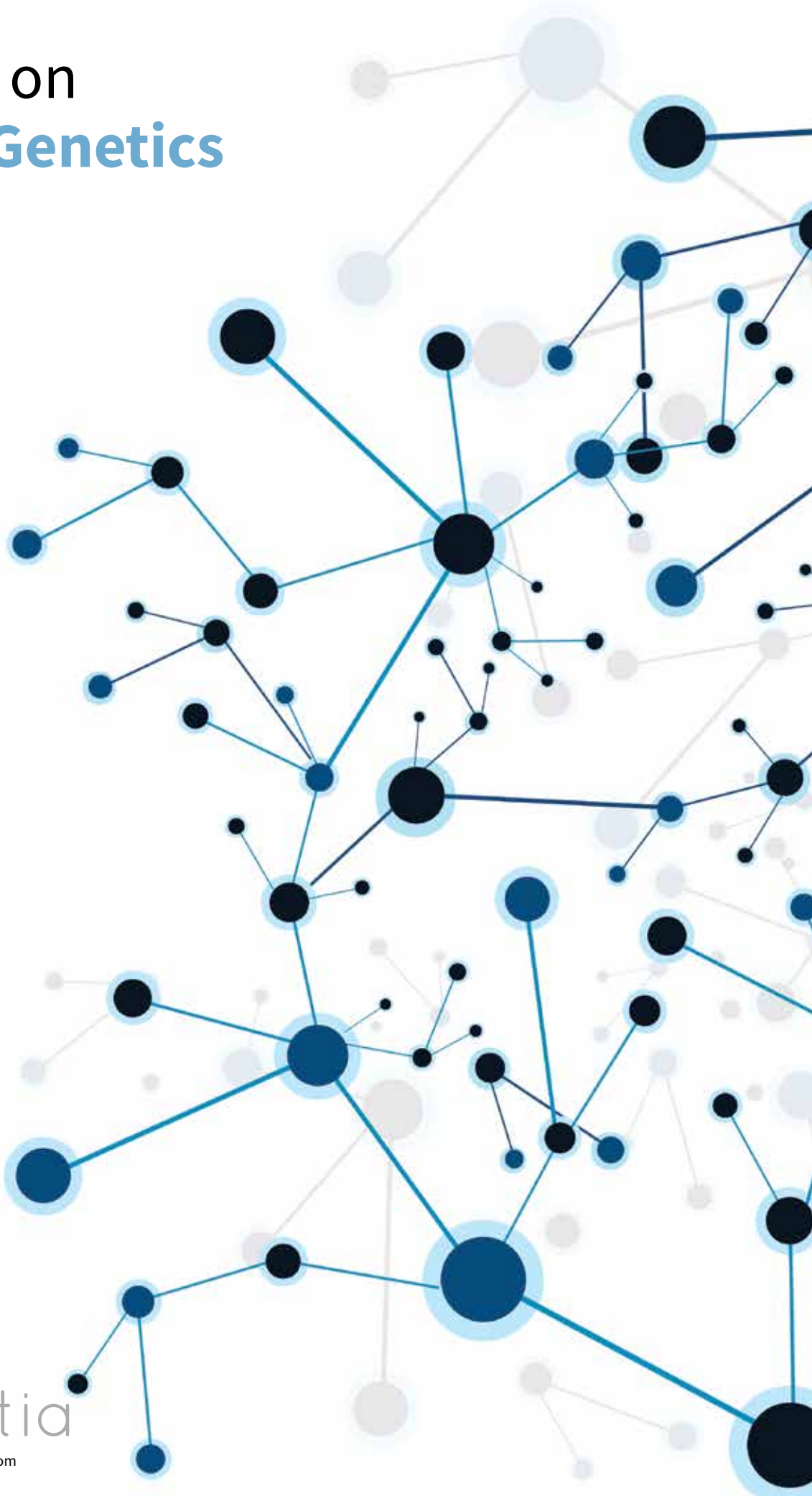
Dwelling on
Suicide Genetics

Dr. Hilary Coon



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Dr. Hilary Coon at the University of Utah is determined to find genetic risk factors predisposing people to commit suicide. Having access to DNA and phenotypic information from more than 4000 suicide victims, she is in an excellent position to fulfil her quest.

For most people, suicide is a topic they prefer to keep at arms distance. How did you become interested in studying the genetics of suicide?

The main focus throughout my research career has been the study of genetic risk factors contributing to psychiatric disease susceptibility. The study of suicide is a natural outgrowth of this interest, as most individuals who commit suicide struggle with mental illness. However, most individuals with mental illness do not commit suicide, which suggests that additional specific risk factors, some of which may be genetic, probably exist. Suicide has not yet been the focus of intense study in the field of psychiatric genetics.

I became aware that the University of Utah had a large, untapped resource of DNA from individuals who had committed suicide. Though these cases are de-identified to our research team, there are database resources in Utah that have allowed the cases to be grouped into high-risk extended family clusters. Knowing that cases are related allows us to search for genetic variation shared among these very distant relatives through their common ancestors. Their family relationships are distant enough to minimize the impact of shared environmental factors. However, since the genetic risk factors recur in each distantly related suicide case, the familial genetic risk is magnified and therefore easier to detect.

I have no illusions that the study of genetic risk factors for suicide will be an easy task. But each of us knows of a friend, relative, or co-worker whose life has been touched in some way by suicide. The repercussions of a suicide are severe and long lasting. Suicide is a potentially preventable tragedy that deserves urgent study.

You state that you wish to identify those who share phenotypic profiles with decedents with known sequence variation? How does this information strengthen your analyses?

Our database collaborators can match cases to electronic data that flags early life risk factors and co-morbid psychiatric and medical conditions. This additional data, combined with shared familial genetic risk, gives us an unprecedented opportunity to study familial genetic risk of suicide. One strategy is to use co-morbidity, a particular demographic characteristic, or particular environmental exposure as a way to select high-risk families and additional non-familial cases. For example, we have ongoing studies of a high-risk family where the proportion of women is unexpectedly high, and we are comparing this family to non-familial female suicides.

What light can the study of families at high risk for suicide shed on suicide in general?

We study the familial cases because familial genetic factors can be detected through their recurrence in families. It is however certainly possible that individuals who are not related, carry the same genetic risk factors. We intend to screen our top genetic findings in as many cases as we can afford to determine their frequency in the more heterogeneous non-familial sample.

What kind of interventions do you believe could spring out of your work?

We will make any finding where we have achieved appropriate scientific validation and replication known through publication and communication with local and national societies and support groups. Without knowing what our findings might be, it is impossible, at this point, to guess if any finding could be related to interventions. In the event a feasible intervention will be apparent, we are poised to take steps to advocate for this intervention. Nevertheless, I'd like to make it clear that our research group has formally declared that we will not seek to profit if a diagnostic test or treatment is developed from our work.

Do you think genetic tests will be part of suicide risk assessment in the future?

It is not certain if any of our findings would translate into genetic testing. From where we stand now, it seems that genetic testing may have a low impact if we are correct in our assumption that there is a high level of genetic heterogeneity, and that any one specific genetic risk factor likely plays out in the context of complex environmental exposures and other background genetic risk, and protective factors.

Our goal is rather to help identify some of the genetic risk factors for suicide to increase our understanding of underlying neurobiological and cellular processes that might be part of the undeniably complex risk landscape of suicide.

The Meticulous Drawing of a Neurobiological Suicide Map

Some people state that becoming a successful researcher requires the bright mind of the scientist, but then also depends critically on fortunate opportunities. For Dr. Coon this opportunity came in the form of access to a unique resource, that became the starting point of an exceptional project – Searching for genes associated with an increased risk of committing suicide.

UNTANGLING A KNOTTY SCENARIO

Studying the genetics of suicide is a "daunting task", to use the words of Dr. Coon. As opposed to genetically simple illnesses such as Huntington's disease, suicide is very heterogeneous. Suicidal behaviour, and more specifically, the completion of suicide, is dependent on a multitude of genetic factors, which are interacting with an unknown amount of environmental stressors. These factors differ between individuals, and many combinations of genetic and environmental factors can lead up to the same endpoint – Suicide.

Being lucky enough to get her hands on what must be one of the largest DNA collections from suicide victims in the world, Dr. Coon set out to do what she does best: studying the genetic risk leading to complex traits. Her research team first obtained ethical approvals from the University of Utah Institutional Review Board (IRB), in addition to IRBs at the Utah State Health Department and Intermountain Healthcare. Through these approvals, this DNA resource was made still more valuable by being linked to the Utah population database, holding medical, demographic and genealogic information. With the help of these data, Dr. Coon and her team hope to identify specific gene variants, while controlling for the influence of other factors such as psychiatric and physical disorders, hence being able to sort out the gene variants that are related to an increased risk of suicide per se.

Dr. Coon was soon able to identify several extended families where suicide was significantly more common than in the general population, providing a dream scenario for a researcher trying to identify genetic risk factors. "We study these familial cases because familial genetic risk factors are magnified through their occurrence over and over in extended families", says Dr. Coon. She is, however, underscoring that the research team doesn't have access to identities of her study subjects or their living relatives. "I'd like to emphasize that we study our data resource from a de-identified perspective; all identifiers are stripped from cases, and familial risk is given as an aggregated, family cluster statistic so that we have no chance of inadvertently identifying any cases or family members."

Suicidal behaviour, and more specifically, the completion of suicide, is dependent on a multitude of genetic factors, which are interacting with an unknown amount of environmental stressors.

Studying high-risk families is therefore a good start for understanding genetics of a specific trait, but findings from these family clusters will also be used to assess risk genes in the unrelated suicide cases. Using the top hits from her search within high-risk families, she also screens all the non-familial cases for the presence of a genetic variant. With the use of more comprehensive screening tools, such as whole genome and whole exome sequencing, Dr. Coon hopes to find variants that are shared between both related and unrelated individuals.

CO-MORBID COOPERATION

Realizing the huge potential of the resource she has access to, Dr. Coon has initiated collaborations with scientists and research institutions, ranging from her departmental colleagues to foreign universities. Among other factors, the joint ventures will be investigating the co-morbidity of suicide and other conditions, such as post-traumatic stress disorder, cardiovascular disorders and and opiate abuse. One of her collaborative efforts deals with the co-morbidity of suicide and asthma, two seemingly very disparate conditions. This research is based on observations that asthma sufferers are at significantly increased risk of suicide when compared to population suicide rates. Looking into the genetics of this co-occurrence will be an important contribution to resolving this medical conundrum.

Understanding how genes and environment interact is one of the most important issues a psychiatric geneticist is facing. Since the likelihood of developing a psychiatric condition is dependent on an abundance of both genetic and environmental risk factors, it is not enough to perform isolated studies of genes or environmental hazards. In yet another collaborative project, Dr. Coon, therefore, studies suicide victims exposed to specific environmental conditions. She believes they might carry genetic factors making them more vulnerable to the particular environmental impact, increasing the risk for suicide.

BRAIN CONTRIBUTIONS

Dr. Coon's close partnership with the Utah State Office of the Medical Examiner has given

her more than DNA samples. After obtaining additional ethical review board approvals, Dr. Coon has recently begun to collect post-mortem brain tissue and skin biopsies from suicide victims. Using brain tissue, it is possible to look for expression of the genes identified in the DNA samples. Gene expression analyses can conversely be used to further guide the DNA analyses, looking at specific genes or gene pathways that show abnormal expression.

Identifying gene expression changes that coincides with changes in DNA would make a result more solid. Given the heterogeneity of suicide, it is, however, crucial to look at the right sample subset. As brain collection from suicide victims is a slow process, Dr. Coon will have to bide her time for this part of the study, banking tissue until she can match tissue with DNA having a specific genetic profile, or when she manages to get her hands on DNA and tissue from the same individuals.

The value of the post-mortem brain tissue doesn't end here. Synaptic dysfunction is implicated in suicide, and studying synaptic characteristics in the brain from the suicide cases might further guide the search for genes involved in the increased risk of suicide. As with the gene expression data, this will be an important complement in the search of genetic variation, governing which genes to focus on.

GOING MORE THAN SKIN DEEP

With the recent advances in stem cell technology, cells from skin tissue can now be converted to stem cells, called induced pluripotent stem cells, or iPSCs. The technique, while still technically difficult and costly, is a huge step forward in medical science. Not only is it now possible to grow neurons from iPSCs but employing iPSC techniques might also answer questions on an individual level. As the study progresses, Dr. Coon plans to use skin fibroblasts from subsets of suicide cases with validated, high-risk gene mutations that have persisted through rigorous statistical and molecular tests, to produce neuronal cell cultures.

This approach, together with the post-mortem brain tissue, will open up a whole new avenue for functional studies. Having living neurons in culture, derived from individual suicide victims, allows studying the functional consequences of an aberrant gene, using electrophysiology and calcium signalling experiments. Also on the agenda are re-expression experiments, reversing a deficiency to study the functional outcomes. On top of that, neuronal cell cultures can also be used to test for potential pharmacological therapies, studying the effects of drugs on the cells.

"In short, we have found many opportunities for creative ways of looking at these data and have only begun to scratch the surface", says Dr. Coon.

Dr. Coon doesn't seem to be the kind of person that sits around waiting for opportunities to come her way. Like a hub in the middle of this suicide centred wheel, she has initiated studies that might answer many of our questions about why some people commit suicide.
It is obvious that it takes more than a lucky break to become successful in research. It also takes a brilliant intellect to realize the potential of a situation and transform ideas into action.

Researcher Profile

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Dr. Hilary Coon is the principal investigator of a research initiative set out to identify genes associated with increased risk of suicide. Her work is focusing on high-risk families where suicide is frequent, and together with a broad network of both national and international collaborators, she also studies the co-morbidity of suicide with lung disorders, cardiovascular disorders and obesity. She also studies the genetics of autism and addiction. Dr. Coon's interest in research ethics has also led to long-term service on the University of Utah Institutional Review Board.

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