

パーキンソン病の遺伝背景解明と その応用

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パーキンソン病

1. 中～晩年期に発症

2. 4大症状(運動障害)

安静時振戦・筋固縮・無動・姿勢反射障害

非運動症状

認知障害、うつ、自律神経症状

3. アルツハイマー病について多い、神経変性疾患

有病率は10万人あたり150人、全国に15万人

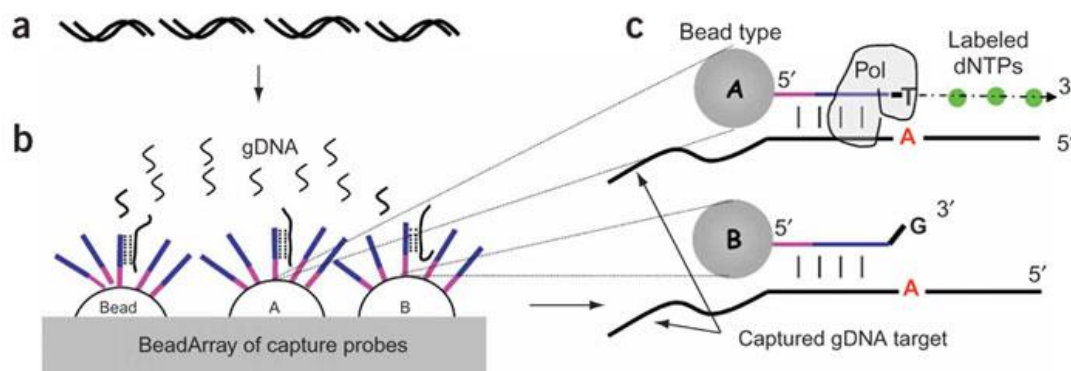
4. 発症様式 5-10%の症例には家族内発症あり

少数のMendel遺伝(単一遺伝性)家系あり

大多数(90-95%)は孤発性発症

ゲノムワイド関連解析

1. 患者1,078検体、対照2,628検体をタイピング
2. 1枚のアレイに56万個のSNP型を判定するビーズを搭載



3. 厳密なQuality Control

Sample QC

Sample CR<0.95 (case), <0.98 (control)

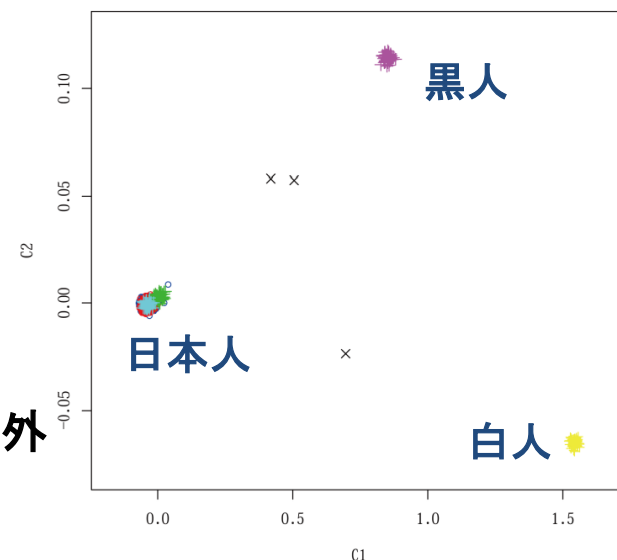
かくれた血縁関係 2度近親まで

かくれた非日本人

→患者988検体、対照2,521検体を検定へ

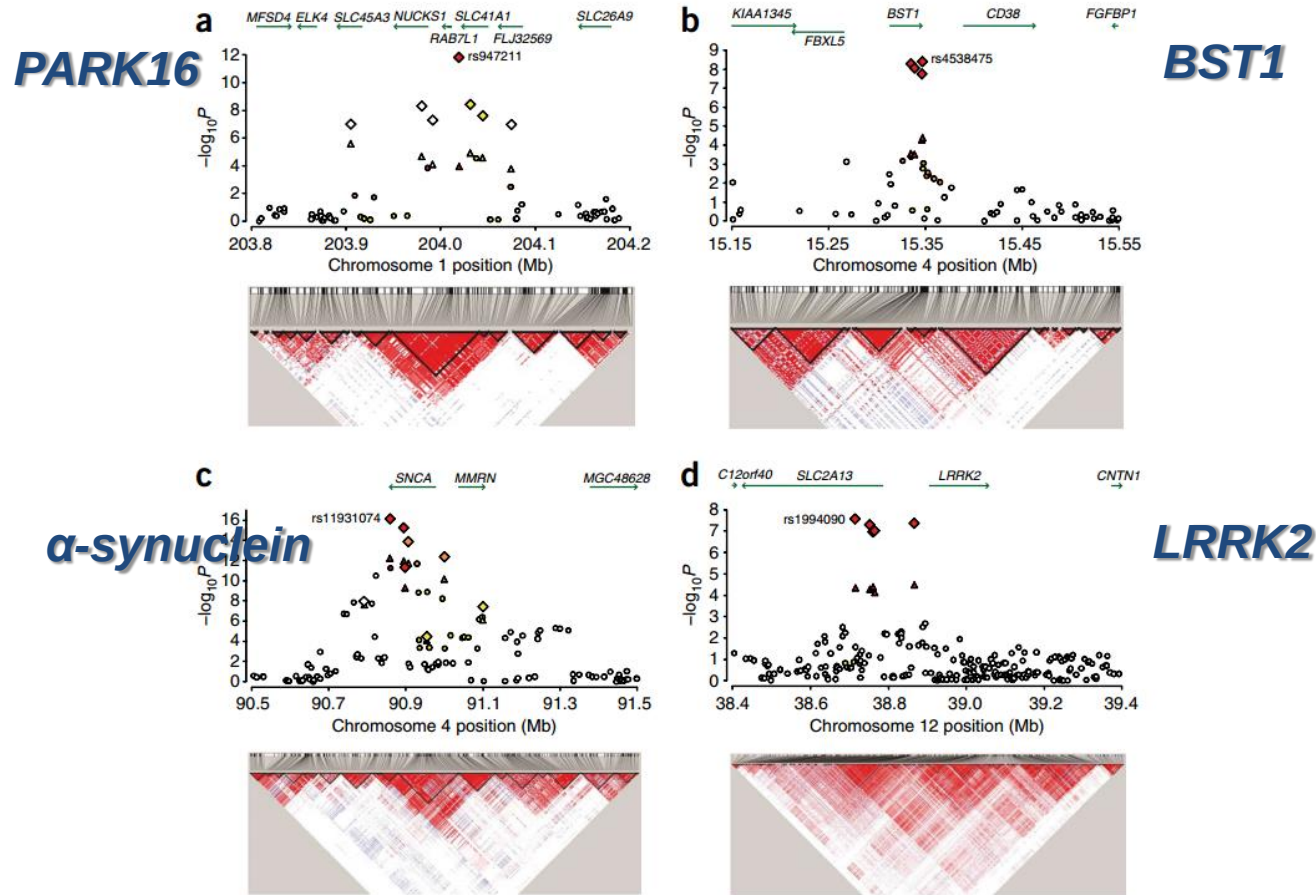
SNP QC; MAF < 0.05 , HWE- $P < 0.001$, SNP CR < 0.95 を除外

→ **435,470 SNP** を検定へ



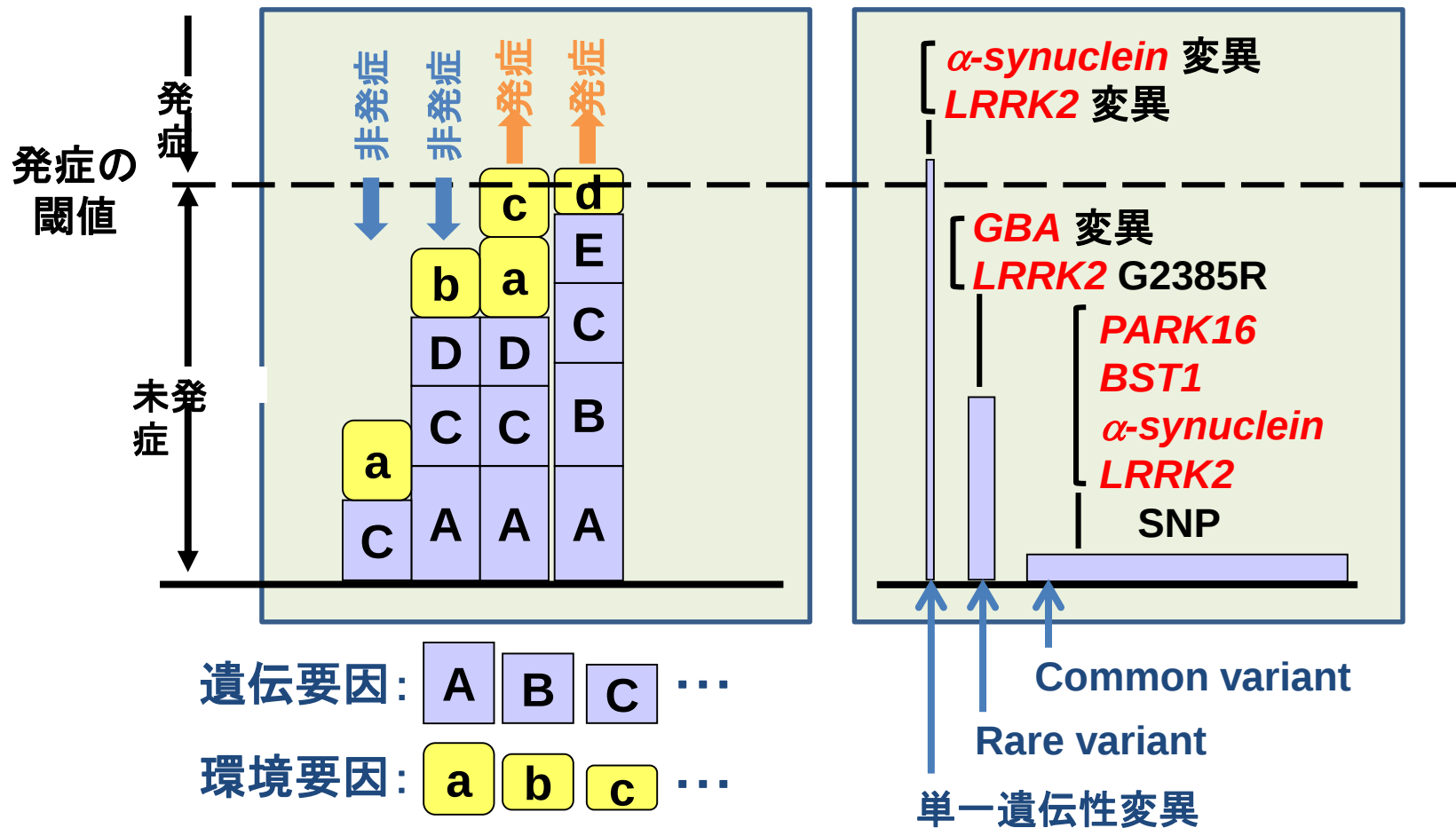
Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

Wataru Satake¹⁻³, Yuko Nakabayashi^{1,2}, Ikuko Mizuta^{1,2}, Yushi Hirota^{1,2}, Chiyomi Ito^{1,2}, Michiaki Kubo⁴, Takahisa Kawaguchi⁴, Tatsuhiko Tsunoda⁴, Masahiko Watanabe⁵, Atsushi Takeda⁶, Hiroyuki Tomiyama⁷, Kenji Nakashima⁸, Kazuko Hasegawa⁹, Fumiya Obata¹⁰, Takeo Yoshikawa¹¹, Hideshi Kawakami¹², Saburo Sakoda³, Mitsutoshi Yamamoto¹³, Nobutaka Hattori⁷, Miho Murata¹⁴, Yusuke Nakamura^{4,15} & Tatsushi Toda^{1,2}



Japanese GWAS identified 4 PD-risks (PARK16, BST1, α -synuclein and LRRK2) with genomewide significance (Satake et al, Nature Genet 2009)

＜孤発性パーキンソン病の遺伝背景＞



(左) パーキンソン病は、複数の遺伝因子と複数の環境因子の積み木の総和が、ある閾値を超えたとき発症する多遺伝性疾患。

(右) 遺伝因子は、患者内での頻度も、発症オッズ比の強さもまちまちであり、common variantとしてPARK16, BST1, α -synuclein, LRRK2, rare variantとしてGBA変異, LRRK2 G2385R

さらなるパーキンソン病遺伝子の発見をめざす

50万ポイント

(1塩基多型、GWAS)

→ 5000万ポイント

(全エクソン解読、エクソーム)

→ 30億ポイント

(全ゲノム)

**次世代
シーケンサー**



Whole exome sequencing using next-generation sequencer

104 443 15 October 2009 | DOI:10.1038/nature08484

nature

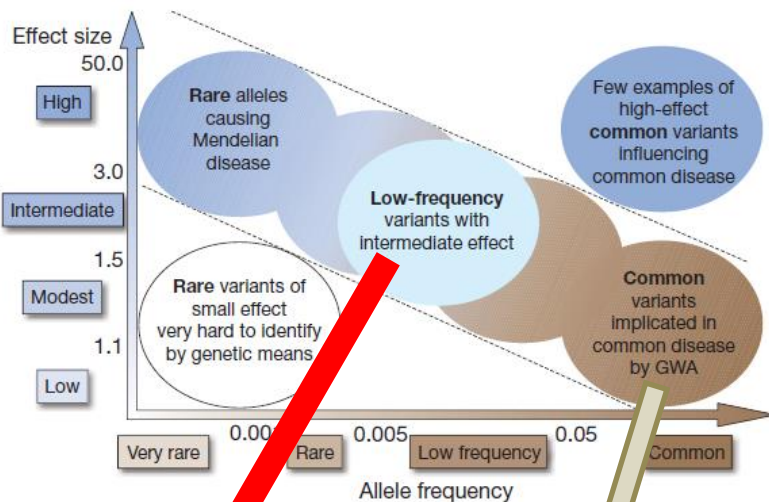
REVIEWS

Finding the missing heritability of complex diseases

Tari A. Manolio¹, Francis S. Collins², Nancy J. Cox³, David B. Goldstein⁴, Lucio A. Hindorf⁵, David J. Hunter⁶, Mark I. McCarthy⁷, Eric M. Ramos⁸, Lon R. Cardon⁹, Aravinda Chakravarti¹⁰, Judy H. Cho¹¹, Alan E. Guttman¹², Augustine Kong¹³, Leonid Kruglyak¹⁴, Elaine Mardis¹⁵, Charles N. Rotimi¹⁶, Montgomery Staton¹⁷, David Valle¹⁸, Alice S. Whittemore¹⁹, Michael B. Zuckerman²⁰, Andrew G. Clark²¹, Evan E. Eichler²², Greg Gibson²³, Jonathan L. Haines²⁴, Trudy F. C. Mackay²⁵, Steven A. McCann²⁶ & Peter M. Visscher²⁷

Genome-wide association studies have identified hundreds of genetic variants associated with complex human diseases and traits, and have provided valuable insights into the genetic architecture. Most variants identified so far confer relatively small increments in risk, and explain only a small fraction of the total heritability. The remaining 'missing heritability' can be explained by several factors, including the presence of rare variants with larger effects, which are not captured by current GWAS. Research strategies, including understanding the biology of these variants, are needed to identify the remaining 'missing heritability' and enhance its potential for understanding the genetic architecture of complex diseases and enhance its potential for understanding the genetic architecture of complex diseases and enhance its potential for understanding the genetic architecture of complex diseases.

(Manolio et al, *Nature* 2009)



**Exome
Association
Study**

2nd GWAS

1. Exon capture
Sureselect 50M/V4/V5
2. High throughput sequencing
HiSeq2000/2500
3. BWA Mapping
4. GATK Calling

