Dissecting the genetic diversity of Japanese's marmoset colonies

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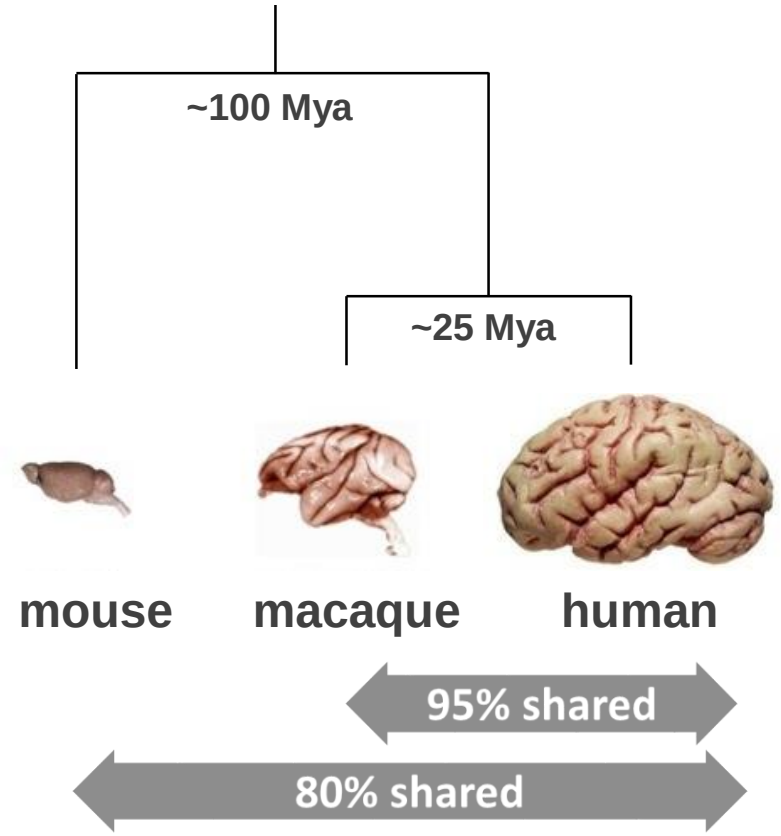
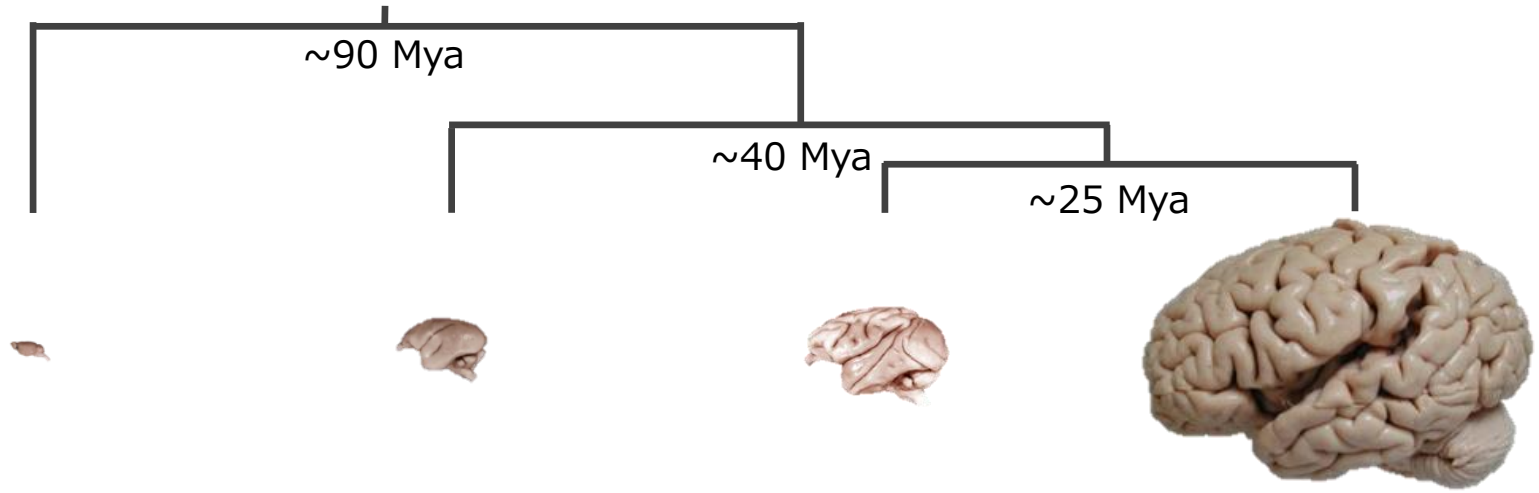
Animal Model for Neuropsychiatric Disord

Conventional Animal Model

Advanced Animal Model



Primate Model for Human Diseases

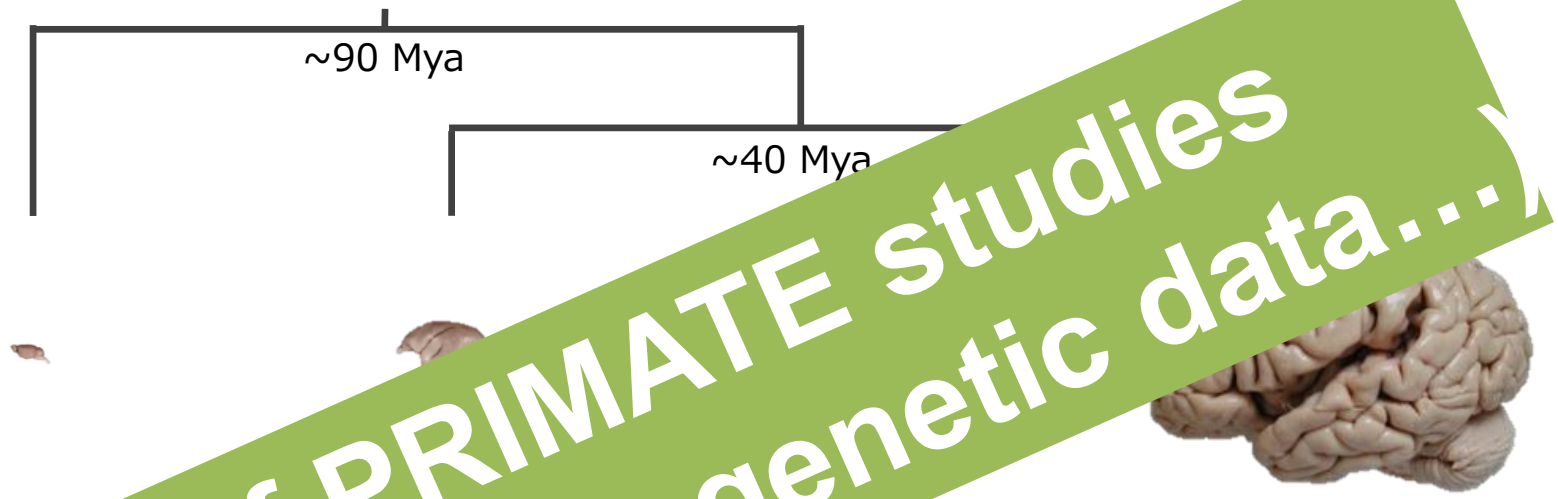


	mouse		marmoset		macaque		human
Brain weight	**0.4 g**	20x	**8 g**	11x	**87 g**	17x	**1500 g**
# neurons	**71** millions	9x	**634** millions	10x	**6376** millions	13x	**86000** millions

Manipulation

Complexity, Specificity

Primate Model for Human Diseases



Lack of PRIMATE studies
methodologies, genetic data…

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Manipulation

Complexity, Specificity

Primate Genomic & Transcriptomic Study

Genome

☞ Identification of **spontaneous mutants** in the neuropsychiatric related genes in macaques & marmosets

Transcriptome

☞ **Brain transcriptome atlas** at macro/mesoscale in marmosets

☞ Brain transcriptome analysis of **disease marmoset model** and elucidating molecular basis of neuropsychiatric disease

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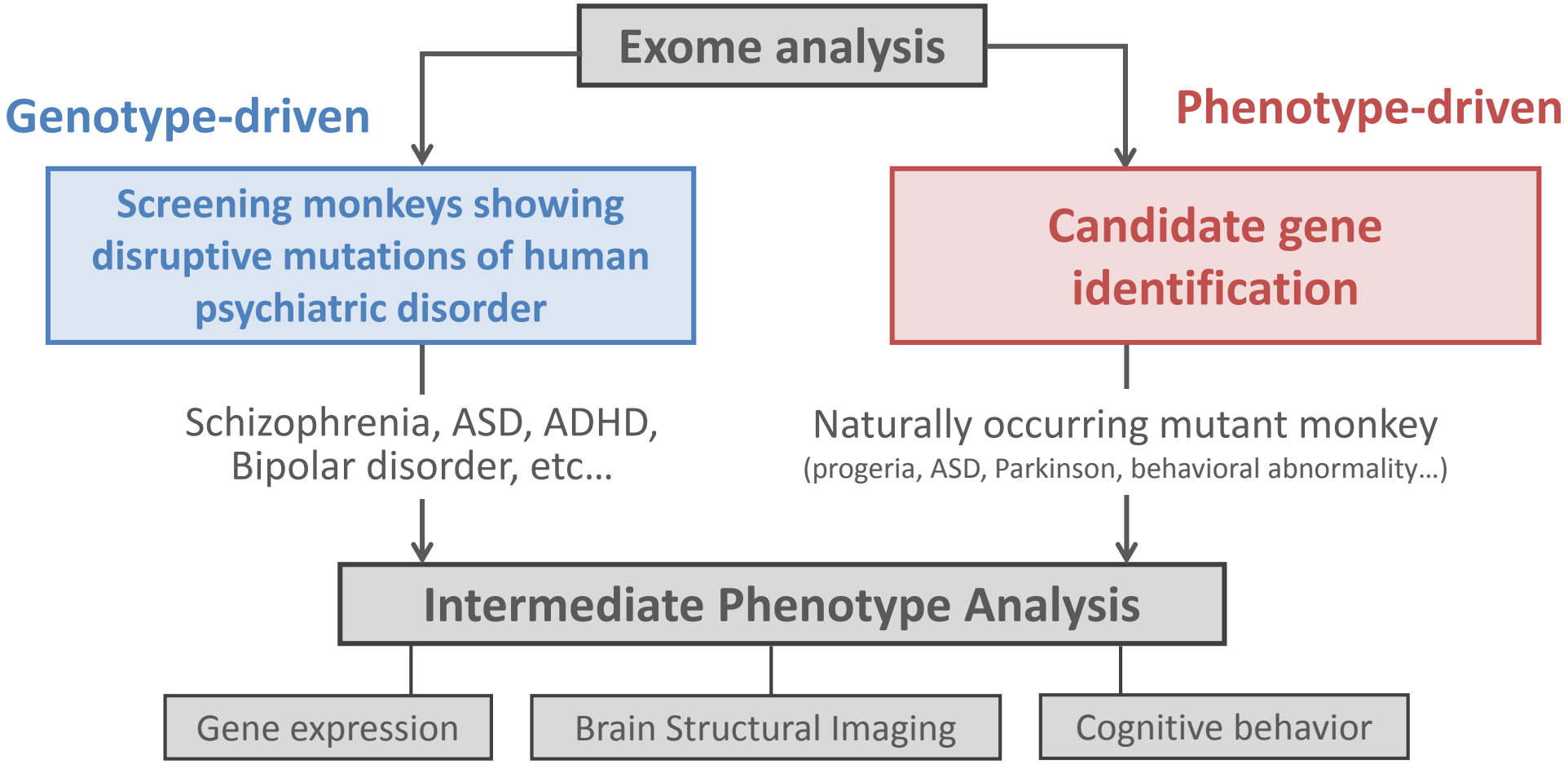
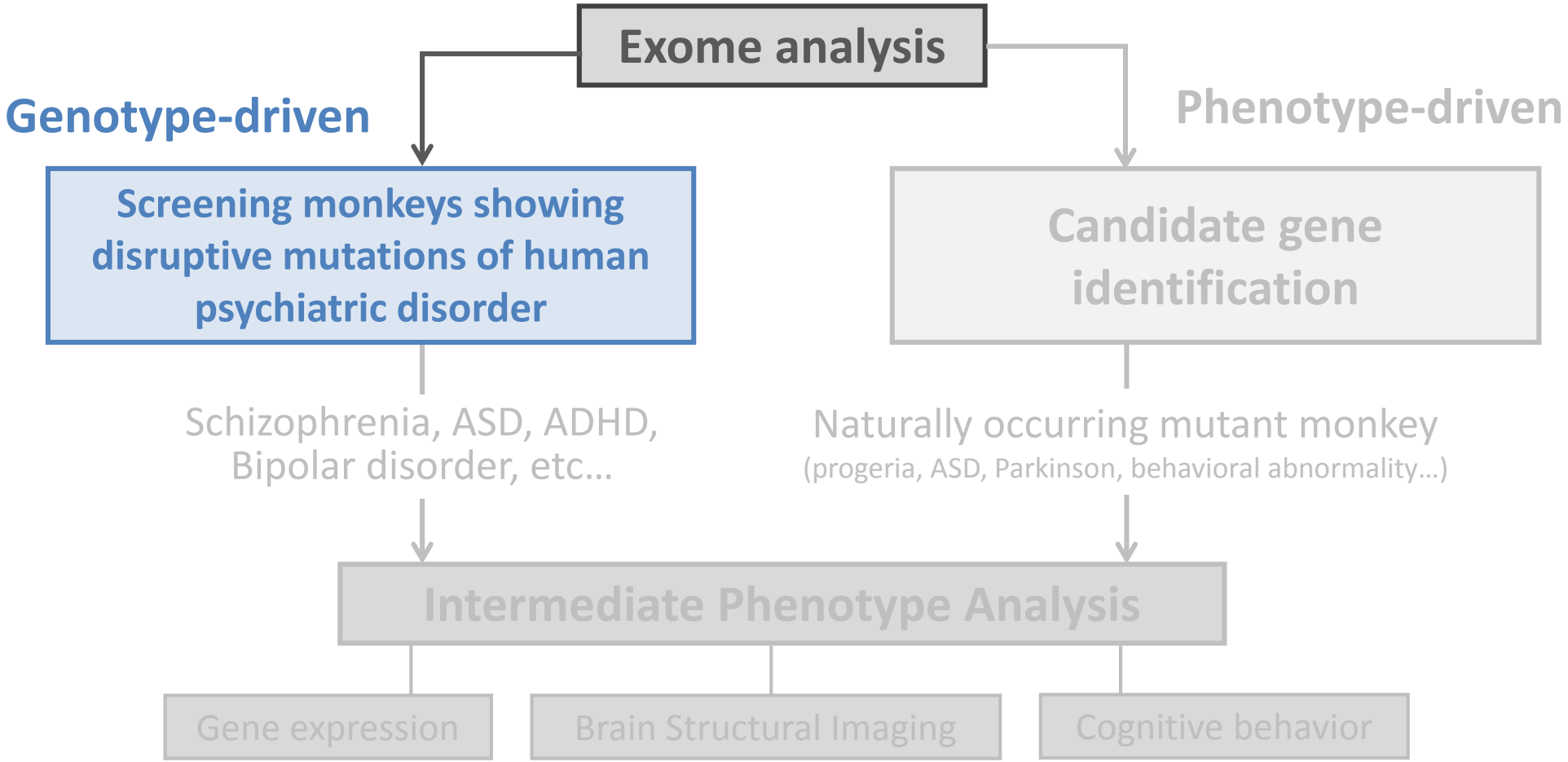
Primate Genomic Study | Two Strategies

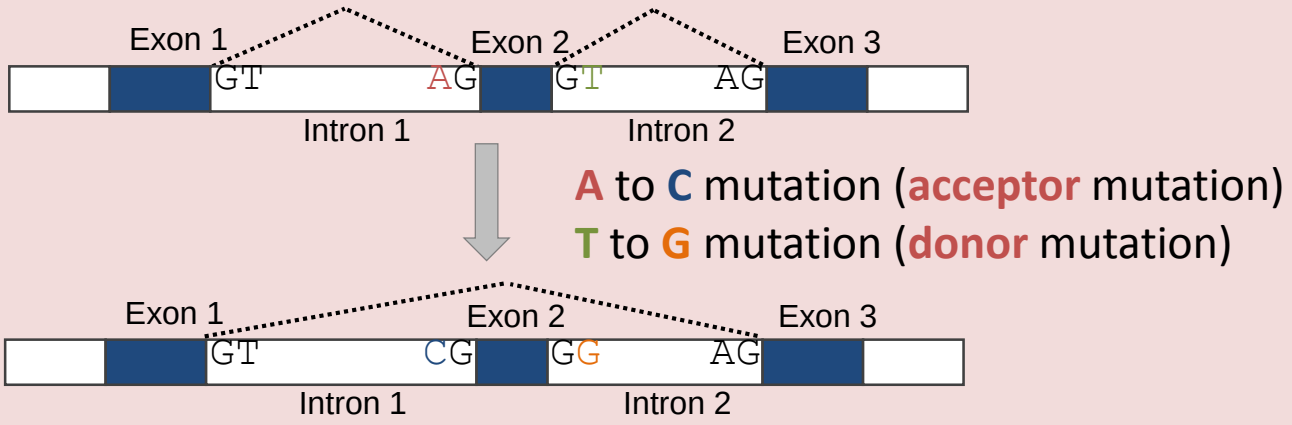


Primate Genomic Study | Two Strategies

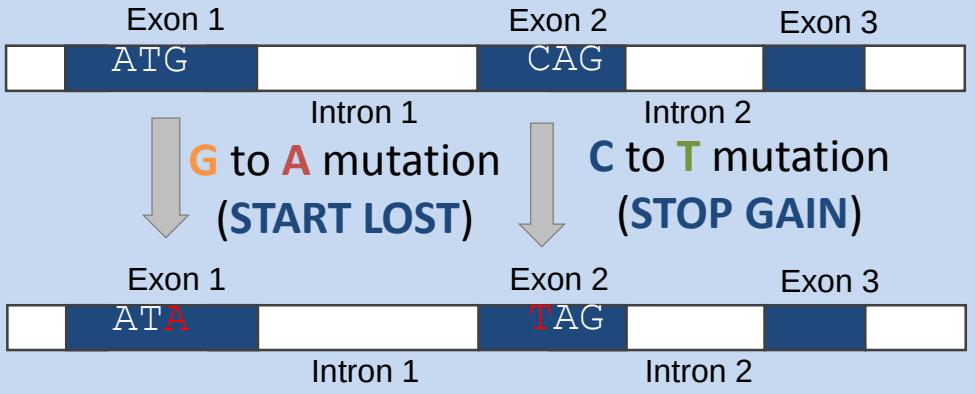


Loss-of-Function (LoF) mutations

splice site mutation



stop gain start lost mutation



Exome Analysis | Marmoset

【GENOTYPE-DRIVEN】

1,328 marmosets x **479** neuropsychiatric related genes

142 genes that show **rare** (< **5** %) **Loss-of-Function** (**LoF**) mutations

127 genes that show **very rare** (< **1** %) **Loss-of-Function** (**LoF**) mutations

【PHENOTYPE-DRIVEN】

Abnormal Eye Movement ⇒ ***MECP2*** (Rett syndrome)

Epilepsy ⇒ ***KCNQ3*** (Juvenile Myoclonic Epilepsy)

Loss-of-Functional mutation genes in marmosets

Gene	Disease (Score*)	LoF type	Genotype (REF Homo, Hetero, ALT Homo)
SHANK2	Autism Spectrum Disorder (19.81)	Stop gain	666, 44, 1
NLGN3	Autism Spectrum Disorder (19.27)	Frame shift	1141, 8, 0
DRD5	Autism Spectrum Disorder (16.34)	Stop gain	1211, 7, 0
NRG1	Schizophrenia (19.01)	Frame shift	1236, 2, 0
SYN3	Schizophrenia (17.63)	Frame shift	1053, 2, 0
SLC1A1	Schizophrenia (17.46)	Frame shift	1190, 1, 0
TPH1	Bipolar Disorder (18.43)	Stop gain	1078, 2, 0
RELN	Bipolar Disorder (15.85)	Stop gain	1073, 1, 0
NRG1	Bipolar Disorder (15.21)	Frame shift	1236, 2, 0
DRD5	Attention Deficit Hyperactive Disorder (19.71)	Stop gain	1211, 7, 0
SETX	Amyotrophic Lateral Sclerosis (20.56)	Stop gain	1152, 1, 0
ALS2	Amyotrophic Lateral Sclerosis (19.76)	Splice donor	1206, 1, 0
TRAK2	Amyotrophic Lateral Sclerosis (16.67)	Stop gain	1129, 1, 0
PRNP	Huntington's Disease (19.25)	Frame shift	1240, 2, 0
SETDB1	Huntington's Disease (16.99)	Frame shift	1229, 2, 0
CASP1	Huntington's Disease (15.88)	Stop gain	1076, 4, 0
DNAJC13	Parkinson's Disease (18.99)	Splice acceptor	859, 9, 0
LRRK2	Parkinson's Disease (17.92)	Stop gain	1128, 1, 0
GIGYF2	Parkinson's Disease (17.72)	Stop gain	1134, 1, 0

*Score > 15 (MalaCards: https://www.malacards.org/)

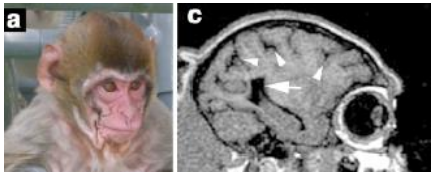
Exome Analysis | Macaque

【GENOTYPE-DRIVEN】

831 macaques x **503** neuropsychiatric related genes

53 genes that show **rare** (<5%) **Loss-of-Function** (**LoF**) mutations

【PHENOTYPE-DRIVEN】



Progeria → **Progeria-related genes** Oishi et al. (2014) *PLoS ONE*

Autism Spectrum Disorder → **Serotonin receptor (*HTR2C*)** Yoshida et al. (2016) *Science Advances*

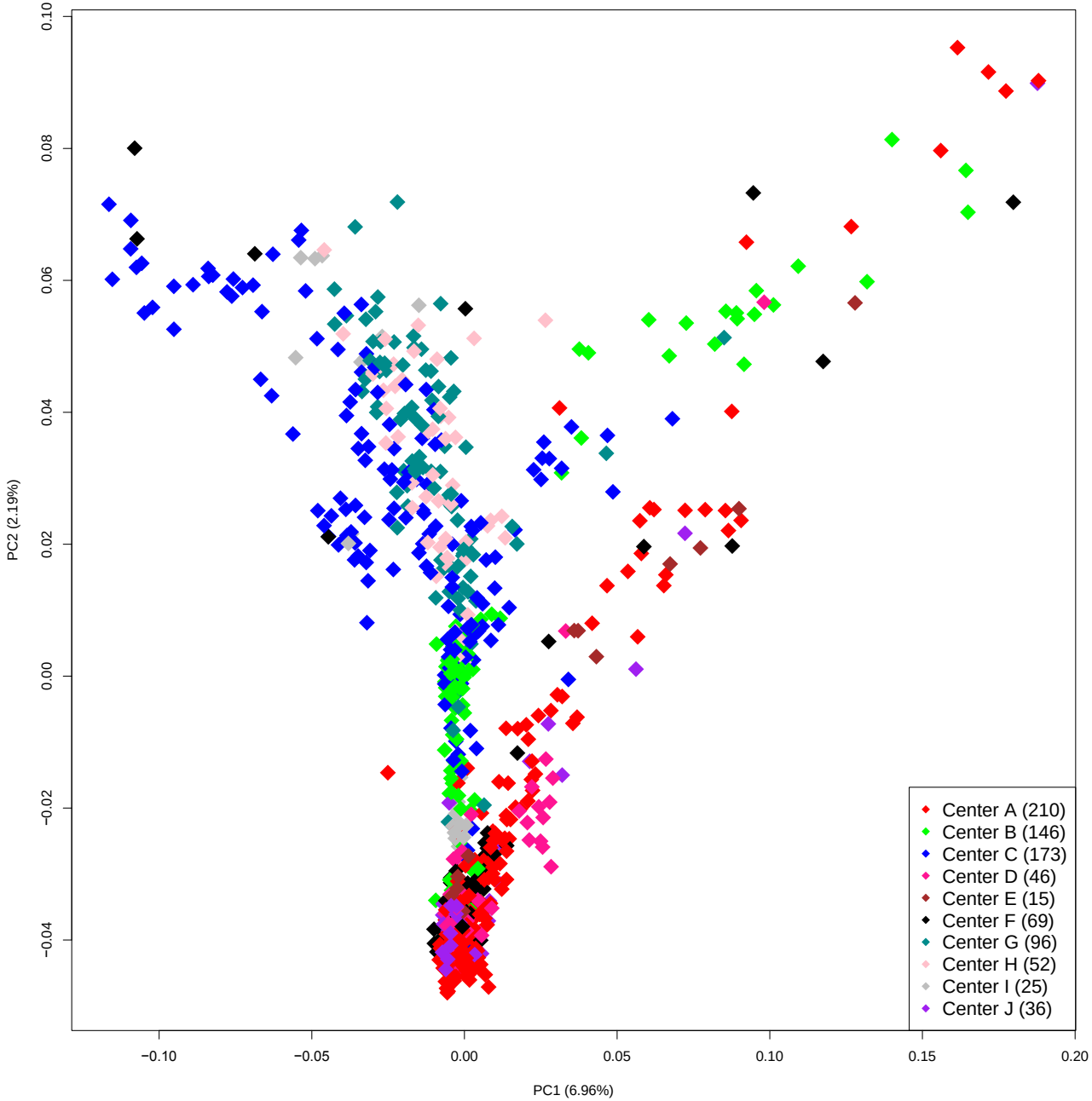
Multiple system atrophy → **Signaling adapter coupled with growth factor receptors in neuron**

McCairn et al. (*unpublished*)

Mucopolysaccharidoses → **Glycosaminoglycans hydrolyzed enzyme**

Oishi et al. (*unpublished*)

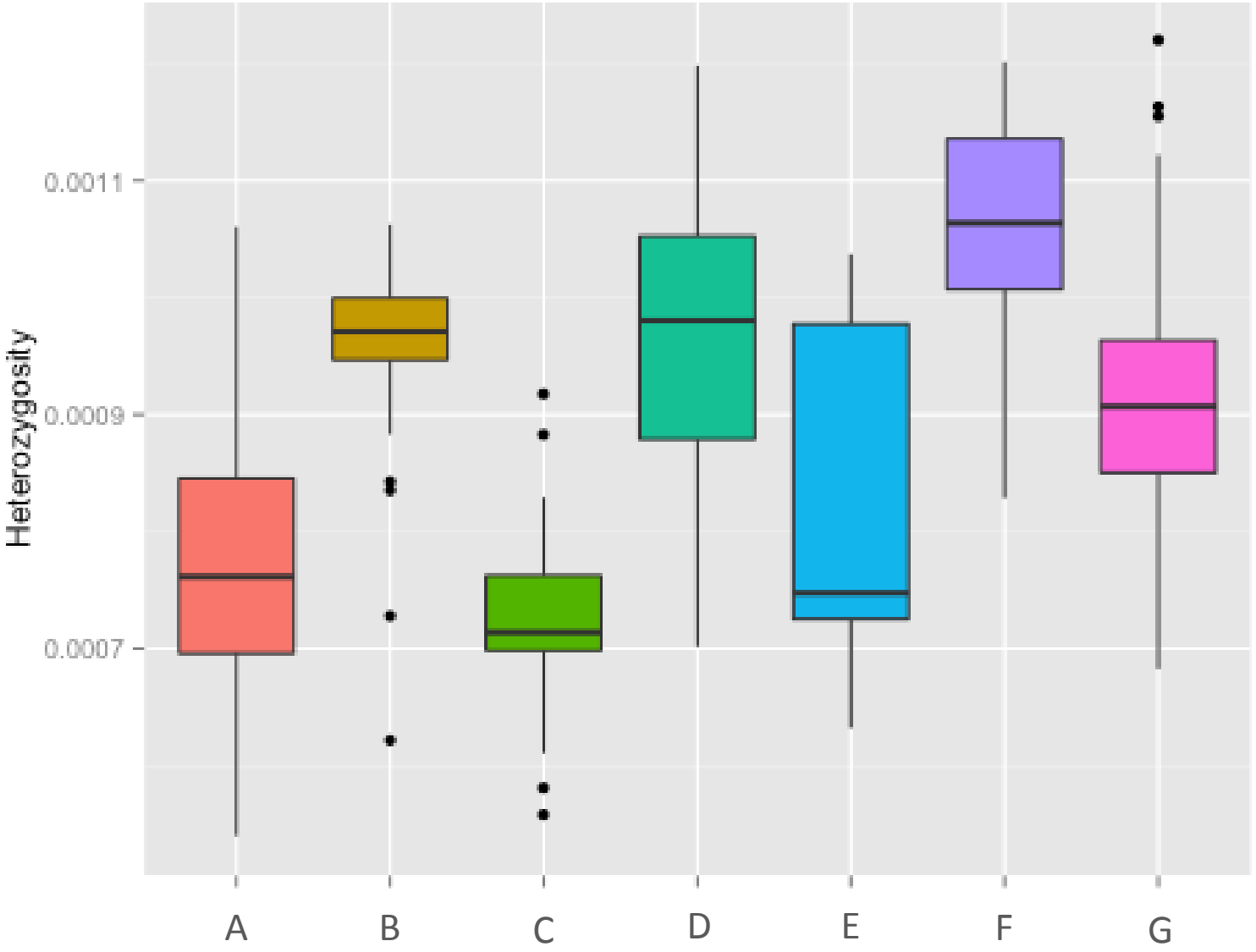
Genetic Diversity of “JAPANESE” marmosets



868 samples

3,335 SNVs

Heterozygosity among marmoset facilities in Japan



NOTE: Heterozygosity

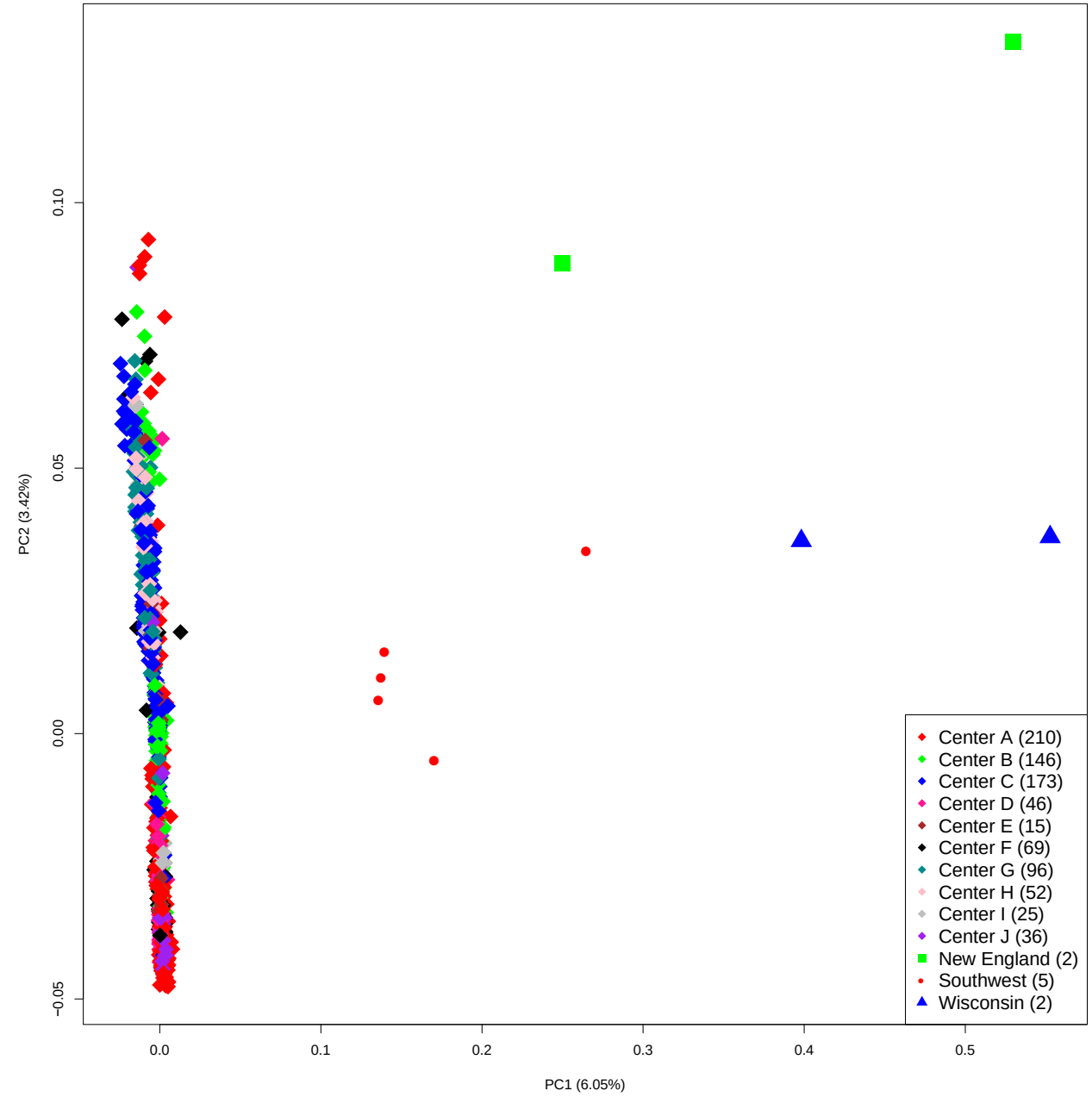
African human = 0.1%

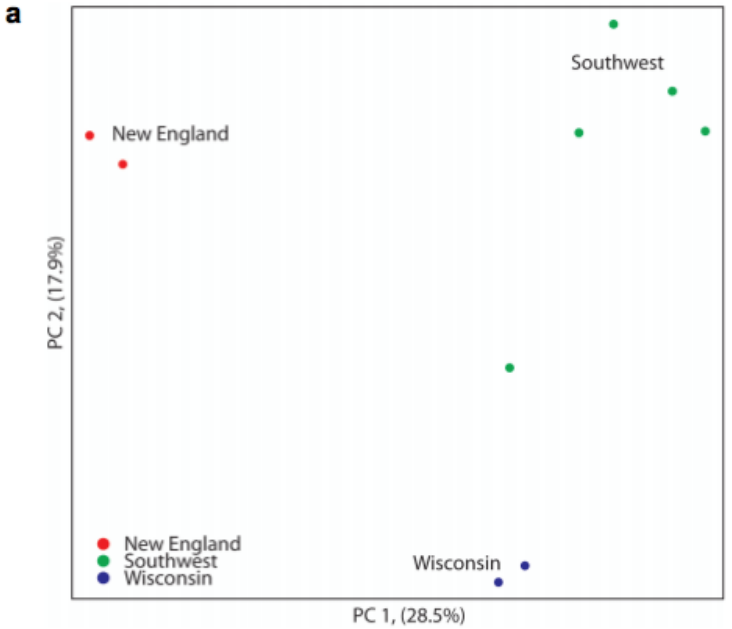
non-African human = 0.077%

Rhesus macaque = 0.21%

Japanese macaque = 0.14%

Genetic Diversity of “JAPAN + US” marmosets

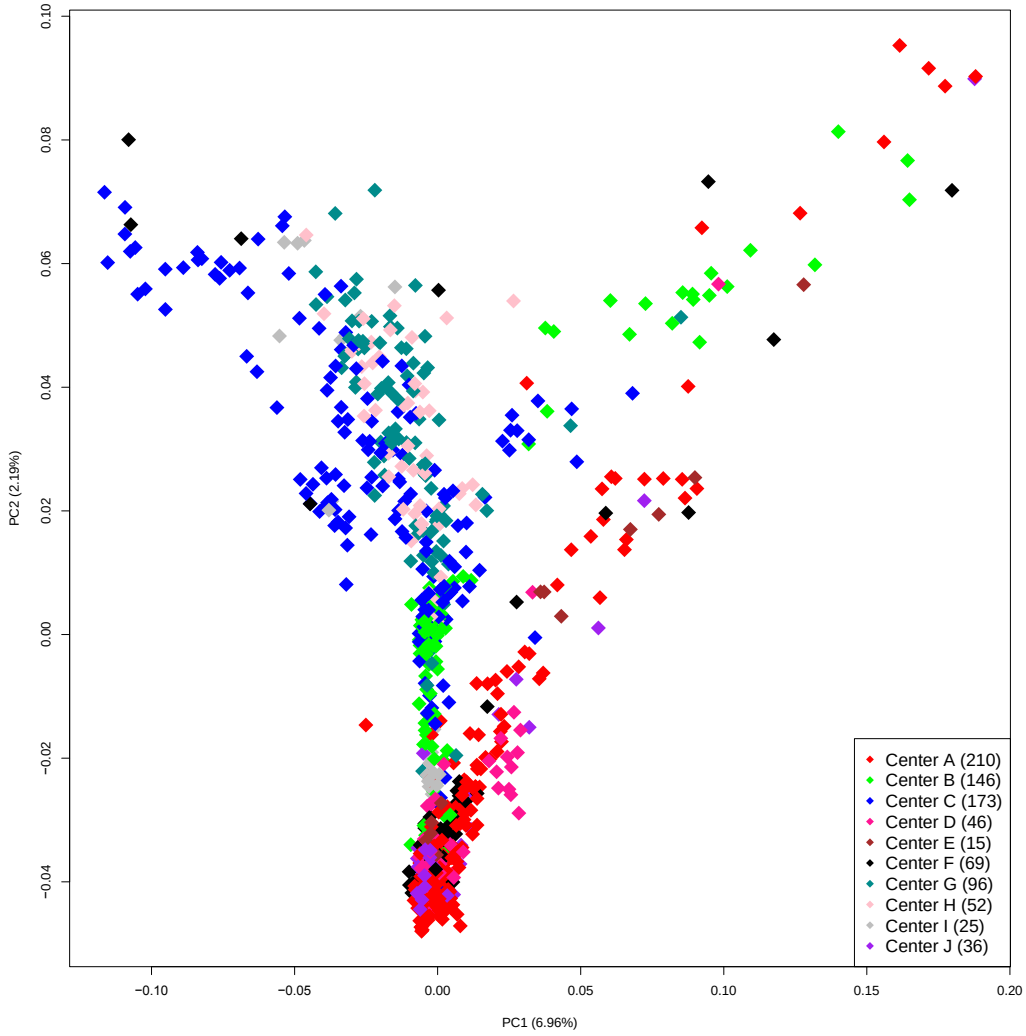




Nature Genetics (2014)

868 (JPN) + **9** (US) samples
3,335 SNVs

Genetic Diversity of “JAPAN + US” marmosets



868 samples
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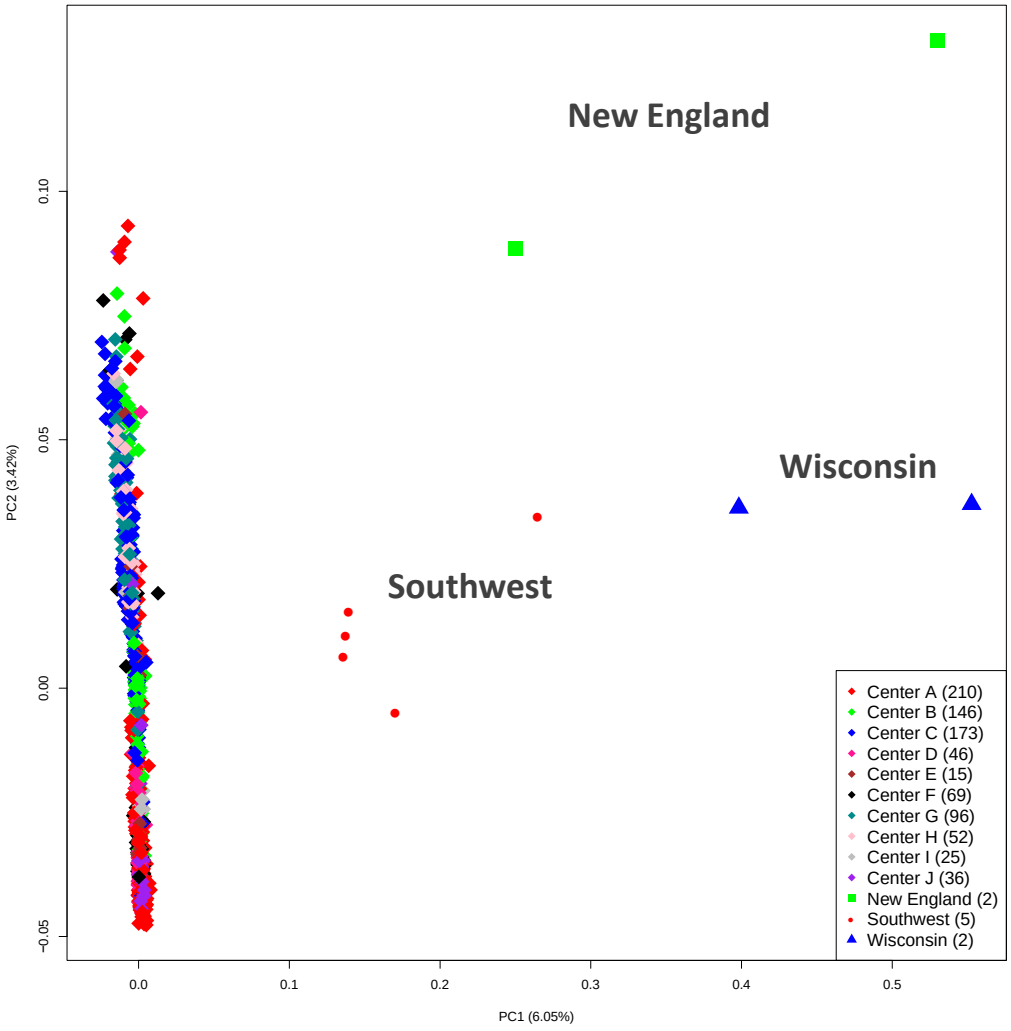

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Summary

Genome

- Genomic analysis of **neuropsychiatric genes** (**~500** genes) in hundreds of monkeys (**macaques**, **marmosets**)
- Loss-of-Function mutations are found in **53** genes (macaques) & **142** genes (marmosets) [**GENOTYPE-DRIVEN**]
- Success of identification of the candidate genes in naturally (spontaneous) mutant monkeys (progeria, ASD, Multiple system atrophy, Mucopolysaccharidoses) [**PHENOTYPE-DRIVEN**]
- Pay attention to the source of DNA in marmosets due to **blood chimerism**
  [PROS] **Blood**: **high amount & quality DNA**, **Nail(Crow)**: **no chimerism**
  [CONS] **Blood**: **high chimerism**, **Nail(Crow)**: **low amout & quality DNA**

Transcriptome

- Brain transcriptome analysis of **disease marmoset model** and elucidating molecular basis of neuropsychiatric disease
- **VPA** marmoset: **Glutamatergic synapse** gene [*SLC1A2*, *GRM2*, *SLC1A6*, *PRKCG*, *SHANK1*, *GRK3*, *SHANK3*], **Circadian rhythm** gene [*NR1D1*, *PER2*, *PER1*, *PER3*, *BHLHE40*]
- **Single cell & Single nuclei RNA-seq** are vigorously in progress.

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NINS

ExCELLS

Brain Individuality

CNSI

Brain/Minds

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JSPS

NIPS

Correlative Gene System

Glia Assemble

Genome Support

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