**SUPPLEMENTARY METHODS:**

Details of RT-ddPCR protocol, based on Cassinari et al 13

For each subject, 2.5mL of blood was collected directly into PAXgene Blood RNA Tubes (Qiagen, Hilden, Germany). Total RNA was isolated from whole blood using the PAXgene Blood RNA kit (Qiagen, Hilden, Germany). RT-ddPCR assays were performed using the One-Step RT-ddPCR Advanced Kit for Probes (Bio-Rad Laboratories, Hercules, CA, USA) and the QX200 ddPCR platform (Biorad). For the target, a 82 bp-amplicon was designed spanning exons 5 and 6 of *APP* (probe and primer sequences available upon request) associated to a FAM-labelled hydrolysis probe containing LNA (Universal Probes Library, Roche), as already described for DNA CNV analyses 14. The 83-bp reference amplicon mapped to exons 15-16 of *DLG4* gene associated to a specific HEX-labelled custom hydrolysis probe Iowa Black quencher and an internal ZEN quencher (IDT DNA). This reference gene was selected due to a level of blood expression comparable to that of *APP* according to the genome tissue expression GTEX database 15. RT-ddPCR mix preparation, droplets generation and amplification were performed with standard protocols according to manufacturer specification. In details, for RT-ddPCR, 4.4 μL of RNA (40 ng) was diluted in a 22 μL final reaction volume containing 5.5 μL of One Step SuperMix (ddPCR supermix for Probes no dUTP, Bio-Rad), 2.2 μL of Reverse Transcriptase, 1.1 μL of 300mM DTT and 3 μL of primers and probes mix (final probe concentration: 250 nM each, final primer concentration: 750 nM each). Then, each sample was partitioned into 11000 to 20000 droplets using the QX200 ddPCR Droplet Generator System (Bio-Rad). PCR amplification was then performed on a T1000 thermal cycler (Bio-Rad). This protocol included an initial retro-transcription step (60 min, 50°C, and 10 min, 95°C) followed by 40 cycles of cDNA amplification, each cycle including a denaturation step (95°C for 30 sec) and a step of annealing and extension at (55°C for 1 min). A final denaturation step was realized at 98°C for 10 min. The droplet reading and quantification were performed using the QX200 droplet digital reader (Bio-Rad) and data analysis was performed using the 2D module of the QuantaSoft-Pro software (Bio-Rad). For each sample, the analyses were performed in at least 3 replicates for the controls and 5 for the proband.

**Data Availability**

All relevant data are available in the article.

Supplemental references:

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14. Cassinari K, Quenez O, Joly-Hélas G, et al. A Simple, Universal, and Cost-Efficient Digital PCR Method for the Targeted Analysis of Copy Number Variations. Clin Chem. 2019;65:1153–1160.

15. Carithers LJ, Ardlie K, Barcus M, et al. A Novel Approach to High-Quality Postmortem Tissue Procurement: The GTEx Project. Biopreservation Biobanking. 2015;13:311–319.