PARKINSON'S PROGRESSION MARKERS INITIATIVE

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Selected Genetic Variants Genotyped using NeuroX array

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Summary

SNP genotyping was performed using Illumina NeuroX array on whole-blood extracted DNA samples collected according to the PPMI Research Biomarkers Laboratory Manual. The NeuroX array is an Illumina Infinium iSelect HD Custom Genotyping array containing 267,607 Illumina standard content exonic variants and an additional 24,706 custom variants designed for neurological disease studies. Of the custom variants, approximately 12,000 are designed to study Parkinson's disease and are applicable to both large population studies of risk factors and to investigations of familial disease and known mutations.

Method

Genotyping on Illumina NeuroX array was performed per manufacturers protocol (Illumina, Inc. San Diego). The Genotyping Analysis Module within Genome Studio version 1.9.4 was used to analyze data. The threshold call rate for sample inclusion was 95%. Quality control of sample handling was determined by comparing the subject's sex reported by Coriell Institute for Medical Research with the genotypic sex estimated from X chromosome heterogeneity. X chromosome heterogeneity calculations were based on common SNPs from the International HapMap Project that had genotypes with missingness <5% and hardy-Weinberg equilibrium (HWE) *p* values >1E-5. Samples containing discrepancies between reported sex and genotypic estimated sex were excluded.

The genetic variants in table 1 below were directly typed using the NeuroX array. This list includes the data dictionary description for each variant; note this field includes the ancestral and minor alleles as defined by dbSNP as of April 10th 2014 (build creation 123, build update 138; http://www.ncbi.nlm.nih.gov/projects/SNP/).

Table 1. Selected single nucleotide variants typed by NeuroX

Variant Name	NeuroX_ID	Locus Name	Other Name	Data Dictionary Entry
rs114138760	NeuroX_dbSNP_rs114138760	*GBA/SYT11*		rs114138760 C/G (FWD) G:Ancestral C:Minor
rs76763715	exm106217	*GBA*	*GBA* p.N370S	rs76763715 C/T (FWD) T:Ancestral C:Minor
rs71628662	NeuroX_rs71628662	*GBA/SYT11*		rs71628662 C/T (FWD) T:Ancestral C:Minor
rs823118	NeuroX_rs823118	*RAB7L1*		rs823118 C/T (FWD) C:Ancestral T:Minor
rs10797576	NeuroX_rs10797576	*SIPA1L2*		rs10797576 C/T (FWD) C:Ancestral T:Minor
rs6430538	NeuroX_rs6430538	*ACMSD/TMEM163*		rs6430538 C/T (FWD) T:Ancestral C:Minor
rs1955337	NeuroX_rs1955337	*STK39*		rs1955337 G/T (FWD) G:Ancestral T:Minor

rs12637471	NeuroX_rs12637471	*MCCC1*		rs12637471 A/G (FWD) G:Ancestral A:Minor
rs34884217	NeuroX_rs34884217	GAK		rs34884217 (G/T) REV T:Ancestral C:Minor
rs34311866	NeuroX_rs34311866	*GAK*		rs34311866 A/G (REV) A:Ancestral C:Minor
rs11724635	NeuroX_rs11724635	*BST1*		rs11724635 A/C (FWD) A:Ancestral A:Minor
rs6812193	exm-rs6812193	*FAM47E/SCARB2*		rs6812193 C/T (FWD) C:Ancestral T:Minor
rs356181	NeuroX_rs356181	*SNCA*		rs356181 C/T (REV) T:Ancestral A:Minor
rs3910105	NeuroX_rs3910105	*SNCA*		rs3910105 C/T (REV) T:Ancestral G:Minor
rs8192591	exm535099	*HLA*		rs8192591 A/G (REV) G:Ancestral T:Minor
rs115462410	NeuroX_dbSNP_rs115462410	*HLA*		rs9275326 (was rs115462410) C/T (FWD) C:Ancestral T:Minor
rs199347	NeuroX_rs199347	*GPNMB*		rs199347 C/T (REV) C:Ancestral G:Minor
rs591323	NeuroX_rs591323	*FGF20*		rs591323 A/G (FWD) G:Ancestral A:Minor
rs118117788	NeuroX_dbSNP_rs118117788	*INPP5F*		rs118117788 C/T (FWD) C:Ancestral T:Minor
rs329648	NeuroX_rs329648	*MIR4697*		rs329648 C/T (FWD) T:Ancestral T:Minor
rs76904798	NeuroX_rs76904798	*LRRK2*		rs76904798 C/T (FWD) T:Ancestral T:Minor
rs34995376	NeuroX_rs34995376	*LRRK2*	*LRRK2* p.R1441H	rs34995376 A/G (FWD) G:Ancestral A:Minor
rs35801418	NeuroX_rs35801418	*LRRK2*	*LRRK2* p.Y1699C	rs35801418 A/G (FWD) A:Ancestral G:Minor
rs34637584	exm994671	*LRRK2*	*LRRK2* p.G2019S	rs34637584 A/G (FWD) G:Ancestral A:Minor
rs35870237	NeuroX_rs35870237	*LRRK2*	*LRRK2* p.I2020T	rs35870237 C/T (FWD) T:Ancestral C:Minor
rs11060180	NeuroX_rs11060180	*CCDC62*		rs11060180 A/G (FWD) A:Ancestral G:Minor
rs11158026	NeuroX_rs11158026	*GCH1*		rs11158026 C/T (FWD) T:Ancestral T:Minor
rs2414739	NeuroX_rs2414739	*VPS13C*		rs2414739 A/G (FWD) G:Ancestral G:Minor
rs14235	NeuroX_dbSNP_rs14235_replciate_1	*BCKDK/ STX1B*		rs14235 A/G (FWD) G:Ancestral A:Minor
rs11868035	exm-rs11868035	*SREBF/RAI1*		rs11868035 A/G (FWD) G:Ancestral A:Minor
rs17649553	NeuroX_rs17649553	*MAPT*		rs17649553 C/T (FWD) T:Ancestral T:Minor
rs12456492	NeuroX_rs12456492	*RIT2*		rs12456492 A/G (FWD) G:Ancestral G:Minor
rs55785911	NeuroX_rs55785911	*DDRGK1*		rs55785911 A/G (FWD) G:Ancestral A:Minor

Cluster plots (below) for these SNPs and mutations typed in PPMI samples were generated by plotting R and Theta metrics abstracted from GenomeStudio (Illumina Inc, CA) using the statistical analysis package R. The resulting plots are shown below and demonstrate good cluster separation and a high degree of confidence in genotype calling (figures 1a-c). Points in grey represent an uncalled sample/genotype, all other points represent called genotypes.

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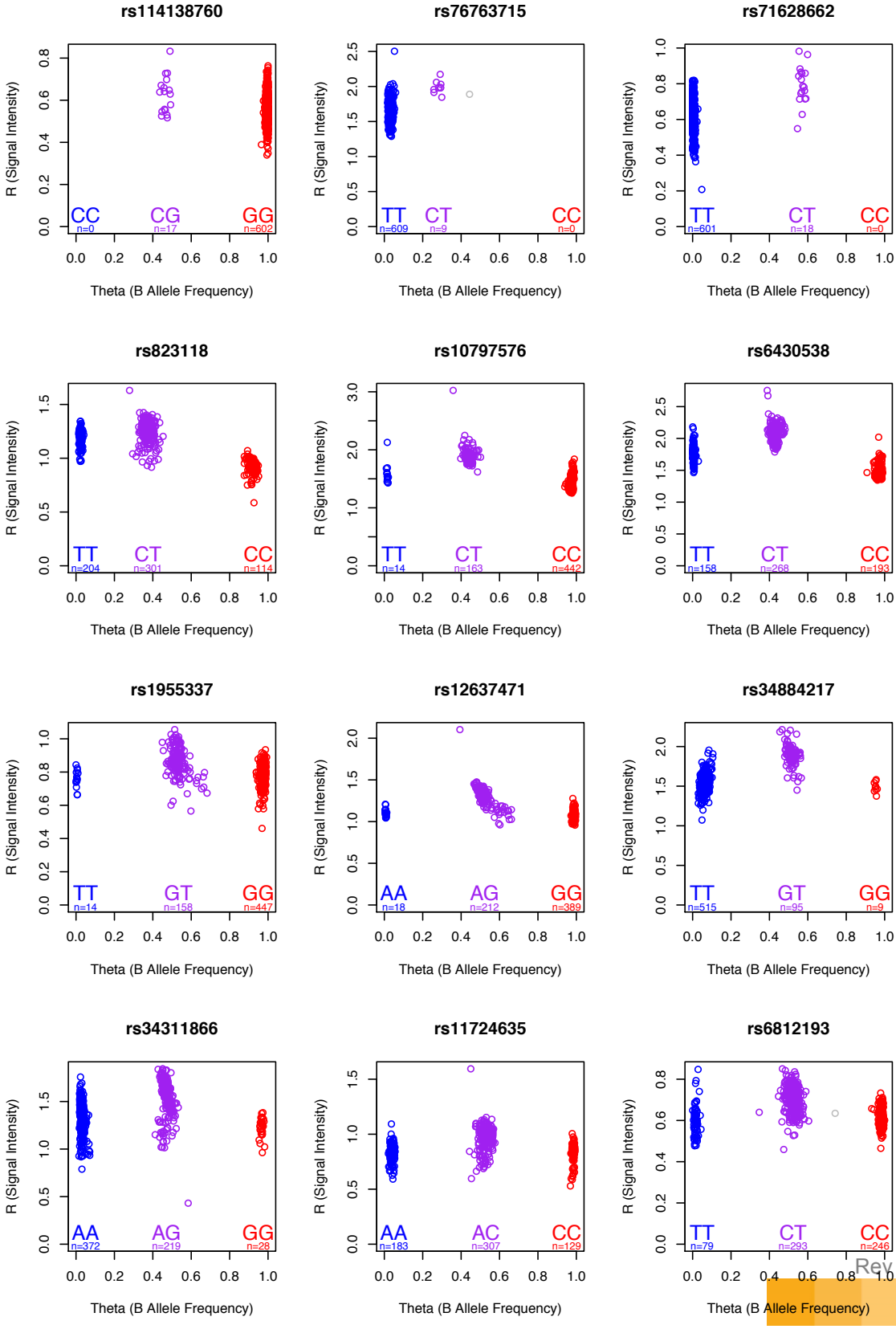

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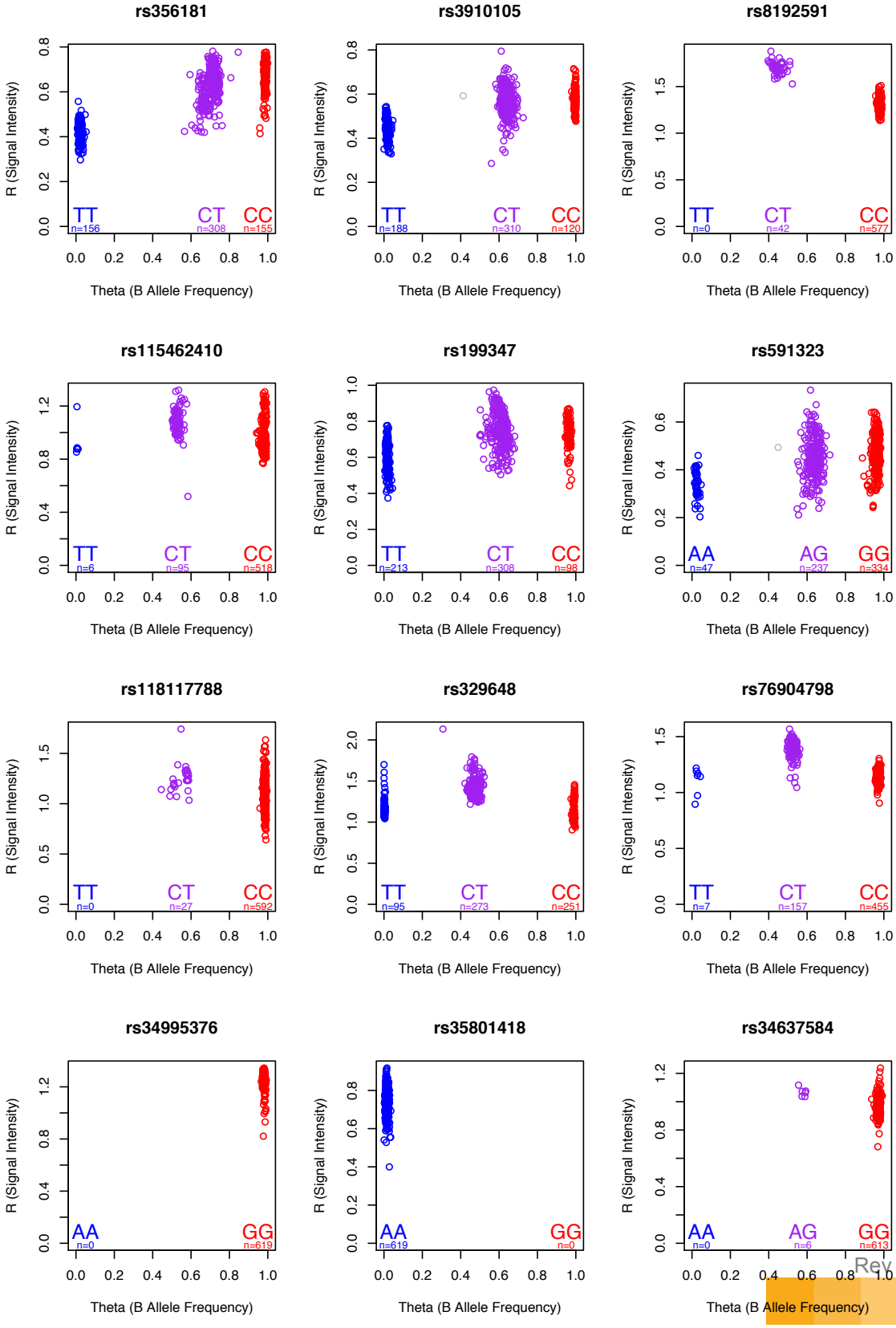

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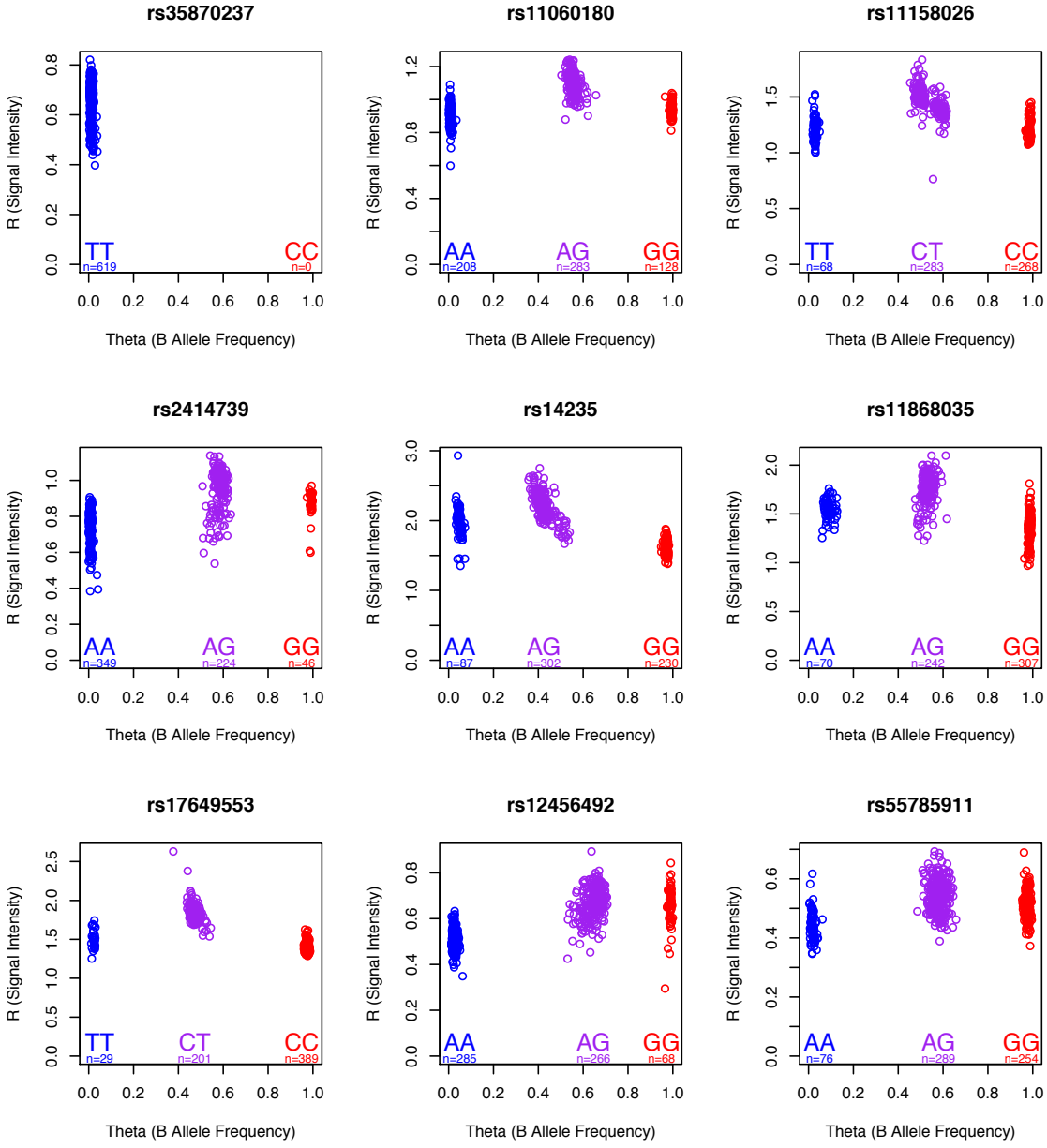

PD risk scores were calculated for each individual within PPMI using risk variants implicated by GWA (rs114138760, rs71628662, rs823118, rs10797576, rs6430538, rs1955337, rs12637471, rs34884217, rs34311866, rs11724635, rs6812193, rs356181, rs3910105, rs8192591, rs115462410, rs199347, rs591323, rs118117788, rs329648, rs76904798, rs11060180, rs11158026, rs2414739, rs14235, rs11868035, rs17649553, rs12456492, and rs55785911), this was performed as previously described [1].

B Allele Frequency and Log R Ratio metrics across chromosome 4 were examined for each PPMI sample typed on NeuroX and ImmunoChip assays to detect possible genomic copy number changes indicative of *SNCA* multiplication mutation.

References

1. International Parkinson Disease Genomics Consortium, Nalls MA, Plagnol V, Hernandez DG, Sharma M, Sheerin UM, Saad M, Simon-Sanchez J, Schulte C, Lesage S, Sveinbjornsdottir S, Stefansson K, Martinez M, Hardy J, Heutink P, Brice A, Gasser T, Singleton AB, Wood NW. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet. 2011;377(9766):641–9.

2. Nalls MA, Pankratz N, Lill C, Do CB, Hernandez DG et al. Large Scale Meta Analysis of Genome-wide Association Data in Parkinson's Disease Reveals 28 Distinct Risk Loci. *Nature Genetics 2014. Under Review.*

3. Parkinson's Progression Marker Initiative Research Biomarkers Laboratory Manual (Biologic Manual) http://www.ppmi-info.org/wp-content/uploads/2011/05/PPMI-Biologics-Manual-April-2011-FINAL.pdf.

About the Authors

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