

DISEASE EXOME, A POWERFUL DIAGNOSTIC TOOL: POST-MORTEM DIAGNOSIS OF DYSKERATOSIS CONGENITA

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CASE REPORT

DYSKERATOSIS CONGENITA, DKC

1. Rare ectodermal dysplasia often presents with the classic triad of:
- Nail dysplasia,
 - Skin pigmentation changes
 - Oral leukoplakia associated with a high risk of bone marrow failure (BMF) and cancer.
2. Onset and progression of manifestations of DKC varies:



3. Diagnosis:
- Telomere length – cytogenetics analysis (ex: FISH)
 - Molecular Diagnosis – mutations known to cause DKC in:

DKC1 TINF2 TERC TERT NHP2 NOP10 WRAP53 CTC1

There are several variants of the disorder, each associated with a different pattern of inheritance

We report on a deceased 60yo male with an undiagnosed systemic disease that presented with liver cirrhosis, pulmonary fibrosis, sick sinus syndrome and thrombocytopenia. Multiple tests had been previously performed with no diagnosis. DNA from *post-mortem* tissue was obtained and disease exome performed.

Exome sequencing has become a powerful diagnostic tool to identify the molecular etiology of genetic diseases in patients with unknown diagnosis.

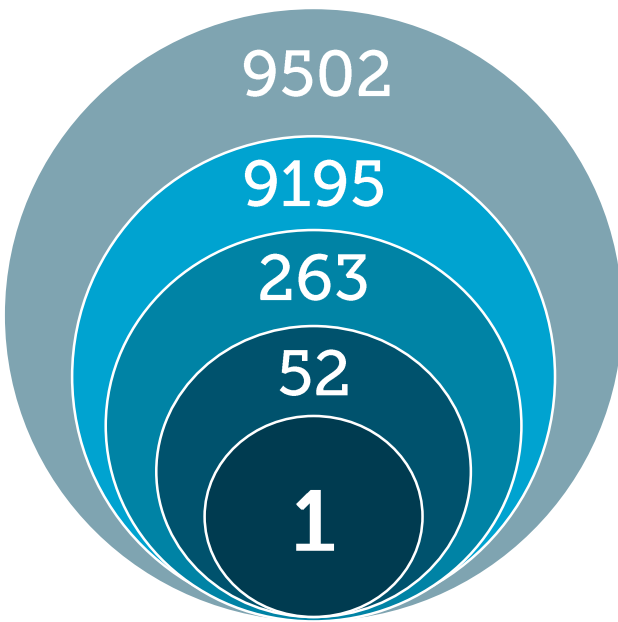
METHODOLOGY

Disease exome was performed by capture of target regions using TruSightOne (Illumina) and subsequent NGS of a panel composed by 4813 clinically-relevant genes. Alignment and variant calling was performed using the Burrows-Wheeler Aligner (BWA) and Genome Analysis Toolkit (GATK), respectively. Variants with minor allele frequency below 1% (MAF<1%) were filtered and processed with bioinformatic analysis tools to assess its pathogenicity and potential to explain the clinical phenotype. Relevant variants were confirmed by Sanger sequencing (Figure 1).

GENETIC ANALYSIS

> PRIORITIZATION OF DISEASE EXOME DATA

EXCLUSION OF:
Low quality reads
Non-genic, intronic and synonymous variants
Variants in in-house variant database
INCLUSION OF:
Variants with less than 1% in population databases
Variants in exonic, splice-site and canonical splice site regions



Heterozygous variant in *TERT* gene
NM_198253.2: c.1492G>A (p.Gly498Arg)

> TERT - Telomerase reverse transcriptase

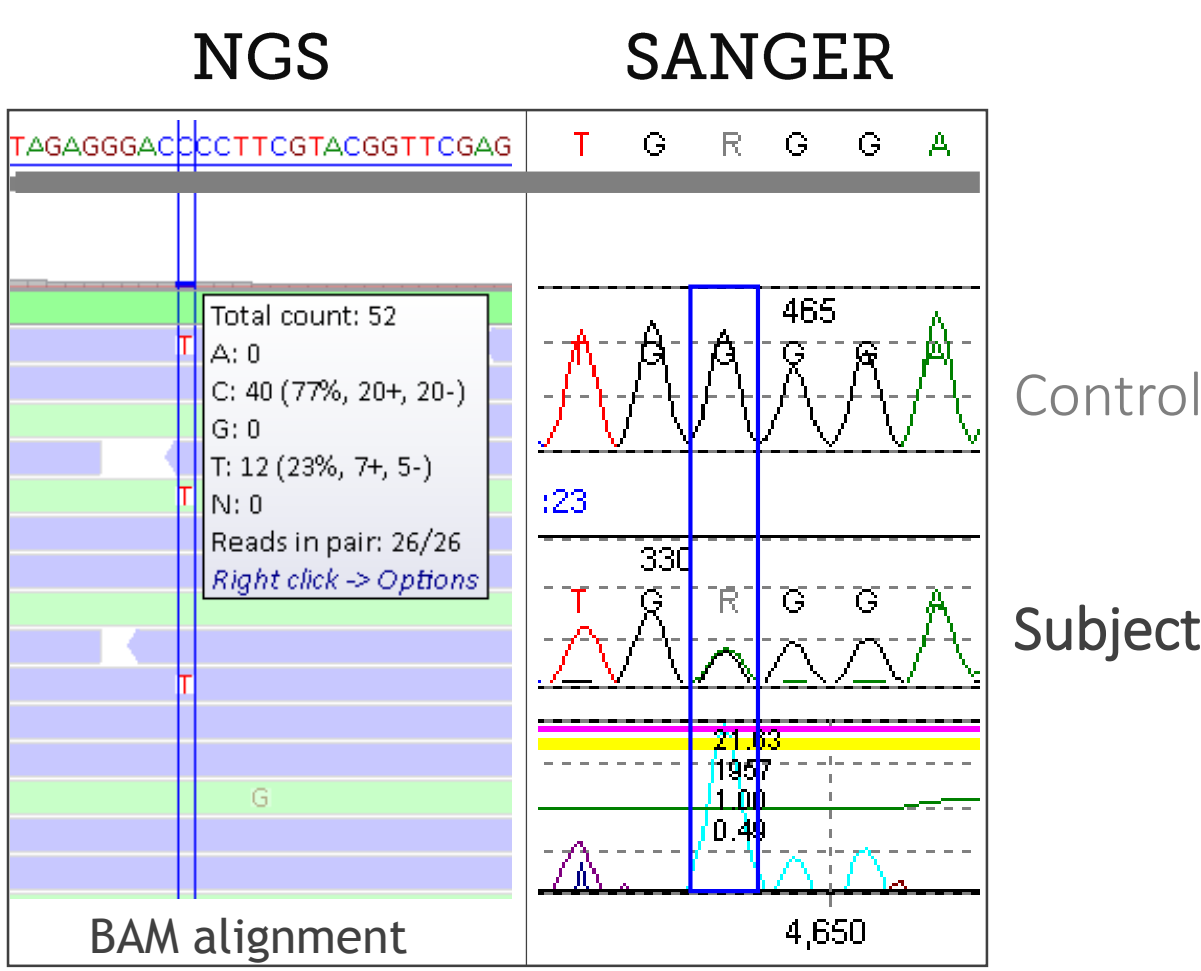
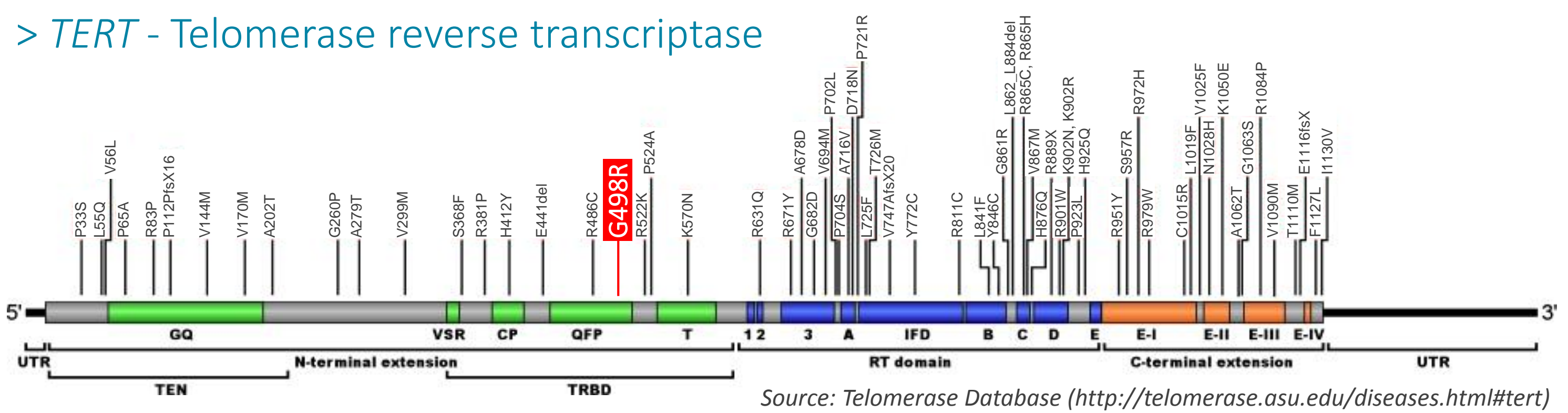


Figure 1: Exome sequencing analysis revealed a novel missense heterozygous variant NM_198253.2: c.1492G>A (p.Gly498Arg) in *TERT* gene, affecting a highly conserved residue located in the RNA-binding region (TRBD). Bioinformatic analysis suggests that the variant is very likely pathogenic (PolyPhen-2: probably damaging; SIFT: deleterious) and is not present in dbSNP, ExAC, 1KGenomes and ESP databases.

Mutations in *TERT* gene, mostly missense, cause autosomal dominant dyskeratosis congenita (DKC type 2; MIM 613989) and autosomal recessive DKC (MIM 613989). Homozygous mutations in *TERT* gene cause a more severe phenotype than heterozygous mutations. However, there is no obvious genotype-phenotype correlation between mutations in *TERT* gene and DKC, possibly because mutations may be subject to inherited telomere length and other genetic and/or environmental factors. In the context of the clinical phenotype of this patient, this result supports the diagnosis of DKC type 2. Segregation studies were not possible as parents and sibs were not available for testing.

DISCUSSION AND CONCLUSION

We report a *post-mortem* diagnosis of DKC type 2 with a novel variant in the *TERT* gene, expanding the mutational spectrum of *TERT*-related DKC. Familial studies, even though not possible for this family, are particularly important as they would allow to evaluate the segregation of the phenotype with this variant, confirming its pathogenicity. Additionally, this result highlights the importance of molecular diagnosis, even *post-mortem*, as establishing the molecular etiology allows proper genetic counselling to at-risk relatives. Finally, this case illustrates the power of clinical exome sequencing in solving complex diagnostic cases in a clinical setting.



ABOUT THE PRESENTING AUTHOR

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