

Project Title: Cryptic Pathogenic Variants in Hereditary Haemorrhagic Telangiectasia: a Whole Genome Sequencing approach

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Research Theme: Genetic bases of Rare Diseases

Hereditary Haemorrhagic Telangiectasia (HHT) is a rare autosomal dominant vascular disease affecting 1:5000/8000 individuals worldwide. The vascular dysplasia related to HHT are mucocutaneous telangiectases and arteriovenous malformations (AVMs) mainly in liver, lungs and brain.

Whole Exome Sequencing (WES) and MLPA analyses search for a pathogenetic variant among the four HHT genes (*ENG*, *ACVRL1*, *SMAD4*, *GDF2*). Unfortunately, in the 10-15% of the clinically diagnosed patients a pathogenetic variant cannot be found.

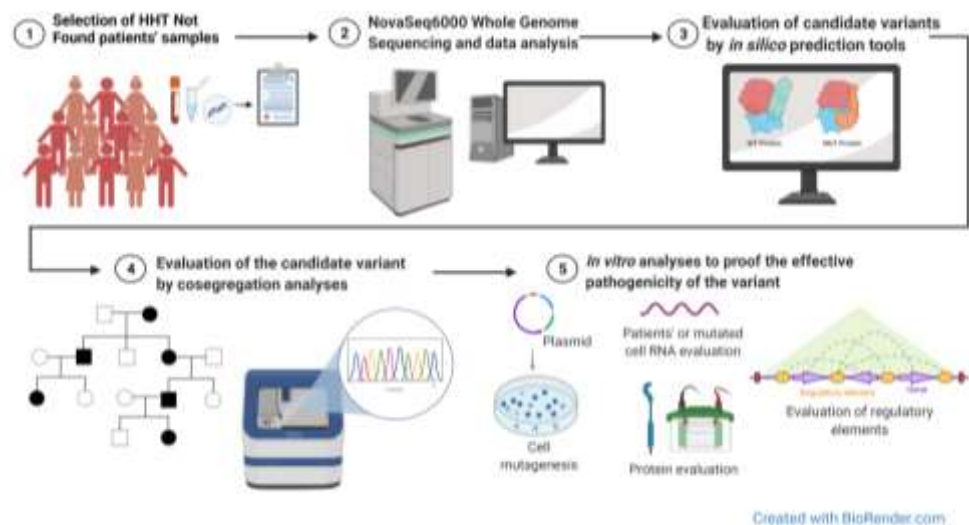
These patients are therefore named "Not Found".

The research project aims to solve the "Not Found" patients, performing Whole Genome Sequencing (WGS) and therefore analysing all those regions excluded from the routinely performed genetic tests.

The project is divided into three main steps: 1) WGS data analysis, selection of candidate variants (prioritizing them for allele frequency, prediction and impact data) 2) variant confirmation by Sanger Sequencing and, when possible, co-segregation studies; 3) *in vitro* and *in vivo* functional studies.

This project is extremely relevant for the patient community: the identification of the disease-causing variant allows to test, in the family, young subjects and individuals with a "suspected" diagnosis in order to address the variant carriers to clinical screening and prevent morbidities related to HHT.

The study also impacts the scientific community: the discover of new pathogenetic mechanisms can pave the way to novel therapeutic strategies.



#### Techniques

WGS data analysis, Sanger Sequencing, cell culture, Gene Reporter Assay, DNA and RNA extraction, RT-qPCR, Minigene assay, Western Blot and immunofluorescence analyses.