

Supplementary Table 1.

Mutation.	REVEL	PON-P2	VarSite Conservation	ProTSPoM. FoldX	Missense 3D Phyre
RAG2 G35V	0.891	0.969	1	-1.27 kcal/mol	Damage G in turn
RAG2 L155P	0.726	0.760	1	-1.79 kcal/mol	Damage buried P
RAG2 R229W	0.947	0.965	0.7	-0.21 kcal/mol	no damage
RAG2 H481D	-	0.929	0.8	-0.11 kcal/mol	no damage
RAG1 R764P	0.958	0.921	1	0.92 kcal/mol	no damage
RAG1 R624H	0.927	0.918	1	-1.11 kcal/mol	no damage

Supplementary Table 2.

Patient #	CD3+ (%), (cells/mm³)	CD4+ (%), (cells/mm³)	CD8+ (%), (cells/mm³)	CD19+ (%), (cells/mm³)	CD56+ (%), (cells/mm³)	CD45+RA (%), (cells/mm³)	CD45+RO (%), (cells/mm³)
1	52, 577	48, 534	2.3, 26	0.28, 3	46, 515	0.19, 1	99.7 , 526
2	ND ND	68, ND	29.9, ND	0.03, ND	4.5, ND	4.8, ND	89.9 ND
3	52, 1168	59, 797	28, 297	14, 286	39, 797	3, 19	81 508
4	69, 185	48, 89	49, 91	0.6, 16	25, 67	5, 5	88, 87
5	1, 11	44, 2	16, 2	0, 0	84.5, 913	0, 0	93, 4
6	66, 4467	64, 4325	2, 145	0, 0	32, 2144	ND, ND	ND, ND

Supplementary Table 3.

RAG Mutation	ClinVar	HGMD	gnomAD	dbSNP
RAG2G35V	likely pathogenic, pathogenic VCV000496618	SCID REF 30	heterozygote 1 male	rs148508754
RAG2 L155P	likely pathogenic VCV000418452	—	heterozygote 2 female Latino	rs1064793250
RAG2 R229W	conflicting	atypical SCID Omenn REF 22	heterozygote 1 male European	rs765298019
RAG2 H481D	—	—	heterozygote 2 male Latino	rs762054841
RAG1 R764P	—	SCID REF	—	—
RAG1 R624H	not provided VCV000068687	SCID	heterozygote (12) 8 male 4 female European, Latino, South Asian	rs199474680

Supplementary Figure 1. Location of the mutations in the context of the RAG recombinase (reference structures PDB-ID 5ZDZ (A and B, representing perpendicular views of the complex) and 2V87 (C)). RAG1 is shown as a green ribbon, RAG2 in orange, a histone peptide with methylated arginine (2MR) and lysine (3MK) in magenta, and a nicked DNA duplex in purple; the active site location is marked by residue E965, and a long loop in RAG2 with extensive interactions with RAG1 is also indicated (RAG1 loop). The mutated residues (labeled in blue) in the core recombinase (A and B) are shown in Van der Waals spheres and as sticks for the PHD domain (C), in CPK colors (carbon in cyan, nitrogen in blue, oxygen in red, sulfur in yellow, Zn in grey).

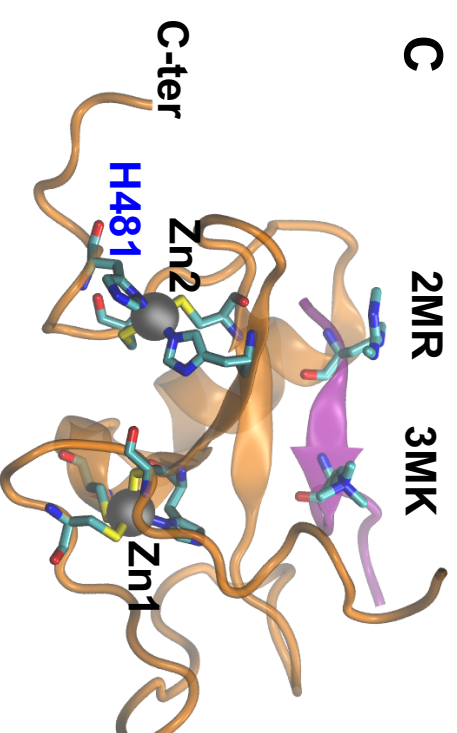
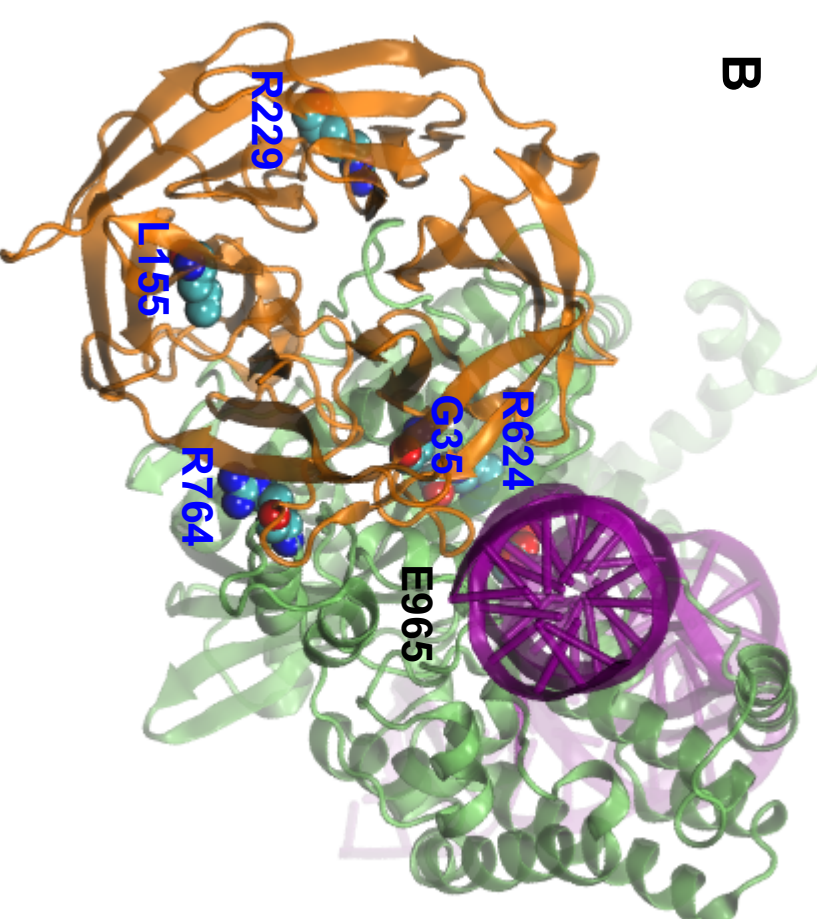
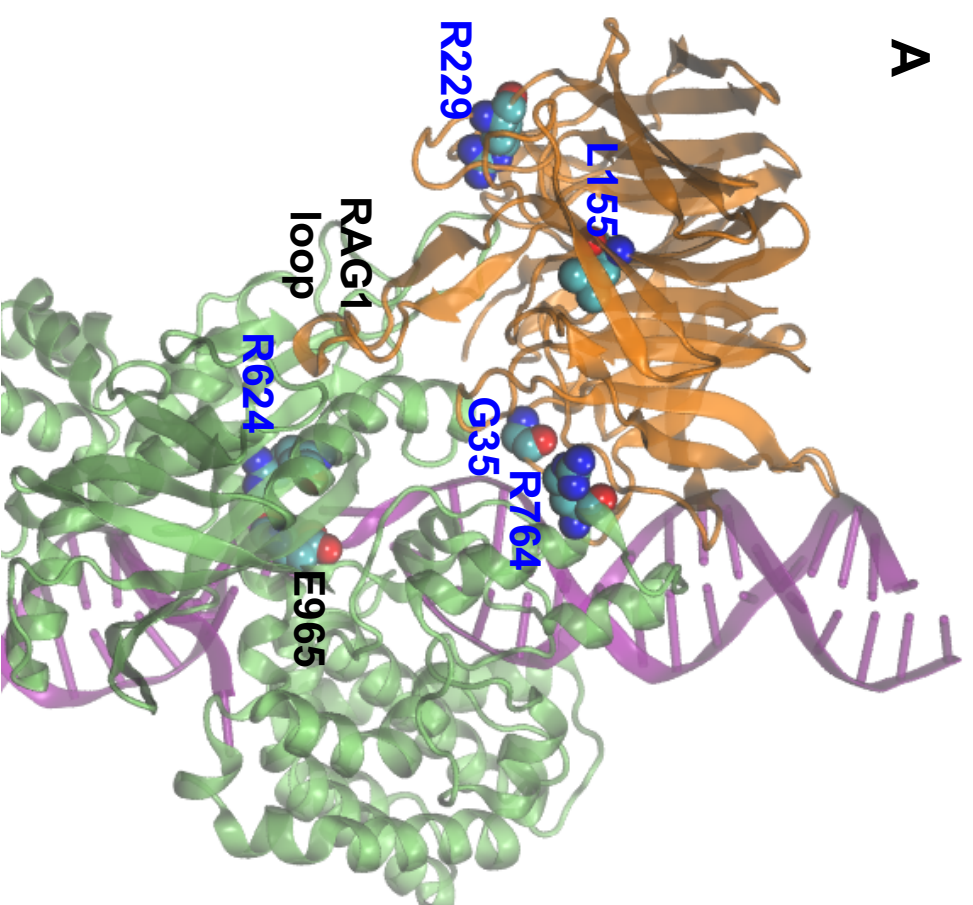


Fig S1