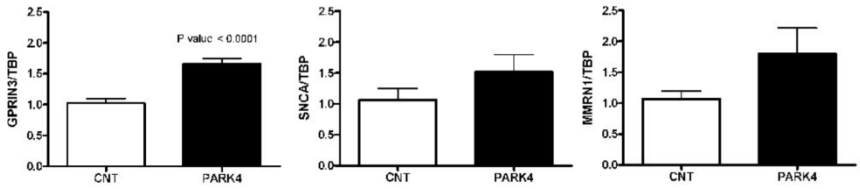
Supplemental Figures and Legends:



FigureS1. Duplication effects on RNA expression levels of the PARK4 family. *GPRIN3*, *SNCA*, and *MMRN1* mRNA levels are increased approximately 1.5 fold by qPCR analysis in blood of PARK4 cases versus control relatives (11 versus 9), although variances and significance differed, corresponding to their gene duplication.

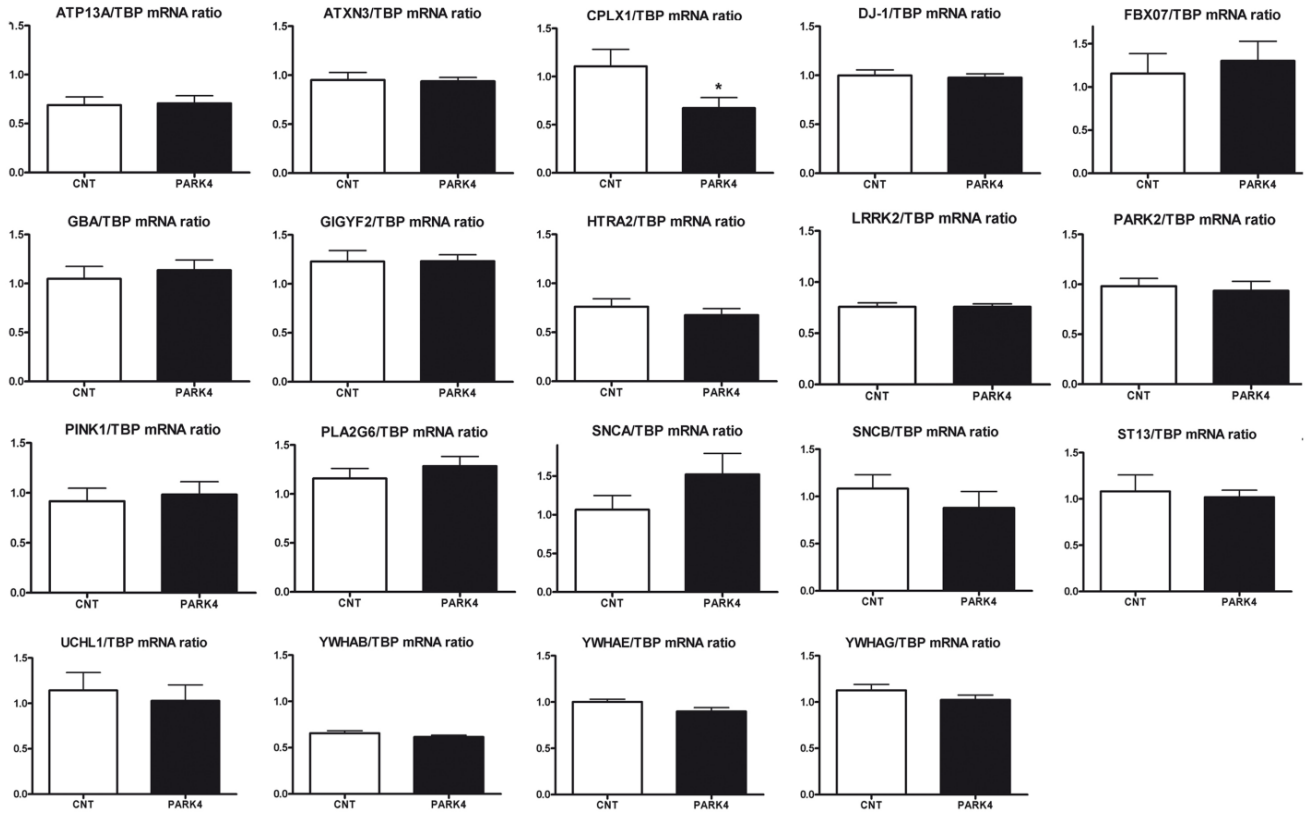


Figure S2. Blood mRNA levels in the PARK4 family. (A) Bar graphs illustrate the expression change direction, effect size and variance for the candidate genes summarized in Figure 2.

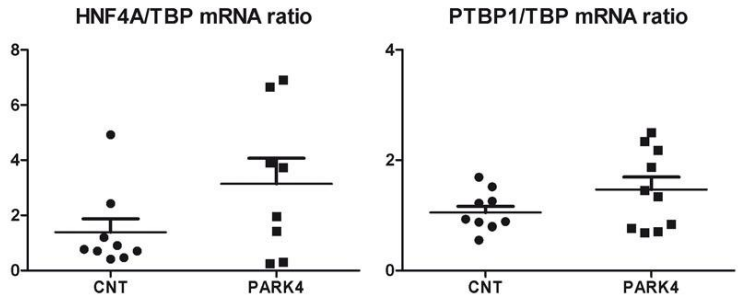


Figure S3. Assessment of longitudinally dynamic biomarkers of PD in blood of prodromal PARK4. Neither *HNF4A* nor *PTBP1* mRNA levels in blood were significantly altered in qPCR analyses (n = 9 control versus 12 PARK4 individuals). The individual value plots show mean and SEM.

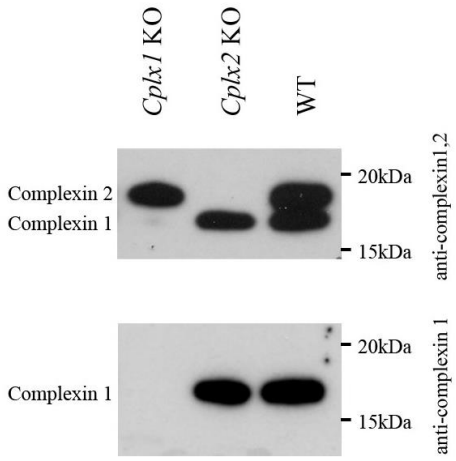


Figure S6. Complexin-1 and complexin-2 detection with specificity in immunoblots. Analysis of the detection properties of commercially available antibodies, demonstrating specific detection of complexin-1/2 (Synaptic systems, Cat no#122 002) versus exclusive detection of complexin-1 (Acris, Cat no#AP51050PU-N) in whole brain tissue RIPA soluble protein extracts from mice with *Cplx1*-KO versus *Cplx2*-KO. The anti-complexin-1 antibody from Acris was further used in the immunohistochemical studies of Lewy bodies (see Figure 6).

Supplemental Table Legends:

Table S1: Ranked gene list of expression changes in whole blood global RNAseq data (5 PARK4 versus 5 matched control relatives) was produced by computing average fold changes and was used as input for GSEA bioinformatics.

Tables S2: GSEA output files with highest significance (0.0 in nominal p-value, 0.0 in FDR q-value and 0.0 in FWER p-value) among the c2 KEGG pathway and c2 REACTOME pathway gene sets.