# RESEARCH PROJECT:

## Telethon undiagnosed disease program - revised proposal

# The aim of the research:

Despite numerous efforts, a number of genetic diseases remain undiagnosed. In families with children affected by severe and unknown diseases, the lack of diagnosis results in significant emotional distress, uncertainty about prognosis and recurrence risk. In addition, it precludes the use of available therapies or promotion of research initiatives and strategies to investigate novel treatments. Current technologies are rapidly evolving, allowing the parallel sequencing of billions of DNA fragments. This technological advance opens up the possibility of understanding the cause of diseases by studying all human genes. Although the process is straightforward, it is not as simple as it may appear to the general public. Analysis of all coding sequences in the human genome detects thousands of genetic variants, many of which are of unknown significance. A major challenge is the identification of the causative gene defect among these variants. This key task is performed through a multi-step process. Firstly, in addition to the undiagnosed patient, unaffected family members are evaluated for the presence of the variants and, secondly, other patients sharing the same pattern of abnormalities and carrying the same variant are searched worldwide. The matching process is the most important step leading to the identification of the disease-causing gene. This project aims at identifying the causes of undiagnosed diseases in 350-400 families selected by three referral clinical centers involved in the program, by combining next generation sequencing, deep phenotyping and comparison with other similarly affected people all over the world.

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