

SUPPLEMENTARY MATERIALS

Neuronal downregulation of *PLCG2* impairs synaptic function and elicits Alzheimer disease hallmarks

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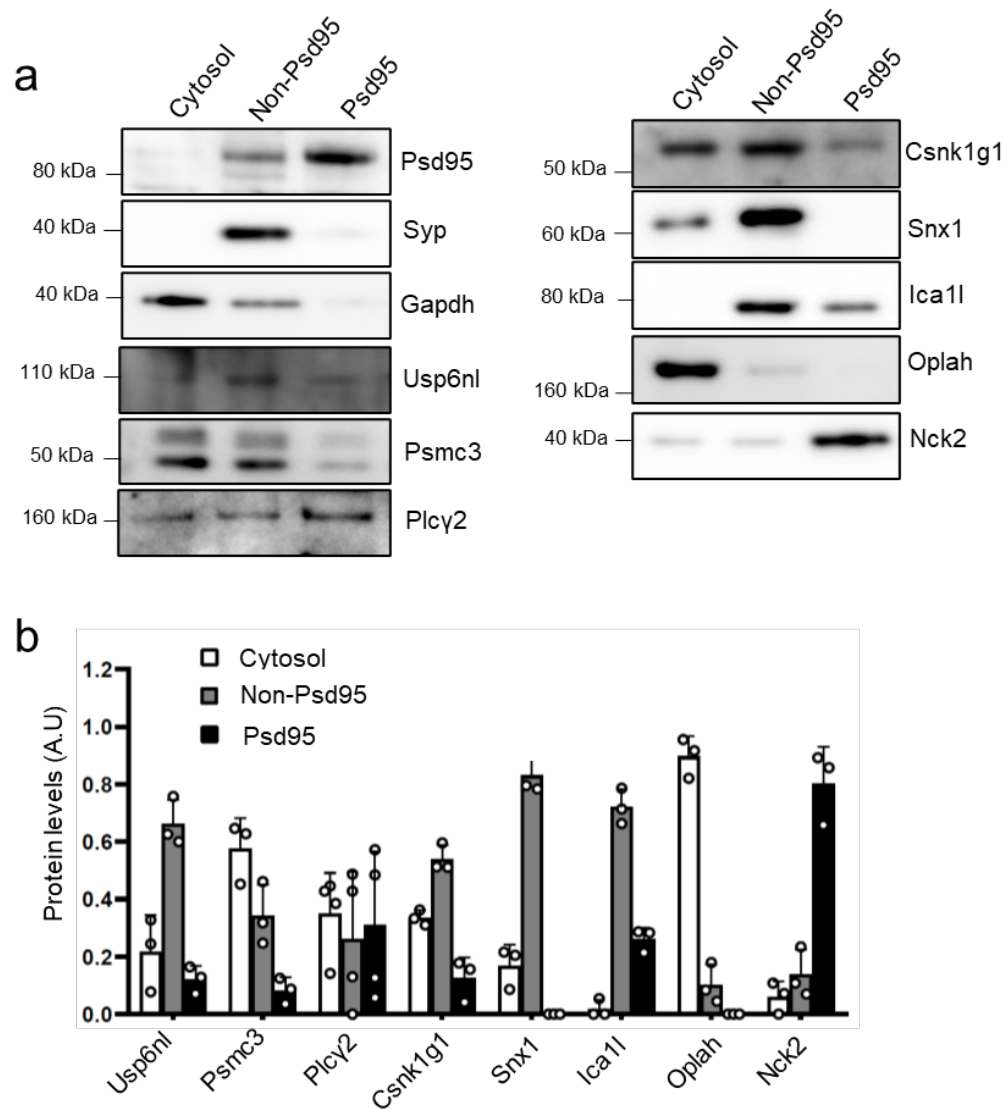
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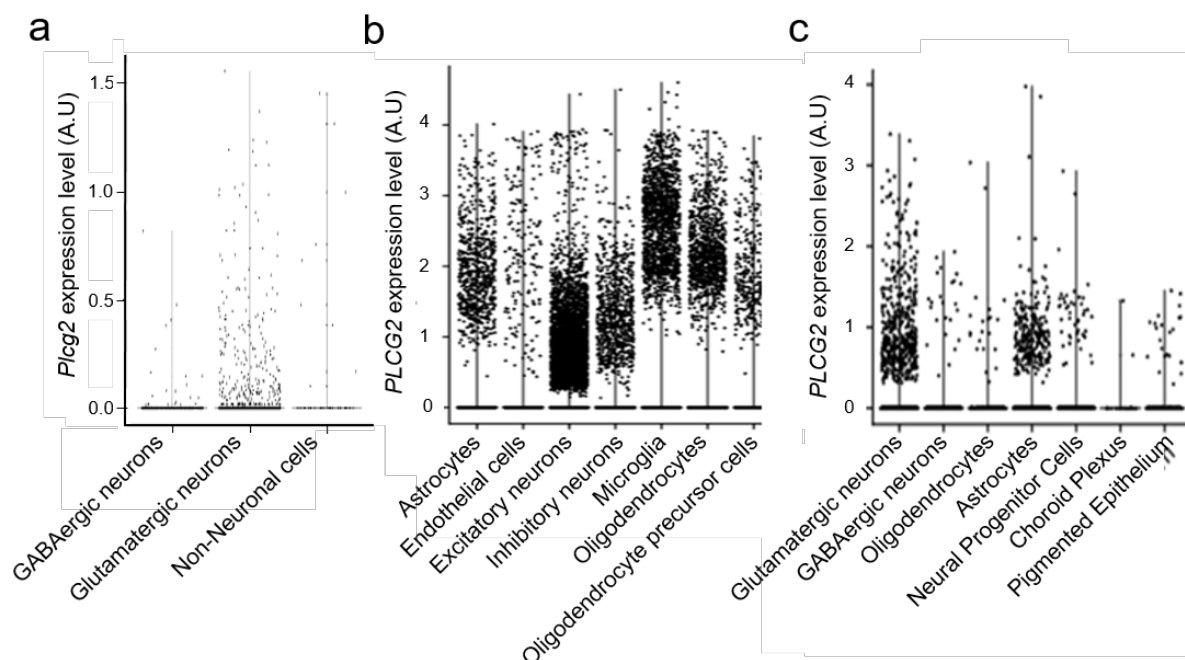
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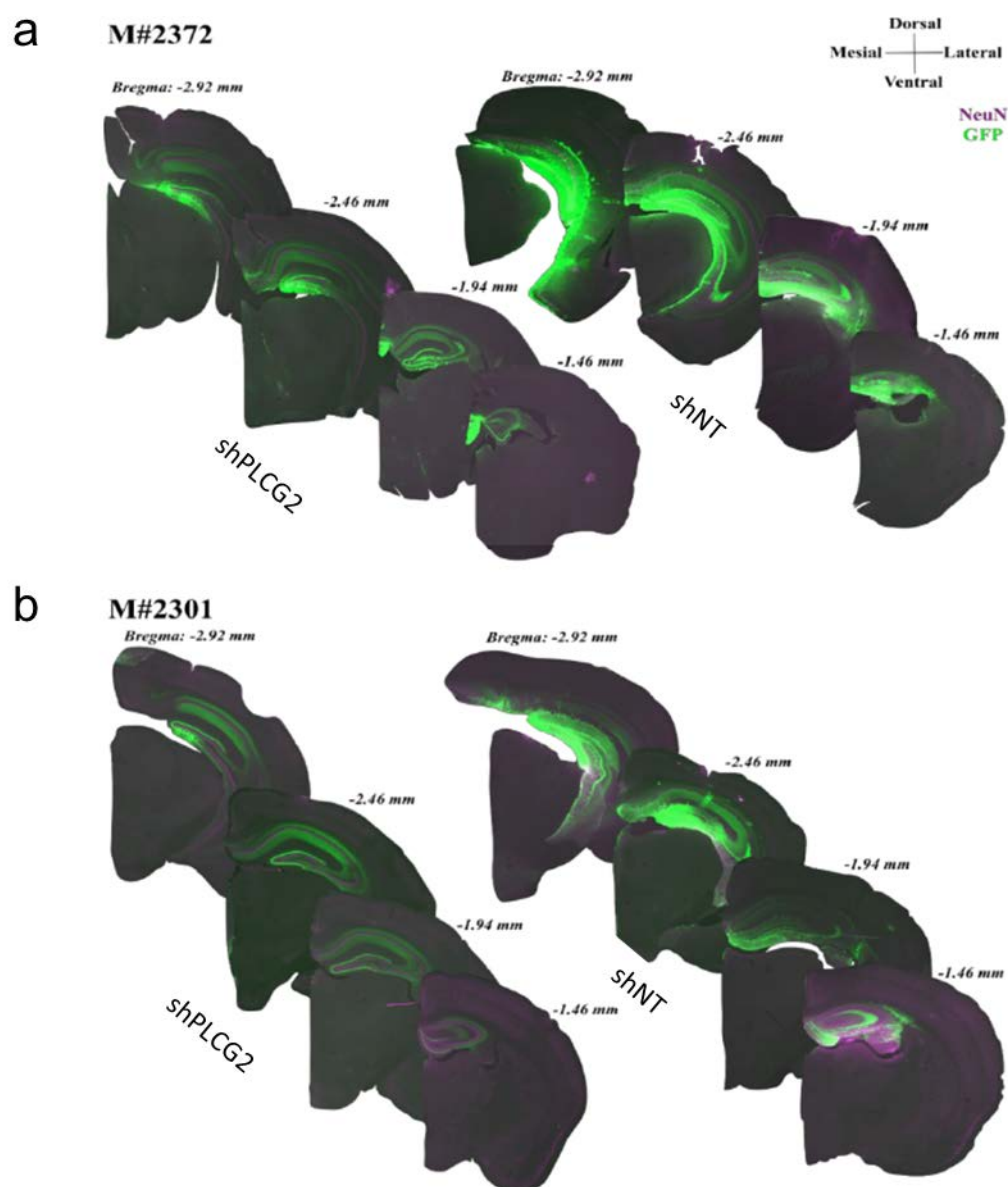
Supplementary Figure S1. Psmc3, Plcy2, Snx1, Ica1l, Csnk1g1, Usp6nl, and Nck2 proteins are expressed in the pre- and/or post-synaptic compartments. Immunoblotting of PSD95 and non-PSD95 fractions in primary rat hippocampal neurons (at DIV21) synaptosomes.



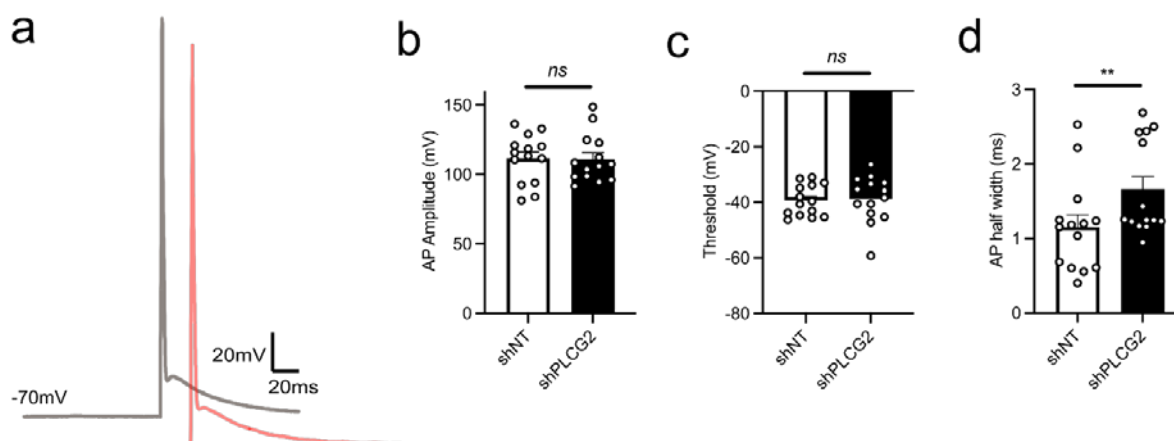
Supplementary Figure S2. *PLCG2* transcripts are expressed in neurons. Levels of expression of *PLCG2* transcripts: (i) in mouse hippocampus **(a)** and human brain **(b)** based on public snRNA-Seq databases (22, 23) and (ii) in iPSC-derived brain organoids **(c)** based on in-house snRNA-Seq data (24).



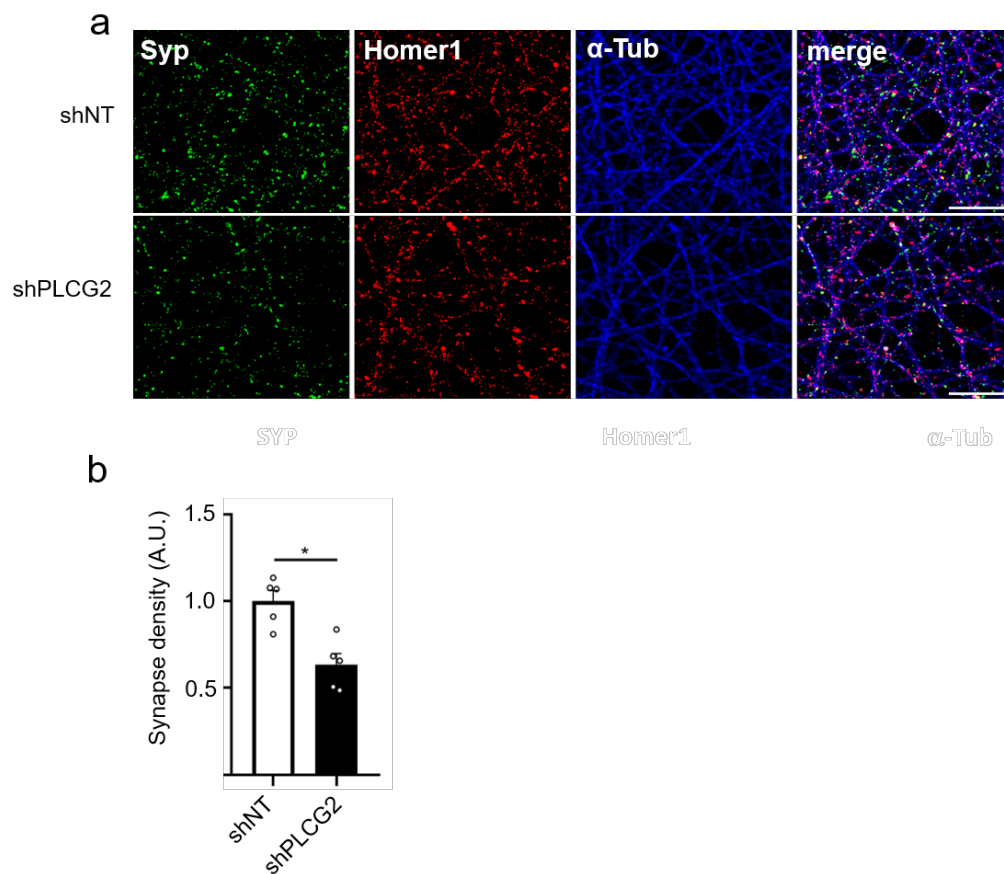
Supplementary Figure S3. Extent of transduction by LV constructs following stereotactic injection in the hippocampus. Representative images of contra-lateral injection of shNT/ shRNA lentiviral vectors in the dorsal dentate gyrus in two different animals (#2372, #2301) (a, b); these images were taken at 10X magnification on an epifluorescence microscope where sections were labeled with NeuN (in magenta) and GFP (in green), arranged from anterior (-1.46 μ m) to posterior (-2.92 μ m).



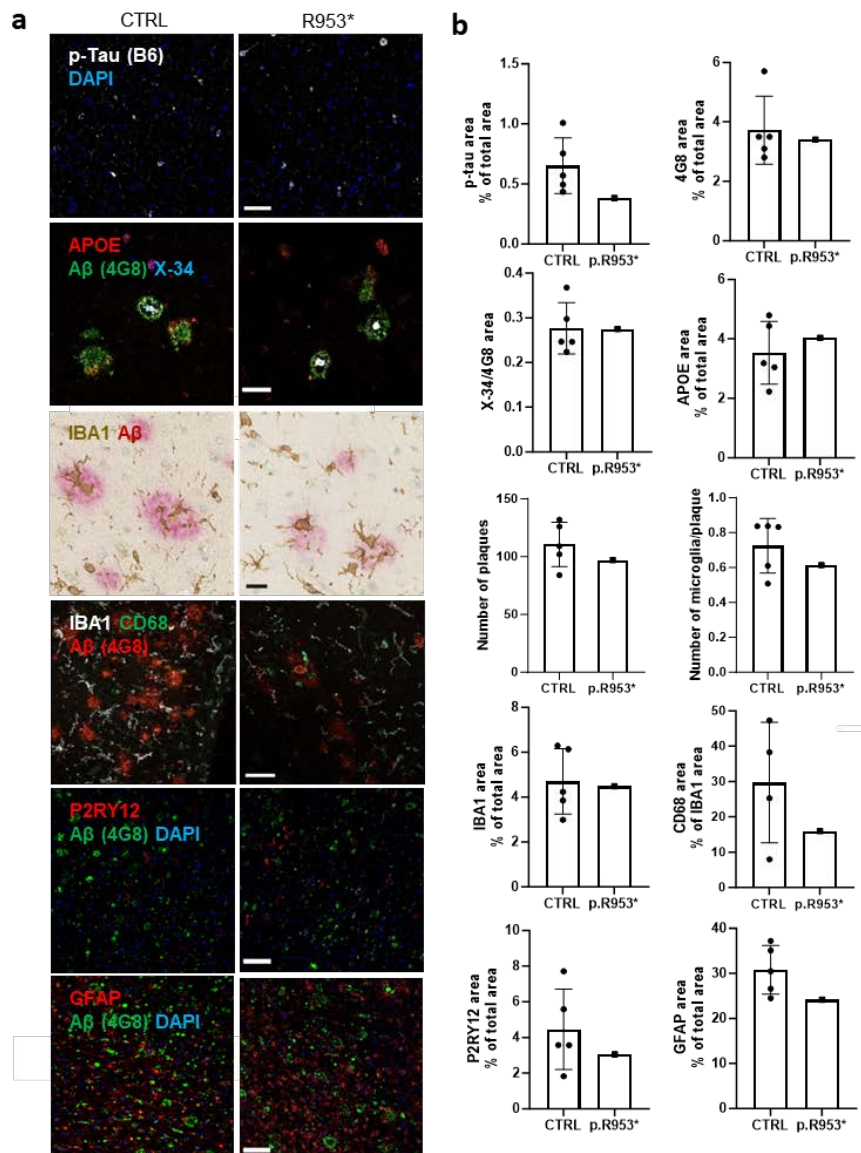
Supplementary Figure S4. Properties of action potentials in shRNA vs. shNT transduced DG granule cells. (a) Traces of action potentials triggered by a short depolarizing pulse from -70 mV in shRNA (red) vs. shNT (grey) transduced DG granule cells. (b-d) Analysis of action potential amplitude (b), threshold for action potential discharge (c) and action potential half-width (d). Mann-Whitney test were applied to compare the average values for shNT (n=15) vs shRNA (n=14) transduced DG granule cells.



Supplementary Figure S5. *Plcg2* downregulation decreases synaptic density in primary rat neurons cultured in microfluidic devices. (a) Immunofluorescence representative images of SYP, HOMER1, and alpha-tubulin markers in shNT and shPLCG2 transduced rat PNCs in microfluidic devices. **(b)** Synapse density quantification for both conditions is shown as mean $\pm$ SEM, $n=4$, $*p<0.05$. Scale bar= 20 μ m.



Supplementary Figure S6. (a) Representative images of brain samples from CTRL and p.R953X carrier showing from top to bottom. Tau phosphorylated at Ser202, Thr205, and Ser208 (p-tau, white) and nuclei (blue); APOE (red), β -amyloid plaques stained with X-34 (blue), and A β stained with 4G8 (green), A β (pink) surrounded by IBA1 positive microglia (brown); A β (red), IBA1 positive microglia (white), and activated microglia stained with microglial lysosomal marker CD68, A β (green), homeostatic microglia stained with P2RY12 (red), and nuclei (blue); A β (green), GFAP positive astrocytes (red), and nuclei (blue). **(b)** Bar graphs show quantification of p-tau, A β (4G8), APOE, IBA1, P2RY12 and GFAP immunopositive area, ratio of compact and diffuse β -amyloid plaques (X-34/4G8), total number of plaques, IBA1 positive microglia within and surrounding the plaque area, and proportion of activated microglia of IBA1 positive microglia. Scale bar 25 μ m for IBA1/A β , 50 μ m for all the others. Data is presented as mean $\pm$ SD.



Supplementary Table S1. Impact of gene knockdown (MOI2 and MOI4) on synaptophysin 1 (Syp) density, HOMER1 density, and synapse density, normalized by shRNA non-targeting (shNT) control. Line without data stands for toxic shRNAs that have been removed from the analysis.

	MOI2 shRNA transduction						MOI4 shRNA transduction					
	mean			SEM			mean			SEM		
	Syp density	HOMER1 density	Synapse density	Syp density	HOMER1 density	Synapse density	Syp density	HOMER1 density	Synapse density	Syp density	HOMER1 density	Synapse density
ABCA1	1.450	1.192	1.638	0.166	0.013	0.209	1.530	1.243	1.880	0.258	0.061	0.365
ABCA7	0.957	0.971	0.850	0.136	0.036	0.195	0.666	0.812	0.645	0.219	0.171	0.297
ABI2	1.256	1.047	1.322	0.055	0.092	0.074	1.525	1.126	1.809	0.308	0.094	0.539
ABI3	1.018	1.033	1.062	0.355	0.194	0.453	0.971	0.928	0.978	0.379	0.182	0.469
ACP2	1.070	1.006	1.091	0.040	0.035	0.015	1.194	0.965	1.214	0.109	0.057	0.138
ACTL6B	0.406	0.896	0.417	0.098	0.044	0.111						
ADAM10												
ADAM17	1.342	1.181	1.519	0.092	0.163	0.208	1.661	1.352	2.053	0.137	0.173	0.266
ADAMTS1												
ADAMTS4	1.076	1.024	0.994	0.041	0.007	0.141						
AGFG2	1.306	0.950	1.214	0.076	0.087	0.103	1.500	0.875	1.374	0.162	0.095	0.133
AKAP9	0.994	0.870	0.998	0.184	0.077	0.233						
ALDOA	0.982	1.130	1.141	0.060	0.132	0.129						
ALKBH5	1.174	0.954	1.182	0.096	0.032	0.129						
ANK3												
ANKH	1.451	1.197	1.638	0.085	0.071	0.081	1.285	0.927	1.441	0.193	0.064	0.299
ANXA6	1.566	1.080	1.616	0.175	0.165	0.252	1.714	1.189	1.800	0.045	0.065	0.120

AP4M1	0.822	1.078	0.920	0.091	0.168	0.154						
APH1B	1.242	1.126	1.347	0.178	0.059	0.229	1.175	1.093	1.297	0.323	0.120	0.369
APOE	1.259	1.045	1.344	0.218	0.063	0.231	1.461	1.055	1.596	0.085	0.071	0.126
APP												
APPL1	0.792	0.944	0.805	0.123	0.016	0.137						
ARFRP1	0.740	0.671	0.577	0.113	0.104	0.142	0.824	0.818	0.737	0.188	0.083	0.208
ASAP2	1.267	1.076	1.388	0.169	0.182	0.295	1.698	1.221	1.964	0.118	0.064	0.160
AZGP1	1.120	0.907	1.099	0.107	0.049	0.123	1.061	0.856	1.016	0.193	0.062	0.205
B4GALT3	0.876	0.891	0.895	0.225	0.089	0.256						
BCKDK	0.824	0.801	0.777	0.122	0.045	0.138	0.896	0.835	0.867	0.063	0.034	0.071
BIN1	0.906	1.027	0.982	0.072	0.080	0.082	0.827	0.895	0.835	0.195	0.066	0.244
C16orf62												
C1QTNF4												
C7orf43												
CARF	1.175	0.910	1.172	0.045	0.050	0.050	1.392	1.098	1.556	0.148	0.076	0.271
CASP2	0.789	0.876	0.778	0.036	0.089	0.030	0.705	0.880	0.714	0.130	0.077	0.152
CASS4	1.257	0.954	1.346	0.131	0.027	0.134	1.152	0.772	1.072	0.150	0.047	0.145
CCDC6	1.167	0.965	1.315	0.085	0.027	0.115	1.260	1.017	1.539	0.146	0.042	0.261
CCNH	0.798	1.274	1.009	0.080	0.189	0.146	0.942	1.163	1.151	0.093	0.008	0.127
CD2AP	1.104	0.937	1.085	0.101	0.077	0.142	1.199	0.981	1.215	0.183	0.015	0.191
CELF1	0.965	0.875	0.975	0.148	0.032	0.158	0.361	0.731	0.355	0.216	0.008	0.233
CHRNA2	0.947	0.949	1.019	0.116	0.082	0.168	0.807	0.895	0.862	0.195	0.089	0.242
CIAO2A	1.429	0.907	1.345	0.094	0.087	0.157	1.309	0.802	1.167	0.112	0.065	0.149
CLU	0.981	0.830	0.892	0.053	0.016	0.053	1.094	0.767	0.989	0.223	0.115	0.145

CNPY4	1.314	1.121	1.432	0.191	0.063	0.193	1.252	1.128	1.370	0.223	0.115	0.288
CNTNAP2	1.385	0.933	1.295	0.169	0.060	0.118	1.255	0.901	1.210	0.376	0.089	0.395
COPS6	0.837	0.898	0.829	0.081	0.129	0.155	0.792	0.914	0.814	0.207	0.090	0.244
CPSF3	0.726	1.094	0.855	0.083	0.188	0.198						
CSNK1G1	0.845	1.008	0.932	0.167	0.036	0.147	0.214	0.907	0.234	0.092	0.014	0.089
CSTF1	1.113	0.918	1.069	0.039	0.071	0.092	1.027	0.746	0.887	0.168	0.119	0.216
CTSB	1.191	0.956	1.250	0.174	0.115	0.226	1.406	1.076	1.524	0.179	0.032	0.267
CTSH	1.248	1.028	1.281	0.117	0.036	0.152	1.473	1.161	1.629	0.058	0.050	0.080
CYB561	0.356	0.667	0.352	0.116	0.199	0.188						
CYC1	1.271	1.235	1.492	0.292	0.051	0.202						
CYP20A1	0.877	0.940	0.952	0.103	0.059	0.118	0.545	0.895	0.554	0.052	0.047	0.068
DAPK2	1.232	0.956	1.146	0.059	0.067	0.117	1.380	0.978	1.365	0.186	0.023	0.208
DDB2	0.557	0.871	0.551	0.088	0.058	0.078						
DDX54	1.429	1.118	1.536	0.067	0.013	0.059						
DGKQ	1.395	0.966	1.414	0.070	0.029	0.078	1.149	0.870	1.107	0.048	0.065	0.086
DOC2A	0.734	1.158	0.832	0.051	0.184	0.019	0.684	1.088	0.720	0.026	0.096	0.011
DTX1	1.314	1.190	1.487	0.127	0.042	0.192	1.199	1.108	1.386	0.108	0.046	0.184
EGFR	1.004	1.084	1.094	0.188	0.130	0.210	0.959	1.120	1.155	0.384	0.167	0.561
EPHA1	0.829	0.857	0.690	0.107	0.023	0.200						
EPHX2	1.040	0.911	1.055	0.055	0.094	0.102	0.954	0.886	0.958	0.410	0.045	0.421
FAM131B	1.094	1.017	1.175	0.068	0.089	0.087						
FDFT1	1.119	0.899	1.121	0.157	0.083	0.224	1.297	1.224	1.439	0.208	0.229	0.453
FERMT2	1.049	1.051	1.131	0.233	0.086	0.237						
FGFRL1	0.735	0.846	0.762	0.125	0.141	0.197	0.799	0.995	0.898	0.116	0.058	0.156

FLII	1.106	1.275	1.355	0.088	0.061	0.090	1.140	1.169	1.418	0.098	0.077	0.218
FNBP4	0.678	0.824	0.612	0.100	0.076	0.129	0.391	0.798	0.340	0.022	0.020	0.028
FRMD4A												
GAK	1.379	0.987	1.437	0.106	0.025	0.115	1.386	1.022	1.558	0.224	0.021	0.314
GAL3ST4	1.397	1.101	1.399	0.048	0.017	0.088						
GAS8	0.980	0.785	0.938	0.070	0.021	0.064	1.205	0.967	1.250	0.116	0.049	0.144
GDPD3	1.009	0.808	0.954	0.173	0.098	0.223	1.375	0.940	1.515	0.322	0.105	0.526
GFPT2	1.291	0.904	1.285	0.073	0.027	0.088	1.324	0.996	1.402	0.071	0.043	0.132
GIGYF1	0.668	0.835	0.691	0.073	0.090	0.116						
GNB2	1.097	0.936	1.039	0.074	0.104	0.124	1.109	0.976	1.058	0.129	0.020	0.133
GNPNAT1												
GPAA1	1.367	1.085	1.504	0.053	0.080	0.113	1.290	1.022	1.505	0.100	0.044	0.189
GPR137C	0.917	0.904	0.881	0.010	0.050	0.107						
GPX3	0.714	0.929	0.780	0.184	0.180	0.245	0.284	1.077	0.382	0.071	0.154	0.160
GRN	0.952	0.882	0.943	0.239	0.085	0.234						
HBEGF	1.355	1.106	1.502	0.244	0.077	0.260	1.646	1.219	1.911	0.252	0.153	0.342
HDAC2	0.786	0.809	0.712	0.143	0.100	0.166						
HIRIP3	0.526	0.795	0.517	0.085	0.034	0.086						
HS3ST1	1.394	1.186	1.510	0.144	0.055	0.171	1.650	1.215	1.834	0.250	0.062	0.288
HS3ST5	1.669	1.149	1.744	0.071	0.056	0.113	1.695	1.055	1.761	0.152	0.070	0.144
HTRA1	1.218	1.294	1.436	0.100	0.236	0.204						
IAH1	0.898	1.027	0.942	0.069	0.131	0.120	0.534	1.292	0.696	0.086	0.244	0.151
ICA1	1.100	0.793	0.974	0.043	0.096	0.100						
ICA1L	1.698	1.234	1.922	0.124	0.049	0.159	1.485	1.196	1.707	0.045	0.089	0.090

IDUA	1.493	1.149	1.609	0.063	0.084	0.096	1.640	1.274	1.940	0.146	0.012	0.247
IL17RD	0.734	0.928	0.787	0.240	0.067	0.258						
IL34	0.957	0.815	0.917	0.051	0.058	0.019	1.048	0.883	1.103	0.130	0.075	0.195
INPP5D												
IQCK	1.477	1.065	1.554	0.062	0.055	0.083	1.882	1.142	2.050	0.170	0.089	0.273
ITGB1BP1	0.669	1.042	0.751	0.125	0.172	0.169	0.544	0.848	0.545	0.288	0.043	0.279
JAZF1	0.776	1.124	0.864	0.052	0.071	0.056						
KAT8	0.820	0.806	0.791	0.077	0.113	0.136	0.625	0.771	0.588	0.180	0.103	0.264
KNOP1												
LAMTOR4	1.101	1.010	1.142	0.047	0.049	0.074	1.254	1.004	1.279	0.176	0.063	0.194
LIME1	1.019	0.976	1.070	0.119	0.036	0.120	0.825	1.071	0.953	0.072	0.135	0.147
LRCH4												
MADD	0.676	1.003	0.726	0.501	0.146	0.546						
MAF	1.243	1.122	1.352	0.131	0.092	0.139	1.290	1.063	1.357	0.146	0.094	0.183
MAF1	0.870	1.052	0.930	0.171	0.104	0.114						
MAPK3	1.154	0.854	1.070	0.081	0.016	0.066	1.254	0.838	1.146	0.092	0.061	0.103
MAPK9	1.290	0.916	1.255	0.110	0.019	0.143	1.188	0.878	1.137	0.072	0.055	0.094
MAPT	1.162	1.042	1.185	0.051	0.040	0.044	1.158	1.036	1.196	0.057	0.052	0.047
MCM7	1.152	0.971	1.156	0.195	0.145	0.250	1.278	1.021	1.346	0.201	0.045	0.223
MME	1.342	1.096	1.386	0.139	0.083	0.232	1.380	1.299	1.611	0.058	0.125	0.149
MOSPD3	1.035	0.962	1.022	0.095	0.091	0.131	1.149	1.002	1.201	0.118	0.014	0.140
MS4A7	0.640	0.849	0.673	0.053	0.141	0.092						
MTCH2	1.330	0.911	1.322	0.051	0.122	0.039	1.645	0.899	1.715	0.230	0.081	0.201
MTHFSD	0.644	0.628	0.531	0.045	0.064	0.071						

MYO15A	0.981	0.959	0.994	0.059	0.016	0.073	0.530	1.004	0.665	0.227	0.107	0.375
N4BP2	1.575	1.106	1.707	0.064	0.049	0.093	1.514	1.065	1.554	0.017	0.062	0.058
NBEAL1	0.928	0.899	0.899	0.112	0.037	0.113						
NCK2	1.575	1.444	1.954	0.193	0.281	0.424	1.768	1.399	2.273	0.224	0.157	0.421
NDUFAF7	1.310	1.113	1.454	0.035	0.088	0.086	1.175	1.099	1.407	0.142	0.180	0.321
NDUFS3	1.208	1.021	1.332	0.082	0.008	0.082	1.535	0.984	1.608	0.158	0.017	0.178
NGEF												
NR1H3	0.825	1.083	0.885	0.250	0.114	0.295	0.797	1.023	0.832	0.290	0.106	0.326
NUP160	1.095	0.967	1.081	0.149	0.028	0.136						
OARD1	1.035	0.868	1.083	0.113	0.060	0.138						
OPLAH	1.524	1.113	1.719	0.098	0.033	0.054	1.868	1.233	2.227	0.131	0.079	0.254
OTULIN	1.524	1.105	1.680	0.060	0.118	0.145						
PCOLCE	0.847	0.934	0.860	0.098	0.013	0.122	0.643	0.852	0.659	0.235	0.084	0.243
PFDN1	1.160	1.038	1.169	0.089	0.078	0.151	1.482	1.131	1.543	0.198	0.041	0.262
PICALM	0.688	0.844	0.704	0.093	0.064	0.111	0.536	0.885	0.566	0.232	0.079	0.240
PILRA	0.889	0.883	0.882	0.081	0.091	0.116	1.239	0.893	1.258	0.234	0.063	0.295
PLCG2	0.314	0.722	0.294	0.052	0.062	0.058						
PLEKHA1	1.285	1.217	1.447	0.072	0.060	0.042	1.204	1.221	1.371	0.164	0.093	0.230
PPIB	1.313	0.882	1.255	0.087	0.057	0.136	1.260	0.840	1.155	0.088	0.125	0.205
PPOX	0.904	1.005	0.915	0.134	0.029	0.133						
PPP1R35	1.052	0.997	1.078	0.113	0.097	0.115						
PPP4C	1.348	0.990	1.429	0.052	0.077	0.055	1.349	0.891	1.376	0.120	0.041	0.172
PRKD3												
PRXL2A	1.257	1.174	1.460	0.131	0.108	0.184	1.260	1.287	1.543	0.080	0.060	0.146

PSEN1												
PSEN2	1.031	1.012	1.064	0.065	0.028	0.096	0.917	0.912	0.928	0.242	0.033	0.251
PSMC3	0.183	0.936	0.216	0.032	0.096	0.049	0.231	0.893	0.257	0.148	0.202	0.185
PSMC6												
PTK2B												
PTPMT1												
QPCT	1.271	1.305	1.551	0.221	0.247	0.323	0.820	1.047	0.951	0.296	0.021	0.396
RABEP1	0.850	1.035	0.831	0.238	0.023	0.243	0.479	0.908	0.447	0.185	0.056	0.206
RASA1	1.114	0.987	1.199	0.069	0.014	0.035	1.075	1.141	1.318	0.304	0.162	0.368
RASAL1	1.396	1.132	1.500	0.145	0.063	0.218	1.602	1.219	1.836	0.187	0.083	0.321
RASGRF1												
RBCK1	0.813	0.901	0.828	0.144	0.040	0.160	0.757	0.994	0.861	0.037	0.050	0.060
RIN3												
RITA1	1.241	1.046	1.308	0.047	0.031	0.055	1.385	1.109	1.531	0.245	0.050	0.333
RPS9	0.924	0.852	0.865	0.094	0.064	0.117	0.838	1.058	0.892	0.137	0.074	0.170
RTEL1												
RTFDC1												
SAP25	0.937	0.806	0.835	0.079	0.031	0.088	1.183	0.725	1.014	0.231	0.134	0.321
SCARA3	1.060	0.888	1.000	0.079	0.072	0.131	1.130	0.928	1.123	0.241	0.058	0.294
SHARPIN	1.400	1.083	1.518	0.105	0.082	0.167	1.352	1.190	1.521	0.054	0.157	0.171
SHMT1	0.624	0.868	0.627	0.039	0.067	0.061						
SLC24A4												
SLC39A13	0.851	0.907	0.877	0.081	0.025	0.095	1.004	0.886	0.999	0.185	0.075	0.239
SNX1	1.480	1.293	1.810	0.102	0.248	0.260	1.253	0.852	1.258	0.002	0.120	0.007

SORL1	0.964	0.935	1.027	0.131	0.067	0.195	1.134	0.969	1.206	0.288	0.079	0.350
SORT1	1.346	1.165	1.566	0.132	0.240	0.345	1.631	1.314	1.986	0.035	0.115	0.114
SPDYE3	1.201	1.054	1.219	0.180	0.078	0.226						
SPI1	1.039	0.980	1.087	0.116	0.047	0.160	0.950	0.969	0.932	0.152	0.024	0.175
SPPL2A	1.118	0.992	1.126	0.042	0.010	0.048	1.160	0.893	1.120	0.107	0.070	0.134
SRC	0.921	0.754	0.785	0.060	0.066	0.099	0.972	0.667	0.776	0.181	0.126	0.227
STAG3	0.724	0.992	0.762	0.090	0.011	0.116	0.655	0.828	0.652	0.205	0.049	0.232
STMN4												
STYX	0.530	0.815	0.515	0.031	0.020	0.011	0.523	0.844	0.503	0.060	0.027	0.050
TAF6	0.503	0.919	0.515	0.149	0.148	0.150						
TANC2	1.061	0.992	1.152	0.125	0.047	0.116	1.265	1.023	1.367	0.280	0.065	0.333
TAOK2	0.611	0.871	0.643	0.014	0.017	0.027						
TBC1D20	0.877	0.779	0.763	0.121	0.107	0.174	0.702	0.819	0.716	0.121	0.121	0.203
TFR2	0.967	0.774	0.869	0.082	0.119	0.152						
TM2D3	0.972	0.918	0.962	0.070	0.045	0.116	1.223	0.921	1.188	0.074	0.013	0.112
TMEM106B	0.835	1.120	0.943	0.329	0.081	0.338						
TMEM175	1.729	1.082	1.742	0.122	0.101	0.199						
TMEM219	1.383	0.983	1.350	0.146	0.157	0.256	1.531	1.043	1.512	0.052	0.099	0.068
TOP3A												
TPCN1	1.271	0.964	1.284	0.079	0.076	0.126	1.725	1.166	1.942	0.199	0.017	0.282
TREM2	1.110	0.955	1.088	0.060	0.089	0.088						
TRIB3	0.809	1.115	0.921	0.175	0.026	0.182	1.187	1.209	1.411	0.006	0.217	0.213
TRIP4	0.887	1.165	1.024	0.120	0.064	0.103						
TSC22D4	0.856	0.934	0.874	0.122	0.061	0.114	0.474	0.946	0.480	0.307	0.115	0.322

TSPAN14	0.920	1.107	1.056	0.095	0.191	0.178						
USP6NL	0.466	0.766	0.465	0.033	0.027	0.042	0.283	0.750	0.244	0.034	0.035	0.019
VRK3	0.703	0.806	0.653	0.080	0.048	0.103	0.815	0.986	0.815	0.097	0.065	0.143
WDR12	1.211	1.176	1.368	0.114	0.116	0.028						
WDR81	0.936	0.734	0.826	0.232	0.137	0.289	0.885	0.590	0.695	0.152	0.163	0.247
WVOX	1.098	0.868	1.009	0.072	0.058	0.106	1.250	0.673	1.048	0.347	0.061	0.347
YPEL3	0.989	1.144	1.124	0.144	0.028	0.145	0.863	1.115	0.962	0.104	0.048	0.102
YWHAQ	0.882	1.164	1.036	0.242	0.045	0.232						
ZCWPW1												
ZKSCAN1	0.720	0.777	0.690	0.080	0.059	0.144						
ZNF3	0.801	0.986	0.848	0.066	0.133	0.080						
ZNF655	0.900	0.922	0.914	0.118	0.055	0.167	1.851	1.068	1.992	0.707	0.129	0.844
ZYX	0.677	0.808	0.682	0.138	0.102	0.168						

Supplementary Table S2. Description of the LoF mutations in *PLCG2* and demographic information of the carriers in ADGEN and ADES.*GRCh37

Consortium sample	Country	chr,	pos*	rs	ref allele	alt allele	annotation	Status	Gender	age	age at onset	APOE
ADER carrier 1	NER	16	81888105	-	C	T	stop_gained	AD	F	75	75	34
ADER carrier 2	NER							AD	F	73	73	44
ADER carrier 3	FRA						p.R84Ter	AD	M	76	73	34
ADER carrier 4	UK							AD	F	73	NA	33
ADER carrier 5	FRA	16	81939026	rs778484571	C	T	stop_gained	AD	F	87	NA	33
ADER carrier 6	FRA						p.Arg461Ter	AD	F	77	72	44
ADER carrier 7	UK							AD	F	78	NA	34
ADGEN carrier 8	FIN	16	81944193	rs745414766	A	T	stop_gained	control	NA	NA	NA	NA
ADGEN carrier 9	UK	16	81946323	-	T	G	splice_donor_variant	AD	F	75	70	33
ADGEN carrier 10	FIN	16	81960714	-	C	T	stop_gained	AD	M	NA	60	34
ADER carrier 11	FRA	16	81968031	-	CAGG	C	splice_acceptor_variant&coding_sequence_variant	AD	M	79	NA	34
ADGEN carrier 12	FIN	16	81969788	rs1278946830	C	T	stop_gained	AD	F	85	73	34
ADER carrier 13	FRA	16	81972519	rs1435372531	G	GAGTA	frameshift_variant&splice_region_variant	AD	F	48	NA	34
ADGEN carrier 14	FIN	16	81990426	rs746342905	TAA	T	frameshift_variant	control	NA	NA	NA	NA
ADGEN carrier 15	FIN						p.Lys1233ArgfsTer5	control	NA	NA	NA	NA

Supplementary Table S3. Quantification of AD hallmarks in brain and CSF of a *PLCG2* p.R953X carrier and matched AD cases (see material and methods as well as Fig. S7). Mean±SD

	p.R953X carrier	AD cases of reference (n=5, immunohistochemical analyses)	AD cases of reference (n=4, CSF analyses)
p-Tau area (% of total area)	0.38	0.65 ± 0.23	
Aβ (4G8) area (% of total area)	3.4	3.7 ± 1.5	
X-34/4G8 area	0.28	0.3 ± 0.06	
APOE area (% of total area)	4.0	3.5 ± 1.1	
Number of plaques	97	111 ± 19	
Plaque size (μm ²)	1003 ± 631	1216 ± 863	
Aβ42 soluble (pg/ml)	296	1528 ± 864	
Number of Microglia/plaque	0.61	0.73 ± 0.16	
IBA1 area (% of total area)	4.5	4.7 ± 1.3	
CD68 area (% of IBA1 area)	16	30 ± 17	
P2RY12 area (% of total area)	3.1	4.5 ± 2.3	
GFAP area (% of total area)	24.2	30.8 ± 5.4	
CSF total Tau (pg/ml)	703		1122 ± 287
CSF p-Tau (pg/ml)	58		121 ± 59
CSF Aβ42 (pg/ml)	415		444 ± 95