*Supplementary Material*

**Mutation Analysis**

Although hereditary hemorrhagic telangiectasia (HHT) can be diagnosed according to the Curacao criteria, the value of gene mutation detection is also emphasized in the international guidelines [1]. Therefore, we further analysed the gene sequencing data of the patient (Supplementary Fig. 1).

*1. Sample preparation and instruments*

DNA was extracted from 2 mL of blood using the Gentra Puregene Blood Kit (QIAGEN, Germantown, Maryland, Germany) following the manufacturer's instructions. The xGen Lockdown Reagents (IDT, Coralville, Iowa, America) was used to capture the whole exome. Paired-end sequencing with a 150-bp read length was conducted using the NOVA system (Illumina, Hayward, America; 99.98% depth). All reads were mapped to the human reference genome (g19).

*2. Analysis process of mutation*

(1) retention of variants: AF (allele frequency) ≥ 10%, AD (allele depth) ≥ 3, 3500 ≥ DP (depth) ≥ 6 and QUAL ≥ 30

(2) retention of variants: crowd frequency less than 0.01

(3) retention of variants that are predicted as deleterious or near splice-site variants and in-frame insertion/deletion

(4) retention of variants: record in OMIM (http://www.omim.org) or HGMD (http://www.hgmd.org) databases, or report more than ten times in the Cosmic databases

(5) retention of variants: pass the filter and pass manual confirmation using the IGV package

(6) Search the mutation in OMIM and HPO (http://hpo.jax.org/app/)

(7) retention of variants: according to the autosomal dominant inheritance mode and record as pathogenic, benign according to ACMG Standards and Guidelines [2]

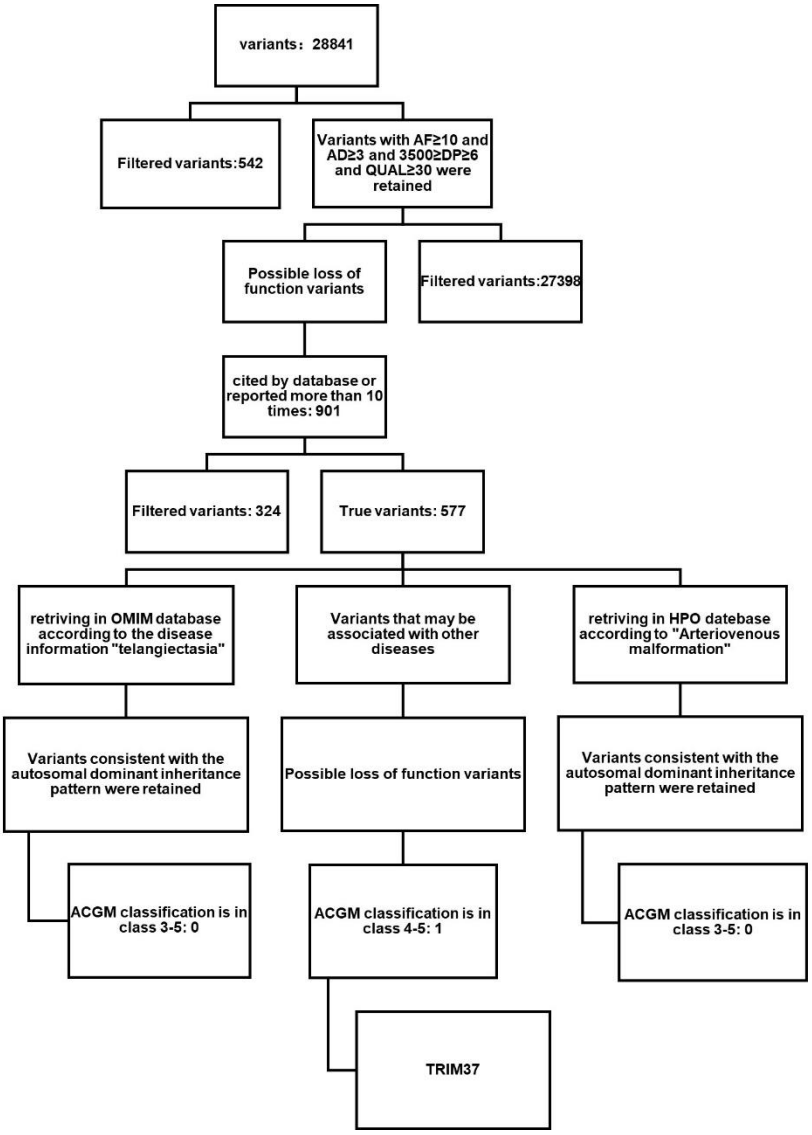
*3. Results*

In total, 28841 variants were identified. A total of 28299 of these variants passed condition (1) and 524 variants were removed from the variant library. According to condition (2) and (3), a focus was placed on variants that were missense, frame-shift, splicing, or stop-gain/stop-loss variants and small indels. Finally, 901 possible loss-of-function variants were obtained, including 811 single nucleotide variants and 90 small indels. Of the remaining 901 variants, 577 were retained for passing the filter and manual confirmation using the IGV package. We searched the mutation in OMIM using the key words: telangiectasia and then retained the variants for adhering to the autosomal dominant inheritance mode. Meanwhile, the detected variants were graded according to ACMG standards and guidelines mentioned in condition (7). However, no variants were found. Using the same method, we searched the mutation in HPO using the key words: arterio-venous malformation, and obtained the same result. By comparing the variants to the OMIM database, we found a deleterious variant located in TRIM37, which is related to Mulibrey syndrome. Common gene mutation types of this disease were not found, indicating that this patient had a specific and unique gene mutation that had not been described to date.

**References**

1. Faughnan ME, Mager JJ, Hetts SW, Palda VA, Lang-Robertson K, Buscarini E, et al. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Ann Intern Med. 2020;173:989-1001.

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24.




**Supplementary Figure 1 Analysis process of whole exome sequencing data from the patient in this case study.**