Table 1 Parkinson's disease risk loci previously reported at genome-wide significance levels

CHR:BP[a]	SNP	Candidate gene[b]	Effect allele/ alternate allele	EAF in 1000 Genomes	$EAF_{cases/controls}$[c]	P_{PDGene}[d]	OR_{PDGene}	P_{PDWBS}[e]	OR_{PDWBS}	$P_{discovery}$	$OR_{discovery}$	$OR_{discovery}$ 95% CI
1:155135036	rs35749011	*GBA*	G/A	0.976	0.979/0.988	6.10×10^{-23}	0.57	5.33×10^{-14}	0.59	2.59×10^{-35}	0.58	0.53–0.63
1:205723572	rs823118	*NUCKS1*, *SLC41A1*	C/T	0.467	0.419/0.443	1.96×10^{-16}	0.89	8.78×10^{-9}	0.90	1.12×10^{-23}	0.89	0.87–0.91
1:232664611	rs10797576	*SIPA1L2*	T/C	0.137	0.145/0.135	1.76×10^{-10}	1.13	7.4×810^{-4}	1.10	8.41×10^{-13}	1.12	1.09–1.15
2:135539967	rs6430538	*TMEM163*,*CCNT2*	T/C	0.488	0.426/0.450	3.35×10^{-19}	0.88	1.5×410^{-6}	0.91	8.24×10^{-24}	0.89	0.87–0.91
2:169110394	rs1474055	*STK39*	C/T	0.881	0.855/0.874	7.11×10^{-16}	0.82	1.11×10^{-11}	0.83	5.68×10^{-26}	0.83	0.80–0.86
3:87520857[f]	**rs115185635**	***CHMP2B***	**C/G**	**0.036**	**0.040/0.039**	$\mathbf{2.2 \times 10^{-8}}$	**1.79**	**0.182**	**1.08**	$\mathbf{1.22 \times 10^{-4}}$	**1.21**	**1.10–1.33**
3:182762437	rs12637471	*MCCC1*	A/G	0.219	0.175/0.198	5.38×10^{-22}	0.84	4.27×10^{-10}	0.86	2.11×10^{-30}	0.85	0.82–0.87
4:951947	rs34311866	*TMEM175*,*DGKQ*	C/T	0.199	0.212/0.184	6.00×10^{-41}	1.26	2.48×10^{-12}	1.18	1.47×10^{-50}	1.23	1.20–1.27
4:15737101	rs11724635	*FAM200B*, *CD38*	C/A	0.437	0.437/0.452	4.26×10^{-17}	0.89	1.0×410^{-4}	0.93	1.22×10^{-19}	0.90	0.88–0.92
4:77198986	rs6812193[g]	*FAM47E*	T/C	0.398	0.351/0.370	1.85×10^{-11}	0.91	1.24×10^{-4}	0.93	1.43×10^{-14}	0.92	0.90–0.94
4:90626111	rs356182	*SNCA*	G/A	0.375	0.406/0.349	1.85×10^{-82}	1.34	1.44×10^{-42}	1.31	5.21×10^{-123}	1.33	1.30–1.36
6:32666660	rs9275326	*HLA-DRB6*, *HLA-DQA1*	T/C	0.114	0.099/0.105	5.81×10^{-13}	0.80	1.04×10^{-3}	0.90	1.26×10^{-13}	0.85	0.82–0.89
7:23293746	rs199347	*KLHL7*, *NUPL2*, *GPNMB*	G/A	0.368	0.389/0.412	5.62×10^{-14}	0.90	8.66×10^{-6}	0.92	3.51×10^{-18}	0.91	0.89–0.93
8:16697091	rs591323	*MICU3*	A/G	0.293	0.258/0.274	3.17×10^{-8}	0.91	1.61×10^{-4}	0.92	2.38×10^{-11}	0.91	0.89–0.94
10:121536327	rs117896735	*BAG3*	A/G	0.012	0.021/0.015	1.21×10^{-11}	1.77	1.75×10^{-9}	1.57	2.23×10^{-19}	1.65	1.48–1.85
11:83544472	rs3793947	*DLG2*	A/G	0.463	0.431/0.442	2.59×10^{-8}	0.91	8.92×10^{-3}	0.95	3.72×10^{-9}	0.93	0.91–0.95
11:133765367	rs329648	*MIR4697*	T/C	0.327	0.369/0.351	8.05×10^{-12}	1.11	9.16×10^{-4}	1.07	1.11×10^{-13}	1.09	1.07–1.12
12:40614434	rs76904798[h]	*LRRK2*	T/C	0.132	0.152/0.137	4.86×10^{-14}	1.16	4.10×10^{-7}	1.14	1.21×10^{-19}	1.15	1.12–1.19
12:123303586	rs11060180	*OGFOD2*	G/A	0.45	0.423/0.449	3.08×10^{-11}	0.91	4.95×10^{-11}	0.88	2.05×10^{-20}	0.90	0.88–0.92
14:55348869	rs11158026	*GCH1*	T/C	0.307	0.309/0.331	2.88×10^{-10}	0.91	2.65×10^{-7}	0.90	4.30×10^{-16}	0.91	0.89–0.93
14:67984370	rs1555399	*TMEM229B*	T/A	0.544	0.518/0.514	5.70×10^{-16}	1.15	0.453	1.01	9.61×10^{-11}	1.09	1.06–1.11
15:61994134	rs2414739	*VPS13C*	G/A	0.292	0.250/0.266	3.59×10^{-12}	0.90	1.1×10^{-3}	0.93	3.94×10^{-14}	0.91	0.89–0.93
16:31121793	rs14235	*ZNF646*, *KAT8*	A/G	0.397	0.388/0.378	3.63×10^{-12}	1.10	0.0339	1.04	5.44×10^{-12}	1.08	1.06–1.10
17:43994648	rs17649553	*ARHGAP27*, *CRHR1*, *SPPL2C*, *MAPT*, *STH*, *KANSL1*	T/C	0.232	0.187/0.221	6.11×10^{-49}	0.77	9.24×10^{-22}	0.80	1.26×10^{-68}	0.78	0.76–0.80
18:40673380	rs12456492	*SYT4*	G/A	0.332	0.336/0.315	2.15×10^{-11}	1.10	5.13×10^{-6}	1.10	5.56×10^{-16}	1.10	1.07–1.12
19:2363319[f]	**rs62120679**	***LSM7***	**T/C**	**0.324**	**0.314/0.310**	$\mathbf{2.52 \times 10^{-9}}$	**1.14**	**0.240**	**1.03**	$\mathbf{6.64 \times 10^{-7}}$	**1.08**	**1.05–1.11**
20:3168166[f]	**rs8118008**	***DDRGK1***	**A/G**	**0.596**	**0.615/0.609**	$\mathbf{2.32 \times 10^{-8}}$	**1.11**	**0.283**	**1.02**	$\mathbf{1.99 \times 10^{-6}}$	**1.07**	**1.04–1.09**

Rows in bold text refer to loci that did not pass the genome-wide significance threshold (5×10^{-8}) in the discovery-phase meta-analysis. [a]Chromosome and physical position according to Hg19. [b]Details regarding the assignment of candidate genes are provided in the Online Methods. [c]Effect allele frequency (EAF) measured in PDWBS controls or cases. [d]*P* value for SNP in the publicly available PDGene data (13,708 cases, 95,282 controls). Publicly available data for the following SNPs include an additional 5,450 cases and 5,798 controls genotyped on NeuroX: rs115185635, rs35749011, rs117896735, rs62120679, rs9275326, rs3793947, rs1555399, rs1474055, and rs8118008. [e]*P* value for SNP in PDWBS (6,476 cases, 302,042 controls). [f]The alternate SNP is genome-wide significant (rs12651582; $P = 3.51 \times 10^{-8}$). [g]The alternate SNP is genome-wide significant (rs76904798; $P = 4.45 \times 10^{-75}$).

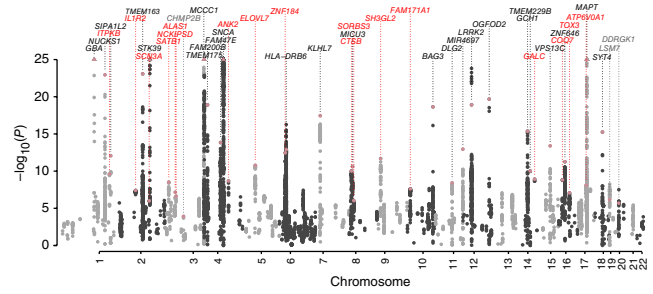

Figure 2 Results of the Parkinson's disease discovery-phase meta-analysis. The top SNPs in associated regions are indicated by pink symbols. Candidate genes for previously associated loci are labeled in black ($P < 5 \times 10^{-8}$ in the discovery phase) or gray text ($P > 5 \times 10^{-8}$ in the discovery phase); candidate genes for newly identified loci are labeled in red. The *y*-axis shows the two-sided unadjusted $-\log_{10}(P)$ values for association with PD. SNPs with $P < 1 \times 10^{-25}$ are indicated by triangles.

To gain insight into the biology, we tested the identified candidate genes in the 41 PD risk loci for association with any pathways or gene sets compared with a background gene list (Online Methods). We investigated whether candidate genes were enriched for pathways previously implicated in PD: autophagy, lysosomal, and mitochondrial biology[1]. PD-associated signals were enriched (at a threshold of $P < 0.05/3 = 0.017$) for lysosomal and autophagy genes ($P = 3.35 \times 10^{-6}$ and $P = 5.71 \times 10^{-3}$, respectively). The addition of candidate genes more than doubled the number of lysosomal genes observed in PD loci and improved the enrichment significance ($P_{\text{all\_loci}} = 3.35 \times 10^{-6}$, $P_{\text{novel\_loci}} = 3.64 \times 10^{-5}$). We also observed that one previously identified gene (*MCCC1*) and two novel candidate genes (*COQ7* and *ALAS1*) mapped to the mitochondrial gene set (**Supplementary Table 11**).

Lysosomal biology and its role in the degradation of protein aggregates emerged as a highly significant pathway in PD risk. Among the five candidate genes linked to lysosomal biology, two were previously identified candidate genes (*GBA* (glucocerebrosidase) and *TMEM175* (transmembrane protein 175)), and three were newly identified candidate genes (*CTSB* (cathepsin B), *ATP6V0A1* (ATPase H^+ transporting V0 subunit a1), and *GALC* (galactosylceramidase)). Glucocerebrosidase is required for normal lysosomal activity and α-synuclein degradation. In addition, *GBA* loss-of-function alleles are a common PD risk factor[31]. *TMEM175* was recently shown to encode a potassium channel that can regulate lysosomal function[32], and the missense variant *TMEM175* M393T is strongly linked to the index variant in the region (**Supplementary Table 8**). *CTSB* is a lysosomal cysteine protease. A PD risk allele is linked to a *cis*-eQTL for *CTSB* in multiple tissues (**Supplementary Table 9**), where the risk allele is associated with reduced levels of *CTSB* mRNA. Double-knockout mice for *Ctsb* and *Ctsl* (cathepsin L) show a tremor phenotype with cerebral and cerebellar atrophy[33]. CTSB is also capable of degrading membrane-bound and soluble α-synuclein in mice[34].

Table 2 Seventeen novel regions associated with Parkinson's disease at genome-wide significance levels

CHR:BP[a]	SNP	Candidate gene[b]	Effect allele/ alternate allele	EAF in 1000 Genomes	$P_{\text{discovery}}$	$OR_{\text{discovery}}$	P_{NeuroX}	OR_{NeuroX}	P_{joint}	OR_{Joint}	OR_{Joint} (95% CI)
1:226916078	rs4653767	*ITPKB*	C/T	0.315	2.40×10^{-10}	0.92	0.017	0.93	1.63×10^{-11}	0.92	0.90–0.94
2:102413116	rs34043159	*IL1R2*	C/T	0.352	3.83×10^{-8}	1.07	1.91×10^{-4}	1.11	5.48×10^{-11}	1.08	1.06–1.10
2:166133632	rs353116	*SCN3A*	T/C	0.385	9.73×10^{-7}	0.94	8.98×10^{-3}	0.93	2.98×10^{-8}	0.94	0.92–0.96
3:18277488	rs4073221	*SATB1*	G/T	0.132	3.02×10^{-9}	1.11	0.583	1.02	1.57×10^{-8}	1.10	1.06–1.13
3:48748989	rs12497850	*NCKIPSD*, *CDC71*	G/T	0.347	6.80×10^{-8}	0.93	0.040	0.94	9.16×10^{-9}	0.93	0.91–0.96
3:52816840	rs143918452	*ALAS1*, *TLR9*, *DNAH1*, *BAP1*, *PHF7*, *NISCH*, *STAB1*, *ITIH3*, *ITIH4*	G/A	0.996	2.25×10^{-7}	0.68	0.095	0.73	3.20×10^{-8}	0.68	0.60–0.78
4:114360372	rs78738012	*ANK2*, *CAMK2D*	C/T	0.106	2.11×10^{-9}	1.14	7.5×10^{-3}	1.12	4.78×10^{-11}	1.13	1.09–1.17
5:60273923	rs2694528	*ELOVL7*	C/A	0.115	1.69×10^{-11}	1.15	6.25×10^{-5}	1.19	4.84×10^{-15}	1.15	1.11–1.20
6:27681215	rs9468199	*ZNF184*	A/G	0.172	3.44×10^{-13}	1.12	0.302	1.04	1.46×10^{-12}	1.11	1.08–1.14
8:11707174	rs2740594[c]	*CTSB*	A/G	0.753	9.54×10^{-11}	1.10	7.95×10^{-3}	1.08	5.91×10^{-12}	1.09	1.07–1.12
8:22525980	rs2280104	*SORBS3*, *PDLIM2*, *C8orf58*, *BIN3*	T/C	0.367	9.06×10^{-7}	1.06	7.87×10^{-3}	1.08	2.53×10^{-8}	1.07	1.04–1.09
9:17579690	rs13294100	*SH3GL2*	T/G	0.371	1.99×10^{-12}	0.91	0.037	0.94	4.84×10^{-13}	0.92	0.89–0.94
10:15569598	rs10906923	*FAM171A1*	C/A	0.306	2.37×10^{-8}	0.93	0.133	0.96	1.35×10^{-8}	0.93	0.91–0.96
14:88472612	rs8005172	*GALC*	T/C	0.424	1.20×10^{-9}	1.08	0.022	1.06	8.77×10^{-11}	1.08	1.05–1.10
16:19279464	rs11343	*COQ7*	T/G	0.454	1.46×10^{-9}	1.07	0.019	1.06	9.13×10^{-11}	1.07	1.05–1.10
16:52599188	rs4784227	*TOX3*	T/C	0.265	8.29×10^{-8}	1.08	1.47×10^{-4}	1.12	9.75×10^{-11}	1.09	1.06–1.12
17:40698158	rs601999	*ATP6V0A1*, *PSMC3IP*, *TUBG2*	C/T	0.699	8.03×10^{-9}	0.93	NA	NA	NA	NA	NA

Summary statistics are shown for the discovery cohort (PDWBS and PDGene), NeuroX (5,851 cases, 5,866 controls), and the joint meta-analysis of the discovery and NeuroX data. Additional summary statistics for NeuroX and the joint meta-analysis are available in **Supplementary Table 5**. EAF, effect allele frequency.

[a]Chromosome and physical position according to Hg19. [b]Details regarding the assignment of candidate genes are provided in the Online Methods. [c]NeuroX and joint statistics are shown for proxy SNP rs1293298.