

Exosomopathy amino acid substitution	Hs EXOSC2		Sc Rrp4	
	G30V	G198D	G58V	G226D
Missense 3D* (Phyre2)	Neutral	Damaging	Neutral	Damaging
PolyPhen-2** (HumDiv)	Possibly Damaging (Score: 1.000)	Probably Damaging (Score: 1.000)	Probably Damaging (Score: 1.000)	Probably Damaging (Score: 1.000)
Provean[†]	Deleterious (-7.938)	Deleterious (-6.35)	Deleterious (-8.981)	Deleterious (-6.517)
SNAP2[‡]	Effect (Score: 91)	Effect (Score: 94)	Effect (Score: 63)	Effect (Score: 92)

***Missense 3D** part of tool suite **Phyre2 (Protein Homology/analogy Recognition Engine)** v2.0; predicts structural changes introduced by an amino acid substitution through three-dimensional protein modeling.

****PolyPhen-2 (Polymorphism Phenotyping)** v2 HumDiv trained model; Naïve Bayes posterior probability that mutation is damaging and qualitative classification as benign, possibly damaging, or probably damaging based on 5%/10% false positive rate (FPR) thresholds (FPR, the chance the mutation is classified as damaging when it is non-damaging).

[†]**PROVEAN (Protein Variation Effect Analyzer)** v1.1; delta alignment scores equal to or below predefined threshold (-2.5), protein variant predicted to have "deleterious" effect on function.

[‡]**SNAP2** predicted score for functional effects of mutations; scores range from -100 strong neutral prediction to +100 strong effect prediction.

Table S3. Summary of *in silico* predictions for pathogenic amino acid substitutions in EXOSC2 and Rrp4.