Table S1. Instruments used to construct ML-derived ASD subtype classifications and scores.

Measures of co-occurring symptoms included parent-reported cognitive impairment, language impairment, cognitive test score, cognitive age level, motor coordination (DCDQ), and adaptive functioning assessed using the Vineland Adaptive Behavior Scales (VABS; Adaptive Behavior Composite, Communication, Daily Living Skills, and Socialization standard scores). Co-occurring neuropsychiatric conditions included parent-reported mood or anxiety disorders, attention or behavioral problems, and attention-deficit/hyperactivity disorder (ADHD).

Category	**Symptom domain**	**Instruments**	Acronym	Scoring and measurement
	Social functioning and communication	Social Communication Questionnaires - Lifetime	SCQ	Higher scores, more severe
ASD core symptom	Repetitive behavior	Repetitive Behaviors Scale Revised	RBS-R	Higher scores, more severe
	Cognitive function	Parent-reported cognitive impairment status		
	Language ability	Parent-reported language impairment level		
	Motor coordination	Developmental coordination Disorder Questionnaire	DCDQ	Lower scores, more severe
Co-occurring symptom	Adaptive function	Vineland adaptive behavior scales	VABS	Lower scores, more severe
	Attention deficit / hyperactivity	Parent-reported medical history	ADHD	
Co-occurring disorder	Mood or anxiety disorders	Parent-reported medical history		

Table S2. Comparison of clustering quality metrics between the three-branch, four-branch DDRTree solutions and k-means clustering.

	Silhouette Score	Davies-Bouldin Index (DBI)	Calinski-Harabasz Index
Definition	Measures how similar each sample is to its assigned cluster compared with other clusters, reflecting both cluster cohesion and separation	Measures the average similarity between each cluster and its most similar neighboring cluster, based on within-cluster dispersion and between-cluster distance	Measures the ratio of between-cluster dispersion to within-cluster dispersion, reflecting how well clusters are separated
Range	[-1, 1]	≥ 0	≥ 0 (no fixed upper limit)
Direction	Higher values indicate better clustering (closer to 1 = compact and well-separated clusters)	Lower values indicate better clustering (closer to 0 = better separation and lower overlap)	Higher values indicate better clustering (larger between-cluster differences relative to within-cluster variation)
DDRTree (N = 3)	0.55	0.79	10231.95
DDRTree (N = 4)	0.43	0.76	7894.26
Kmeans	0.25	1.40	3258.58

Table S3a. Assessment of reliability on projected subtype scores in SSC across different neighborhood sizes in k-NN. We assessed the standard deviations of projected subtype scores among 5 bootstrap replicates.

k	HSN score	EBSN score	LSN score
2	0.0297	0.0332	0.0266
3	0.027	0.0307	0.0241
4	0.0241	0.0276	0.0217
5	0.0234	0.0272	0.0212

Table S3b. Assessment of reliability on projected subtype assignments in SSC across different neighborhood sizes in k-NN. We assessed the agreement of projected subtype assignments among five bootstrap replicates across neighborhood sizes from 2-5.

k	Agreement in all 5 replicates (high reliablity)	Agreement in 4 replicates (moderate reliablity)	Agreement in ≤3 replicates (low reliablity)
2	78.21%	11.59%	10.20%
3	78.17%	12.08%	9.75%
4	78.65%	10.68%	10.67%
5	78.06%	11.60%	10.34%

Table S4. Cell-type heritability enrichment analyses among ASD subtype scores.

Cell-type heritability enrichment was evaluated using stratified LD score regression (S-LDSC) based on GWAS summary statistics derived from logit-transformed Low-support-need, Behavioral-support-need, and High-support-need subtype scores. CT-FM-derived candidate cis-regulatory element (cCRE) annotations were manually curated into canonical cell-type groups, followed by LD-score recalculation and subtype-score-specific enrichment analysis. For Zhang atlas annotations, numerical suffixes denote distinct chromatin-accessibility clusters within the same annotated cell type and do not correspond to standardized neuronal subtype nomenclature. Cell types with non-negative coefficient Z-scores and nominally significant enrichment P values ($P < 0.05$) are reported for each subtype score.

Subtype score	Stage	Cell type	Source	Enrichment *P* value §
HSN	Fetal/embryonic	Excitatory neuron 10	Zhang et al. 2021	1.41E-02*
	Fetal/embryonic	Astrocyte 3	Zhang et al. 2021	1.62E-02*
	Fetal/embryonic	Excitatory neuron 9	Zhang et al. 2021	3.42E-02*
	Adult/general	C4-2B from prostate cancer cell line	ENCODE: ENCSR270DBB	4.38E-02*
EBSN	Fetal/embryonic	Endodermal cell	ENCODE: ENCSR136BIR	3.60E-02*
	Adult/general	Motor neuron	ENCODE: ENCSR215ISZ	4.92E-02*

§ *P < 0.05.

Table S5. Associations between polygenic scores and continuous ASD subtype scores in the SPARK and SSC cohorts.

Associations between standardized polygenic risk scores (PGS) and continuous subtype scores were evaluated using linear regression. PGS were standardized using Z-score transformation. Logit-transformed subtype scores were modeled as the outcome, with PGS as the predictor of interest while adjusting for sex, age, and the first ten ancestry principal components. Analyses were performed separately in the SPARK and SSC cohorts. Regression coefficients (Beta), standard errors (SE), and P values are reported.

Outcome	PGS	SPARK			SSC		
		Beta	SE	*P* value §	Beta	SE	*P* value §
HSN score	Cognitive function	-0.0780	0.0160	1.08E-06***	-0.0089	0.0154	5.65E-01
	Schizophrenia	0.0566	0.0186	2.33E-03**	0.0267	0.0168	1.13E-01
	ASD	0.0225	0.0177	2.04E-01	-0.0166	0.0155	2.83E-01
	Major depressive disorder	-0.0114	0.0176	5.18E-01	0.0011	0.0182	9.51E-01
	Anxiety disorders	0.0222	0.0131	8.99E-02	0.0067	0.0142	6.39E-01
	Bipolar disorder	-0.0106	0.0150	4.80E-01	0.0213	0.0153	1.64E-01
	Attention-deficit/hyperactivity disorder	-0.0088	0.0150	5.54E-01	-0.0044	0.0157	7.77E-01
EBSN score	Cognitive function	-0.0439	0.0156	4.93E-03**	-0.0213	0.0131	1.04E-01
	Schizophrenia	-0.0464	0.0181	1.04E-02*	0.0086	0.0143	5.45E-01
	ASD	-0.0066	0.0172	7.01E-01	0.0129	0.0131	3.27E-01
	Major depressive disorder	0.0939	0.0171	4.25E-08***	0.0322	0.0154	3.65E-02*
	Anxiety disorders	0.0109	0.0127	3.91E-01	0.0004	0.0120	9.75E-01
	Bipolar disorder	0.0023	0.0146	8.78E-01	0.0044	0.0130	7.34E-01
	Attention-deficit/hyperactivity disorder	0.0787	0.0145	6.39E-08***	0.0280	0.0133	3.52E-02*
LSN score	Cognitive function	0.1243	0.0160	9.47E-15***	0.0243	0.0163	1.36E-01
	Schizophrenia	-0.0464	0.0187	1.30E-02*	-0.0330	0.0178	6.38E-02
	ASD	-0.0062	0.0178	7.29E-01	0.0159	0.0164	3.31E-01
	Major depressive disorder	-0.0487	0.0177	5.93E-03**	-0.0239	0.0192	2.13E-01
	Anxiety disorders	-0.0335	0.0131	1.07E-02*	-0.0136	0.0150	3.66E-01
	Bipolar disorder	0.0082	0.0151	5.86E-01	-0.0251	0.0162	1.20E-01
	Attention-deficit/hyperactivity disorder	-0.0413	0.0150	6.02E-03**	-0.0214	0.0166	1.96E-01

§ *P < 0.05; **P < 0.01; ***P < 0.001.