iPSYCH

The Lundbeck Foundation Initiative for

Integrative Psychiatric Research

LUNDBECKFONDEN

Contents

Centre director

Psychiatry concerns us all

Over the course of our lives, more than 40 per cent of us will be treated at a psychiatric department with a mental disorder. Approximately 15 per cent will be treated before the age of 18, and 25-30 per cent of all children will have a parent or sibling who receives treatment for a mental disorder.

The actual numbers are in reality much higher as a significant proportion of us will only be treated by our general practitioner rather than by the hospital mental health system.

The numbers speak for themselves: Few people go through life without being affected by mental disorders in some way or another.

Nevertheless, we still know far too little about why so many people suffer from a mental disorder. This was the driving force behind iPSYCH, a national project to find the causes of, and forge the foundation for better treatment and prevention of autism, ADHD, schizophrenia, bipolar disorder and depression.

Have we reached our goal? No, not at all, but we have come a long way. When iPSYCH was started ten years ago, our knowledge of mental disorders was far from what it is today.

Of course, we cannot take all the credit for the current level of understanding of mental disorders, but our contribution has made an impact: When we discuss the genetic causes of mental disorders, we no longer discuss just one or a few genetic variants. We are all predisposed to these disorders that can be affected by thousands of common genetic variants, each of which can slightly increase the risk of developing a disorder. In short, we are all at risk and the many people affected by the disorders are not so different from those who are not.

IPSYCH has made a significant contribution as the first study of its size to combine register data with data from biobanks to shed light on the hereditary and environmental causes of mental disorders. Our work will contribute to future Danish research into diseases, including diseases that have nothing to do with psychiatry.

Most of the knowledge we have produced has been basic research, but we have also conducted studies of children of parents with schizophrenia and bipolar disorder, and these studies have already provided us with valuable knowledge about how we can best help these families.

There is still a need for more basic research to better understand the mechanisms behind these disorders. We will conduct this research with the help of Danish and international researchers recruited and trained by the iPSYCH project.

We have always collaborated with many of the world's leading researchers and research groups. This collaboration has raised the level of Danish psychiatric research and placed iPSYCH at the heart of many international projects.

I have absolutely no doubt that the knowledge iPSYCH has contributed will be of enormous benefit for people with mental disorders.

Enjoy the read

Preben Bo Mortensen

The Lundbeck Foundation's Initiative for Integrative Psychiatric Research, called iPSYCH, was founded back in 2012 when the project received its first grant from the Lundbeck Foundation. iPSYCH received grants totalling DKK 361 million from the Lundbeck Foundation in 2012, 2015 and 2018. These are the largest grants ever awarded for psychiatric research in Denmark.

The researchers

iPSYCH was founded by leading researchers within psychiatry and genetics. The research project consists of six research groups, each with its own principal investigator covering areas within psychiatry, psychology, statistics, genetics and registry data.

The research groups

Merete Nordentoft's group
Merete Nordentoft is a professor of psychiatry at the University of Copenhagen and a consultant at the Mental Health Services Centre of the Capital Region of Denmark.
Among other things, her group has worked on questions such as: What significance do genetic and environmental factors have on schizophrenia, affective disorders and the interplay between an individual's hereditary genes and environment, such as e.g. drug abuse or suicidal behaviour?

Anders Børglum's group
Anders Børglum is a professor of medical genetics at the Department of Biomedicine, Aarhus University. His group has been concerned with identifying and characterising the genes that play a role in mental disorders and developmental disorders with a focus on autism, ADHD, schizophrenia, bipolar disorder and depression. We have identified genetic risk variants that are specific to the individual diagnosis, and risk variants that are shared across multiple psychological diagnoses. We have made an initial characterisation of the risk genes to understand the biological disease mechanisms and to point to possible molecular targets for treatment. By studying the subjects' overall genetic risk profiles, we were able to split them into diagnostic categories and disease pathways in order to define the prognosis and create a better basis for developing more personalised treatment and support.

Preben Bo Mortensen's group
Preben Bo Mortensen is a professor and centre director at the National Centre for Register-based Research (NCRR) at Aarhus University and the scientific director of iPSYCH.
His group focuses primarily on risk factors and causes of autism, ADHD, schizophrenia, bipolar disorder and depression. They conduct epidemiological research based upon the Danish registers, and also combine this with biological measures from bloddsamples in biobanks. In particular, the group has studied the environmental factors that contribute to the risk of disease and how the disease progresses. The group has also used and developed measures of the genetic liability towards developing disase, and have used these measures in studies examining how hereditary and environmental factors interact.

Thomas Werge's group
Thomas Werge is a professor at the University of Copenhagen and the director of the Institute of Biological Psychiatry at the Sct.Hans psychiatric hospital, which is part of the Mental Health Services in the Capital Region of Denmark. His group has utilised genetic studies to uncover and identify the biological causes that contribute to the development of serious mental disorders. The goal has been to standardise and utilise the breakthroughs over the last decade to understand the hereditary and environmental basis for mental disorders so as to be able to predict disease risks, the course of diseases and treatment response.

Ole Mors' group
Ole Mors is a professor of psychiatry at the Department of Clinical Medicine, Aarhus University and consultant at Aarhus University Hospital, Psychoses Research Unit.
His groups conducts research into identifying genetic and environmental risk factors for mental disorders and our areas of work include psychiatric diagnostics and classification, clinical and epidemiological studies of the effects and side effects of drugs, the ethics of genetic testing and epigenetic studies of the genome.

David M. Hougaard's group
David M. Hougaard is head of the Department for Congenital Disorders, Statens Serum Institut (SSI). Among other things, his group has tried to find out: How do genetic variations affect newborn babies? And how can changes in newborn babies blood composition and risk factors in the environment have an influence on the development of autism, ADHD, schizophrenia, bipolar disorder and depression later in life?

From left Preben Bo Mortensen, David M. Hougaard, Anders Børglum, Ole Mors, Merete Nordentoft and Thomas Werge.

Q&A

Jan Egebjerg, director of science at the Lundbeck Foundation:

Why did Lundbeck Foundation choose to support iPSYCH?

"We funded iPSYCH because we wanted to support psychiatric research. There was a wish to identify and understand the biological mechanisms that affect patients with mental disorders, and thereby better understand the brain and possibly open the door for new and better treatments. 'Bringing discoveries to lives' is the ethos of the Lundbeck Foundation. We know the symptoms of mental disorders, but don't understand the biology behind them. The only anchor we have is genetics. Since Denmark has some of the world's finest registers and biobanks, which make it possible to get DNA from well-diagnosed patients, and because sequencing technology is undergoing rapid development, we wanted iPSYCH to enable researchers to gather detailed genetic information about psychiatric disorders and risk factors."

What has iPSYCH achieved?

"iPSYCH has been very successful at identifying genes that increase the risk of mental disorders. The project has shown that the genetic risk of mental disorders is borne by small contributions from many different genes, and this creates a basic biological challenge to understanding how polygenic genes together increase the risk of mental disorders."

What is the next step?

"The next challenge is finding out how we can utilise the extensive genetic knowledge generated by iPSYCH to understand how signalling in the brain is affected. The goal now is to improve research environments and collaborations between different disciplines in order to establish the necessary knowledge to understand our most complex organ: The brain."

FACTS

MENTAL DISORDERS IN NUMBERS

When we talk about mental disorders, it is important to emphasise that it is too be understood broadly. It covers the entire spectrum of psychiatry, such as schizophrenia, depression, bipolar disorder and developmental disorders such as autism and ADHD.

One in ten Danes have a mental disorder and more than 40 per cent will receive treatment by the mental health services during their lifetime. Research does not yet have an unambiguous answer as to why

The iPSYCH project aims to find the causes of autism, ADHD, schizophrenia, bipolar disorder and depression - and forge the foundation for better treatment and prevention.

Mental disorders transcend gender and age. They can occur simultaneously or in succession. The disorders come at a high personal and societal cost, and they often have a significant impact on individuals and their families.

Approximately half of all mental disorders have their onset before the age of 14, and 75 per cent before the age of 24. One to two children in every classroom have issues of such significance that they need professional help.

25 per cent of enquiries at general practices are related to psychological issues. Life expectancy for people with serious mental disorders is 15 to 20 years shorter than average. Patients with schizophrenia have the shortest life expectancy, but high excess mortality can be seen in most diagnostic groups. This may be due to several reasons, for example shortages of hospital beds, lack of treatment, lifestyle diseases, suicide and adverse effects from medicine.

iPSYCH IN NUMBERS

Since 2012, iPSYCH researchers have published more than 1.000 scientific articles on mental disorders.

By examining the genes and risk factors of more than 150.000 Danes - both with and without mental disorders - iPSYCH has helped shed light on how the interplay between heredity factors and the environment can result in some people developing a mental disorder.

The researchers have looked at the disorders from many angles; from genes to cells, from animal models to population studies, from fetuses to adult patients, and from causes to symptoms.

iPSYCH is one of the world's largest studies of the genetic and environmental causes of mental disorders, and more than 150 researchers within psychiatry, genetics and register-based research have contributed to the project.

THE FIVE DISORDERS

Autism is an innate developmental disorder that affects how a person perceives their surroundings and the way in which they interact with others. Autism is a different way of sensing, understanding and navigating the world, and it has a major impact in social contexts and greatly affects how a person communicates with others. Autism is referred to as pervasive, which means that everything a person says, thinks and does is affected by autism. Three per cent of boys and one per cent of girls are diagnosed with autism.

Attention Deficit Hyperactivity Disorder, ADHD, emerges early in life and is characterised by hyperactivity, attention issues, inner restlessness and impulsive actions. Five per cent of boys/men and two per cent of girls/women are diagnosed with ADHD.

Schizophrenia and schizophrenia-like diseases have affect the thoughts, emotions and senses of a person. Symptoms may include hallucinations and delusions, for example hearing voices or a feeling of being followed. Language may be affected with speech becoming incoherent and difficult to understand, and a lack of initiative and reduced ability to sense and express emotions often make it difficult for the afflicted to take care of themselves.
The risk of developing schizophrenia is 1.9 per cent for men and 1.6 per cent for women. Overall, the risk of schizophrenia and schizophrenia-like diseases is 3.8 per cent for men and 3.7 per cent for women. The typical age for the onset of schizophrenia is between the ages of 17-23 for both sexes.

Bipolar disorder (formerly called manic depression) is a mental disorder that typically emerges during adolescence. The disorder is characterised by periods of mania or slight mania. These periods are characterised by unnatural euphoria and increased energy, activity and self-esteem, succeeded by depressive periods. Manic and depressive symptoms may also occur simultaneously or with rapid shifts. 1.3 per cent of men and 1.8 per cent of women are either hospitalised or receive ambulatory treatment for bipolar disorder during their life.

Depression is one of the most common mental disorders. The symptoms of the disorder are low spirits and low energy levels, paired with lowered self-esteem. People with a depression share a feeling of things being insurmountable. Depending on the symptoms, the severity of a depression is categorised as mild, moderate or severe. The risk of requiring hospitalisation due to depression is nine per cent for men and 16 per cent for women.

Health data is the mainstay of iPSYCH

iPSYCH was established in 2012 and quickly became one of the world's largest studies of the genetic and environmental causes of mental disorders and developmental disorders such as autism, ADHD, schizophrenia, bipolar disorder and depression. Access to Danish health data has been paramount in getting closer to determining the causes of these disorders.

We have heard it before: 'The Danish health registers are something very special', and in an international context, Denmark's registers and biobanks are unique. Together, they contain a wealth of health data that iPSYCH has relied on heavily in its quest to answer some of the most challenging riddles in psychiatry.

"This project wouldn't exist if we didn't have access to the Danish health data. This data has been the starting point for all our research activities," says Anders Børglum, research director at iPSYCH and professor at the Department of Biomedicine at Aarhus University.

Health data is information about our DNA, habits and treatments we have received by the healthcare system. Data that can be used for research, statistics and analyses. Danish health data is stored in a number of different registers and biobanks.

iPSYCH has had access to health data on more than 150.000 Danes with and without mental disorders.

"The data has given us a remarkable opportunity to shed light on the complex interaction between heredity factors and the environment which results in some people developing a mental disorder," says Anders Børglum.

Diagnosis is a private matter

In general, you can divide the data used by iPSYCH into two groups: Biological data and registry data. The biological data is often based on analyses of the archived heel blood samples taken from all newborns in Denmark. Register data is information about people's medical conditions. Researchers have particularly used the information available in the National Patient Register and the Danish central register for mental disorders.

"The genetic data would be useless if we weren't also able to compare it with registry data and see how genetics affect the development of mental disorders. Having access to information about specific diagnoses was absolutely crucial," explains Anders Børglum, and he stresses that there have also been challenges in using the health data.

"The information we've been working with contains very sensitive personal data. For example, a schizophrenia diagnosis is very private and confidential information. The same applies for genetic data. This is why data is stored and processed under very strict security," he says.

Data is encrypted

The researchers used data that had been pseudonymised. This means that any information that could identify an individual had been replaced by a code stored separately.

"When we compared the genetic data we'd accumulated from the biological samples with the subjects diagnosed with a disorder, there was never any information that would've identified a specific person. There were no civil registration numbers, names, addresses, etc. that would have identified the people we were studying. The only thing that we researchers were able to see was an individual with a specific diagnosis code," says Anders Børglum.

"We go far beyond what is required by legislation, to ensure that no results can be exported from a computer without specific authorisation."

There is a reason why Anders Børglum and his colleagues are so careful with the Danish health data; the data is a scientific and healthcare goldmine.

"The Danish public healthcare system basically covers the entire population, and registers all of our health data. The registers contain information about the health of an entire population over many years, and that's unique," he says. They provide a unique opportunity for research to produce results that can benefit patients and their relatives, which is the crucial long-term goal," he says.

Bonus information:

The data on a single person's DNA takes up 100-200 gigabytes.

iPSYCH has made genetic studies representative

When the topic of genetic epidemiology arises, Professor Thomas Werge uses the words "a new mindset". Because for the study of genetics to be beneficial and to be used in practice on patients, it is not enough to know which genetic variants are linked to mental disorders, we also have to know how they are linked. In other words: how big is the risk at population level?

The answer to that comes quickly from Thomas Werge, who has recently given a presentation about the genetic disposition for schizophrenia and 22q11.2 deletion syndrome, which are caused by the most common chromosome abnormality found in children. At the time, the clinical assessment was 50/50. There was a mother in the audience who had just been told that her son had 22q11.2 deletion syndrome, which is characterised by a great distance between the eyes, an elongated, narrow face and a high forehead. She approached Thomas Werge after the presentation. She was unhappy. Unhappy about the prospect of her son having a 50 per cent risk of developing the very serious mental disorder schizophrenia during his lifetime. That encounter is burned into Thomas Werge's memory.

Studies to benefit all

Today, he would not use those numbers in a presentation. The only reason he would include those numbers in a presentation would be to illustrate how much we have learned over the past 15 years. We will get back to that, but first we'll be turning the clock back to circa 1995 because that was when some researchers linked 22q11.2 deletion syndrome to the risk of developing schizophrenia.
In 2010, the research result of a case-control study conducted abroad showed that there is a 50 per cent risk of developing schizophrenia if you have the chromosome abnormality related to 22q11.2 deletion syndrome. These are big numbers. And it was these numbers that the mother was reacting to. Some years later, Thomas Werge, in collaboration with other iPSYCH researchers, conducted a pilot study of people with 22q11.2 syndrome. However, in contrast to previous studies that used completely healthy control subjects, the control group for this study was the entire Danish population. This reduced the risk of developing schizophrenia to approx. 7 per cent. In a third study, researchers turned the whole study design upside down. Instead of comparing people with and without schizophrenia, the researchers examined what illnesses in the Danish population were caused by the genetic 22q11.2 risk factor. The latest research result shows that the risk of developing schizophrenia is two per cent if you have 22q11.2 deletion syndrome.

A new perspective

"That study is an example of how genetic studies can be used to more precisely calculate who is at risk of developing a mental disorder. Moreover, the study concludes that some of the gene variants that have a well-established, documented and high risk of contributing to the development of mental disorders are actually carried by a higher number of healthy people than previously assumed," says Thomas Werge, who emphasises that many people live with the genetic 22q11.2 mutation without any noticeable symptoms. However, people without noticeable symptoms are naturally harder to identify.
According to Thomas Werge, the team behind iPSYCH have done something very simple, but very important within genetics.

"We have quite simply applied classical epidemiological methods of research to the field of disease genetics. We've gone from finding genetic disease variants, so-called gene discovery, to quantitatively understanding how these genetic factors impact the level of illness for an entire population.
iPSYCH has shown how important it is to study genetics at population level," says Thomas Werge.

Patients and students

Studying genetics at population level is different to what researchers have traditionally done and continue to do to some extent, i.e. study the genetics of people who are willing to participate. This would typically be very ill people who are then compared to students, blood donors or others who volunteer as control subjects.
"At iPSYCH, we have studied large, very rare, changes in our genome, but we have also examined the many millions of common genetic variants that all people have. And in both cases, we have demonstrated that the risk assessments created by using classical epidemiological analyses can be significantly different from the risk assessments created using traditional comparisons of people who are very ill and people who are healthy in case-control studies."
Thomas Werge emphasises that traditional genetic research is very important when trying to understand what causes a disease. However, we should be aware that that type of research is not optimal when it comes to determining the risk of developing a disease and should not be used to guide the efforts of the healthcare system.

Knowledge must (also) be countable

"If you want to use the genetics you discover in a clinical context at a hospital, then it's important to not only know how the genetic variants are connected to a certain disease, but know the degree to which they are connected to a certain disease, i.e. know how great the risk of developing the disease is."
All measures taken by the healthcare system in relation to preventing and treating diseases are based on a reasonably accurate risk assessment.
"iPSYCH has undoubtedly generated knowledge that will define how we understand genetics, especially in Denmark and the other Nordic countries. Genetics is on its way into the healthcare system and will be used by it. Which is why we need to remember what we learned in epidemiology. If we want to use our knowledge of a risk factor, we also need to know something about how it functions at population level. If we don't, then we risk launching health initiatives that'll miss the mark by a mile," says Thomas Werge..

Risk factors and registers

We do not know exactly why some people develop mental disorders, even though there are a number of identifiable risk factors such as genetics, effects during foetal development and childhood, social conditions, etc. iPSYCH has used the Danish registers to study a wide range of these factors.

"Anyone can develop a mental disorder because we all have a built-in vulnerability that can be weaker in some people than in others," says Professor Preben Bo Mortensen. For the past many years, he has worked on the risk factors and causes of mental disorders. He uses the Danish registers to study the environmental factors that increase the risk of becoming ill.

In 2000, Preben Bo Mortensen and his colleagues began collaborating with Statens Serum Institut to study blood samples from heel prick tests of newborns to identify risk factors such as signs of infections and inflammations.

"We always had to weigh the risk factors we could study against the genetic factors that we knew could increase the risk of illness," says Preben Bo Mortensen.

However, the researchers lacked adequate tools to measure the hereditary component in order to see if the links with other factors, such as birth complications, could in reality be due to the fact that people with a high genetic risk also experienced more complications, and that it was therefore the heredity components and not the complications that caused the illness.

"You can only study this if you can measure genetic predisposition. However, the only measure of genetic predisposition that we had at our disposal was information about the mental disorders of parents and siblings. iPSYCH has radically changed this state of affairs," he says.

Many genes play a role

We now know that mental disorders are not caused by just a few high risk genes. Rather, they are caused by many different genes that each contribute slightly to an increased risk. However, when you combine all risk variants across the genome, you will begin to see a target for the genetic disposition. A target that could open the door to new ways of studying environmental risk factors.

"Perhaps environmental risk factors act similarly to the many genes. Each of them slightly increase the risk. No individual factor increases the risk significantly, but each factor increases the risk a little bit and they seem to do so relatively independently of each other," explains Preben Bo Mortensen.

According to him, the impact of the many different risk factors cannot be explained by genetic predisposition at all, or can only be partly explained by genetic disposition. He also emphasises that the only certainty we have is the statistical correlation between the many different factors. The next important step is to use new methods to determine whether certain risk factors actually cause certain disorders.

This information will hopefully lead to the prevention of mental disorders in the future. The data and knowledge that iPSYCH has generated will be a key element in this research for a long time to come.

FACTS

Several factors can lead to psychological problems and mental disorders. Both hereditary and environmental factors can play a role in increasing the risk of developing a mental disorder. Despite the progress made over the past few years, most genetic risk variants have still not been identified.

GENETIC RISK

Research has shown that mental disorders and developmental disorders such as autism, ADHD, schizophrenia, bipolar disorder and severe depression share some genetic components.

Researchers from iPSYCH have shown that some people are more genetically predisposed to developing depression. A study based on 34,573 Danes showed that people with a high genetic risk are 2.5 times more likely to require treatment for depression at a psychiatric hospital. However, it is not certain that a person will develop depression just because they are at high risk. On the contrary, the majority of people with a high genetic risk never develop a disorder.

All mental disorders are polygenic, which means that they are caused by the combined action of more than one gene. There are in fact thousands of common genetic variants that each contribute to increasing the risk of developing a disorder such as depression or schizophrenia. There are also several very rare risk variants that can increase the risk of developing a disorder 50 times. In other words, there are several genes that determine whether a person is predisposed to developing a depression or another mental disorder.

OTHER BIOLOGICAL RISK FACTORS

There are biological factors other than genetics that can cause the development of a disorder.

A study from iPSYCH showed a correlation between low vitamin D levels in pregnant women and the later development of schizophrenia in their children. The study was based on blood samples from heel prick tests from 1,301 children who later developed schizophrenia compared with blood samples from 1,301 children who did not develop schizophrenia. Based on this comparison, it was possible to conclude that people who develop schizophrenia often have low vitamin D levels at birth.

Professor John McGrath from Australia received a Niels Bohr Professorship at the National Centre for Register-based Research (NCRR) at Aarhus University. The NCRR is part of the iPSYCH consortium. This enabled him to work with researchers at both NCRR and Staten's Serum Institut to establish the world's largest study of the possible correlation between vitamin D levels in pregnant women and a later risk of mental disorders in their children.

ENVIRONMENTAL RISKS

Research from iPSYCH indicates that the environment a person grows up in can affect the probability of them developing a mental disorder later in life. For example, air pollution is statistically linked to an increased risk of developing a mental disorder, while access to green areas has the opposite correlation. We do not yet know whether this is a causal correlation or whether it is due to other underlying factors.

What is GWAS?

Researchers from iPSYCH use a very particular method to study the three billion building blocks and millions of variants that make up the human genome. A method that perhaps sounds more like a computer game.

GWAS, genome-wide association study, is the most popular tool among researchers studying the genetic causes of illnesses and disorders.

"GWAS has made it possible for us to compare variants in the genome of hundreds of thousands of people, I mean even millions of people, and compare these variants with the risk of developing different disorders," says Professor Anders Børglum.

GWAS uses a relatively simple technique to study the genetic code of a DNA sample. This technique is then combined with statistical computer programs to calculate the correlation between the identified variants and the risk of developing different disorders.

Ander Børglum is in no doubt that this simple technique can have an enormous impact.

"GWAS is the foundation for developing future treatment of hundreds of diseases, including mental disorders."

Deviations are often irrelevant

Even though the vast majority of the human genome is the same for everyone, there are still a million small differences in each of us caused by differences in the building blocks of our DNA. When some people have a building block located in a specific part of the genome and others don't, researchers call it "a genomic variation"

Most variations have a negligible or nonexistent impact on the body, which means differences in building blocks do not matter. The result is the same.

However, researchers have in recent years discovered that some common variants in the genome increase the risk of a number of mental disorders.

iPSYCH was founded at a time when the hunt to map the genetic architecture behind serious mental disorders such as schizophrenia, depression and bipolar disorder was gaining momentum, and the project participated in these international efforts from the outset.

Impact on bipolar disorder

iPSYCH's efforts have resulted in the identification of 33 new genetic variants that affect bipolar disorder.

Researchers studied the DNA profiles of more than 413,000 people: 42,000 patients with bipolar disorder and 371,000 people without bipolar disorder. The pathogenic variants were identified by comparing 42,000 patients with bipolar disorder with 371,000 people without bipolar disorder.

This more than doubled the number of mapped genetic variants/risk factors linked to bipolar disorder explains Associate Professor Thomas Damm Als, who was behind the Danish contribution to the study.

"We have completed three studies, and before we began the third study, we had identified about 31 variants, so we have significantly increased our knowledge of the genetic architecture of the disease," he says.

The environment also matters

After examining DNA from people who have a particular disorder and comparing the results with DNA from people who are not affected by it, we can then use a 'genetic variant library' to see if certain variants are present in connection with the disorder.

However, genetic variants are not the only explanation behind why a person develops bipolar disorder.

"They are contributing factors in various ways, but environmental factors also play a role. A similar cocktail of heredity and environmental factors is also likely the cause of other mental disorders such as schizophrenia and depression," explains the researcher.

In fact, it appears that genetics variants do not affect any other organs or tissue, they only affect brain cells. Some of the variants are therefore part of genes that regulate how other genes are expressed in the brain, while others influence the signalling between nerve cells in the brain.

More studies of the genome

This knowledge extends our understanding of bipolar disorder, and may also provide ideas for the development of new medical treatments for the disease. However, this is in no way a more detailed explanation of bipolar disorder.

While GWA studies give researchers a better idea of where the variant is located, the analysis does not tell us which gene is affected by the variant and what the function of the gene is. By integrating GWA results with functional data about where, when and how much genes are expressed in the brain, we can learn more about the biology involved.

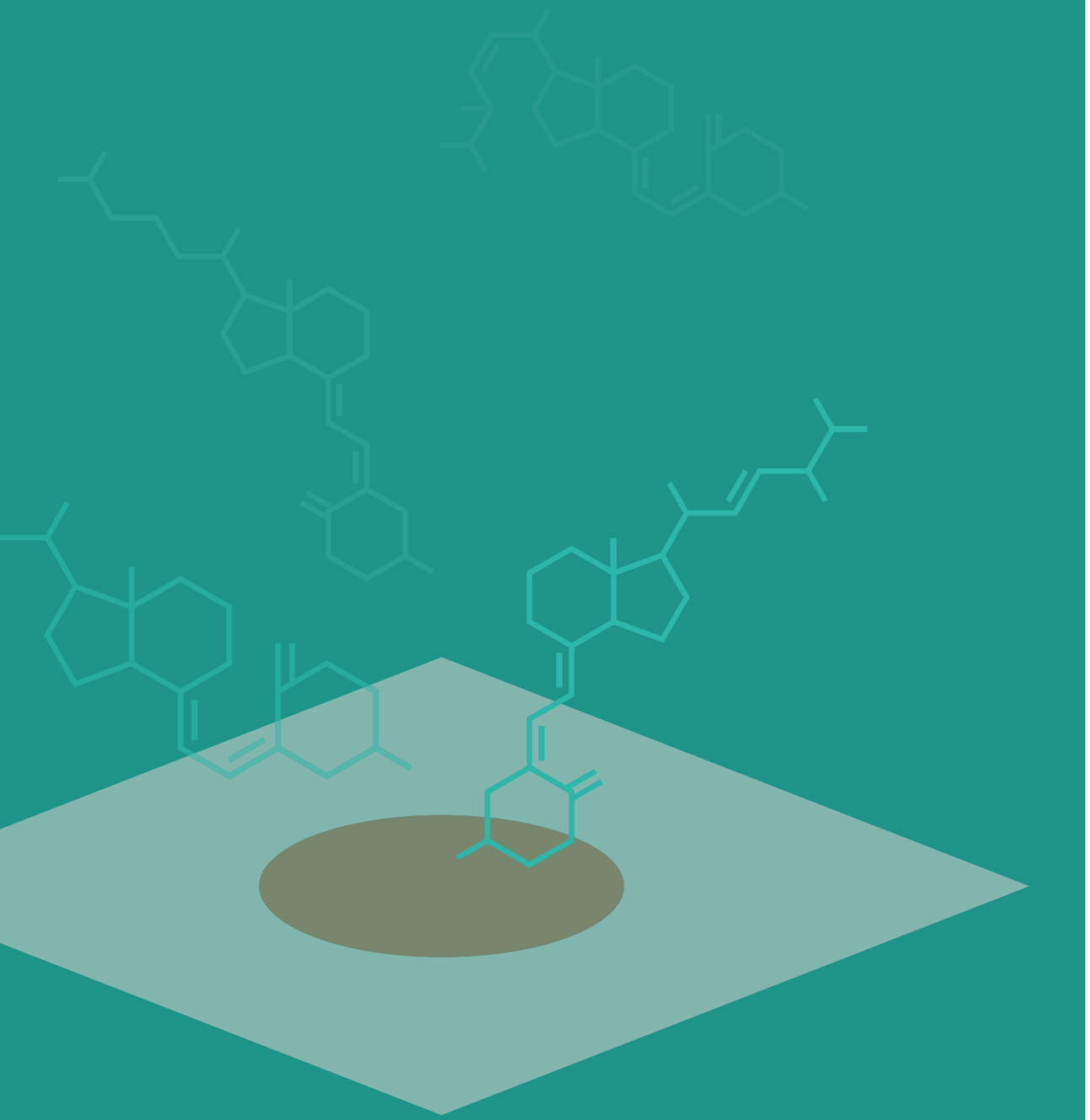
"Today, we know that bipolar disorder is more hereditary than e.g. depression, but how genetic factors and the environment interact is something we still need to understand. And we've still got a long way to go before we've identified all relevant genetic variants," says Thomas Damm Als.

According to the researcher, the road towards a greater understanding of disorders will require even more DNA studies.

"This is true of all psychiatric disorders. A study needs to be of a certain size to have any hope of finding genetic variants that can also be designated as risk factors," adds Thomas Damm Als.

GWAS

The Human Genome Project Organisation was established 1994. It was a global collaboration centred on mapping the human genome. In 2001, the project presented an almost final version of the complete genome. This was also the beginning of the wave of GWA studies. Researchers discovered that many of our individual variants in the genome are linked to each other. So having one specific variant means that you also have several others. This means that researchers only need to know about one of the body's three billion building blocks in order to have an idea about what the rest of the genome looks like and what common variants a person has.



Biobanks create new knowledge

Biological samples contribute to research into why some people develop a disorder while others do not, and into how we can better prevent diseases and take action even earlier to provide better and more effective treatment. Denmark has one of the largest biobanks in the world.

If you were born after 1982, some drops of your blood are most likely locked in a secure freezer at the Danish National Biobank at Staten's Serum Institut. All new parents are given the option to have a heel prick test carried out on their child. The blood sample from the test can show whether the child has an increased risk of a number of congenital diseases and will therefore require additional testing.

"Once all the analyses in the screening of the newborn have been completed, the remaining blood sample material is stored and can be used for research," says David M. Hougaard, head of the congenital disease department at Staten's Serum Institut.

Drops of blood on filter paper

There are more than 2.5 million filter papers with blood samples in the freezers at Staten's Serum Institut. A few droplets of blood from the heel of a newborn are invaluable to research.

For example, iPSYCH has analysed the blood samples of almost 90,000 people with a mental disorder and 50,000 random Danes in order to examine the genetic difference.

"We've discovered that many genes play a role, not just one. I think our genetic studies have been quite unique. We've shown that many genes are different when you have autism or ADHD, for example. We've also shown that there are many people who have a number of autism or ADHD genes without developing either disorder," he says and emphasises that any research that uses biological samples from the biobank has been approved by the National Committee on Health Research Ethics, the Danish Data Protection Agency and the biobank's Scientific Board.

According to David M. Hougaard, the rapid pace of Danish research is due to, among other things, the biological samples that are ready to use for future research.

"It's a unique resource that is of great benefit to research into the causes of diseases, their prevention and treatment."

THE FRONT LINES AGAINST FUTURE EPIDEMICS

The work done with the thousands of samples by iPSYCH contributed significantly to the ability of Statens Serum Institut to carry out genetic analyses on an industrial scale. This development will greatly benefit future research regardless of whether it is about complex diseases or new epidemics.

In order to effectively combat and control diseases, we need to learn more about the viruses and bacteria that surround us. Covid-19 was no exception.

We don't know what we'll be researching tomorrow, but when viruses erupt, new knowledge is needed fast. Researchers from Statens Serum Institut were some of the first to publish new knowledge about Covid-19 with the help of thousands of collected samples.

Up-and-coming researchers

There has never been need for persuasion to join this project: researchers have been queuing up. iPSYCH has been a magnet for talented young researchers in particular.

Think big. This has been the mantra. At least if you ask Professor Michael Eriksen Benros from Mental Health Services in the Capital Region of Denmark.

"The project has helped ensure that young researchers have the courage to think big. This has made us feel that something that would otherwise seem insurmountable can be accomplished with the right support from foundations and close collaboration between researchers," he says.

Michael Eriksen Benros is in no doubt that iPSYCH has been extremely valuable to psychiatric research in Denmark and has also become a recognised brand internationally.

"iPSYCH has helped give a generation of psychiatry researchers, myself included, an extensive national and international network with interdisciplinary collaboration. And most importantly for me, permanent collaborations and new learning."

Career boost

In addition to an extensive network and cross-disciplinary collaboration, iPSYCH has also been good for careers. Associate Professor Katherine Musliner is clear evidence. The American researcher started in iPSYCH immediately after her PhD, and today she is an associate professor.

"This has been a fantastic opportunity as a researcher, because this type of data set is not found anywhere else in the world. And it's given me the opportunity to investigate research questions that I wouldn't otherwise be able to do," she says.

According to Katherine Musliner, iPSYCH has boosted her career as a researcher and made it possible for her to publish articles in prestigious international journals.

"I've also successfully attracted my own external funding. So far, I've applied for and received three grants based on iPSYCH data. iPSYCH gave me ample opportunity to meet with other researchers, share ideas, and enter into new collaborations that continue to this day. The articles and grants formed the basis for my research career," says Katherine Musliner, who is now employed as an associate professor at the Department of Clinical Medicine at Aarhus University.

The word abroad

"On many levels, iPSYCH has been a remarkable program of research. It set ambitious goals – to do world-class research related to the causes of mental disorders. To do this, it has built uniquely informative data sources that have made major contributions to our understanding of mental disorders. Most importantly, it has strengthened and grown research capacity in Denmark – so many brilliant PhD students and post-docs have worked on iPSYCH-related research projects. This legacy will extend well beyond the timeframe of the grant. At the international level, it is widely recognized that iPSYCH has been remarkably productive and influential. I congratulate the senior investigators and the wider family of iPSYCH staff and students."

Professor **John McGrath** from the University of Queensland, who was awarded a Niels Bohr professorship in 2016.

"iPSYCH is a unique and ground-breaking project that has already made important and internationally significant contributions to conditions such as ADHD, autism and schizophrenia. The platform that has been created will be of huge future benefit to researchers in Denmark allowing them to continue to deliver highly impactful research in psychiatry and psychology. This research will ultimately benefit the many who experience challenges to their mental health and wellbeing."

Professor **Sir Michael Owen** from Cardiff University and member of the iPSYCH Advisory Board, whose task has been to provide strategic and scientific advice.

"Denmark has made a very large contribution to the world's knowledge of early life psychiatric disorders through iPSYCH. For example, the project yielded the first genome-wide significant loci for autism spectrum disorders and ADHD. This high value work remains most of what we know about the contribution of common genetic variants to these neurodevelopmental conditions."

Director of the Stanley Center for Psychiatric Research, **Steven E. Hyman**, Broad Institute.

7, 11 and 15 years old: A study of children with parents with serious mental disorders

How do mental disorders develop? And how can a genetic predisposition for schizophrenia and bipolar disorder affect a child's development and risk? These questions were explored in The Danish High Risk and Resilience Study, which included the VIA 7, VIA 11 and VIA 15 studies.

In 2013, 522 children and their parents were invited to participate in VIA 7. The children were seven years old at the time, as the name of the study suggests. The majority of the children were born to parents who had been diagnosed with schizophrenia or bipolar disorder, and there was a control group of 200 children of parents without those diagnoses.

Included in the study were interviews, assignments and questionnaires about the children's mental health, motor functions, social skills and cognitive abilities i.e. intelligence, memory, language, problem solving, etc. The children's quality of life, home life and the mental health and ability of their parents were also included in the study. At the age of 11, the children were given an MRI scan and blood samples were collected. 89 per cent of all families involved in the first data collection, VIA 7, also participated in the second round of data collection, VIA 11.

"It's really incredible to be able to follow up on so many families," says Professor Ole Mors from Aarhus University, "and the fact that all the children are the same age when we examine them, and that the families are all from the registers, and are therefore representative, make the VIA studies something completely unique, also internationally."

What are the most important results from your studies?

"We have now documented that children from families with a history of developing mental disorders begin to show signs of psychological vulnerability at the age of seven. Several of the children in the two risk groups met the criteria for psychiatric diagnoses at the ages of 7 and 11, and the children's cognitive abilities were affected, especially those who were predisposed to schizophrenia. These children were also at an increased risk of growing up in environments that did not contain the degree of support and stimulation that they needed, and those children had a harder time interacting socially. However, it's important to point out that these results are at group level, and approximately half of the children with a genetic predisposition did just as well as the control group. In other words, it's sub-groups of particularly vulnerable children who do poorly, but not all children," emphasises Professor Anne Thorup from the University of Copenhagen.

Have you also collected biological samples from the children and their parents?

"Yes, the children were asked to give a small hair sample each time, as hair can show the stress hormone levels of the past three months. Furthermore, both parents and children provided saliva or blood samples that could be used to analyse genes and epigenetic factors, and to shed light on the children's physical health. We've also measured the children's physical activity level via a chip in their legs, which showed that, at the age of 11, the children who are predisposed to mental disorders are less physically active in their everyday life compared to the control group," says Anne Thorup.

What can the results be used for?

"In many ways, we have placed these vulnerable children on the agenda of research, mental health services and the primary sector because our results have emphasised that these children are at increased risk. We have also learned much more about the problems that the families and especially the children face during childhood and adolescence. Knowledge that can be used to improve early detection and to develop initiatives that can prevent mental disorders. And if we have the opportunity to follow the children into adulthood, we'll really be able to say something about the childhood factors that precede mental disorders later in life. At the moment, we're examining the now 15-year-olds," says Professor Merete Nordentoft from the University of Copenhagen.

VIA IN FIGURES

A total of six senior researchers from both Aarhus and Copenhagen are leading The Danish High Risk and Resilience Study (Professor Marete Nordentoft, Professor Anne A. E. Thorup, Senior Researcher and postdoc Nicoline Hemager, Professor Ole Mors, Associate Professor Vibeke Bliksted, Senior Researcher and postdoc Aja Greve). More than 30 researchers and employees have been affiliated with the project over the years. By 2022, 11 PhD dissertations and more than 40 scientific articles have been written about the project.

Explain epigenetics

Your environment can affect how your genes are expressed. This is called epigenetics. The VIA project is a good example of these studies. Professor Ole Mors, who specialises in epigenetic research will explain.

Can you tell us a little about what 'epigenetics' is?
"Sure: Epi means 'on or above' and refers to the mechanisms through which chemical changes take place without fundamentally changing the actual DNA sequence, but where the function of a gene is changed. For example, the function of the gene can be turned off or upregulated."

Some of these changes take place in the prenatal state and last throughout life. Some cells become brain cells and not skin cells due to epigenetic regulation, which is controlled by the DNA chain.

But Ole Mors explains that other changes are dynamic and can be changed in the course of life. Epigenetic modification – as researchers call it – plays a key role in the development and function of the normal brain, and therefore also in brain diseases.

"We already know that epigenetic mechanisms are affected by the environment, for example smoking, antidepressants and antipsychotic drugs, pollution, stress and diet. A person's biological age can also be determined epigenetically. We therefore no longer need to contact people to ask if they smoke, as long as we have a blood sample. Smoking can be measured in the blood via an epigenetic mechanism. So, via a blood sample, we can often measure a specific environmental influence on the DNA.

Throughout his research career, Ole Mors has been interested in how nature and nurture could affect each other to increase or decrease the risk of mental disorders. It was not until epigenetics were discovered that we suddenly had a specific biological mechanism that described how this could be done.

Earlier intervention

"iPSYCH has carried out several epigenetic studies. IPSYCH initially spent a lot of time on a series of methodological studies just to be able to analyse the epigenetic changes in the small amounts of DNA in heel prick tests. We then examined DNA from heel prick tests from just over 2,000 people who developed ADHD and/or autism and from heel prick tests of a control group. We identified epigenetic changes in specific genes that are important for the development of the brain."

Another example is iPSYCH's epigenetic studies in the VIA project: Because the epigenetic 'landscape' is dynamic and changes throughout life, it is important to follow the same people over time in order to identify changes that end up causing disease.

"If we only examined them once they had fallen ill – the changes could be due to consequences of the disease, for example treatment – and not the causes of the disease. The VIA project is therefore extremely important, and we're currently conducting epigenetic analyses on children who participated in the VIA project when they were seven and eleven years old. We're comparing the environmental influences on the children with changes in their epigenetic landscape and with symptoms and impacts on cognitive functions," he explains, and continues:

"This data is unique because of the measurement at two ages, the large number of children, and the integration of genetic and epigenetic data with environmental influences over time. We hope that the results will contribute to a greater understanding of how early environmental influences interact with the genome and lead to early signs of the potential development of mental disorders in the future. The perspectives are that early detection will allow for early intervention."

Several mental disorders originate from shared genes

Eight of the most common mental disorders have a common genetic structure. Researchers from iPSYCH and the Psychiatric Genomics Consortium are behind the results, which could help to develop more precise diagnoses and improved treatment.

Over the course of a year, one out of five Danes suffer a mental disorder, and in general, psychological disorders are one of the biggest public health challenges in Denmark. These disorders are also a challenge for research, and there is still much to be understood about the basic mechanisms before we can pinpoint the biological processes that are out of balance in the brain. Now, we may have come a little closer to understanding such mechanisms and processes. At any event, a team of international researchers with contributions from Danish iPSYCH have found 109 genetic variants that affect the risk of suffering from more than one mental disorder.

"That we've identified genetic variants which affect the risk of having more than one mental disorder is an important step towards improved diagnosis and treatment of these disorders," says Professor Anders Børglum, who has headed the research team behind the Danish contribution.

Anders Børglum and his colleagues analysed the genetic data from healthy control subjects and people diagnosed with at least one of eight psychiatric disorders; autism, ADHD, depression, schizophrenia, bipolar disorder, Tourette syndrome, compulsive disorders and anorexia.

The results have been published in the journal Cell, and according to Anders Børglum they can tell us something about the extent to which these disorders have a common biology.

"When we know how disorders are related on a biological level, we can classify and diagnose mental disorders more precisely," he explains.

An important discovery

Certain diagnoses had many genetic variants in common, which made it possible for the researchers to categorise three groups of genetically-related disorders; disorders characterised by compulsive behaviour such as anorexia, compulsive disorders and, to a lesser extent, Tourette's syndrome; mood and psychotic disorders such as bipolar disorder, severe depression and schizophrenia; and developmental disorders such as autism, ADHD and Tourette's syndrome.

The study also identified several genetic variants that had a particularly widespread impact on the risk of a range of mental disorders. This may turn out to be an important finding in relation to preventing and treating mental disorders.

"In so far as these genes can have broad-ranging effects, they could be potential targets for developing new treatments which may benefit multiple disorders," says Anders Børglum before continuing: "As the same biological components are partly involved in the development of several of the diseases, treatment directed at these common components may be able to have an effect on all of the diseases."

Background for the results

The data set consists of genetic data from 494,162 healthy control subjects and 232,964 persons diagnosed with at least one of eight psychiatric disorders; autism, ADHD, depression, schizophrenia, bipolar disorder, Tourette syndrome, compulsive disorders and anorexia.

The study was carried out in collaboration with researchers from the Psychiatric Genomics Consortium.

Autism and ADHD share genes

Researchers from iPSYCH have discovered that the similarities between ADHD and autism can be linked to mutations in the same genes. In other words, children with ADHD have a genetic overlap with children with autism, and vice versa.

Autism and ADHD are two of the most common mental health diagnoses in children. In Denmark, approximately two per cent of schoolchildren have autism and three to five per cent meet the criteria for an ADHD diagnosis. Autism and ADHD are different developmental disorders, but they can have certain common symptoms. For example, children with autism can demonstrate violent or aggressive behaviour, be impulsive, and have problems in school and with social relations - and these same symptoms may be shared by children with ADHD.

Researchers from iPSYCH have now discovered that the similarities between the two diagnoses can be linked to mutations in the same genes, and this new knowledge tells us something about the biological causes of the two mental health diagnoses in children.

"The very fact that mutations are found to the same extent and in the same genes in children with autism and in children with ADHD points towards the same biological mechanisms being involved," says Ditte Demontis, associate professor at Aarhus University and one of the researchers behind the study. The study was carried out in collaboration with the Broad Institute and Harvard Univeristy.

The same gene is linked to ADHD and autism

The study is the largest study to date of rare mutations in the genome of people with ADHD and autism.

"This is the first time that the genome has been mapped so comprehensively for both ADHD and autism, and the discovery that children with ADHD have the same amount of gene-destructive mutations in their DNA as children with autism is both striking and someone surprising," says Associate Professor Jakob Grove, who is behind the study.

The findings point directly towards the biological causal mechanisms shared by ADHD and autism.

"In the study, the gene that is most frequently affected by mutations in people with ADHD or autism is the so-called MAP1A gene. The gene is involved in the formation of the physical structure of nerve cells – their inner 'skeleton', so to speak – and is important for the development of the brain," explains Jakob Grove.

This is the first time that this gene has been linked to the development of ADHD and autism, and the mutations found by the researchers give a significantly increased risk of developing autism and/or ADHD.

"We discovered a build-up of mutations that destroy the MAP1A gene in those with ADHD and autism, while very few of the control subjects had changes in the gene," explains Ditte Demontis.

This means that the risk of ADHD and autism increases by more than 15 times for people who carry such a mutation. The researchers have analysed the genes of approximately 8,000 people with autism and/or ADHD, and 5,000 people without either of the two disorders, all from Denmark. The study also incorporated genetic data from approx. 45,000 international control subjects who did not have any psychological disorders.

"The study shows that many more genes for ADHD and autism can be identified directly by studying more people in a similar way with extensive DNA sequencing, thereby providing a more complete picture of the biological causal mechanisms and possible approaches to medical treatment," explains the researchers.

Background for the results

The data set consisted of 3,962 people with autism, 901 with both autism and ADHD, 3,477 with ADHD and 5,002 control subjects without any of the above-mentioned diagnoses.

The genome was analysed in detail in what is known as whole exome sequencing. This maps out in detail the building blocks of the genes.

The study was conducted in collaboration with researchers from the Broad Institute and Harvard in Boston, USA.