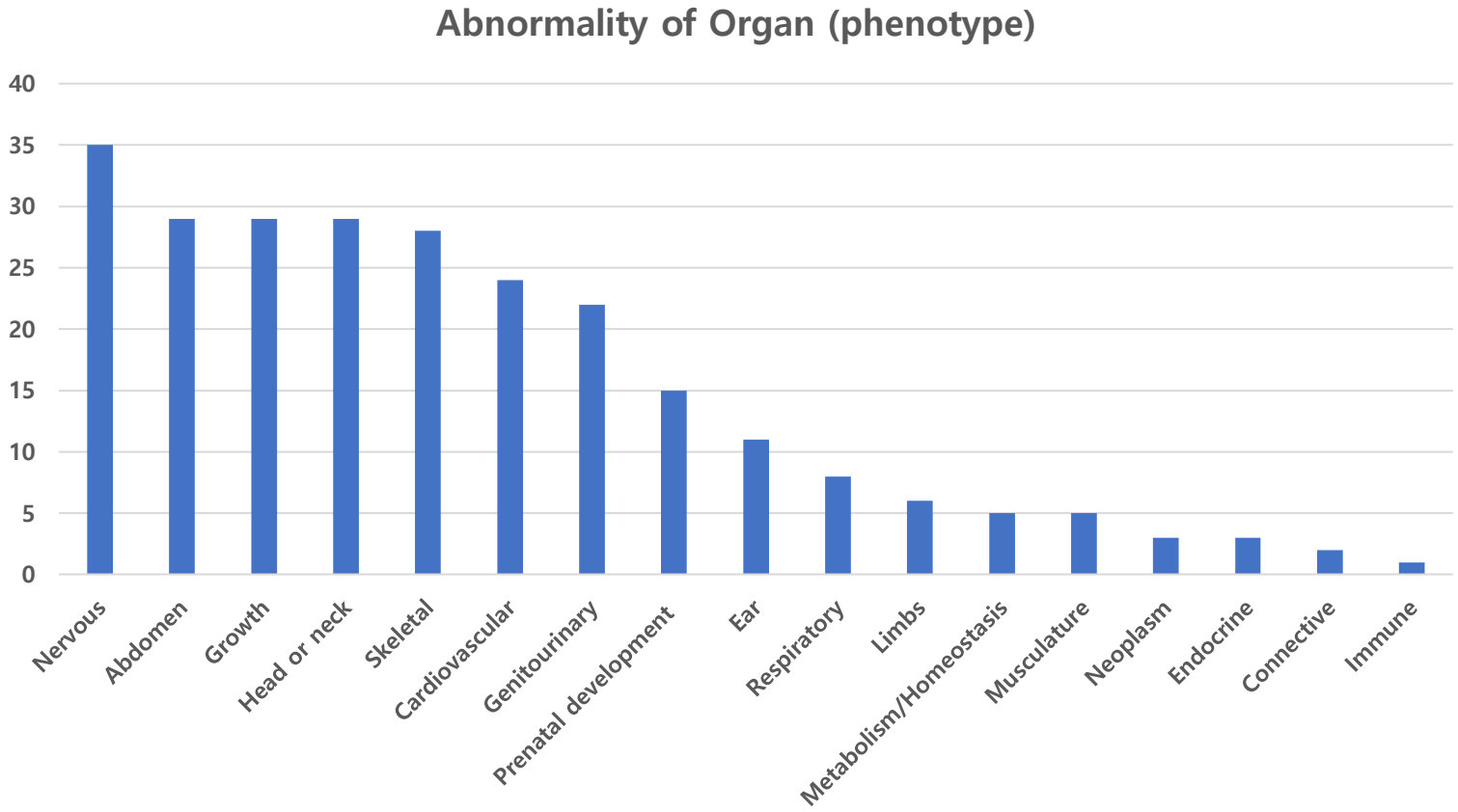
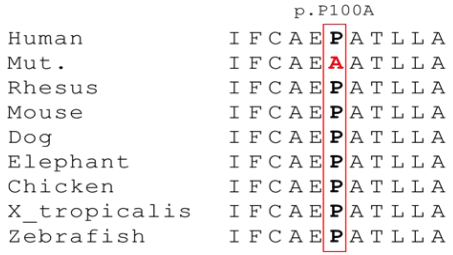
Supplementary Fig. 1. Phenotype distribution of patients with congenital anomaly. The x-axis represents the subgroup of abnormal phenotype and y-axis represents the number of patients with each phenotype. All participants have multiple anomalies with four or more phenotypes. Abnormality of the nervous system is the top phenotypic subgroup followed by several organs/phenotypes such as abdomen, growth, head or neck, skeletal, cardiovascular and genitourinary.



Supplementary Fig. 2. Pathogenicity of causal genetic variants in *NRXN1*and *RARS1*. (A-C for NRXN1, D-F for RARS1). (A, D) Phylogenic conservation of amino acids (AA) in all species. Mut. designates the sequence of AA from genomic DNA variation. (B, E) Protein structural change originated from AA change by genomic DNA variation, predicted by DynaMut2 software using protein sequence of PDB or AlphaFold. (C, F) Change of interaction (C) and hydrogen bond (F) between WT/Var. and neighboring AAs

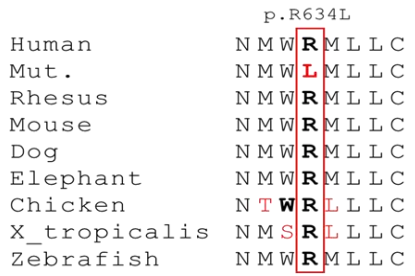
(A)



(C)

Interaction with 100th aa	WT (Pro)	Var (Ala)
Hydrophobic	4	1
Polar	2	2
Carbonyl	1	1

(D)

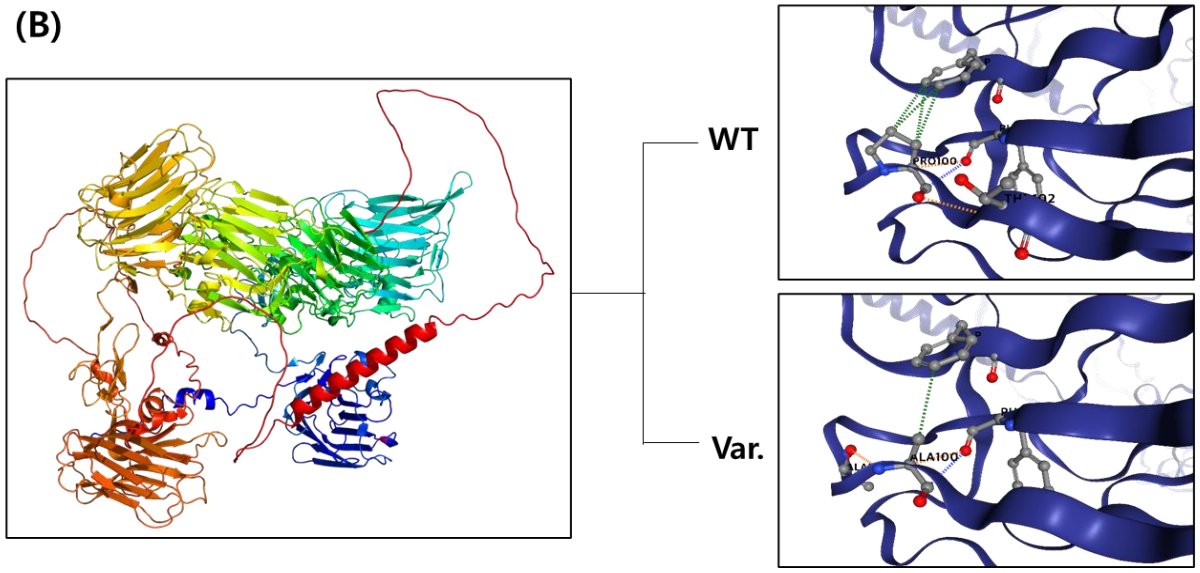


(F)

Interaction Types	WT (Arg)	Var. (Leu)
Carbonly	1	1
Hydrophobic	5	15
Polar	5	9
Ionic	4	0
VDW	1	2
Clash	4	4

Hydrogen bond with 634th aa	WT (Arg)	Var. (Leu)
Cys617	1	2
Asn631	2	1
Leu637	1	2
Gln571	2	0
Cys615	1	0
Cys638	0	1

(B)



(E)