GENCODYS Patient Meeting

Sunday 1 June 2014, Milan

ESHG EMPAG 2014

Milano Congressi - Milan, Italy - May 31 - June 3

VSOP DUTCH GENETIC ALLIANCE

EGAN
Patients Network for Medical Research and Health

Genetic and Epigenetic Networks in Cognitive Dysfunction
GENCODYS

SEVENTH FRAMEWORK PROGRAMME

About GENCODYS

Cognitive disorders can be caused by environmental as well as genetic factors. At the moment a definite diagnosis can only be made in about half of the patients with moderate to severe intellectual disability, and only in 20% of the mildly affected patients. Thus, for the majority of patients, a cause cannot be found, which creates an enormous burden for families confronted with such a disorder. The GENCODYS consortium aims to help these families by identifying the genetic causes of cognitive disorders using next generation sequencing techniques. Individual mutations leading to intellectual disability are often rare, but they may disrupt similar pathways. The GENCODYS consortium also examines these pathways in order to take first steps towards therapy development.

Sunday 1st June

Venue: Milano Congressi, Viale Eginardo, Gate 2, Suite 3

Program

10.00 – 10.15	Welcome by dr. Cor Oosterwijk (director VSOP, secretary general EGAN) Personal introduction round **General introduction** by dr. Cor Oosterwijk **Aims of the meeting** by dr. Tessa van der Valk (policy officer VSOP)
10.20 – 10.35	**New sequencing technologies: implications for research and future directions** by prof. dr. Hans van Bokhoven (Radboud University Medical Centre, The Netherlands)
10.35 – 11.50	**The patient perspective**, by Helene Cederroth (Wilhelm Foundation, Sweden)
11.50 – 12.05	Questions and short discussion
11.20 – 11.35	Break
11.35 – 11.50	**New sequencing technologies: implications for the clinical practice in intellectual disabilities** by dr. Tjitske Kleefstra (Radboud University Medical Centre)
11.50 - 12.05	**Developments in research: Down syndrome,** by Luc Stuit (AFRT; French Association for Research on Down Syndrome)
12.05 – 13.00	**Questions, discussion, conclusions, next steps, closure**

Attendees: L. Stuit (AFRT; French Association for Research on Down Syndrome), O. de Compiègne (Xtraordinaire), R. Barbon Galluppi (UNIAMO), H. Cederroth (Wilhelm Foundation), M. Cederroth (Wilhelm Foundation), H. van Bokhoven (Radboud University Medical Centre), T. Kleefstra (Radboud University Medical Centre), K. Karsenberg (VSOP), M. Nijnuis (VSOP), C. Oosterwijk (VSOP), T. van der Valk (VSOP).

General introduction and aims of the meeting (C. Oosterwijk & T. van der Valk)
VSOP is the Dutch umbrella organisation for patients with rare disorders. About 70 patient organisations representing specific rare and/or genetic disorders are a member of VSOP. According to the international definition, diseases are considered rare if the prevalence is lower than 1 in 2000. There are over 7000 specific rare disorders, and for most of them standards of care and effective therapies are not available. Rare disorders are often diagnosed very late: 25% of the patients receive a definite diagnosis after 5 to 30 years. At least 20% of patients with a rare disorder are intellectually disabled. The GENCODYS project aims to provide these patients with a genetic diagnosis using next generation sequencing technologies. Within GENCODYS, gene mutations found in patients with a cognitive disability are introduced in animal models (fly- and mouse models), in order to further examine the networks that are disrupted in these patients. Eventually, this research should lead to the identification of compounds that might be used in the treatment of patients with intellectual disabilities. The project overview is shown in Figure 1.

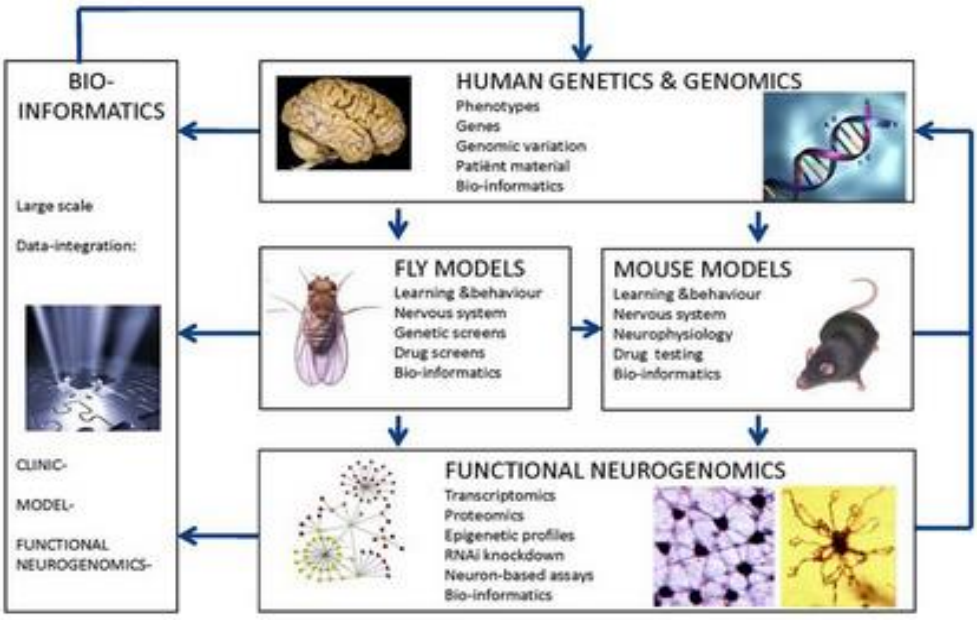

Figure 1: Overview of the GENCODYS project

Networking with patient organisations in the field of rare, genetic, cognitive disorders is an important task in the project. The project finishes in May 2015, and in the last 1,5 years of the project meetings with patient representatives will be organised in 2 to 3 different countries (Italy, Germany and, hopefully, Spain). This morning's meeting in Milan is the first of these

meetings in which we aim to facilitate interaction with patient organisations. Topics for discussion include the importance of new sequencing technologies for patients, patient access to these technologies, how to facilitate research into genetic (cognitive) disorders and how to effectively put forward the needs of patients in the future.

New sequencing technologies: implications for research and future directions (Prof. dr. Hans van Bokhoven)

The human genome consists of about 6 billion nucleotides. A mistake in just one of these can cause a severe disease. The question that prof. dr. Hans van Bokhoven poses in this regard is *'How do we find a needle in a haystack?'*. Next generation sequencing techniques have enabled researchers to speed up the search for a mutation from many years to several weeks. For intellectual disabilities (ID), over 450 mutated genes have already been identified and a thousand other genes might still be there to discover. Intellectual disabilities roughly fall into three important categories: X-linked, autosomal recessive, and autosomal dominant. On the X-chromosome, over 100 ID-genes are already known. When only traditional sequencing methods were available, families with more than one affected person were needed to find recessive mutations. These families are rare, except in populations with high consanguinity-rates (for instance in countries such as Iran and Pakistan, where 2 partners in the GENCODYS consortium are located). It is very difficult to diagnose patients in case of consanguinity, because these patients often have several mutations. Next generation sequencing techniques have made it more feasible to diagnose sporadic cases, which include both recessive mutations and *de novo* dominant mutations (i.e. dominant mutations that the parents of the patient neither possessed or transmitted). A challenge with diagnosing these sporadic cases is how to confirm causality: does the detected mutation really cause the intellectual disability of the patient? To be more sure, findings in a single family or patient always need to be confirmed in another family or patient, on the genetic as well as on the phenotype-level. Databases that are available worldwide are used by researchers to confirm individual mutations that may cause cognitive disorders.

The patient perspective: Wilhelm Foundation (Helene Cederroth)

Wilhelm foundation (http://www.wilhelmfoundation.org) in Sweden was founded to help children that suffer from an undiagnosed brain disease. Its founders, Helene and Mikk Cederroth, have lost their three children to an undiagnosed brain disease. Even though their children, Wilhelm, Emma and Hugo, suffered from similar symptoms, physicians doubted whether the disease was indeed hereditary. As of today clinical geneticists have not been able to find the cause of the disease (even though many had promised to do so). According to the foundations estimation 3 out of 10.000 children suffer from undiagnosed brain diseases. Especially children with degenerative brain diseases are very difficult to find and include in research. There is no international support group. Parents worldwide now turn to Wilhelm Foundation for support, for instance to be able to visit a specialized hospital abroad (such as the NIH Clinical Center in Bethesda Maryland, that collaborates with SWAN USA).

New sequencing technologies: implications for the clinical practice in intellectual disabilities (dr. Tjitske Kleefstra)

Since the discovery of DNA in the 1950s, there has been rapid progress in the area of sequencing. Nowadays, next generation sequencing technologies can be used to analyse exomes (coding regions; about 1% of the DNA). In Nijmegen, the procedure starts with generic exome sequencing, followed by disease-specific data analysis. This last step is continuously updated according to the most recent insights into the possible genetic causes of a disease. So called 'incidental findings' are discussed in a committee and only reported back to the patient if this committee agrees to do so. In the US, a minimum set of about 50 'actionable genes' has been compiled, which patients should always be informed about. Informing parents about the procedure and the possibility of incidental findings is a challenge. Patients and families often really want to know the genetic cause and recurrence risk and are under the impression that after next generation sequencing, they will know all there is to know about their health. While intellectual disabilities are common, each case is rare: individual patients often have different rare mutations that lead to intellectual disabilities. Over 50% of patients with intellectual disabilities can now be diagnosed using next generation sequencing. These advances have caused an increase in the number of novel syndromes. By collaborating worldwide, researchers can bring patients and families together with the same mutation or syndrome. An important challenge is how to collect and store information for patients and their families. Nowadays, information is exchanged online on Facebook or discussion forums, and a lot of this information gets lost, causing different parents to discuss the same topics over and over again. Researches are also in need of a good infrastructure to exchange ideas. There are many international collaborations, but this is not structured: there is no general overview of who is working on what.

Developments in research: Down Syndrome (Luc Stuit, MD)

Luc Stuit draws everyone's attention to the question *"Why is research on Down Syndrome so slow?"*. Down Syndrome was already known in 1830, but still basic data such as the number of patients suffering from the disease are unknown. Better understanding of the neurological pathways involved in the disease is very important to advance towards development of therapies. For patients with Down Syndrome and their families, being able to increase the IQ score by 10 points makes a big difference. There are promising results in mice. To test potential therapies in humans, it might be important to administer the therapy early on in life, as younger patients might respond differently to therapies than older patients who may have incurred irreversible damage. Negative results of research, for example the results of a trial that did not confirm the effectiveness of a new drug, are also important but often not published.

Progress in research on Down Syndrome may be reinforced by research in other diseases. There are common clinical aspects in Down Syndrome and early Alzheimer disease. Many genes on chromosome 21 may also be involved in Alzheimer disease. Also, while changes in cognitive functions are difficult to evaluate in a clinical research setting, there may be other aspects of the disease that are also important for daily life and are more easily evaluated (such as sleep or sense of smell).

Discussion and concluding remarks

Key points in the discussions included:

- At the moment, next generation sequencing of patients within the GENCODYS project is paid from the research budget. This budget will no longer be available when the project ends halfway into 2015. It is at this moment unclear if this will pose a threat to patient access to next generation sequencing. In other countries, the accessibility of next generation sequencing may also be problematic. The currently ongoing process of designating European reference networks and European centres of expertise may facilitate patient access.
- Cohorts of patients are needed, described / characterized and ready to participate in possible future clinical trials. At the moment clinical trials are ongoing in fragile X patients, and the results so far seem to be disappointing. Novartis has stopped the development of its compound. Fragile X is one of the more common cognitive disorders and for patients with other, more rare disorders, this is also not very promising (if it is so difficult to find effective therapies for fragile X it is likely to be even more difficult to find therapies for these more rare cognitive disorders). One of the reasons for these disappointing results so far could be that patients are included who are older, and where the disease has already caused irreversible damage. This shows the importance of including patients early on in life (or at an early stage of the development of their disease), which is more difficult as this decreases the size of the potential study population. Also, in some countries the regulations for conducting clinical trials in minors are more strict.
- It is very important to effectively collaborate and share available resources. Worldwide there are different registries of patients with rare cognitive disorders and some are freely accessible, while others are not. Also, the kind of data stored in these registries is not always optimal for facilitating further research. It is very important to know who is doing what, and this goes for researchers as well as physicians. This is also an important reason why Wilhelm foundation aims to organise a world congress on undiagnosed brain diseases.

To conclude, and taking up some of the key points in the discussion, the idea is launched to organise a meeting in 2015 about a European reference network for patients with undiagnosed cognitive diseases, to try to more effectively coordinate research into these diseases and care for these patients in Europe.