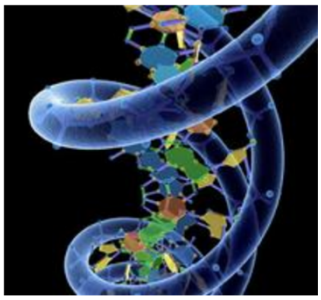
SUDCRRC
SUDC Registry and Research Collaborative

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 ~ 30,000 genes whose function and precise control are essential to human health. Together, those genes 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?

Sequencing the parts of the genome that specifically code for protein (the exome) 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. 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).

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: http://sudc.org/Research/SUDCRRC.aspx Ph: 800-620-SUDC or 646-754-2230 Email: laura.gould@nyulangone.org
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What specific genes will SUDCRRC evaluate?

Whole exome sequencing and additional genetic analyses as indicated will be performed. Analysis includes characterized genetic etiologies that have been associated with sudden death.

Are there different types of variants that can be found?

Variants can fall into two general categories: inherited and '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 would not be at risk of having the de novo variant.

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 mutation 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.