Project Description for People with 9 P Minus Syndrome

Title:  Using genomic analysis to define the molecular causes of symptoms in patients with Chromosome 9 P Minus Syndrome

Understanding the relationship between the deleted genes and patient characteristics in 9P minus syndrome.

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The goal of our research project is to identify the specific genes that are deleted in people with 9 P Minus Syndrome and correlate these genetic abnormalities with specific characteristics of each affected person to gain the insights needed to develop therapeutic strategies.

People with 9 P Minus Syndrome have a number of characteristics in common, while other symptoms are present in only some affected individuals. For example, many people with 9 P Minus syndrome have an unusual head shape at birth (a rounded forehead), low muscle tone, widely spaced eyes, developmental delay and intellectual disability, as well as unusual ear shape. Fewer have birth defects of the heart, diaphragm, and the muscles in the front of the abdomen. The exact length of the chromosomal deletion can vary widely among people with 9 P Minus Syndrome, accounting for the different characteristics observed in affected individuals. Correlations between the size and location of the 9 P chromosome deletion with the unique characteristics of that individual have been difficult because earlier methods could not precisely determine the sets of genes that were missing, nor detect pieces of other chromosomes that can sometimes take the place of the deleted region and lead to additional problems. For this project, we propose to use a personalized medicine strategy that takes advantage of advanced DNA sequencing technologies as well as cellular-based experiments to help understand precisely which genes are most critical in defining specific characteristics of individuals with chromosome 9 P Minus Syndrome.

Each person with 9 P Minus Syndrome who chooses to participate in this research project (or her/his parent or legal guardian) will need to provide informed consent to become a research subject. Each individual will also need to provide a detailed summary of her or his medical and family histories and specific characteristics through a standardized examination and/or questionnaire. They will also need to provide a blood sample drawn from the arm and placed in a special blood tube that we will provide. DNA will be extracted from each person’s blood sample and state of the art gene code deciphering (called whole genome sequence analysis) on
as many as 100 affected people will be used to determine the exact location of the deleted region of the 9th chromosome in each person. This determination will be much more detailed than a chromosomal microarray analysis (CMA) provides and will identify the exact genes that are deleted in each person as well as any other accompanying chromosomal abnormalities. We anticipate that our analysis will help us identify a core set of deleted genes that are consistently associated with specific characteristics of people with 9 P Minus Syndrome. Once the set of deleted genes is in hand, we will use genetic methods, including gene editing technology, to develop new insights into how the missing genes function to alter cells. These studies will be supplemented using blood cells that we will store from the original blood sample to investigate, at a molecular level, how the deletion of these genes causes the specific characteristics observed in chromosome 9 P minus patients. In this project, we plan to perform a pilot of these functional experiments using a small number of samples. All samples will be analyzed to identify their deleted genes and correlate them with patient characteristics, but this second step of functional analysis will only be performed on a smaller number of samples. The results from these early studies will allow us to obtain additional research funding to expand the project and, hopefully, eventually perform this second step (i.e., the functional studies) on the full archive of samples. Through these studies conducted over the next several years, we plan to identify the most important missing genes as they will serve as high priority targets in development of future treatment strategies for people with chromosome 9 P Minus Syndrome.