Gene Hunting - A Genetic Thriller!

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More often than granting superpowers, genetic mutations are a common cause for genetic diseases. Couples often attend genetic counseling to learn about possible genetic risks before conceiving with a child, but there are still some diseases where the causing mutation is not yet known. An example for such a disease is the "progressive cerebellocerebral atrophy (PCCA)" recently discovered in Jewish Moroccan and Jewish Iraqi families in Israel, causing severe retardation, involuntary movement, small head size and brain atrophy that worsen with time. What is a genetic mutation? Our DNA is a giant code for the construction of... us, basically. It is "written" with 4 "letters" called bases: A, C, G and T. Now, it's true that every person is unique and all that, but genetically, we're all near-identical. A genetic mutation is a variation from the common code such as base deletion or addition or a change of one base with another. How are mutations found? - Not easily. In just one of the two complete sets of chromosomes inherited from each parent, there are about 3 billion bases. From a scale perspective, finding a disease-causing mutation within those bases is like uncovering a $1m^2$ treasure chest, buried by the Victual Brothers, in the entire island of Gotland. Obviously, the search area must first be narrowed down a bit... For starters, not every mutation is expected to cause a disease. About 98.5% of the human genome is non-coding (arguably dubbed "Junk DNA") where mutations often roam free without making a fuss, so disease-causing mutations are likely to be within the 1.5% coding DNA, that is, within a gene. Then there's the inheritance pattern. Diseases like PCCA where affected individuals can be of either gender and have healthy parents and siblings, are said to have an "autosomal recessive" inheritance pattern, meaning that both homologous chromosomes must have a mutation in the same gene for the disease to affect an individual. Assuming there's only one type of PCCA causing mutation (an assumption based on the seclusion and relatively small number of Moroccan Jews), affected individuals are expected to have the same mutation in both genes, while their healthy siblings are expected to have either just one mutated gene or none at all. Now, when the parents' chromosomes get shuffled to divide between the eggs or sperms, areas closer to each-other on a chromosome have a better chance of traveling together to the same egg or sperm cell. So sick siblings are expected to share not only the two mutations, but the areas around them too, while healthy individuals will share no more than one of these areas with their affected siblings. These areas include the those non-coding regions with the abundant mutations - many of which are known and can be checked in DNA of family members to help identify which areas came from which parent and are shared by which sibling, that is, to determine the inheritance pattern of each area. The results are analyzed in a computer to indicate the areas where the found inheritance pattern matches that of the disease. Those become the suspected location of the mutation. More families that are suspected of carrying the same mutation can help in narrowing down the suspected area as well. In the case of PCCA, the suspected area was thus reduced to only 6 regions on 4 chromosomes with input from 3 Jewish Moroccan Families. Finally, the gene-hunt begins. All genes in the suspected area (33 in this case) are sequenced from the sick individuals' DNA and compared with the known genome one by one until the mutation is found. Sequencing 33 genes can be tedious so it is wise to start with genes that are associated with the symptoms of the disease. So far, 5 genes were thus either fully or partially sequenced in PCCA patients, but no mutation was found. Hopefully, this process will soon be completed.

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