

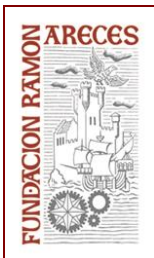
**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

1. [Intellectual Disability: Clinical and epidemiological aspects. Feliciano Ramos](#)
2. [Molecular networks in intellectual disability. Hans van Bokhoven](#)
3. [Systematic analysis of the mammalian synaptic proteome uncovers its evolution and role in cognitive disorders. Alex Bayes](#)
4. [Intellectual disability and autism: the role of rare genetic variants. Bru Cormand](#)
5. [Intellectual Disability and arrayCGH. Laia Rodriguez](#)
6. [Genetic Investigation for adults with intellectual disability. Lucy Raymon](#)
7. [Phenotypic Variability of Genomic Disorders and Rare Copy-Number Variants. Hilde van Esch](#)
8. [Use of array CGH in prenatal diagnosis: main clinical indications and clinically significant genomic alterations. Eugene Pergament](#)
9. [Validation of ArrayCGH and Next Generation Sequencing for Diagnosis in Preimplantation Genetic Diagnosis. Harvey Stern](#)
10. [Identification of novel intellectual disability genes by exome sequencing. Xavier Estivill](#)
11. [Exome and massively parallel targeted resequencing identifies a spectrum of genes recurrently mutated across developmental disorders. Brian O'Roak](#)
12. [Animal Models. Yolanda de Diego](#)
13. [Normalization of DYRK1A to improve cognitive performance in Down syndrome subjects: the TESDAD study. Rafael de la Torre](#)
14. [Clinical trial in Fragile X Syndrome. Ernest Balaguer](#)
15. [Ethical aspects of the use of next-generation sequencing technologies and research involving vulnerable subjects. Teresa Pampols](#)



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

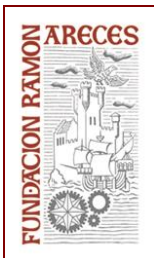
## Intellectual Disability: Clinical and epidemiological aspects. Feliciano Ramos

Intellectual disability (ID) is a disability characterized by limitations in intellectual functioning and resulting in the need for extraordinary supports for the person to participate in activities involved with typical human functioning. It results in impairments to the brain (e.g., body functions and structures) that causes activity limitations and participation restrictions. The term 'mental retardation,' that has been used in parts of the world, has increasingly become stigmatizing and rejected by professionals, advocates and affected families. Intellectual disability is known to cause significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. Intellectual disability is one of a set of disabilities that can result from impairment to the Central Nervous System that manifest in limitations to general cognitive functioning. The definition reflects the three essential definitional elements of intellectual disability: a) significant limitations in intellectual functioning, b) behavioral restrictions in adapting to ecological demands, and c) diagnosis prior to age 18. Although an increasingly contentious issue, the commonly accepted means of determining limitations in intellectual functioning continues to be through the administration of intelligence tests, which yield an intelligence quotient or IQ score. Universally, and depending of the degree of severity, five levels of ID are considered: a) borderline, b) mild, c) moderate, d) severe, and e) profound. Around 2% of the general population has ID of any degree, although about 75% is borderline to mild. Despite there are many known causes of ID, in almost half of the affected individuals no etiology can be ascertained. Genetic syndromes/diseases are an important cause of ID in children and genetic test should be performed to confirm the diagnosis and offer an accurate genetic counselling.

[VOLVER/ RETURN](#)

## Molecular networks in intellectual disability. Hans van Bokhoven

Intellectual disabilities (ID) comprise a highly diverse group of cognitive disorders. To date, mutations in some 500 genes have been associated with ID and this number is rapidly increasing driven by next generation sequencing



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

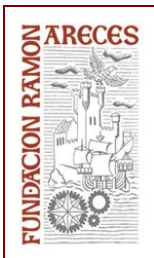
efforts. We are applying various exome sequencing strategies to identify novel gene mutations in X-linked, dominant and recessive cases of ID. These studies have revealed a wide variety DNA variants, which presents a challenge for identification of the true causative mutation. To establish causality, there is a need for standardized protocols for the collection, storage and exchange of genetic and clinical data across Genetic Centers. In addition, we perform in vitro and in vivo investigations of mutated genes to further substantiate causality of DNA variants and to provide mechanistic insight into underlying pathologies of ID.

While mutations in numerous genes give have been linked to ID, a more limited number of pathways is emerging whose disruption appears to be shared by groups of ID genes. Such common networks include Ras- and Rho-GTPase signaling, post-synaptic density proteins, and proteins acting as regulators of chromatin structure. I will provide an overview of our current research aims to gain more insight into mechanisms by which disruptions of these networks give rise to ID. In-depth knowledge about this network should allow the design of rational strategies to treat groups of ID disorder with different genetic etiologies, but that share a common disrupted molecular network.

[VOLVER/ RETURN](#)

Systematic analysis of the mammalian synaptic proteome uncovers its evolution and role in cognitive disorders. Alex Bayes

Genetic studies performed in the past few decades have identified an important number of genes causing Intellectual Disability (ID). Furthermore, next-generation sequencing technologies are uncovering new genes causing ID at a much rapid pace, and many more causal genes are likely to be identified in the near future. Therefore, we should soon be able to have a much deeper understanding of these disorders at the molecular level. In the past few years it has become clear that an important number of genes causing ID are found expressed at synapses, suggesting a key role of these neuronal structures in cognitive disorders. We have extensively studied the postsynaptic proteome of glutamatergic synapses in human and other animal species to scrutinize the



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

role of the postsynaptic proteome in disease. We have focused on two large protein complexes, the postsynaptic density (PSD) and the MAGUK-associated signalling complex (MASC), to experimentally prove that indeed these molecular machines are particularly relevant to many forms of ID. Our work suggests that a detailed understanding of the synaptic molecular pathophysiology in the context of ID can provide important insight on these disorders. Finally, the molecular evolution analysis we have performed on the postsynaptic proteome have discovered that it presents a very high level of conservation, further supporting the central role of this molecular machinery in health and disease.

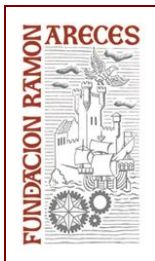
[VOLVER/ RETURN](#)

#### Intellectual disability and autism: the role of rare genetic variants. Bru Cormand

Autism spectrum disorders (ASD) are severe neurodevelopmental disorders characterized by impaired verbal communication, limited reciprocal interaction, restricted interests and repetitive behavior. Although they are among the most heritable neuropsychiatric disorders, the underlying genetic factors remain largely unknown. In some cases, autism presents with intellectual disability (ID), whereas in others (High Functioning Autism) the intellectual quotient is normal.

Our work focuses on rare genetic variants that have been inspected in ASD and ID through whole-exome sequencing (WES) and also by deep screening of specific candidate genes. The results indicate that rare truncating variants may have a major role in the etiology of ASD and their frequency in individuals with this psychiatric condition correlates with the degree of intellectual disability.

[VOLVER/ RETURN](#)



**Simpósio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

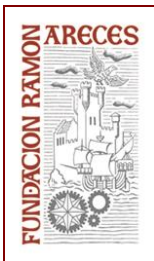
## Intellectual Disability and arrayCGH. Laia Rodriguez

Genome-wide copy-number detection using microarray testing became to be an indispensable genetic analysis in the diagnosis of idiopathic developmental delay/intellectual disability and autism spectrum disorders. Guidelines for molecular karyotyping in constitutional genetic diagnosis have been already published and a consensus statement has been achieved becoming the chromosomal microarray analysis as the first-tier test for clinical diagnosis of individuals with developmental disabilities, congenital anomalies and autism spectrum disorders. The frequency with which chromosome abnormalities and/or genomic rearrangements are detected by using this technique mainly depends on the patient inclusion clinical criteria and the microarray design. Detection rates are much higher in patients with developmental delay/intellectual disability that also present malformations or dysmorphic features and more severe retardation. On the other hand, most current clinical chromosomal microarray analysis platforms can detect copy number changes with a lower limit of resolution of ~400 kb throughout the genome, representing a  $\geq 10$ -fold improvement in resolution in comparison to G-banded karyotyping. This level of resolution provides a broad genomic survey and reliably identifies all known recurrent microdeletion and microduplication syndromes mediated by segmental duplication architecture and most nonrecurrent pathogenic imbalances that are unequivocally pathogenic.

[VOLVER/ RETURN](#)

## Genetic Investigation for adults with intellectual disability. Lucy Raymon

Intellect is normally distributed around an IQ ~100 in the population. At the extreme low end of the IQ range it is associated with diseases that have a high genetic abnormality rate. The recurrence risks of 5-10% in males and 3-4% in females are composite empiric figures that reflect a combination of i) de novo rate of pathogenic CNVs ii) de novo autosomal dominant rates of reproductive lethal genes iii) the presence of high penetrant X-linked recessive alleles in



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

*Barcelona, October 3-4, 2013*

males and iv) increased penetrance of abnormal variants in males compared to females.

The talk will discuss current methods of detecting the cause of disease and present a diagnostic pathway. Examples will be discussed from adult cases and specific syndromes presented.

[VOLVER/ RETURN](#)

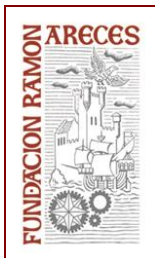
#### Phenotypic Variability of Genomic Disorders and Rare Copy-Number Variants. Hilde van Esch

During the past 8 years, copy number variation (CNV) has emerged as a highly prevalent form of genomic variation. These CNVs account both for normal variation between individuals, but also variations that are associated with certain medical conditions or genomic disorders (large CNVs involving different genes). Some of these CNVs are recurrent, while others are unique or very rare. With increasing resolution of array platforms, even very small CNVs (< 1kb) are nowadays detected, and correct interpretation remains a challenge, especially in a clinical setting.

Some CNVs are associated with a quite consistent core-phenotype (e.g. Williams-Beuren syndrome), while for other CNVs a high phenotypic variability is observed, or even more, they are also detected in the normal population.

In this talk, we will focus on some of the more rare CNVs and discuss the genotype-phenotype relationship and the associated phenotypic variability. We will give examples on how this knowledge can be implemented in pre- and post-natal genetic counselling.

[VOLVER/ RETURN](#)



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

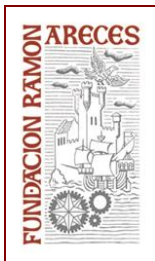
Use of array CGH in prenatal diagnosis: main clinical indications and clinically significant genomic alterations. Eugene Pergament

There are three main clinical indications for the application of array CGH in prenatal diagnosis: 1) Increased nuchal translucency, which has been associated with an increased risk for chromosome abnormalities, both numerically and structurally, for cardiac malformations, and for a series of developmental syndromes in which normal integration of major organ systems fails; 2) The presence of a structural abnormality identified by ultrasound, involving single or multiple organ systems, e.g., the central nervous; and, 3) Any pregnancy undergoing diagnostic testing, even with a normal karyotype after conventional chromosome analysis. Specific examples will be cited.

There are multiple challenges and unresolved issues in the routine application of array CGH in prenatal diagnosis: 1) Distinguishing pathogenic versus benign imbalances in copy number variations, which at present requires considerable subjective judgment; 2) Using currently available datasets, the appropriate interpretation of array CGH in prenatal diagnosis with respect to intellectual function and neurocognitive impairment, specifically, autism; 3) The growing but unsettled, data regarding specific copy number variants and the capacity of array CGH in the prenatal period to anticipate intellectual and neurocognitive impairment and risk of dysfunctional behavior; 4) The need to evaluate the educational, counseling and psychosocial implications of microarray testing as it is introduced as a standard prenatal diagnostic procedure and analysis, particularly as the focus is anticipated to shift from identifying established syndromes centered on physical development to functional deficiencies associated with intellectual and behavioral disabilities; and 5) the introduction of array CGH to discriminate intellectual capacities by means of non-invasive prenatal testing technologies.

[VOLVER/ RETURN](#)





**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

## Validation of ArrayCGH and Next Generation Sequencing for Diagnosis in Preimplantation Genetic Diagnosis. Harvey Stern

PGD was first offered clinically by Handyside and colleagues in 1990 for the detection of Y-chromosome sequences in embryos from a woman who carried the X-linked disorder ornithine transcarbamylase deficiency. Since then, PGD has been employed as a prenatal diagnostic test for a wide range of genetic disorders, chromosome rearrangements and aneuploidy testing to improve the outcome of IVF. More sophisticated molecular technologies are currently being used in PGD analysis including chromosome microarrays and Next Generation Sequencing (NGS). This lecture will look at the current state of PGD for detection of genetic disorders and chromosome aneuploidy. With the introduction of NGS based PGD there is the potential for a more accurate method to access for the presence of chromosome aneuploidy along with sequence level detection of genomic alterations. It is probable that NGS technology will be used to determine the chromosome status of embryos along with selected microdeletions or CNVs with strong disease association. Ethical issues exist about the potential of this technology to be used to create “designer babies”.

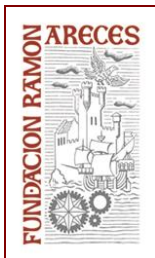
[VOLVER/ RETURN](#)

Identification of novel intellectual disability genes by exome sequencing. Xavier Estivill<sup>1</sup>, Laura Domènech<sup>1</sup>, Oliver Drechsel<sup>2</sup>, Anna Puig<sup>1</sup>, Maja Gehre<sup>1</sup>, Stephan Ossowski<sup>2</sup>, Irene Madrigal<sup>3</sup>, Marina Viñas<sup>4</sup>, Montse Milà<sup>3</sup>, Miriam Guitart<sup>2</sup>, Raquel Rabionet<sup>1</sup>

<sup>1</sup>Centre Genomic Regulation (CRG), UPF, and CIBERESP, Barcelona; <sup>2</sup>Centre for Genomic Regulation (CRG) and UPF, Barcelona, <sup>3</sup>Servei de Genètica, Hospital Clínic de Barcelona, Barcelona; <sup>4</sup>Laboratori Genètica, UDIAT-Centre Diagnòstic, Corporació Sanitària Parc Taulí, Sabadell, Catalonia, Spain

Intellectual disability (ID) is a genetically heterogeneous disorder affecting 1-3% of population. About 30% of cases of ID can be explained by structural variants, and more than 100 genes have been implicated in its pathophysiology. Nevertheless, a large proportion of cases remain unexplained. A recent study has shown that *de novo* point mutations are a frequent cause of ID, which





**Simpósio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

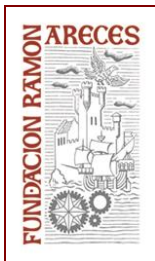
Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

would make next generation sequencing technologies (NGS) extremely powerful to identify rare *de novo* genetic causes of ID. We recruited 33 trio cases and 6 sibling pairs affected with idiopathic ID, all of them negative for the fragile X expansion and without cytogenetically visible abnormalities. Exome sequencing was performed in the trio samples and non-synonymous variants present in the cases were selected and filtered based on their frequency in known databases. Then, *de novo* variants were identified, as well as potential X-linked or recessive genes (carrying homozygous or compound heterozygous variants in the case), their functionality score was predicted (Condel), and they were annotated against a list of known ID-related genes. Novel variants were also filtered for their presence in an in-house database of exomic data. We detected an average of 8,520 non-synonymous variants in the cases, of which an average of 27 were considered *de novo*. Frequency and functionality based filtering reduced the number of potential candidate ID genes harboring *de novo* variants to 0-10 per case. The presence and *de novo* state of the identified candidate variants was confirmed by Sanger sequencing. In four cases we confirmed the presence of a *de novo* variant in previously described ID genes, and in seven additional families, nine genes with damaging *de novo* variants were considered as potential novel ID genes. In three cases, we detected mutations that would lead to known ID syndromes. Three male cases carried X-linked variants in known ID genes and two cases were homozygous or compound heterozygous for rare potentially damaging variants in ID genes. In six cases we identified X-linked (2) or recessive (3) candidate novel ID genes, one X-linked gene was mutated in two families. Of the 14 potential novel ID genes, 11 have functions related with neurite outgrowth, gene silencing or epigenetic control of gene expression, making them good candidates for novel ID genes. Further evidence for their involvement in ID is obtained by analysis of interaction networks, brain expression analysis, and targeted resequencing in additional isolated ID cases.

Supported by European Commission projects (Geuvadis, ESGI and Techgene).

[VOLVER/ RETURN](#)



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

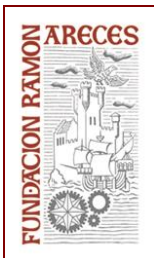
Exome and massively parallel targeted resequencing identifies a spectrum of genes recurrently mutated across developmental disorders. Brian O'Roak

The genetic intractability of complex genetic heterogeneous disorders, such as autism spectrum disorder (ASD), intellectual disability (ID), and broadly defined developmental delay, has been challenged in recent years; first by the application of genomewide platforms to detect copy number and more recently sequencing of the entire protein-coding genome (aka exome). Recent exome sequencing studies of families with simplex or “sporadic” ASD and ID has highlighted the importance of *de novo* mutations and led to the discovery of novel candidate genes. However, most genes are only disrupted once. To address the problem of locus heterogeneity, we have optimized an ultra-low-cost (amortized reagent costs <\$1/sample/gene) resequencing method based on modified molecular inversion probes (MIPs) and a statistical framework for evaluating the likelihood of recurrent mutations at individual genes (O’Roak *et al.*, *Science*, 2012). We extended this paradigm further by screening 64 genes (202 kilobases/sample) in >4,000 ASD probands and >2,200 unaffected siblings. These candidate genes were selected based on *de novo* mutations discovered in the exomes of 1,100 probands with ASD or ID. Preliminary results show severe mutations in ~3% of ASD probands and implicate several novel risk loci. Our data strongly support a major role for recurrently disrupted genes in sporadic ASD many of which span diagnostic boundaries, such as ID and epilepsy, and provide a model for discovering and rigorously validating bona fide genetic risk loci for sporadic, genetically heterogeneous neurodevelopmental disorders

[VOLVER/ RETURN](#)

Animal Models. Yolanda de Diego

Animal models are important tools in the discovery and development of treatments for rare diseases, particularly given the small populations of patients in which to evaluate therapeutic candidates. We will provide a compilation of



**Simpósio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

mammalian animal models for orphan-designated conditions based on information gathered from a review of the literature. We will discuss the predictive value of the models and their advantages and limitations with the aim of highlighting those that are appropriate for the preclinical evaluation of novel therapies, thereby facilitating further drug development for rare diseases. An specific example of translational research on rare disorders will be explained related to our experience on a mouse model for the fragile X syndrome.

[VOLVER/ RETURN](#)

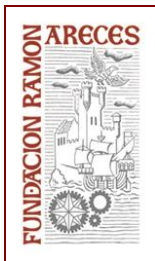
Normalization of DYRK1A to improve cognitive performance in Down syndrome subjects: the TESDAD study. Rafael de la Torre

DYRK1A (Dual specificity tyrosine-phosphorylation-regulated kinase 1A) is one of the major candidate genes for Down syndrome. Its triplication in transgenic mice is sufficient to recapitulate most of the DS cognitive phenotype. In fact, normalization of DYRK1A activity reverses the cognitive impairment in trisomic and transgenic mice. EGCG is an inhibitor of DYRK1A that we have tested in Ts65Dn and TgDyrk1A leading to phenotype rescue.

We present a phase II clinical trial (TESDAD) assessing the efficacy of EGCG combined with cognitive stimulation in improving cognitive performance in DS patients.

86 (44 males and 42 females) DS subjects aged 17-34 y (mean 23.4 y) were randomly divided into two treatments: placebo or a green tea extract (200mg EGCG per capsule, 7-10 g/kg dose b.i.d, p.o.). All randomized subjects entered in a standardized cognitive stimulation program (2-3 times per week one hour session) delivered through a telematics platform ([www.feskits.com](http://www.feskits.com)).

Subjects were evaluated with a battery of cognitive tests as well as several biomarkers were tested based on their relationship with the pathogenesis of DS cognitive impairment and on the treatment (EGCG) targets. The cognitive battery was administered and biomarkers were analyzed at baseline, and after 3, 6 and 12 months of treatment. A subgroup of 24 subjects additionally were explored with neuroimaging (fMRI) and neurophysiological (TMS) techniques. Subjects will be asked after one year of treatment to discontinue it for a further evaluation 6 months later to evaluate the sustainability of treatment benefits. The study is in its last phases and results should be available by the end of



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

*Barcelona, October 3-4, 2013*

2013. It is expected that encouraging preliminary results obtained in a previous pilot study will be confirmed in the ongoing one.

This work was supported by Fondation Jérôme Lejeune, Fondo de Investigaciones

Sanitarias-ISCIII PI11/00744, Spanish Ministry of Economy (SAF2010-16427), ERare-EU/FIS PS09102673, 2009SGR1313, CIBERER and CIBEROBN

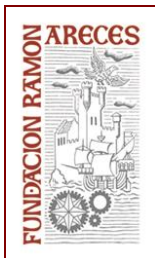
[VOLVER/ RETURN](#)

### Clinical trial in Fragile X Syndrome. Ernest Balaguer

Currently several drugs are being tested and in the treatment of patients with fragile X syndrome, both pediatric age and adult age. In the last years, the number of ongoing clinical trials in this pathology is increasing. So, in the official web “www.clinical trials.org” we can access to data of 47 clinical trials, majority of them active in September 2013.

We can observe in this web 3 highlighted drugs: the so named Mavoglurant (AFQ056, Novartis), Arbaclofen (STX209) and STX107 (both of Seaside Therapeutics) and finally RO4917523 (Roche). These drugs have similarities in their mechanisms of action. They can produce a negative allosteric modulation of metabotropic receptor of Glutamate (mGluR5), in order to normalize excessive protein synthesis related to neurotransmitter disorder in X fragile syndrome.

Mavoglurant is evaluated in 6 clinical trials (phase I & phase II studies) seeking to evaluate its efficacy and safety. This allosteric modulator receptor of metabotropic receptor, mGluR5, has been administered in pediatric and adult population, including ages from 3 years to 55 years old. Primary and secondary outcomes include to compare changes, from basal to final evaluation, in several neuropsychological scales, including autism rating, CGI changes and other abnormal motor behavior scoring, with a prominent role of the caregiver's impression. Doses ranged from 25 mg to 100 mg, twice a day, with a good tolerance.



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

Arbaclofen (STX209, a GABA-B agonist) could correct inhibitor deficit of neurotransmission and also obtain an additional improvement by indirect reduction of the activation in mGluR5 pathway. In 4 clinical trials (phase II and III) investigators are evaluating safety and efficacy in adolescents and in adults, by comparing changes in irritability scores and social withdrawal. This studies include both core and open label protocols, and they are also evaluating biomarkers. STX107 is a potent and selective mGluR5 antagonist and acts only in this way, like negative allosteric modulator of mGluR5. A phase I study has been performed to evaluate safety and tolerability of single oral doses of STX107, administered via an oral suspension.

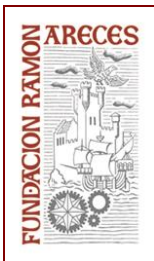
There are 3 clinical trial (phase II) with another inhibitor of mGluR5, named RO4917523. This drug is evaluated in pediatric and in adult patients (from 14 to 50 years old) to compare, also in a placebo-control study, its safety and efficacy, including changes in anxiety, depression and mood scales, and other secondary outcome measures. Oral doses (0.5 mg to 1.5 mg) were administered only once a day, during 12 weeks

Other experimental drugs, evaluated in ongoing clinical trials, include Ampalex (CX-516, positive allosteric modulator of glutamatergic AMPA receptors), and Ganaxoxone (CCD-1042, neuroactive steroid also positive allosteric modulator GABA-A). In the other hand, some drugs, marketed for other indications, have been tested in X fragile Syndronme, like Acamprosate, Sertraline, Minocycline, Donepezil, Aripiprazole, Oxytocin, Memantine and antioxidants (vitamins C and E).

Finally there are other clinical trials in biochemical aspects, gynecological disorders (premature ovaric failure) and response to diet and vitamins.

We can highlight the notable efforts to demonstrate the efficacy and safety of antiglutamatergics drugs in several clinical trials (1). Our Clinical Trials Unit is working on these lines of clinical research in the past 2 years, in both adult and pediatric population, with a strong cooperation with neuropsychiatry, genetists and patients associations.

[VOLVER/ RETURN](#)



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** *Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies*

Barcelona, 3 y 4 de octubre de 2013

*Barcelona, October 3-4, 2013*

Ethical aspects of the use of next-generation sequencing technologies and research involving vulnerable subjects. Teresa Pampols

In the context of intellectual disability research, there are two issues, which deserve special mention:

1. The ethical complexity raised by use of next-generation or massive parallel sequencing technology that expands duties of researchers concerning the return of findings to research participants.
2. The involvement of children and people with diminished decision making capacity, likely to be vulnerable to coercion or undue influence, and the specific aspects on the return of individual research findings in paediatric genomic research.

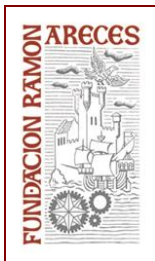
These issues involve duties of researchers and the protection of rights of participants and are concerned by the four relevant ethical principles in medicine: Respect for the autonomy of persons; Beneficence; Non-maleficence and Justice (Wertz Dc et al. 2003)

1. Exists an ethical duty to return individual genetic research subject to the existence of proof of validity, significance and benefit ( Knoppers BM et al 2006), that is supported by the principles of justice, beneficence and respect for persons. For a review of international norms covering both general and individual return of research results see Lévesque E et al 2011.

In genomic research, currently there is an important debate on the return of individual findings to research participants and if so, *under what criteria, to whom, when, how and by whom*, genomic information should be disclosed to individual participants and their families (Zawati MH et al. 2011) (Bush LW and Rothemberg KH 2012)

The data sought for the researchers to answer their research hypothesis includes results related to the original question for which genomic study was





**Simpósio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

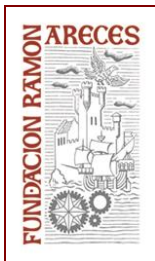
indicated but also a lot of “incidental information”. *The management of these incidental findings is a central question in the genomic research context.*

Incidental finding is “a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study” (Zawati MH et al. 2011).

Incidental findings are endemic to human research involving humans, and incidental or unexpected findings are consubstantial with genetic research and clinical practice, but probability of incidental findings increases proportionately with information collected and genomic research has increased exponentially the possibility of discovering incidental findings. Multiple abnormal genomic findings are analogous to the “incidentalomas” that are often discovered in radiological studies, physicians can be overwhelmed by its complexity, patients could be subjected to unnecessary follow up tests and the costs of genomic medicine will increase substantially with little benefit for patients or physicians, thus throwing into question the overall societal benefit of genome based medicine (Kohane IS et al. 2006). False positive incidental findings are of particular clinical concern: Erroneous annotations in the databases, limited accuracy of *in silico* prediction tools for missense variants, sequencing errors, incorrect penetrance estimates and multiple hypotheses testing across millions of variants, are main sources of false positive, providing misleading or incorrect diagnostic or prognostic information with clear and imminent potential of harm (Kohane IS et al 2012) (Green RC et al. 2012).

Currently the literature addresses three types of incidental findings: *Findings with strong net benefit* that researcher should disclose to research participants unless the latter have chosen not to know (non-disclosure has associated a potential risk of harm that should also be considered). *Findings with possible net benefit* or non-fatal conditions that are likely to be grave or serious but that cannot be ameliorated or avoided, letting the decision to disclose to discretion of the researcher and *Findings with unlikely net benefit*, that means a condition that is unlikely to be of serious health or reproductive significance, recommending a no disclosure policy (Wolf SM 2008)

(Zawati MH et al. 2011). Bearing in mind that providing health related information might be more credible when coming from a health professional (physician, genetic counsellor); researchers should to direct participants to a qualified professionals when necessary. For a review of international norms on



**Simpósio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

incidental findings in genomic research, including Spain's Law 14/2007, of 3 July, on Biomedical research see Zawati et al. 2011

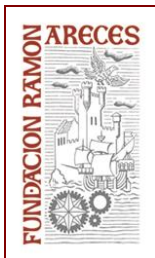
Other relevant issues are the *disclosure of results to health people*. The fact that depending of the development of the tools and resources for genomic interpretation a *genome sequence can be interpreted and used over the lifetime of the patient* (Biesecker L 2012). The *increasingly unrealistic total protection of privacy* in an era in which direct-to-consumer genetic testing is offered in internet, with an active genetic social networking; the specific requirement of population genome research with sharing of databases and the bioinformatics possibilities of re-identification, that raises *the necessity of an international code of conduct for data shearing*, establishing principles and procedures: Quality. Accessibility. Responsibility. Security. Transparency. Accountability and Integrity (Knoppers BA et al. 2011).

*Informed consent is a key step* in any research project as well as in the clinical setting

(Pampols T et al. 2012) and preparation of informed consent for whole-genome sequencing all these question must be carefully considered ( Ayuso C et al. Eur J Hum Genet 2013).The National Institute for Health of US Department of Health and Human Services is a very useful resource for the preparation of informed consent for genomic research (<http://www.genome.gov>)

In summary with the use of genomic technologies we are seeing an unprecedented expansion of researcher's "duties" and it is very important to develop guidelines for a proportionated approach to the responsibilities of stakeholders (Zavati MH et al. 2011)

2. There are specific international regulations directed to *protect rights of research participants and limit to enrol children and other vulnerable subjects in research studies*: Direct benefit, minimal risk, or minor increase overall minimal risks, reasonable relationship between risk and anticipated benefits, the participation in the informed consent process according to the degree of comprehension. *The use of genomic technologies raises specific issues on preserving research participant wishes or autonomy, disclosing results and communication of incidental findings* (Hens K et al 2011)( Groisman J et al.



**Simposio Internacional:** Discapacidad intelectual: desafíos diagnósticos en los array de CGH y la secuenciación de nueva generación

**International Symposium:** Intellectual disabilities: diagnostic challenges in array CGH and next generation sequencing studies

Barcelona, 3 y 4 de octubre de 2013

Barcelona, October 3-4, 2013

2012) (Wilfond B and Carpenter KJ ) . When the participant is a child, *the triadic relationship between the researcher, child participant and parent makes considerations more complicated. Biobanking* is not a specific issue to be discussed in this talk, nevertheless it deserves to be mentioned that the storage of samples in a biobank is often associated to genomic research projects and paediatric biobanks has also specific requirements: *Children have right to an open future* and parents do not have the right to access any genetic data that a biobank holds on their children ( Hens K et al.2011). *The scope of parental consent is limited* and young adults have the right to decide on the fate of their samples when they reach the age of maturity. Research and science are not completely value-free and *children should be given the opportunity to express their values* also in this respect (Hens K et al 2011). Of course mentally retarded children cannot express on these aspects but they apply to the healthy family related children or young people often also included in the research project.

[VOLVER/ RETURN](#)

\*Todos los derechos de propiedad intelectual son del autor. Queda prohibida la reproducción total o parcial de la obra sin autorización expresa del autor.

© FUNDACIÓN RAMÓN ARECES. Todos los derechos reservados.

\*All intellectual property rights belong to the author. Total or partial reproduction of the work without express permission of the author is forbidden. © FUNDACIÓN RAMÓN ARECES. All rights reserved.