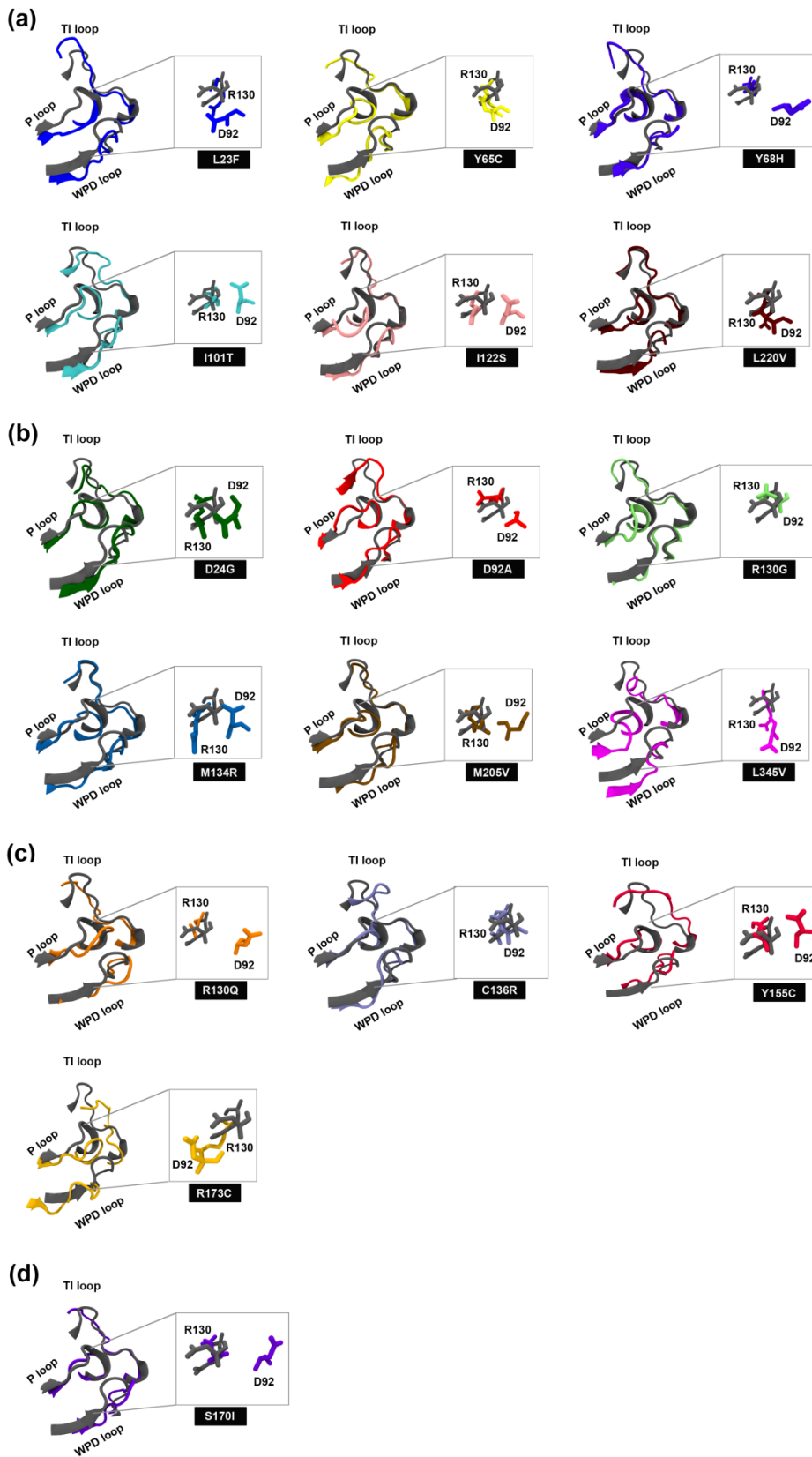


Figure S1. Human PTEN sequence and ASD- vs. cancer-associated mutations at

structure level. (a) Primary amino acid sequence of human PTEN and (b) 17 germline *PTEN* missense mutations (spheres) mapped to the three-dimensional structure of WT PTEN. The P-, WPD-, and TI-loops are highlighted in cyan, brown, and purple, respectively. ATP-binding motif type A (residues 60-73) is indicated in pink (type B, residues 122-136 overlaps the P loop). Inter-domain region motifs 1, 2, 3, and 4 are highlighted in dark blue, red, orange, and yellow, respectively.



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Figure S2. Conformational analysis of catalytic active site in ASD- vs. cancer-associated mutations. The catalytic P-, WPD-, and TI-loops illustrate the conformational changes in (a) ASD (only), (b) cancer (only), (c) mutations shared across both phenotypes, and (d) one mutation with coexisting phenotypes in comparison to WT PTEN. Catalytic residues D92 and R130 are indicated in the separate exploded box depicting the orientations as a result of the mutation and subsequent conformational change.

Table S3. Patient Cohort Median and Age Ranges

	No. of Patients	Mean or Median Age	
		Median	Range
ASD (only)	6	17	10 – 31
Cancer (only)	6	60	52 – 71
ASD or Cancer (shared)	22	44	8 – 80
ASD and Cancer (coexisting)	1	30	30

Table S3. Rigid vs. Flexible Inter-domain region – Disease Burden

Cancer (only) n=6								
Genotype	Phenotype							
	Breast	Cervical	Endometrial	Leukemia	Skin	Thyroid	Uterine	
p.D24G			✓	✓				
p.D92A	✓							
p.R130G	✓							
p.M134R						✓		
p.M205V	✓	✓						
p.L345V	✓				✓		✓	
ASD or Cancer (only) n=4								
Genotype	Phenotype							
	ASD	Breast	Cervical	Endometrial	Esophageal	Ovarian	Skin	Thyroid
p.R130Q	✓	✓	✓		✓	✓		
p.C136R	✓	✓		✓				✓
p.Y155C	✓	✓						
p.R173C	✓					✓	✓	✓
ASD and Cancer (coexisting) n=1								
Genotype	Phenotype							
	ASD	Endometrial	Ovarian	Thyroid				
p.S170I	✓	✓	✓	✓				