The American Journal of Human Genetics, Volume *99*

Supplemental Data

Bi-allelic Mutations in *KLHL7* Cause a Crisponi/CISS1-like Phenotype Associated with Early-Onset Retinitis Pigmentosa

Andrea Angius, Paolo Uva, Insa Buers, Manuela Oppo, Alessandro Puddu, Stefano Onano, Ivana Persico, Angela Loi, Loredana Marcia, Wolfgang Höhne, Gianmauro Cuccuru, Giorgio Fotia, Manila Deiana, Mara Marongiu, Hatice Tuba Atalay, Sibel Inan, Osama El Assy, Leo M.E. Smit, Ilyas Okur, Koray Boduroglu, Gülen Eda Utine, Esra Kılıç, Giuseppe Zampino, Giangiorgio Crisponi, Laura Crisponi, and Frank Rutsch

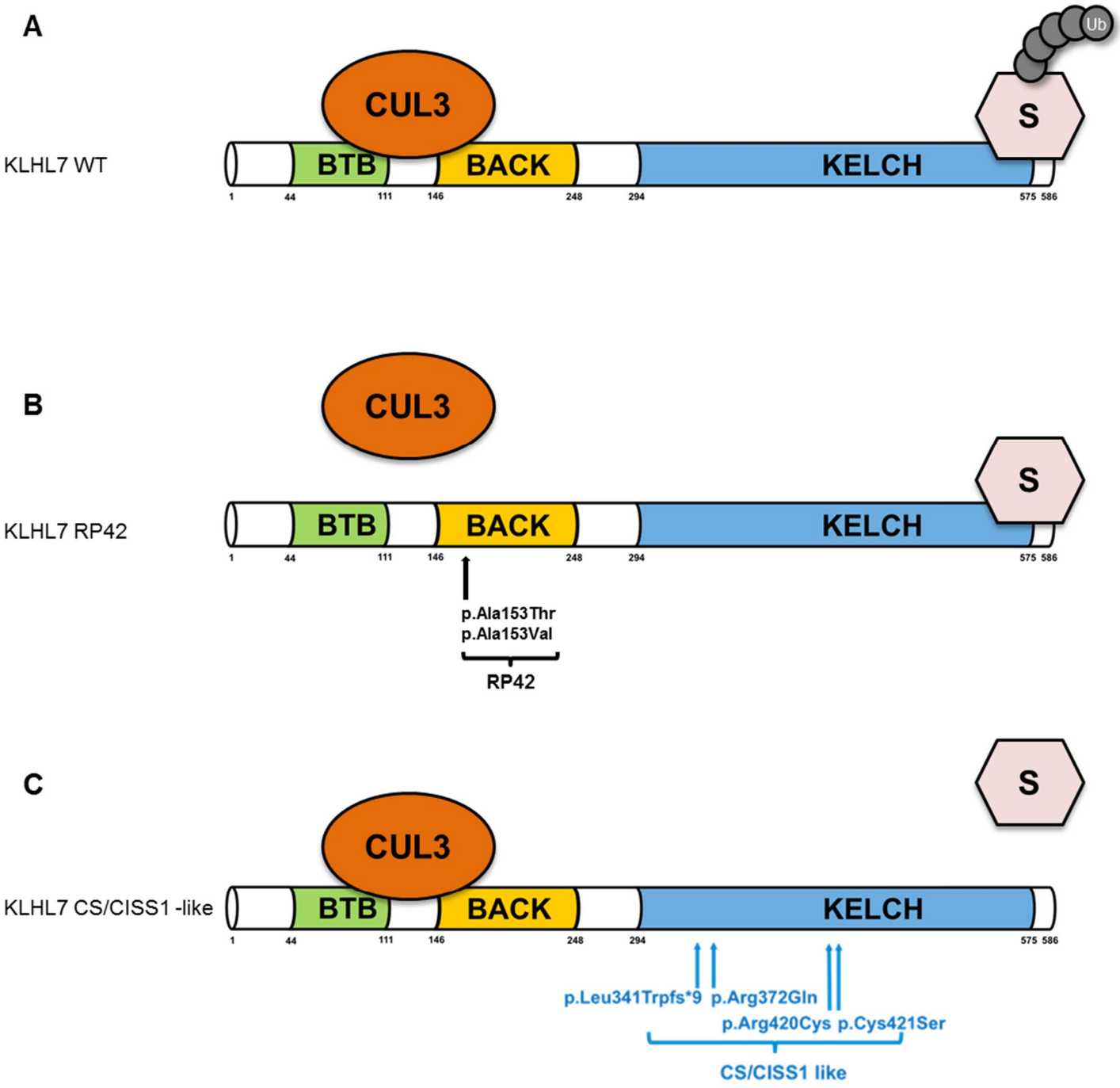

Figure S1: Proposed pathomechanism of KLHL7 mutations in adRP and Crisponi/CISS1-like phenotype. (A) In KLHL7 WT, CUL3 binds to the protein via the BTB/BACK domain and the target substrate(s) that bind to the Kelch domain are ubiquitinated and degraded by proteasome. (B) In KLHL7 mutated in adRP, CUL3 does not bind to the protein, and the target substrate(s) that bind to the Kelch domain are not ubiquitinated and accumulate. (C) In KLHL7 mutated in CS/CISS1 like, CUL3 binds to the protein while the target substrate(s) could not bind to the Kelch domain and are not ubiquitinated and accumulate.

Table S1. Number of variants identified in the whole exome sequencing.

	CS - Fam C	CS - Fam F	CS - Fam G
Annotated variants	178148	194431	127389
Total high quality variants in the family (GATK Hard Filters PASS Variants)	165377	174850	118995
Filtered by MAF	19226	22314	11023
Filtered by feature (frameshift - nonframeshift - startloss - stoploss - stopgain - splicing2bp - missense - 3'UTR - 5'UTR)	7397	7800	4246
Filtered by feature (No UTRs)	1792	1946	941
Filtered by autosomal recessive model	80	42	250
Recessive homozygotes	50	27	82
Heterozygous compound	30	15	168
Filtered by false positives	68	37	202
Novel variants (No rs)	20	12	52
Candidate gene(s)	1	1	1

Table S2. Pathogenicity score of the three missense mutations found

Family code	CS ï Fam C	CS ï Fam G	CS ï Fam L
Proband code	CS_144	CS_260	CS_169
Chromosome	7:23207538	7:23207535	7:23205495
Gene	*KLHL7*	*KLHL7*	*KLHL7*
DNA change	c.1261T>A	c.1258C>T	c.1115G>A
aa change	p.Cys421Ser	p.Arg420Cys	p.Arg372Gln
dbSNP (rsID)	no rs	rs780705654	no rs
SIFT	Tolerated	Damaging	Damaging
PolyPhen-HDIV_pred	Probably damaging/Benign	Probably damaging	Probably damaging
PolyPhen-HVAR_pred	Probably damaging/Benign	Probably damaging	Probably damaging
LRT	Damaging	Damaging	Damaging
MutationTaster	Disease causing	Disease causing	Disease causing
MutationAssessor	Neutral	High	Medium
FATHMM	Tolerated	Deleterious	Tolerated