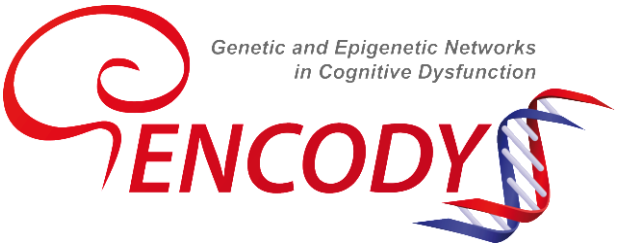
GENCODYS Patient Meeting

Saturday the 1st of November 2014, Berlin



About GENCODYS

Cognitive disorders can be caused by environmental factors 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 the first steps towards therapy development.

Saturday the 1st of November

Venue: TRYP Hotel, Berlin Mitte, Room Dali 1

Program

11.00 – 11.25	**State of the art of preclinical and clinical research towards better diagnosis and treatment of cognitive disorders** (Dr. Annette Schenck, Radboud University Nijmegen Medical Centre, The Netherlands)
11.25 – 11.50	**Next generation sequencing and the clinical context: how can patients benefit?** (Dr. Christiane Zweier, Institute of Human Genetics Friedrich-Alexander-University Erlangen-Nürnberg)
11.50 – 12.05	**Access to genetic diagnostics in Germany – Status quo** (Dr. med. Christine Mundlos)
12.15 – 12.45	Lunch
12.45 – 13.15	**Discussion on possible ethical questions in Next generation sequencing** (dr. Cor Oosterwijk)
13.20 – 13.40	**Progress towards therapy development and the involvement of patient organisations in Fragile X** (dr. Jörg Richstein, Interessengemeinschaft Fragiles-X e.V.)
13.45 – 14.05	**Progress towards therapy development and the involvement of patient organisations in Tuberous Sclerosis** (Anja Klinner, Tuberöse Sklerose e.V.)
14.10 – 14.25	Coffee break
14.25 – 16.00	**Discussion**

Attendees:

A. Klinner (Tuberöse Sklerose e.V. / ACHSE e.V.), A. Schenck (Radboud University Nijmegen Medical Centre), C. Zweier (Institute of Human Genetics Friedrich-Alexander-University Erlangen-Nürnberg), C. Leber (Bundesverband Williams-Beuren-Syndrom e.V.), C. Mundlos (ACHSE e.V.), G. Wehr (Selbsthilfe Ichthyose e.V.), J. Richstein (Interessengemeinschaft Fragiles-X e.V. / ACHSE e.V.), M. Südbeck (LEONA e.V.), C. Oosterwijk (VSOP), T. van der Valk (VSOP).

General introduction and aims of the meeting

Within GENCODYS, gene mutations found in patients with an intellectual disability (ID) 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.

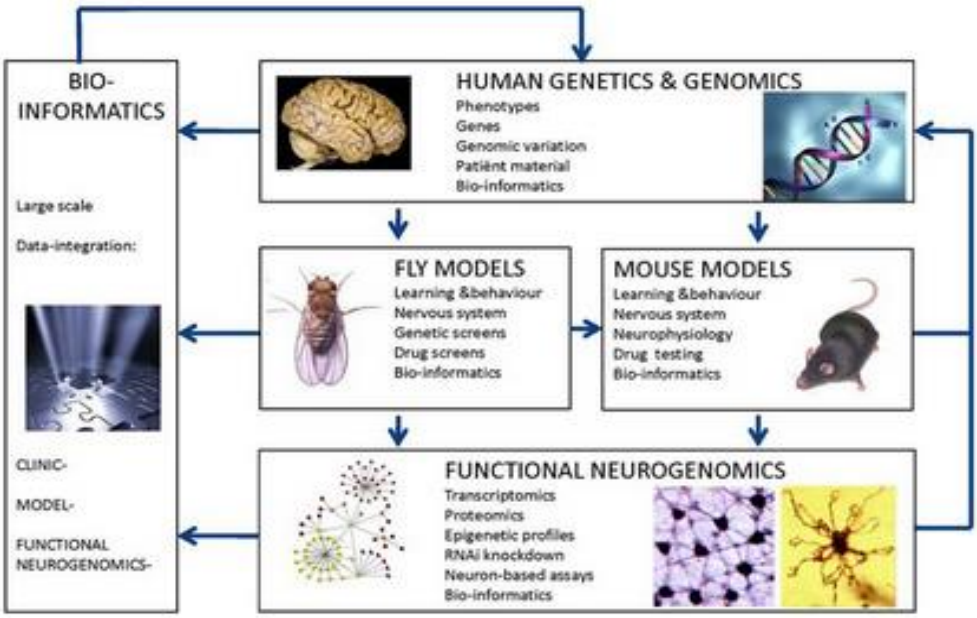


Figure 1: Overview of the GENCODYS project

Networking with patient organisations in the field of rare, genetic, cognitive disorders is an important task in the project. VSOP, the Dutch umbrella organisation for rare, genetic disorders has this responsibility. The project finishes in May 2015, and so far meetings with patient representatives have been held in the Netherlands, France, and Italy. Topics for discussion today 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. After today's meeting in

Berlin, we hope to organise a final meeting in Madrid, right before or after the EURORDIS meeting.

State of the art of preclinical and clinical research towards better diagnosis and treatment of cognitive disorders (Dr. Annette Schenck)

About 700 genes are known to play a role in ID. If we can find out what functions these genes have and what goes wrong in patients, clues for therapeutic intervention could be discovered. Studying gene defects in animal models is an important step. Within the GENCODYS project, mice and drosophila are used to mimic the gene defects found in patients with ID. Dr. Schenck's work within the project focuses on drosophila. Drosophila offers many advantages: relevant behaviour can be studied, as well as mechanisms at a (sub)cellular and molecular level within the brain. Also, studies in drosophila allow to test whether cognitive defects are reversible in adulthood. For example, studies into Kleefstra Syndrome in drosophila have shown that defects in learning and memory can be (at least partly) reversed by reversing the underlying molecular deficits. About ¼ of the patients with Kleefstra Syndrome have a defective EHMT gene. The genetic diagnosis of many other patients is still unknown. It is expected that these patients have other gene defects, but that these genes disrupt the same pathways: rare gene defects are related by the pathways they disrupt and lead to similar phenotypes. Similar molecules might be used to reverse the disruption of a pathway, regardless of the specific rare gene defect.

Next generation sequencing and the clinical context: how can patients benefit? (Dr. Christiane Zweier)

From a clinical perspective, the heterogeneity within the group of patients with ID is very high: some patients only have mild learning disabilities, while others have many additional health problems. For about half of the patients, the genetic cause is still unknown. While chromosomal aberrations can be detected quite reliably in our days, monogenic aberrations are still difficult to detect as they are extremely heterogeneous and as the number of known ID genes is still incomplete. When coming to the clinic, patients and families have many questions: what is the cause of the disease? How high is the risk that a subsequent child will also have the disease? What can be expected in terms of development and general health? And is there a therapy available? The answer to the last question is often 'no'. For patients and their families, obtaining a diagnosis is very important, and knowing more about the causes of ID could help researchers to discover new therapies. To provide patients and families with a diagnosis, both gene panels and whole-exome sequencing can be used. If a specific, but genetically heterogenous disorder is suspected, a specific panel of genes can be analysed. For patients with a unspecific phenotype, whole-exome sequencing is more helpful, often in a trio-approach to use the parental DNA to filter for de novo mutations. In such sporadic cases, finding other patients with mutations in the same gene and with a similar phenotype is crucial. In general, analysing a panel of genes is a good diagnostic option if a defect in a certain group of genes is suspected. If this is not the case, whole-exome sequencing provides more flexibility, as a larger number of genes, both known and so far unknown ID genes, can be tested, and as the sequence data can be stored and re-examined if

further patients with a similar phenotypes are found. If more patients can be diagnosed, more patients and families will know what to expect in terms of health problems and quality of life.

Access to genetic diagnostics in Germany - Status quo (Dr. med. Christine Mundlos)

In Germany, as well as in many other countries, there is inpatient and outpatient billing of health care services. Inpatient billing is based on Diagnosis Related Groups (DRG). In outpatient billing statutory health plans and private health funds are relevant.

Standard genetic diagnostic procedures in Germany comprise cytogenetic analyses, array-CGH and Sanger gene sequencing. These standard genetic diagnostic methods are in principle covered by the national health insurance. The budget of regionally organised associations of insurance funds depends on the resources of the region concerned. If the budget of a certain medical service has been fully spent, further will be reimbursed at a reduced rate.

In practice, patients in the hospitals hardly ever receive genetic diagnostics, as this is too costly to be covered by the insurance reimbursements as these are based on Diagnosis Related Groups. The reimbursement for genetic counselling is sufficient for standard situations but does not cover the often complicated and time consuming procedures in clinical genetics. Counselling is mandatory in cases of predictive testing (testing of healthy individuals for disease risks) and optional for all other genetic testing. It can be provided by human geneticists of other physicians with basic knowledge in Human Genetics. In private health plans, genetic diagnostic services are only covered if they influence therapy. Patients need to hand in a "specific individual request" that will be decided on after evaluation.

Next generation sequencing (NGS) services in general cannot be billed (with exceptions). They can only be used in a research setting or after approval from a health care insurer, based on a 'specific individual request'. In practice, patients can only benefit from NGS services if they happen to be able to participate in a clinical research study.

Discussion on possible ethical questions in Next generation sequencing (dr. Cor Oosterwijk)

For patients it is important that they have the option to be diagnosed as early as possible. The positives for early diagnosis are: prevention of diagnostic delay, avoiding uncertainty and stigmatization and gaining access to research and reimbursed treatment. A diagnosis can also be relevant for reproductive choices, to be made by the patient or his or her family members. Compared to traditional diagnostic procedures, next generation sequencing poses specific ethical questions. One important ethical question concerns so-called 'incidental findings', i.e. genetic defects found in next generation sequencing, but not related to the disease symptoms for which a diagnosis was originally sought.

The American College of Medical Genetics (ACMG) has spurred the debate on incidental findings, by compiling a list of genetic disorders that patients always need to be informed about. At first it was not possible to opt out: patients did not have the right not to know about these genetic defects. Also related to the issue of incidental findings is whether or not to do a targeted analysis. The results of next generation sequencing can be analysed in full, or

only those genes can be analysed in which a defect is expected (if such an expectation can be made). Targeted analysis would decrease the chance of incidental findings. Another issue is patient access to data and who is in control of this data.

In the EU and within individual European countries, there is no consensus on how to deal with incidental findings and patient access to data. A statement from the perspective of patients should be formulated to feed the debate.

For patients and families, adequate communication and support are always important. After diagnosis, patients and families are (too) often abandoned when they should be referred to the relevant patient organisation. Networks are needed that can support patients and families that have not yet been diagnosed. Progress of research into the genetic background of diseases and patient care are both important and the quality of life of individual patients and their families should always be leading.

Progress towards therapy development and the involvement of patient organisations in Fragile X (dr. Jörg Richstein)

Fragile X is caused by an expansion of a repetition that affects the Fragile X Mental Retardation gene (FMR1) on the X chromosome. Depending on the length of the repetition, a person may have a premutation or a full mutation. In the latter case, the fragile X mental retardation protein is not expressed and the person is affected by the syndrome. In subsequent generations, a premutation may develop into a full mutation. Genetic testing to determine the number of repetitions can be done to provide patients with a diagnosis. The prevalence of Fragile X is estimated at 1 in 4000 and affects males more as they only have one copy of the X-chromosome. Individuals with Fragile X are often intellectually disabled, some are affected by autism and have difficulties communicating. But they also have special abilities (they are very friendly and open to the feelings of others) and in daily life they are not ill.

Preclinical trials in Fragile X were very promising, but in 2014 phase II-b clinical studies by Roche and Novartis were discontinued. A strong placebo effect occurred in the control groups. A major underlying problem is the lack of adequate outcome measures and difficulties in patient recruitment. Patient organisations should become involved to develop adequate outcome measures and study designs in collaboration with industry.

Interessengemeinschaft Fragiles-X e.V. is now involved in several Horizon 2020 project proposals. There are also hurdles in some of these collaborations, notably insufficient communication or not being allocated a fair share of budget. Guidelines are needed to facilitate the involvement of patient organisations in EC-funded and other research projects (could be similar to the guidelines that apply to SMEs).

Progress towards therapy development and the involvement of patient organisations in Tuberous Sclerosis (Anja Klinner)

Tuberous sclerosis is a genetic, multisystem disorder that causes growth of benign tumors in the brain or in other vital organs. Two gene mutations have been found that cause tuberous sclerosis (TSC1 and TSC2). The disorder has an autosomal dominant pattern of heritability,

but in most cases (2/3) it is caused by sporadic mutation of one of the two genes involved. The estimated incidence is 1 in 6.000 to 1 in 10.000.

Since 2012, there is a therapy available for the treatment of SEGA (brain tumor) and ALM (kidney tumor) caused by tuberous sclerosis, marketed by Novartis (Afinitor®, everolimus). The benign brain tumors and the dysplasia of the brain that occur in patients with tuberous sclerosis can cause seizures. Everolimus has been shown to reduce tumor size in patients, but whether or not the product might also reduce the number of epileptic seizures or influence the mental abilities has not been examined (whilst it was proposed to Novartis to include this outcome measure). Epileptic seizures are one of the first symptoms of tuberous sclerosis, and early treatment with anti-epileptics may be beneficial for the cognitive development. The international Epistop project focusses on the pathophysiology of epilepsy and its consequences. Further research also examines the possibility of relatedness of this disease with other rare diseases, most notably fragile X and NF1 and other disorders associated with PTEN mutations (part of the network that is disrupted in tuberous sclerosis patients).

Next generation sequencing is applied in a research project in Germany in order to find a cause for the disease in patients that do not have mutations in the TSC1 or TSC2 genes (15 to 20 % of all patients). A complicating factor is that some patients are genetic mosaics.

Discussion and concluding remarks

The cases of research on fragile X and tuberous sclerosis have both shown that not involving patients in research (and especially in developing and deciding on outcome measures of clinical research) can contribute to suboptimal or even disappointing results. Off course, not all individual patient organisations are able to provide this input. To facilitate involvement of patient organisations in research, international networks need to be set up to enable exchange of knowledge between patient organisations. This does not have to be expensive; budget is needed to organize at least one face to face meeting each year and to set up a website to share knowledge online. In the fourth quarter of 2015 the procedure will start to establish European Reference Networks. Patient organisations will need to be part of these networks and need to have the competences to adequately take up this role. Quality criteria for patient organisations could be useful in this respect.

In the end, multidisciplinary research networks are needed in which patient organisations at least participate but they should also be able to become actively involved and take up the role of coordinator. Many organisations might not be able to fulfil this important role, but it is also not an easy task for academics. Patient organisations that are well equipped can bring research organisations together and facilitate collaboration. Guidelines for the involvement of patient organisations in these multidisciplinary networks should be set up, notably in regard to finances (for instance by adding 10% of the project budget for patient involvement). The European Patient Forum could facilitate the development of such guidelines.