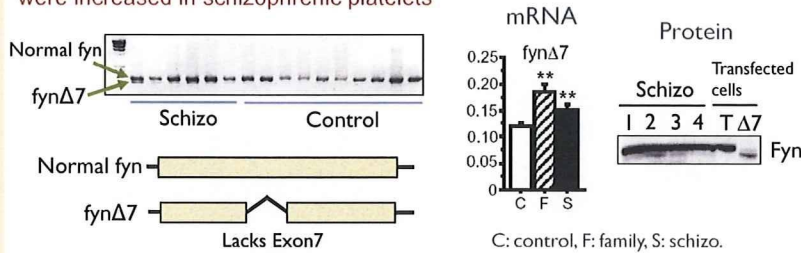
Hattori et al., JBC, 2006

Fyn protein levels were decreased in schizophrenic platelets.



Hattori et al., Psychiatry Res. 2009

Ratios of fynΔ7, a defective splice variant were increased in schizophrenic platelets

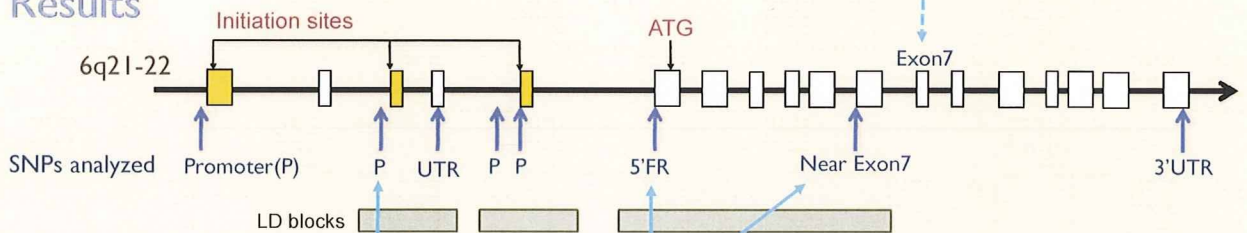


C: control, F: family, S: schizo.

Methods

Sample	Nos	8 TagSNPs genotyped
Schizo	497	→
Depression	528	
Bipolar	138	
Control	932	

Results

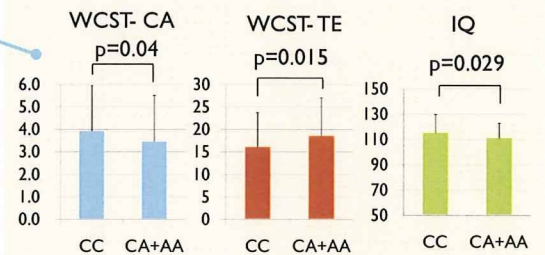


Association with bipolar disorder

	MAF	p-value
Bipolar	0.32	0.047
Control	0.25	

Haplotype p=0.047

Association with cognitive function



Discussion

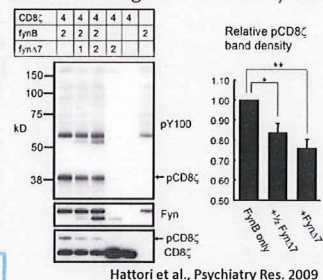
Phenotypes of Fyn KO

- Emotional deficits (fearful)
- Cognitive deficits

SNPs that affect fyn's expression

- Bipolar, Schizophrenia
- Cognition

Dominant-negative effect of fynΔ7



Hattori et al., Psychiatry Res. 2009

SNPs that affect splicing

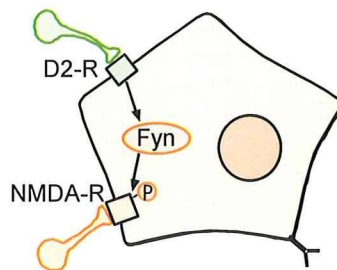
Limitation: small sample size of Bipolar patients

Fynチロシンキナーゼの統合失調症・気分障害における解析

国立精神・神経センター
神経研究所 疾病研究第3部

○服部功太郎、内山博文、山本宜子、飯嶋良味、藤井崇、堀弘明、寺石俊也、巽雅彦、大森まゆ、岡本長久、有馬邦正、樋口輝彦、功刀浩

FynはドーパミンD2受容体とNMDA受容体の橋渡しをする鍵分子

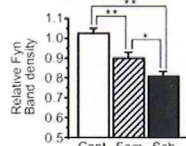


Hattori et al., JBC, 2006

統合失調症血液ではFynタンパクが減少している

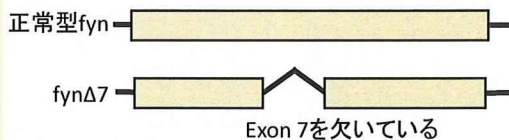
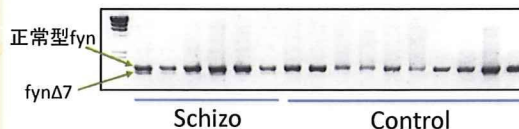


Schizophrenia 109
Family 74
Control 120

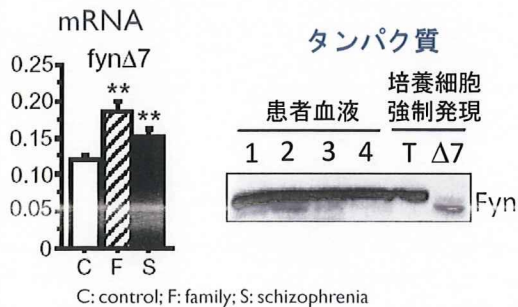


Hattori et al., Psychiatry Res. 2009

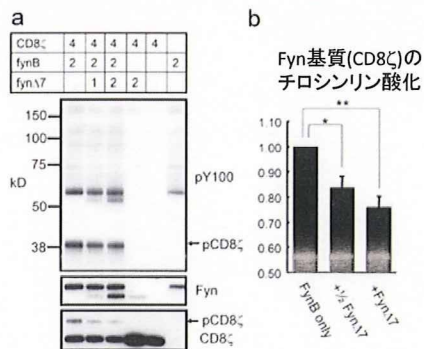
fyn mRNAのRT-PCR



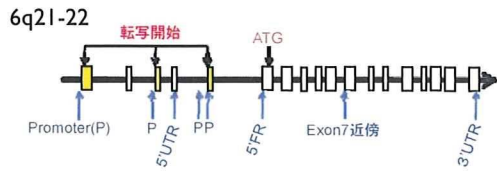
統合失調症血液におけるfynΔ7のmRNAとタンパク質



FynΔ7のDominant-negative効果

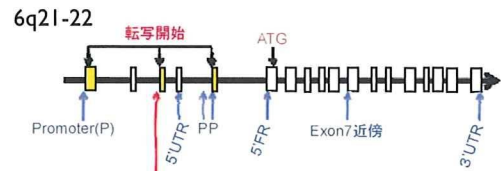


Fynゲノムの解析



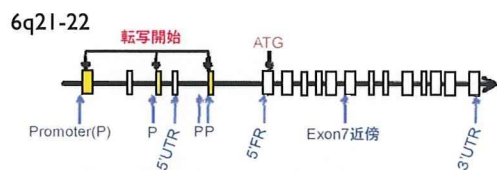
• 対象
Schizo 497, BD 138, Dep 528, Control 932
→ TaqMan assay

Fynゲノムの解析



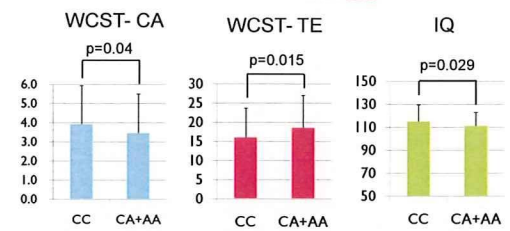
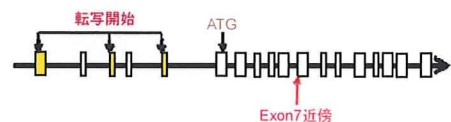
MAF
BD 0.32 (n=104) $p=0.047$
Cont 0.25 (n=927)

Fynゲノムの解析

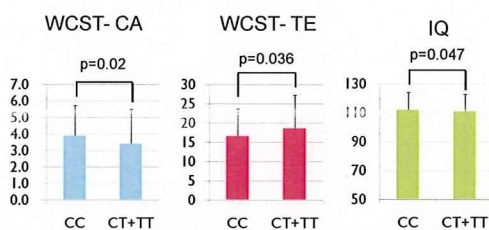
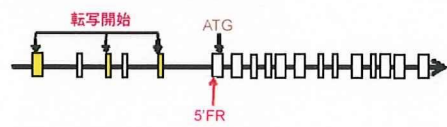


LD blocks
T A
BD 0.32 $p=0.049$
Cont 0.25

Fynゲノムの解析

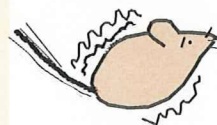


Fynゲノムの解析



Fynゲノムの解析

Fyn欠損マウス



- 情動異常 (こわがり)
→ BD? Dep? Sz?
- 学習能力異常
→ WCST?, IQ?

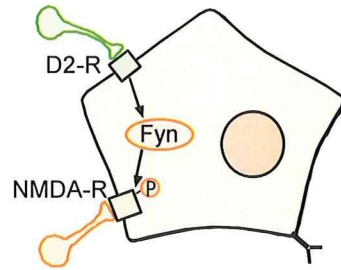
→ 死後脳・血液におけるFyn発現量

統合失調症・気分障害のゲノム・死後脳を用いたFynチロシンキナーゼの解析

国立精神・神経センター
神経研究所 疾病研究第3部

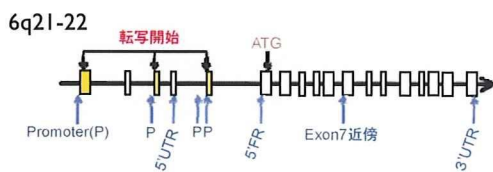
○服部功太郎、田中治子、内山博文、山本宜子、飯嶋良味、藤井崇、堀弘明、寺石俊也、木下裕紀子、松尾淳子、川本由実子、有馬邦正、功刀浩

FynはドーパミンD2受容体とNMDA受容体の橋渡しをする鍵分子



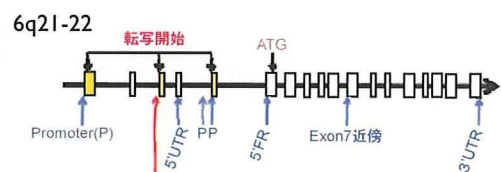
Hattori et al., JBC, 2006

Fynゲノムの解析



- 対象
Schizo 497, BD 138, Dep 528, Control 932
→ TaqMan assay

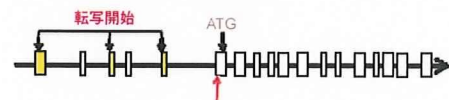
Fynゲノムの解析



MAF

BD	0.32 (n=104)	p=0.047
Cont	0.25 (n=927)	

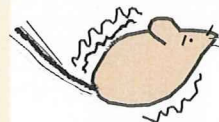
Fynゲノムの解析



WCST- CA	WCST- TE	IQ
p=0.02	p=0.036	p=0.047

Fynゲノムの解析

Fyn欠損マウス



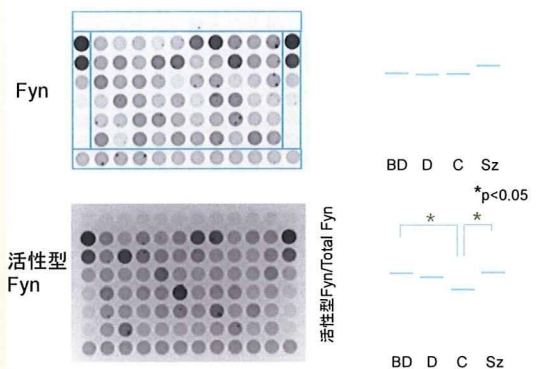
- 情動異常 (こわがり)
→ BD? Dep? Sz?
- 学習能力異常
→ WCST?, IQ?

→ 死後脳・血液におけるFyn発現量

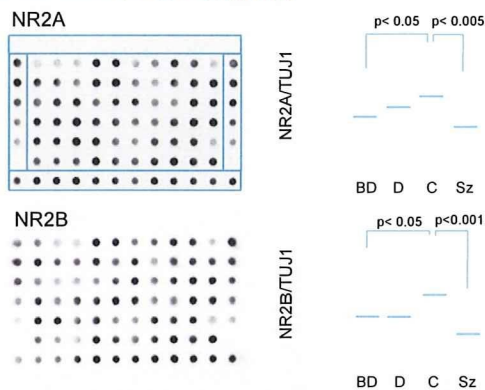
スタンレー死後脳の解析

- 60検体：Sz, BD, Dep, Cont各15例
- 年齢、性別、pH等をマッチ
- ブラインドで測定
- 測定結果を登録後、対応表が送られる

ELISAによる解析



Dot-blotによる解析



まとめ

- Fynゲノム
 - Szとは関連-, BDと関連
 - 認知機能と関連
- 死後脳(スタンレーBA6)
 - Sz, BDで活性型Fynの量・割合が亢進
 - Sz, BDでNMDA-Rサブユニットの減少

Genetic variations of fyn-tyrosine kinase and schizophrenia

Hattori K, Iijima Y, Uchiyama H, Yamamoto N, Fujii T, Hashimoto R, Horii H, Teraishi T, Arima K, Kinoshita Y, Matsuo J, Kawamoto Y, Kunugi H

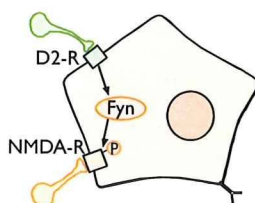
Dept Mental Disorder Research, National Inst Neurosci, Nat Center Neurol & Psychiatry, Japan

Summary

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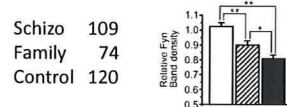
Introduction

Fyn kinase is a key mediator of the crosstalk between D2-R and NMDA-R



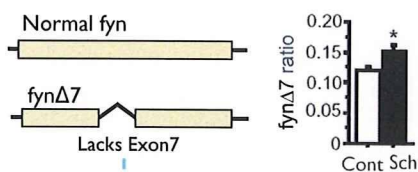
Hattori et al., JBC, 2006

Fyn protein levels were decreased in schizophrenic platelets.



Hattori et al., Psychiatry Res. 2009

Ratios of fynΔ7, a defective splice variant were increased in schizophrenic platelets

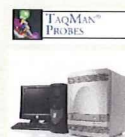


Method

Genomic DNA

Sample	Nos
Schizo	497
Dep	528
Bipolar	204
Control	932

8 TagSNPs genotyped

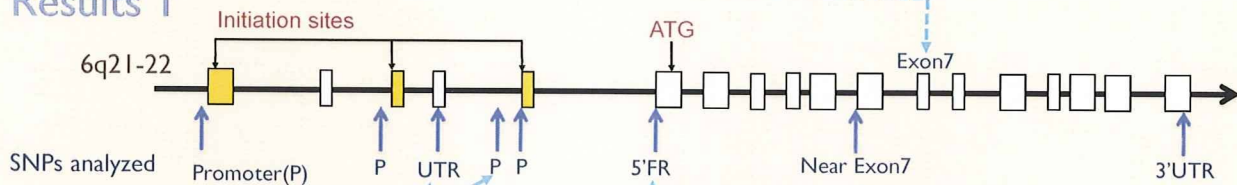


Blood mRNA

Sample	Nos
Schizo	158
Dep	49
Bipolar	31
Control	409

Quantitative-PCR (TaqMan probes) fyn, fynΔ7

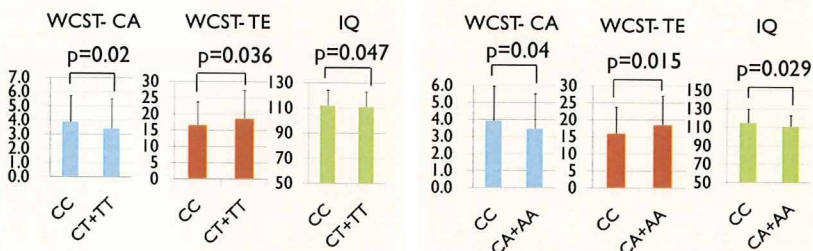
Results I



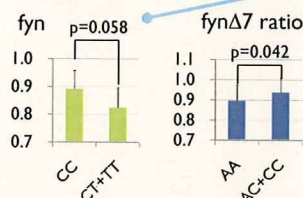
Association with bipolar disorder

	MAF	p-value
Bipolar	0.32	0.06
Control	0.25	

Association with cognitive function



Association with fyn, fynΔ7 expression levels



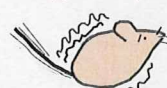
Decreased expression of fyn, fynΔ7 mRNA in schizophrenia

Dx	n	fyn		fynΔ7		fynΔ7/fyn	
		Mean	p	Mean	p	Mean	p
Schizo	158	0.753	0.027	0.681	0.038	0.959	1
Dep	49	1.05	1	1.01	1	1.1	1
Bipolar	31	0.735	0.24	0.697	0.753	1.05	1
Control	409	0.907		0.823		0.991	

ANCOVA (age, sex), bonferroni

Discussion

Phenotypes of Fyn KO

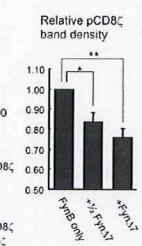
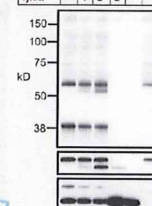


- Emotional deficits (fearful)
- Cognitive deficits

SNPs that affect fyn's expression
Bipolar, Schizophrenia
Cognition

Dominant-negative effect of fynΔ7

CD8c	4	4	4	4	4
fynB	2	2	2	2	2
fynΔ7	1	2	2		



SNPs that affect splicing

