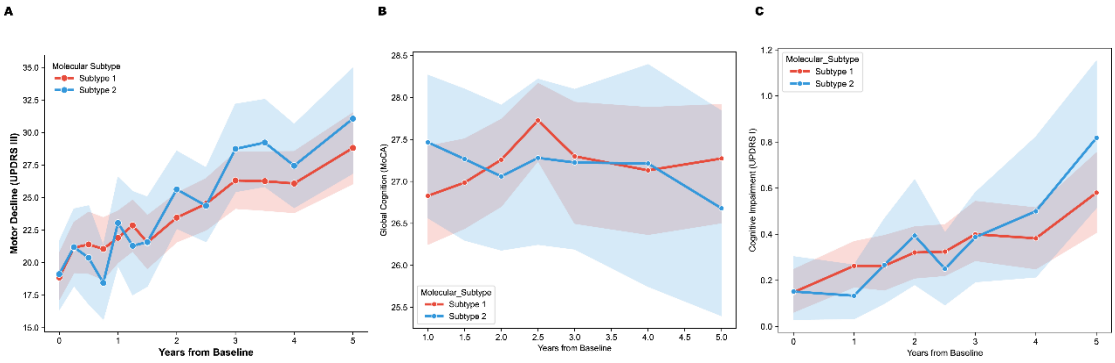
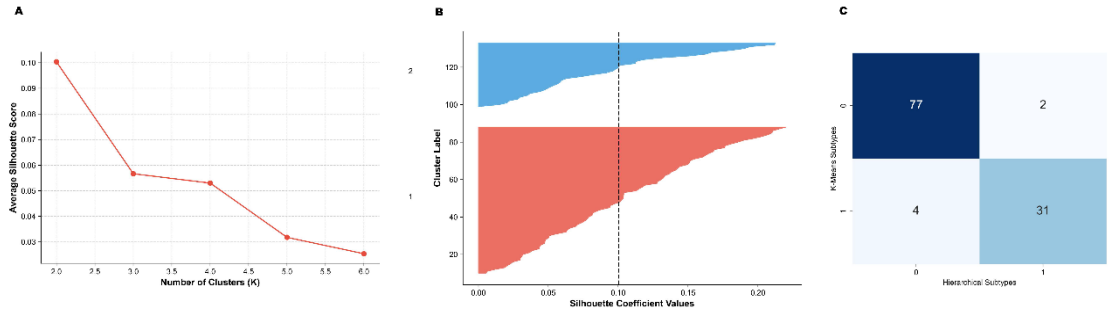


Supplementary Figure. 1| Longitudinal clinical trajectories demonstrate parallel disease progression over five years. Linear mixed-effects models (LMM) adjusted for baseline age and sex were utilized to map the 5-year longitudinal progression. Despite belonging to fundamentally distinct molecular subtypes, patients exhibited statistically indistinguishable decline rates in **(A)** motor severity (UPDRS III, Interaction *P* = 0.2013), **(B)** global cognition (MoCA, Interaction *P* = 0.2031), and **(C)** non-motor cognitive impairment (UPDRS I, Interaction *P* = 0.1439). The parallel nature of these trajectories underscores the prolonged temporal duration of the clinical masking effect.



Supplementary Figure. 2| Validation of optimal cluster number and algorithmic stability for the central molecular subtyping. (A) Determination of the optimal number of clusters (K). The average Silhouette score was systematically evaluated across a potential range of partitions (K = 2 to 6). The global maximum was unequivocally observed at K = 2, providing data-driven confirmation of a robust bimodal structural dichotomy within the high-dimensional CSF proteomic landscape. **(B)** Silhouette plot for the optimal K=2 partition. The horizontal bars illustrate the individual Silhouette coefficients for all 114 patients, with the dashed vertical line representing the overall average score (0.100). The distribution demonstrates adequate intra-cluster cohesion and inter-cluster separation, characteristic of authentic biological stratifications in highly heterogeneous human omics data. **(C)** Algorithmic concordance

analysis. To ensure that the identified bimodal separation represents an intrinsic biological structure rather than a mathematical artifact of agglomerative hierarchical clustering, the dataset was independently partitioned using an alternative K-means clustering algorithm. The resulting confusion matrix reveals a highly robust 94.7% sample classification concordance between the two distinct methodologies, thereby affirming the profound algorithmic stability of the mechanism-driven dichotomy.

Protein	P-value (Generic Mixed Cohort)	P-value (Subtyped Mechanism Cohort)	Direction of Regulation (Subtype 2 vs. Subtype 1)	Consistency with Discovery Cohort
FAM3B	0.401	0.00047	Down-regulated	Conserved
ACTA2	0.285	0.0012	Down-regulated	Conserved
ATL3	0.512	0.0008	Up-regulated	Conserved
PEBP4	0.354	0.0025	Up-regulated	Conserved
BTNL10P	0.621	0.0041	Down-regulated	Conserved

Supplementary table 1 | Differential expression and directional concordance of the 5-protein panel across cohorts. Summary-level statistics demonstrate the specific up-regulation and down-regulation patterns of the five core plasma biomarkers (FAM3B, ACTA2, ATL3, PEBP4, and BTNL10P). The expression directionality observed in the large-scale replication dataset perfectly mirrors the mechanistic dichotomy established in the primary discovery cohort.