Supplementary Data

CADD score analysis

CADD analysis (Scaled C-score) [1] was performed.

RTEL1 variants identified by WES in FPF families

FAMILY A : scaled C-score=28.4
FAMILY B : scaled C-score=35
FAMILY C : scaled C-score=12,95
FAMILY D : scaled C-score=25

RTEL1 missense variants >0.1% in EA population (> 8 variants found in 8000 individuals)

20:62322290	rs190887884	G>A	A=113/G=8185

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62322290	G	A	0.010755	2.497

20:62293272	rs3848668	A>G	G=712/A=7888

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62293272	A	G	-1.792082	0.002

20:62293862	rs41297642	C>T	T=43/C=8555

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62293862	C	T	0.183848	4.293

20:62309621	rs143550996	T>C	C=9/T=8591

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62309621	T	C	-0.637851	0.073

20:62321128	rs35640778	G>A	A=152/G=8430

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62321128	G	A	3.329118	22.7

20:62324290	rs61736615	G>A	A=318/G=8266

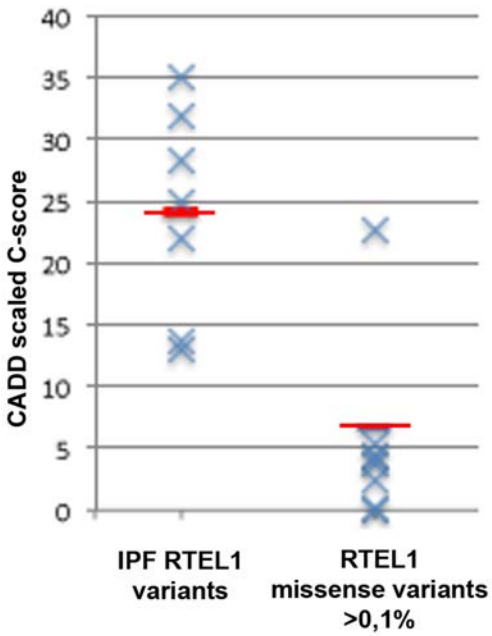
#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62324290	G	A	0.189811	4.359

20:62325833	rs115610405	C>A	A=163/C=8391

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62325833	C	A	0.274745	5.283

20:62326110	rs3208008	A>C	C=6574/A=1972

#Chrom	Pos	Ref	Alt	RawScore	PHRED
20	62326110	A	C	0.143789	3.855



Supplementary reference :

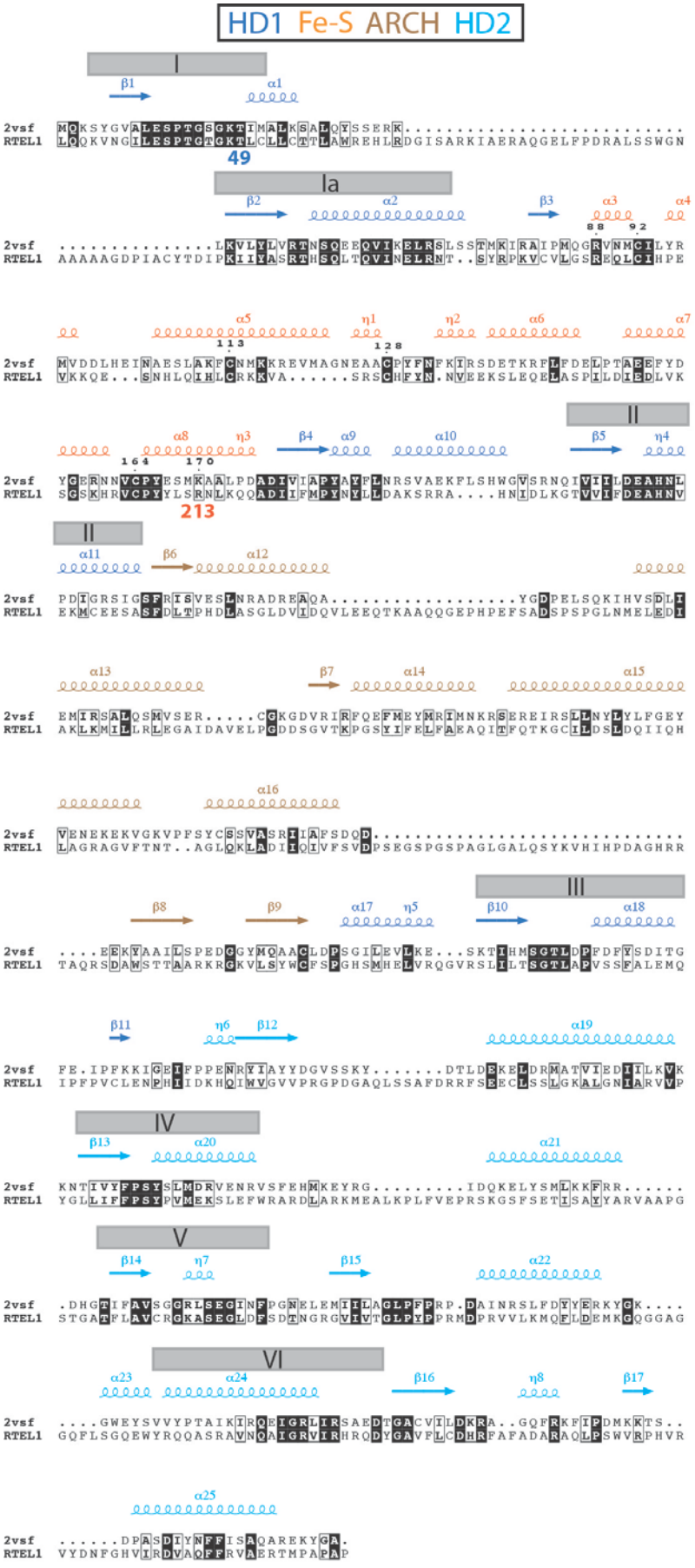
1.Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet*. **2014** Mar;46:310-315.

Molecular modelling and 3D structure visualisation

Alignment of the human RTEL1 sequence with that of the T. acidophilum XPD, whose 3D structure is known (pdb 2vsf and 4a15). Secondary structures are indicated above the alignment and are colored according to their domains (indicated at top), as reported in [1]. The two mutations reported here are indicated below the RTEL1 sequence. They belong to highly conserved regions.
The alignment was deduced from the results of HH-PRED [2], Phyre2 [3] and I-TASSER [4], and was refined for the most divergent regions (especially the ARCH domain) using Hydrophobic Cluster Analysis [5] (and our unpublished results).

Supplementary references :

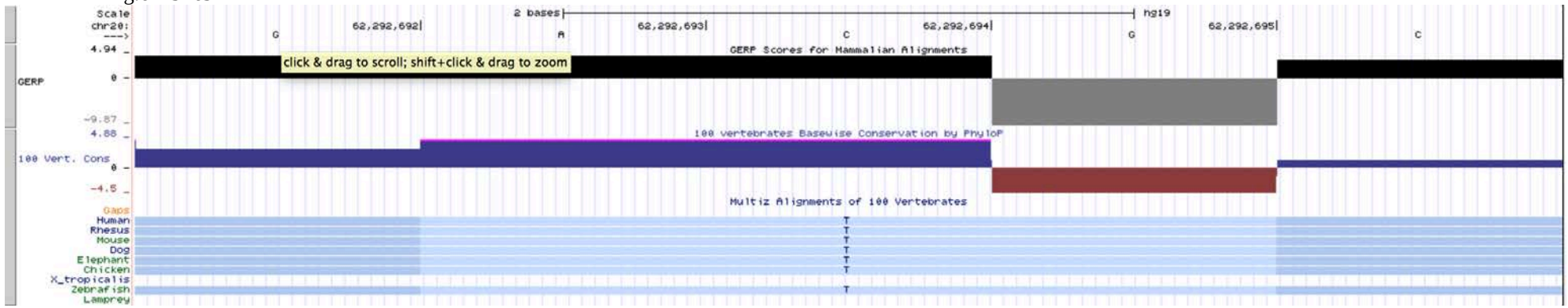
1. Wolski SC, Kuper J, Hanzelmann P, Truglio JJ, Croteau DL, Van Houten B, Kisker C. Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD. *PLoS Biol* 2008; 6: e149.
2. Soding J, Biegert A, Lupas AN. The HHpred interactive server for protein homology detection and structure prediction. *Nucleic Acids Res* 2005; 33: W244-248.
3. Kelley LA, Sternberg MJ. Protein structure prediction on the Web: a case study using the Phyre server. *Nat Protoc* 2009; 4: 363-371.
4. Yang J, Yan R, Roy A, Xu D, Poisson J, Zhang Y. The I-TASSER Suite: protein structure and function prediction. *Nat Methods* 2015; 12: 7-8.
5. Callebaut I, Labesse G, Durand P, Poupon A, Canard L, Chomilier J, Henrissat B, Mornon JP. Deciphering protein sequence information through hydrophobic cluster analysis (HCA): current status and perspectives. *Cell Mol Life Sci* 1997; 53: 621-645.


HD1 Fe-S ARCH HD2
I
Ia
II
II
III
IV
V
VI
2vsf
RTEL1
49
213

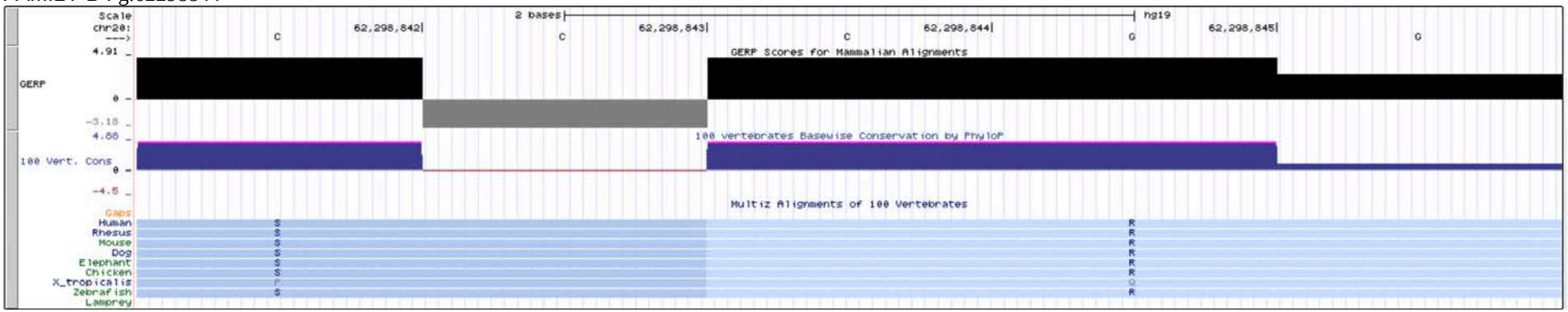
Conservation

GERP scores analysis of nucleotides targeted by RTEL1 mutations were obtained on UCSC genome browser based on their position in hg 19 human genome version. Chr20 (Hg19/GRCh37)

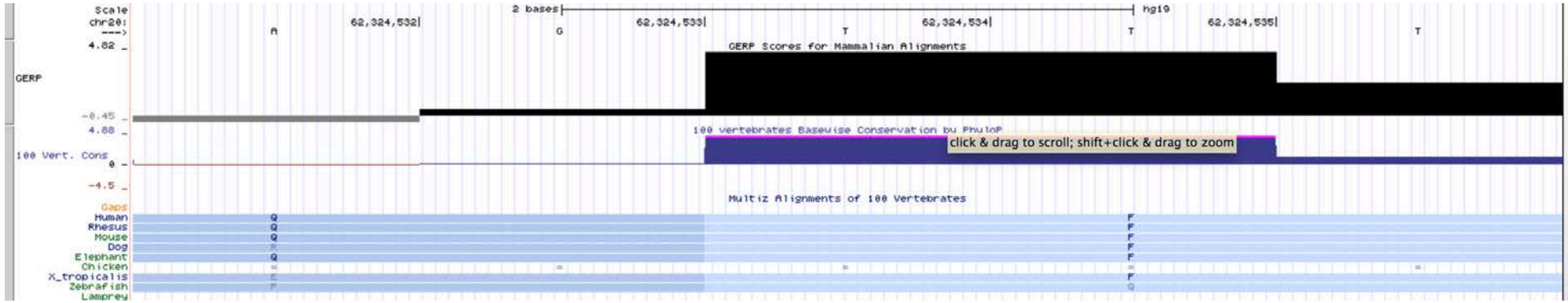
FAMILY A : g.62292694



FAMILY B : g.62298844



FAMILY C : g.62324534



FAMILY D : g.62326565