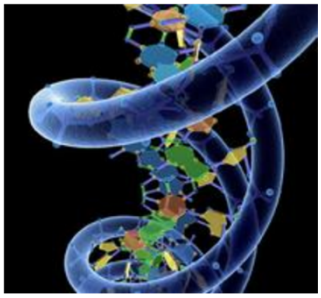
SUDCRRC
SUDC Registry and Research Collaborative

Frequently Asked Questions about Genetics



What is the human genome?

The human genome is the complete set of genetic information for humans. Within the nucleus of each human cell are 46 chromosomes each containing a long sequence of DNA. Positioned along this DNA strand are an estimated 3 billion base pairs whose function and precise control are essential to human health. Together, those base pairs write the four letter code of the DNA to make up the human genome. Although the full sequence of the human genome has been almost completely determined by DNA sequencing, it is not yet fully understood.

Your personal genome is essentially a tightly regulated set of instructions that your body follows throughout your life in order for proper development and maintenance to occur. Each person's genome is slightly different and we call these differences "genetic variation".

At this time, it is well accepted that genetic variation in particular parts of the genome can cause or lead to increased risk of disease. For this reason, identifying the types of genetic variation found in SUDC victims can be very important in determining what specific genetic variation may have contributed to their deaths. For more information, go to: http://www.infohow.org/wp-content/uploads/2012/11/The-Human-Genome.jpg

What is whole exome sequencing and how can it help with investigating SUDC?

While sequencing an entire genome can take significant time and money, sequencing the parts of the genome that specifically code for protein (the exome) is more practical and cost-effective in comparison. This approach has been immensely successful in clinical genetics because although these regions make up only 1.5% of the genome, they contain 85% of known disease-causing variants. There are about 20,000 genes in our exome. Given this, it makes sense to use whole exome sequencing as a tool to try to better understand SUDC on both a patient level (being able to provide precise explanations or contributory factors for SUDC occurrence in a particular child) as well as a cohort level (improved understanding of SUDC genetics overall, leading to the improvement of screening for variants that may help evaluate the risk of SUDC in the living). Although we know a lot about the genes in our exome, there is a lot that we do not know. Of the approximately 20,000 genes in our exome, only about 6-7,000 of those genes are characterized.

How does the SUDCRRC make sense of so much data?

Given that a person has several thousand genetic variants of interest that might be identified through exome sequencing, how is it possible to narrow down the list to one or several variants that may cause or contribute to a SUDC outcome? We adopt a framework that takes into account genes that we think might possibly be associated with an SUDC event. There are a fair number of genes that are already known to be associated with epilepsy and heart disorders and are likely to be at play in some SUDC deaths. However, there are also other genes whose dysfunction may cause or contribute to SUDC occurrence but have not yet been as thoroughly researched by the scientific community. Exome sequencing allows us to sequence the protein coding portions of all of these genes, regardless of how much is currently known about them, and will ultimately allow us to determine if particular genes and variants are contributing to SUDC. It is important to note that as discoveries are made in identifying new genetic variants known to cause disease, the data from whole exome sequencing can be reanalyzed with this new information as well.

For more information on the SUDC Registry and Research Collaborative, please go to:
Web: https://sudc.org/research-medical-info/sudc-registry-research-collaborative Ph: 646-754-2230 Email: laura.crandall@nyumc.org

What specific genes will SUDCRRC evaluate?

Whole exome sequencing is the type of genetic testing performed. Analysis includes genes that have been associated with sudden death. As we learn new information over time, we will continue to analyze new genes that we learn to be associated with sudden death.

Are there different types of variants that can be found?

There are different types of variants that can be found. Variants can be classified as pathogenic/likely pathogenic, benign/likely benign, or uncertain. Variants that are pathogenic or likely pathogenic are changes in the DNA that are known or highly certain to be disease causing. Variants that are benign or likely benign are changes in the DNA that are known or highly certain to not cause disease. We all have this type of variation in our genes. That is why we are all different. A variant of uncertain significance is a change in the DNA that does not have enough evidence at the time to know if the variant is a normal variation or if it is disease causing. When we see a variant of uncertain significance, it is typically the first time we are seeing the variant, so we do not have a lot of information about the variant. Over time, we hope to re-classify the variant as either benign/likely benign or pathogenic/likely pathogenic.

Variant can also be inherited or de novo. Inherited variants come from parents and have often been passed down through generations. De novo variants are variants that are found in the child but are absent from the parents. A child with a de novo variant did not inherit it from either parent. Instead, a de novo variant occurs randomly as a mutation in one specific egg or sperm cell before conception, or in the fertilized egg at the very beginning of development. Because the de novo variant is present only in the child but not in either parent, other siblings are unlikely to be at risk of having the de novo variant.

The conditions associated with the variants in genes can have different types of inheritance patterns. We have two copies of most of the genes in our body: one copy is inherited from our mother and one copy is inherited from our father. For conditions that are inherited in an autosomal dominant pattern, one disease causing variant is enough to have or to be at risk of developing the condition. For conditions that are inherited in an autosomal recessive pattern, there must be a disease causing variant on each copy of the gene in order to have the condition. The parents of the affected person who only have one disease causing variant are called carriers and are not thought to be at risk of developing the condition. There are also a number of genes on the X chromosome. Girls have two X chromosomes and boys have an X chromosome and a Y chromosome. Boys only have one copy of the genes on the X chromosome. There are some conditions that are caused by disease causing variants of genes on the X chromosome. These conditions are typically present only in males and female are silent carriers. For boy with these conditions, one disease causing variant on the one copy of the X chromosome is enough to present with the condition. Some conditions can have reduced penetrance and/or variable expressivity. Reduced penetrance means that not every person who has a disease causing variant will develop the condition. Variable expressivity means that people who have the same condition can present differently. Individuals may have different symptoms or different severity of the condition, even within the same family.

What types of variants are reported?

The variants that are reported by the SUDCRRC are variants that are believed to be disease causing or potentially disease causing, at that point in time. These variants are in genes that are thought to potentially have a contributing factor to the sudden death. The SUDCRRC reports variants in line with recommendations by the American College of Medical Genetics and Genomics (ACMG). We all have variations in our genes, and that is why we are all different. The SUDCRRC does not report variants that are thought to be harmless, or variants that do not have strong evidence to support that they are harmful at the time. The interpretation of variants may change over time as we learn new information.

Why does SUDCRRC want to study the DNA from parents and some relatives of a SUDC child?

Sequencing parents and some relatives of an SUDC child allows researchers to identify variants that are unique to the child as well as those that are shared with their relatives. This allows us to determine if variants observed in the child are likely to cause disease or not. This can be particularly important when analyzing genetic variation found in the SUDC child. If both parents are healthy, then we can evaluate if the SUDC child has a suspicious combination of their parent's variants, or if they have a de novo mutation. Sequencing parents will enable us to identify these special informative occurrences and identify clear patterns of genetic variation inherent to SUDC victims only. Additionally, if an SUDC child has a sibling, then the genetic variants shared between them can be very informative in the clinical care of that sibling.

How can you tell whether a variant is harmless or if it is likely to cause health problems?

We know that some variants are harmless and found in the general population, while others are much less common in the general population and may cause or increase the risk of disease. Therefore, it is important to distinguish variants known to be harmless from those that may be potentially harmful to an individual.

There are multiple traits that can often distinguish a variant that is highly likely to be causative of disease from a variant that has no apparent effect (harmless variant). The first is that the variant changes the actual sequence of the protein that normally occurs in that location. The second is that the variant is not seen in the general population and therefore, by definition, is unusual. The third is that the variant is in a gene, or a region of a gene, where changes normally do not occur. The fourth criteria is that the variant is predicted to significantly alter protein function. The final criteria is that there is some feasible biological explanation for how the dysfunction of the gene that the variant falls in could cause the disease. Typically, protein-coding variants that are causative of disease meet the majority of the traits described above.

What if I have more questions?

For assistance, please do not hesitate to contact the SUDCRRC at the contact information below at any time.