SUPPLEMENTARY APPENDIX

Marked overlap of four genetic syndromes with dyskeratosis congenita confounds clinical diagnosis

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Supplemental information:

Marked overlap of four other genetic syndromes with dyskeratosis congenita confounds clinical diagnosis

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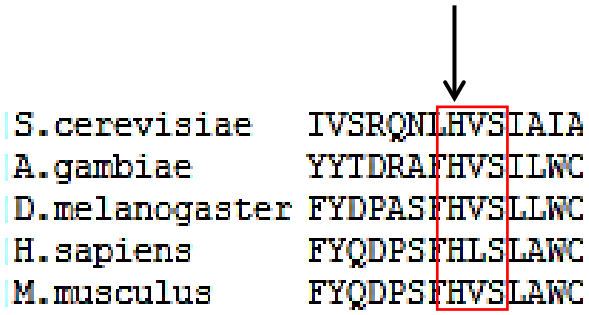
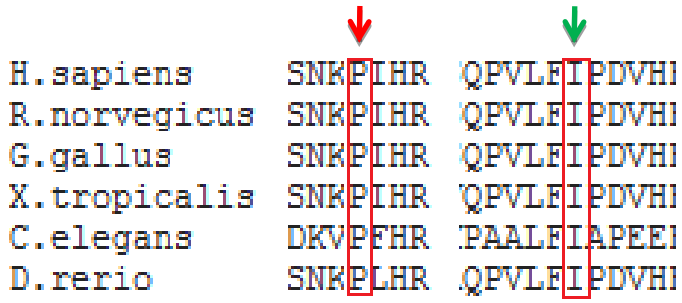
Supplementary Figure 1



The p.His208Arg homozygous USB1 mutation identified in Family 7 and Family 8 causes disease. Clustal alignment (http://www.ebi.ac.uk/Tools/msa/clustalo/) identifies the highly conserved HxS motif (red box). The arrow indicates the amino acid of interest. The accession numbers used are NP_013233, XP_307963, NP_649911, NP_078874 and NP_598715 respectively.

Supplementary Figure 2



Clustal alignment for GRHL2 demonstrated that the amino acids in the red boxes are highly conserved. The red arrow highlights the p.Pro405Thr substitution identified in Family 10 and the green arrow highlights the p.Ile482Lys substitution seen in Family 9. The accession numbers used are NP_079191, NP_001127999, XP_004940038, NP_001011338, NP_490837 and NP_001076541 respectively

Supplementary Table 1: List of genes included in the targeted sequencing assay

Gene	Approved HGNC name	MIM
ACD	Adrenocortical dysplasia homolog	609377
ANKRD26	Ankyrin repeat domain 26	610855
CEPBA	CCAAT/enhancer binding protein alpha	116897
CTC1	CTS telomere maintenance complex component 1	613129
DDX41	DEAD-box helicase 41	608170
DKC1	Dyskerin pseudouridine synthase 1	300126
DNAJC3	DnaJ heat shock protein family (Hsp40) member C3	601184
DNAJC21	DnaJ heat shock protein family (Hsp40) member C21	NA
ERCC6L2	Excision repair cross-complementation group 6 like 2	615667
ETV6	ETS variant 6	600618
FANCA	Fanconi anemia complementation group A	607139
FANCC	Fanconi anemia complementation group C	613899
FANCG	Fanconi anemia complementation group G	602956
GATA2	GATA binding protein 2	137295
GRHL2	Grainyhead like transcription factor 2	608576
LIG4	Ligase IV, DNA, ATP-dependent	601837
NHP2	NHP2 ribonucleoprotein	606470
NOP10	NOP10 ribonucleoprotein	606471
PARN	Poly(A)-specific ribonuclease	604212
PAX5	Paired box 5	167414
RECQL4	RecQ like helicase 4	603780
RMRP	Mitochondrial RNA-processing endoribonuclease, RNA component	157660
RTEL1	Regulator of telomere length 1	608833
RUNX1	Runt related transcription factor 1	151385
SBDS	SBDS ribosome assembly guanine nucleotide exchange factor	607444
SRP72	Signal recognition particle 72kDa	602122
TERC	Telomerase RNA component	602322
TERT	Telomerase reverse transcriptase	187270
TINF2	TERF1 (TRF1)-interacting nuclear factor 2	604319
TP53	Tumor protein p53	191170
USB1	U6 snRNA biogenesis phosphodiesterase 1	613276
WRAP53	WD repeat containing, antisense to TP53	612661

NA – not available

Supplementary Table 2: Biallelic calls identified in Families 9-12 that underwent WES, after filtering for possible causal variants

Family	Gene	Gene name	MIM	Variant	Status	Biallelic variants in the same gene in additional families
9	*GRHL2*	Grainyhead-like 2 (Drosophila)	608576	c.T1445A:p.I482K	Homozygous	Family 10
9	*PAM*	Peptidylglycine alpha-amidating monooxygenase	170270	c.2585_2590del: p.862_864del	Homozygous	No
9	*TENC1*	Tensin like C1 domain containing phosphatase (tensin 2)	607717	c.A3563G:p.Q1188R	Homozygous	No
10	*FREM1*	FRAS1 related extracellular matrix 1	608944	c.5845-2A>G	Homozygous	No
10	*GRHL2*	Grainyhead-like 2 (Drosophila)	608576	c.C1213A:p.P405T	Homozygous	Family 9
10	*INPP5F*	Inositol polyphosphate-5-phosphatase F	609389	c.A2884G:p.R962G	Homozygous	No
10	*NKRF*	NFKB repressing factor	300440	c.A83G:p.K28R	Homozygous	No
10	*SHROOM2*	Shroom family member 2	300103	c.G227A:p.G76E	Homozygous	No
10	*SSC5D*	Scavenger receptor cysteine rich domain containing (5 domains)	NA	c.G5A:p.R2K, c.A493G:p.N165D	Compound heterozygous	No
11	*C5orf60*	Chromosome 5 open reading frame 60	NA	c.T167C:p.L56P, c.C163T:p.R55C	Compound heterozygous	No
11	*GSE1*	Gse1 coiled-coil protein	616886	c.C3202G:p.L1068V, c.A3233G:p.Q1078R	Compound heterozygous	No
11	*LIG4*	Ligase IV, DNA, ATP-dependent	601837	c.1271_1275del:p.424_425del, c.C2440T:p.R814X	Compound heterozygous	Family 12
12	*LIG4*	Ligase IV, DNA, ATP-dependent	601837	c.1271_1275del:p.424_425del, c.C2440T:p.R814X	Compound heterozygous	Family 11