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Molecular Genetics of Intellectual Disability

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1. Introduction

The goal of this chapter is to review the current knowledge of the genetic causes of intellectual disability, focusing on alterations at the chromosomal and single gene level, with particular mention to the new technological developments, including array technologies and next-generation sequencing, which allowed an enormous increase in yield from genetic studies. The cellular and physiological pathways that seem to be most affected in intellectual disability will also be addressed. Finally, a brief analysis of the contribution of the genetically modified animal models for the study of the pathogenesis of intellectual disability and for the development and testing of novel therapeutic approaches, with unexpectedly good results, previously thought to be impossible to achieve. The chapter will close with some considerations on the relevance and future perspectives of genetic testing in patients with intellectual disability.

2. Intellectual disability – definition and classification

Intellectual disability is one of the most frequent and disabling neurological impairments in school-age children, with an estimated prevalence of 1.5-2% in Western countries (Leonard and Wen, 2002). In developing countries it tends to be even more frequent, due to environmental factors such as poor health care and malnutrition, among others (Durkin, 2002). The diagnosis of intellectual disability is built upon three main criteria: I) significant sub-average general intellectual functioning; II) limitations in adaptive behaviour in at least 2 of the following skills: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety; III) onset of the symptoms before 18 years of age (Salvador-Carulla et al., 2008). According to the International Classification of Disease, intellectual disability is defined as a “condition of arrested or incomplete development of the mind, which is specially characterized by impairment of skills manifested during the developmental period, skills which contribute to the overall level of intelligence, i.e. cognition, language, motor and social abilities” (World Health Organization, 2007). The classification of intellectual disability is mostly based on the measurements of Intellectual Quotient (IQ) tests. In the general population IQ is normally distributed with a mean at approximately 100. It is accepted that when an individual

presents an IQ lower than 70, this person is classified as intellectually handicapped. The severity of intellectual disability can be divided into mild (IQ between 50 and 69), moderate (IQ of 35-49), severe (IQ of 20-34) and profound intellectual disability (IQ lower than 20) (Salvador-Carulla et al., 2008). Severe to profound intellectual disability has an estimated prevalence of 0.3-0.5% (Leonard and Wen, 2002).

Conventionally, and from a clinical perspective, intellectual disability may be subdivided into two major categories - syndromic, characterized by associated clinical, radiological, metabolic or biological features, and non-syndromic forms of intellectual disability in which the cognitive impairment represents the only manifestation of the disease. This distinction is very useful from the clinical perspective, although some studies have shown that the boundaries between syndromic and non-syndromic forms are not strict. Several genes have been identified that are associated with both types of phenotypic presentation (Frints et al., 2002). Although this may be an artificial classification, for discussion purposes some researchers have also defined three major groups of intellectual disability associated disorders: metabolic syndromes, syndromes with intellectual disability and associated malformations/dysmorphisms and syndromes with intellectual disability and neurological/neuromuscular symptoms (Chiurazzi et al., 2008).

3. Metabolic causes of intellectual disability

Metabolic disorders or inborn errors of metabolism (IEM) designate a wide group of diseases caused by genetic defects leading to alterations of metabolism. These are estimated to be responsible for 1- 5% of non-syndromic intellectual disability (García-Cazorla et al., 2009). The majority arise from mutations in single genes that code for enzymes, resulting in abnormal or reduced enzyme activity. As a consequence, some undegraded substrates may accumulate and built up to toxic levels. It can also occur that some compounds that are required for normal cellular metabolism cannot be produced. As with many genetic conditions, inborn errors of metabolism are individually rare but as a group can reach an incidence of 1:4000 (Applegarth et al., 2000).

Although intellectual disability is a common theme in metabolic disorders, very few present intellectual disability as the only clinical feature. Other neurological findings such as regression, ataxia, seizures, movement disorders or behavioural problems are usually present, as well as other organ related symptoms. Taking into consideration what is currently known about intellectual disability related genes, it is accepted that intellectual disability can stem from two broad mechanistic themes: dysfunction of neurodevelopmental programs and alterations in synaptic organization and plasticity (Vaillend et al., 2008; Kramer and van Bokhoven, 2009). Metabolic alterations present in metabolic disorders can theoretically affect both mechanisms, depending on the age at which the toxicity/deficiency begins to manifest (prenatal, early or late infancy, adolescence), and the specific defect itself (energy deficiency, storage disorders). For instance, diseases of energy availability, such as creatine and glucose transport deficits, are associated with mild/moderate intellectual disability. On the other hand, altered production of neurotransmitters in glycine, serine and biogenic amine disorders, is usually associated with severe mental and motor deficits (García-Cazorla et al., 2009). In inborn errors of metabolism leading to storage of toxic compounds, such as urea cycle disorders, organic acidurias, or lysosomal storage disorders, the level and duration of

exposure to toxic agents can dictate different degrees of mental disability. The most common inborn error of metabolism associated with intellectual disability is Phenylketonuria (PKU), with an average worldwide estimated prevalence of 1:10000 (Hardelid et al., 2008). Phenylketonuria results from deficient activity of the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine (Kahler and Fahey, 2003). Other less common disorders include deficiency of the creatine transporter SLC6A8 (Salomons et al., 2001) and mutations involving the thyroid hormone transporter MCT8 (Dumitrescu et al., 2004) and the *ATP7A* gene, which is implicated in occipital horn syndrome, a mild variant of Menkes syndrome (OMIM 309400) (Tümer et al., 1999).

4. Chromosomal rearrangements in intellectual disability: From classic syndromes to the discovery of new microdeletions and microduplications

Chromosomal aberrations can be numeric or structural. Numeric aberration can stem from the loss/gain of an entire chromosome (leading to the monosomy or trisomy) or of the whole chromosome complement (given rise to triploidy and tetraploidy). In general, the absence of a chromosome is far more drastic than its excess. These consequences are not the same for autosomal and sexual chromosomes since the absence of an entire autosomal chromosome is not compatible with life whereas the same alteration in a sexual chromosome may result in a live born female (e.g. 45,X - Turner syndrome). Structural variation is a term used to describe all types of genomic rearrangements, including deletions, duplications, insertions, inversions, translocations, loss of heterozygosity and more complex alterations. Structural abnormalities are a consequence of double-strand breaks and inappropriate DNA repair. The most common form of structural variation in the genome are copy number variations - CNVs.

4.1 Classic syndromes

Classic syndromes are usually associated with chromosomal abnormalities and large structural variations, since this type of alterations is far more likely to lead to additional phenotypic presentations other than intellectual disability alone. Moreover, from a historical perspective, classical cytogenetic methodologies (karyotyping, fluorescent *in situ* hybridization) are poorly suited for the detection of very small alterations. The most common single cause of intellectual disability is Down syndrome (trisomy 21; OMIM 190685), with an estimated prevalence of 1:750-1:800 and described for the first time in 1866, by J. Langdon Down (Down, 1995). In addition to mental impairment, Down syndrome patients may present other phenotypic characteristics such as the easily recognizable facial appearance, congenital malformations, hearing loss and early onset Alzheimer's disease (Epstein, 2001). The identification by Jérôme Lejeune of trisomy of chromosome 21 as the cause of this syndrome opened the way to genetics studies and genotype-phenotype correlations in patients with intellectual disability. Although other alterations are far less common than trisomy 21, cytogenetically visible chromosomal alterations are estimated to account for up to 15% of intellectual disability cases (Leonard and Wen, 2002). Other well-known syndromes with recognizable clinical features include: Prader-Willi, Angelman, Smith-Magenis, Miller-Dieker and DiGeorge (Ropers, 2010). Table 1 summarizes some examples of syndromes and chromosomal alterations associated with intellectual disability.

Syndrome	Chromosomal abnormality	OMIM	Clinical hallmarks
Down	trisomy 21	190685	Intellectual disability and characteristic facies, congenital malformations of the heart (30-40%), significant hearing loss (90%), early onset Alzheimer disease
Prader-Willi	del15q11-q13	176270	Diminished fetal activity, obesity, muscular hypotonia, intellectual disability, short stature, hypogonadotropic hypogonadism, and small hands and feet
Angelman	del15q11-q13	105830	Intellectual disability, movement or balance disorder, characteristic abnormal behaviours, and severe limitations in speech and language
Smith-Magenis	del17p11.2	182290	Brachycephaly, midface hypoplasia, prognathism, hoarse voice, speech delay with or without hearing loss, psychomotor and growth retardation, and behavioral problems
Miller-Dieker	del17p13.3	247200	Classic lissencephaly, microcephaly, cardiac malformations, hypoplastic male external genitalia, growth retardation, and intellectual disability with seizures
DiGeorge	del22q11.2	18840	Neonatal hypocalcemia, susceptibility to infection, cardiac malformations, micrognathia may be present, low set ears, short philtrum, small mouth, short stature, variable mild to moderate learning difficulties
Edwards	trisomy 18	-	Kidney malformations, structural heart defects at birth, intestines protruding outside the body, esophageal atresia, intellectual disability, developmental delay, growth deficiency, microcephaly, micrognathia, cleft lip/cleft palate, upturned nose, narrow eyelid folds, drooping of the upper eyelids clenched hands
Williams-Beuren	del7q11.23	194050	Supravalvular aortic stenosis, intellectual disability, and distinctive facial features: „elfin face“

Table 1. Examples of syndromes and chromosomal alterations associated with intellectual disability.

4.2 New microdeletion and microduplication syndromes

For many years, genomic DNA copy-number variants (CNVs) such as deletions and duplications were assumed to be few and to have limited impact on the total content of human genetic variation. With the development and improvement of genome-wide analysis tools to study the genome, such as array comparative genomic hybridization (see below), it has been shown that copy-number variants are relatively frequent, spread throughout the genome and represent a very significant source of genetic variation in human populations. As of now, thousands of heritable copy number variations have been identified, in regions of potential variability corresponding to 14.3% of the human genome (Li et al., 2009). These are often sporadic and caused by *de novo* rearrangements. It is accepted that these types of variations can occur at a 1000 to 10,000 higher frequency than point mutations (Kumar, 2008). Although copy-number variants occur at similar frequencies between populations, several significant differences in the frequency of some CNVs were found between different populations in the world, suggesting that variations in the genomic architecture account not only for disease, but also for ethnic differences and selective evolution (Li et al., 2009). The developments in array comparative genomic hybridization technologies allowed genome-wide studies in patients with intellectual disability, and as a consequence, the rate of discovery of new microdeletion and microduplication syndromes has substantially increased. For instance, several studies were able to identify new pathogenic copy-number variants in up to 15% of patients with non-syndromic intellectual disability and normal karyotype (Friedman et al., 2006; Koolen et al., 2009; Jaillard et al., 2010). A current search on the DECIPHER database of submicroscopic chromosomal imbalance (<http://decipher.sanger.ac.uk/>) yields 46 entries/syndromes with intellectual disability. Some of these copy-number variants are surprisingly common, such as the microdeletion in the 1p36.1 region, found in 1% of non-syndromic patients (Battaglia et al., 2008).

4.3 Array comparative genomic hybridization technology

Microarray technology was developed more than a decade ago and has now become a routine tool in genetic research. This methodology was first used in the Clinical Genetics field for the analysis of copy-number variants in all human telomeres in patients with intellectual disability. Since then, array comparative genomic hybridization (aCGH) has been adopted by hundreds of genetic laboratories, using platforms that now target the entire genome (Heller, 2002).

In an aCGH experiment, DNA from a test sample (e.g. patient with intellectual disability) and a reference DNA (healthy individual) are labelled with different fluorescent dyes and hybridized with DNA probes that can represent either regions or the entire genome. These arrays are generally performed on glass slides, silicon or plastic substrates and can contain hundreds to many thousands of probes. The construction of the array slides involves the physical immobilization of previously selected and synthetically generated probes onto specific sites of the solid support (Ylstra et al., 2006). As reference and test samples are labelled with different fluorophores, hybridization with genomic probes will result in distinct fluorophore intensity for test and reference DNA. It is this fluorescence ratio that translates the amount/type of copy number variation present in the sample.

The majority of aCGH data available today in public databases and published articles originated from studies using Bacterial Artificial Clone-based CGH (BAC arrays). BAC probes vary from 150 to 200 Kb and require high amounts of DNA for hybridization, having been superseded by oligonucleotide-based arrays (oligo arrays), which are considered to have large advantages over the BAC arrays. These platforms are characterized by single-stranded oligonucleotides (25 to 85 bp in length) attached to the array slide, allowing the detection and analysis of copy-number variation with a much higher resolution (Neill et al., 2010). The development of the aCGH platforms has led to an important increase in the detection of copy number variations. The spatial resolution of the array is determined by the sensitivity, the number, the chromosomal distribution and the length of the probes in the array. As such, platforms with shorter probes will allow more probes in the same space, leading to higher resolution. With the increasing awareness of the impact of copy number variations in disease and the growing number of international databases and population studies regarding pathogenic and non-pathogenic variations, these higher resolution platforms are now widespread and used in routine procedures. aCGH is currently the recommended approach for diagnosis of intellectual disability by international guidelines and is already used as a first-tier test in the USA and several European countries (Li and Andersson, 2009). The successful implementation and use of aCGH technologies requires the use of techniques for synthesis and spotting of the probes in the most effective locations, detection of hybridized samples and many statistical methods and informatic analysis of the resulting data. The informatic analysis usually requires the detection of the ratio of the signal generated at each probe location in the test and control sample. Several bioinformatic tools have been developed and are now available to transform the complex aCGH data and artefacts into useful information (van de Wiel et al., 2009; van Wieringen et al., 2007; Gai et al., 2010).

5. Monogenic forms of intellectual disability: X-linked and autosomal

5.1 X-linked intellectual disability

X-linked intellectual disability (XLID), although a heterogeneous group, is perhaps the most widely studied form of intellectual disability. This is mostly due to the fact that the X-linked mode of inheritance is easy to identify and also because, although the human X-chromosome only harbours about 4% of the protein coding genes of the human genome, X-chromosomal defects are estimated to account for approximately 10% of the intellectual disability seen in males (Ropers and Hamel, 2005). In fact, the use of target sets of XLID or simply X-chromosome genes to screen for new X-linked intellectual disability mutations or genes in undiagnosed patients has proved to be an effective approach (de Brouwer et al., 2007; Tarpey et al., 2007). To date more than 90 genes have been associated with XLID, either syndromic, non-syndromic forms of intellectual disability or both. For instance, mutations in the *ARX* gene, the second most common cause of X-linked intellectual disability (after *FMR1*/Fragile X) can be associated with both syndromic and non-syndromic intellectual disability (Gécz et al., 2006).

The most common form of X-linked intellectual disability, and also “overall” monogenic intellectual disability, is the Fragile-X syndrome which is estimated to affect up to approximately 1:2500 individuals (Hagerman, 2008). This syndrome is characterized by intellectual disability, development delay, hyperactivity, hypersensitivity to stimuli, mood

instability and autism. The Fragile-X syndrome is caused by the expansion of the trinucleotide repeat CGC at *FMR1* gene in the X chromosome, leading to the absence of FMRP protein. FMRP is an RNA binding protein that shuttles between the nucleus and the cytoplasm. It is thought that FMRP plays an important role in synaptic plasticity through regulation of mRNA transport and translational inhibition of local protein synthesis at synapses (Fatemi and Folsom, 2011). Studies in patients and animal models of Fragile-X syndrome have identified increased spine density and an excess of abnormal long, thin and immature spines which are indicative of alterations in synapse development and/or function in these patients (Krueger and Bear, 2011).

5.2 Autosomal intellectual disability

As intellectual disability affected individuals commonly possess low reproductive fitness, severe autosomal dominant intellectual disability is most often due to *de novo* mutations. Taking into account the high frequency of *de novo* pathogenic copy-number variations found in non-syndromic intellectual disability, autosomal dominant intellectual disability is unlikely to be rare. However, while several well-known autosomal dominant disorders such as neurofibromatosis, tuberous sclerosis and myotonic dystrophy are often associated with intellectual disability of varying severity (Nelson, 2009), very little is known about the gene defects underlying non-syndromic autosomal dominant intellectual disability. On the other hand, mounting epidemiological data suggests that autosomal recessive forms may also be very common, although frequencies for each individual gene should be rare (Ropers, 2007). More than 1400 autosomal intellectual disability genes are estimated to exist (Raymond, 2010). For instance, a search for the terms “mental retardation” or “intellectual disability” on OMIM (Online Mendelian Inheritance of Man; <http://www.ncbi.nlm.nih.gov/omim>) yields 815 entries for conditions with known molecular basis or gene on autosomal chromosomes, while an unrestricted search for the same terms yield 1308 entries for autosomal chromosomes. The classical approach for identifying autosomal recessive intellectual disability associated genes is homozygosity mapping in consanguineous families. This has made the search for new autosomal recessive intellectual disability genes very difficult as in Western societies, where most research takes place, families are usually small and most patients are isolated cases. In countries such as Iran, where consanguinity is more common, several studies revealed more than 30 loci for autosomal recessive intellectual disability, highlighting the heterogeneous character of this condition (Ropers, 2010). The massification of high resolution aCGH and the maturation of next generation sequencing technologies (see below), will certainly provide a new thrust to the identification of novel intellectual disability-associated genes.

6. Recent technological advances: Massive Parallel Sequencing

Technological advancements in the last decade have brought enormous progress, not only in the field of array-technology, but perhaps even in a more striking way in DNA sequencing. Sanger sequencing has for decades been the standard method for DNA sequencing. However, despite several improvements throughout the years, its basic process is not adequate for fast and complete sequencing of one or multiple genomes (Schuster, 2008). Several new and improved technologies have emerged in recent years to cope with these new expectations – fast, low cost and high-throughput – so called Next Generation

Sequencing or Massive Parallel Sequencing (NGS/MPS). Massive Parallel Sequencing technologies have fundamental differences compared to conventional Sanger sequencing, relying on different technical approaches and usually requiring a previous enrichment step. MPS is based on sequencing clonally amplified single molecules of genomic DNA that need between 10-50 reads of the same base to reliably identify heterozygous sequence variants since every read shows only one of the possible two alleles in the sequence.

Massive parallel sequencing has led to the development of new strategies in the analysis of monogenic diseases, allowing the identification of causative mutations in diseases in which they were previously impossible to identify through classical linkage analysis or positional cloning due to insufficient family information. Moreover, it can also be applied to the detection of copy-number variants and provide an effective replacement for aCGH (Medvedev et al., 2009). When speaking of MPS, one must take into consideration that it can be applied not only to the sequencing of a complete genome, but also to a subset of genomic regions of a set of target genes, which due to factors such as cost/speed can be much more effective approaches than full genomic sequencing. Exome sequencing for instance, comprehends the capture, sequencing and analysis of only the protein-coding regions of the genome (1% of the whole genome) and has seen increasing adoption by researchers for the identification of new disease genes. The use of exome capture to focus on a critical part of the human genome, allows the study of larger numbers of samples than those currently practical to analyse with whole-genome sequencing (Teer and Mullikin, 2010).

Since current classical approaches seem incapable of identifying/explaining a huge amount (60%) of the genetic aetiology of intellectual disability (Rauch et al., 2006), these technologies are already having a great impact in the field. In recent years, exome sequencing has allowed researchers to identify several new genes involved in intellectual disability, encompassing diverse models of inheritance and phenotype (Hoischen et al., 2010; Ng et al., 2010; Vissers et al., 2010). Unlike standard strategies, by avoiding the use of a predefined set of target genes or genomic regions, the likelihood of finding new genes acting in unexpected biological pathways is greatly increased. Moreover, these studies are often successful in the analysis of very few or even single disease patients, which is of relevance since many cases of intellectual disability occur as isolated cases in families without previous clinical history. Although the advantages of massive parallel sequencing seem very clear, there are many challenges brought up by these technologies that need to be overcome. Due to the fact that MPS approaches generate vast amounts of data, the biggest challenge is, of course, interpretation. Researchers need to be able to accurately distinguish the disease-associated variations from the benign and evolution-related aspects of the genome. This will be facilitated by the adoption of standardized analytical procedures and the development of catalogues or databases of genetic variance in both diseased and healthy individuals from different ethnic backgrounds. In the following years, as the affordability and practical implementations of these technologies improves, massive parallel sequencing will theoretically allow us to identify mutations in patients with intellectual disability, regardless of inheritance and frequency of phenotype.

7. Cellular pathways involved in intellectual disability

The increasing number of genes identified over the last years associated with intellectual disability suggests that this phenotype can emerge as the final common pathway of many

different types of abnormal cellular processes, putting to rest the hypothesis of a single main general mechanism responsible for the disease. This is in a way consistent with the complexity of intellectual processing in humans. To date, taking into consideration what is currently known about intellectual disability related genes, in particular monogenic forms of intellectual disability, it is considered that this disease can stem from two broad mechanistic themes: dysfunction of neurodevelopmental programs and alterations in synaptic organization and plasticity (Vaillend et al., 2008; Kramer and van Bokhoven, 2009).

7.1 Neurogenesis

During development, neurogenesis and cell migration occurs in a tightly controlled spatio-temporal manner, during which neurons form intricate axonal and dendritic connections. The accuracy of this process results from both intrinsic genetic characteristics and functional cell-to-cell interactions. Small disruptions in any of these processes during development can lead to cognitive dysfunction in children.

During embryonic development, the first formed neurons arise from two different daughter cells: one that gives rise to a neuron that will migrate to the cortex, and another cell that continues to proliferate as a stem cell. It is now known that although in the cerebral hemispheres the majority of neurogenesis occurs in the first half of gestation, neurogenesis also occurs in the olfactory bulb, sub-ventricular zone and hippocampus in adults (Diaz and Gleeson, 2009). Defects in the control of neuronal number, from excess or defects in germinal epithelial proliferation can lead to disorders such as macro- or microcephaly. These diseases comprise a heterogeneous group of disorders that can be *de novo* or familial, often associated with increased incidence of cognitive impairments (Adachi et al., 2011).

Microcephaly is characterized by a reduced frontal-occipital head circumference, more than 3 standard deviations below the mean of age and sex-matched controls. It can be classified as primary or secondary (acquired or traumatic). Patients with primary microcephaly usually display small but architecturally normal brains or with mildly simplified gyral patterns, and have mild intellectual disability (Clowry et al., 2010). Microcephaly is known to be associated with mutations in at least 4 genes (*MCPH1*, *ASPM*, *CDK5RAP2* and *CENPJ*), all associated with cell division and cell cycle regulation. But whereas microcephalin (*MCPH1*) is a DNA damage response protein that plays a role into preventing premature entry into mitosis (Alderton et al., 2006), *ASPM*, *CDK5RAP2* and *CENPJ* are located to the spindle poles of mitotic cells and are involved in mitotic spindle dynamics and cellular abscission (Bond et al., 2005; Fish et al., 2006; Paramasivam et al., 2007). The role of adult neurogenesis in cognition is still a matter of debate, but it is possible that milder disruption of genes involved in neurogenesis, even if it does not disrupt development of the nervous system, may impair cognition through yet unknown mechanisms (Bruehl-Jungerman et al., 2007).

7.2 Neuronal migration

Diseases of neuronal migration comprise a heterogeneous group of disorders of the nervous system development and represent a significant cause of intellectual and developmental disability and epileptic seizures in childhood (Verrotti et al., 2010). After neurogenesis, post-

mitotic neurons are organized in columns and migrate away from the ventricular zone in a radial pattern to their final destination in the forming cerebral cortex (Diaz and Gleeson, 2009). Strict regulation of the timing and pattern of neuronal migration is essential for a correct development and intellectual functioning. Abnormal migration dynamics leading to incorrect distribution of neurons in the cerebral cortex is the cause of several disorders characterized by cortical dysgenesis, such as lissencephaly.

Lissencephaly (which literally means “smooth brain”) refers to the occurrence of a smoother brain surface without *gyri* or *sulci* and it is associated with severe intellectual disability and refractory epilepsy (Verrotti et al., 2010). Classical type 1 lissencephaly can be caused by mutations in *LIS1* and *DCX* genes, among others. *LIS1* is an autosomal gene that encodes the LIS1 protein, a microtubule associated protein. LIS1 is known to interact with cytoplasmic dynein, phosphoprotein NDEL1 and kinetochore CLIP-170, as part of a complex important for neuronal migration (Wynshaw-Boris, 2007). *DCX* on the other hand is an X-linked gene exclusively expressed in post-mitotic neurons. *DCX* encodes the doublecortin protein, proposed to be involved in vesicle trafficking and the growth of neuronal processes (Friocourt et al., 2003). *TUBA1* ($\alpha 1$ tubulin) is also a lissencephaly-associated gene, which reinforces the role of microtubule associated proteins in the processes of neuronal migration (Keays et al., 2007).

Type of Lissencephaly	Associated syndrome	Underlying genes
Type I Lissencephaly	· Isolated lissencephaly sequence · Miller-Dieker syndrome	· <i>LIS1</i> , <i>DCX</i> , <i>TUBA1A</i> , · <i>LIS1</i> and <i>YHAWAE</i> deletion
Cobblestone Lissencephaly	· Walker-Warburg syndrome · Muscle-Eye-Brain disease · Fukuyama congenital muscular dystrophy	· <i>POMT1</i> , <i>POMT2</i> , <i>FKTN</i> , · <i>FKRP</i> · <i>LARGE</i> , <i>FKTN</i>
X-linked lissencephaly with agenesis of corpus callosum (XLAG)	· Lissencephaly	· <i>ARX</i>
Lissencephaly with cerebellar hypoplasia (LHC)	· Lissencephaly	· <i>RELN</i> , <i>VLDLR</i>
Microlissencephaly	· Norman-Roberts syndrome · Barth syndrome · Primordial osteodysplastic dwarfism and microcephaly (MOPD type 1)	Not described

Table 2. Classification of lissencephalies, syndromes and associated genes. Adapted from (Verrotti et al., 2010b).

Another well studied intellectual disability gene is *RELN*, associated with lissencephaly with cerebellar hypoplasia and rare forms of pachygyria. Reelin, however, is not related to

microtubules: it is an extracellular matrix protein of migrating neurons. Reelin, along with Dab1, participates in a signalling pathway critical for the end stage of neuronal migration (Kerjan and Gleeson, 2007).

Other diseases associated with the Reeling pathway are the cerebellar ataxia, intellectual disability, and dysequilibrium syndrome (CAMRQ1, OMIM 221050), and the Uner Tan syndrome, characterized by a similar phenotype and possessing quadrupedal locomotion (Uner Tan, 2010). CAMRQ1 and Uner Tan syndrome are caused by mutations in the *VLDLR* gene which encodes the very low density lipoprotein receptor (Ozcelik et al., 2008). In mice, *Vldlr* has been shown to be a direct binding partner of Reelin and lack of *Vldlr* impairs Reelin-induced Dab1 phosphorylation (Trommsdorff et al., 1999).

7.3 Synaptic function

Chemical synapses regulate the electrical communication within neurons and allow the flow of information from presynaptic axon terminals to postsynaptic dendritic regions. Most excitatory synapses in the brain are formed at tiny dendritic protrusions called dendritic spines (Hotulainen and Hoogenraad, 2010). The molecular architecture of chemical synapses consists of presynaptic axon terminals harbouring synaptic vesicles and a postsynaptic region (on dendrites) containing neurotransmitter receptors. The presynaptic and postsynaptic sites are separated by the synaptic cleft (10 to 25 nm) and a variety of cell adhesion molecules (CAMs) hold them together at the proper distance (Price et al., 2006). These cell adhesion molecules, such as neuroligins and neuroligins, are involved in the formation of functional presynaptic regions specialized in vesicle fusion to the plasma membrane and correct release of the neurotransmitters to the synaptic cleft. While neuroligins are presynaptic receptors, neuroligins are the ligands of neuroligins located in the postsynaptic side. Mutations in *NLGN3/4* (neuroligin 3/4) gene were found in patients with intellectual disability and/or autism spectrum disorders (ASDs) (Vaillend et al., 2008). *NLGN4* is involved in formation of active regions at presynaptic terminals through interactions with its presynaptic receptor β -neuroligin. It is worth noting that other proteins belonging to the neuroligin superfamily, such as CNTNAP2 or interaction proteins such as APBA2 have been implicated in autism spectrum disorders and schizophrenia, suggesting that synaptic dysfunction may be a common theme among these disorders (Ropers, 2008). Interestingly, some molecules known to be involved in axonal pathfinding are now known to play a role also in synapse stabilization, one example being ephrins (Shen and Cowan, 2010).

On the presynaptic region, neurotransmitters such as glutamate or γ -aminobutyric acid (GABA), are produced and stored in synaptic vesicles. The docking and fusion of the vesicles to the membrane is controlled by the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex. Many other presynaptic proteins play a role not only in the synaptic vesicle fusion process but also in other steps of synaptic vesicle trafficking such as targeting, docking and priming (Lin and Scheller, 2000). Information about the mechanisms of synaptic vesicle docking and fusion are a key to understand synaptic transmission itself and also to discover the transmission modifications that may play a role in synaptic plasticity, learning and memory (Chechlacz and Gleeson, 2003).

Gene	Protein	Locus	Function
<i>NRXN1</i>	NRXN1	2p16.3	Cell adhesion molecule
<i>NLGN4</i>	NLGN4	Xp22.33	Cell adhesion molecule
<i>STXBP1</i>	Syntaxin-binding protein 1	9q34.1	Synaptic vesicle docking and fusion, release of neurotransmitters
<i>GDI</i>	GDI α	Xq28	Regulator of Rab GDP-GTP state, vesicle trafficking, release of neurotransmitters
<i>RAB3GAP1</i>	Rab3-GAP	2q21.3	Regulator of Rab GDP-GTP state, vesicle trafficking, release of neurotransmitters
<i>GLIA3</i>	Glutamate receptor 3	Xq25	Ionotropic glutamate neurotransmitter receptor
<i>SAP102/DLG3</i>	Synapse-associated protein 102/ Discs large homolog 3	Xq13.1	Guanylate kinase, clustering of NMDA receptors
<i>SHANK2</i>	Synapse-associated protein 102	11q13.2	Molecular scaffolds in the postsynaptic density of excitatory synapses
<i>IR1RAPL</i>	Interleukin-1 receptor accessory protein-like 1	Xp22.1-p21.3	Regulation of calcium-dependent exocytosis, secretion and presynaptic differentiation
<i>DMD</i>	Dystrophin	Xp21.2	Synapse stabilization, anchoring of postsynaptic receptors and transducing signals
<i>PAK3</i>	Serine/threonine-protein kinase PAK 3	Xq23	Regulator of synapse formation and plasticity
<i>PRSS12</i>	Protease, serine, 12	4q28.1	Serine protease, neuronal plasticity
<i>GRIK2</i>	Glutamate receptor, ionotropic, kainate 2	6q16.3-q21	Ionotropic glutamate neurotransmitter receptor

Table 3. Examples of ID-associated genes coding for synaptic proteins.

STXBP1 (syntaxin-binding protein 1) encodes a neuronal specific syntaxin-binding protein and has been found to be mutated in patients with autosomal dominant intellectual disability and epilepsy (Hamdan et al., 2009). *STXBP1* is also a regulatory protein of VAMP2, syntaxin 1 and SNAP, key elements of the synaptic vesicle docking and fusion machinery (Lin and Scheller, 2000). The key regulator of vesicle trafficking is Rab GTPase activity, which is under the control of specific GAPs (GTPases-activating proteins), GEFs (guanine-nucleotide-exchange factors) and GDIs (guanine-nucleotide-dissociation-inhibitors). These molecules mediate vesicle trafficking and fusion by modulating the association/dissociation of Rab proteins to vesicles through control of their GDP-bound state (Renieri et al., 2005). Several intellectual disability related proteins are known to intervene in this process. Of notice, the *GDI* gene, associated with X-linked intellectual disability, encodes the GDI α protein which regulates the sequestration of GDP-bound Rab proteins. Moreover, studies in mice models have shown that lack of GDI α leads to altered

Rab4/5 distribution and impaired short-term memory (D'Adamo et al., 2002). Rab3 for instance, has been shown to be regulated by Rab3 GAP, a protein involved in Warburg Micro syndrome, characterized by abnormal brain development and severe intellectual disability (Aligianis et al., 2005). In animal models, mutated Rab3 GAP has been shown to lead to accumulation of GTP-bound Rab3 and result in inhibition of glutamate release and altered short-term plasticity (Sakane et al., 2006).

The dendrites are home to the post-synaptic machinery/density, which includes neurotransmitter receptors (e.g. glutamate receptors), cytoskeleton components, adapter proteins, endocytic machinery, chaperones as well as members of numerous regulatory pathways involved in differentiation of the post-synaptic regions and establishment of functional synapses (Vaillend et al., 2008). Approximately 20 X-linked intellectual disability associated genes code for postsynaptic proteins (Laumonnier et al., 2007). Some of these genes code for components or regulators of glutamate receptors, such as GluR3, SAP102 and PLP1. GluR3 for instance is a subunit of post-synaptic AMPA receptors, which plays a role in fast excitatory transmission, and has been involved in neurodegenerative disorders such as Parkinson's and Huntington's disease (Jayakar and Dikshit, 2004). As for SAP102, it is a member of membrane associated guanylate kinase (MAGUK) family of proteins and is required for recruitment of NMDA receptors. MAGUKs play a role in the regulation of the number of glutamate receptors at the synapse as well as the synaptic trafficking of these receptors during the morphological changes that are associated with synapse plasticity (Elias and Nicoll, 2007). Other components of the post-synaptic machinery are the Shank proteins - multidomain scaffold proteins connecting neurotransmitter receptors and other membrane proteins with signaling proteins and the actin cytoskeleton (Boeckers et al., 2002). They participate in morphological changes, leading to maturation of dendritic spines and synapse formation. Mutations in the *SHANK2* (SH3 and multiple ankyrin repeat domains 2) gene have recently been described to be associated with intellectual disability and autism spectrum disorders (Berkel et al., 2010).

7.4 Transcription regulation

Gene expression and consequent protein synthesis is a tightly regulated process determined by the interplay of chromatin dynamics, transcriptional activators/repressors and the regulation of RNA splicing, export and degradation. Alterations in these mechanisms may result in the deregulation of gene expression. If this abnormal expression of genes occurs at critical developmental stages, it is likely that it will lead to defective brain development and/or functioning. Neurons are highly specialized cells in which some specific aspects of RNA metabolism play critical roles for their function specially, during development, when trafficking of mRNAs to growth cones (axonal and dendritic) regulates neuronal growth (Hengst and Jaffrey, 2007). After synapse formation, mRNAs continue to be transported to dendrites and axons where they are locally translated at the synapse (Martin and Zukin, 2006). This process has extreme importance for synaptic plasticity, thought to be the biological correlate of memory/learning, and its deregulation can have an important impact on cognition.

In fact, there are many examples of intellectual disability-associated genes that code for regulators of signal transduction pathways, transcription factors and cofactors involved in chromatin remodelling, gene expression and protein maturation (Santos et al., 2006; McClung and Nestler, 2007; Renieri et al., 2005).

	Gene	Locus	Protein Function	Associated Phenotype
Chromatin remodelling	<i>ATRX</i>	Xq13	ATPase/helicase	Alpha-thalas semia syndrome
	<i>CHD7</i>	8q12.1	ATP-dependent chromatin remodeler	CHARGE syndrome
	<i>ERCC6</i>	10q11	ATPase/helicase	Cerebrooculofacioskeletal syndrome
DNA methylation	<i>CDKL5</i>	Xp22	Dnmt1 phosphorylase	West syndrome; Rett-like variant
	<i>DNMT3B</i>	20q11.2	NA methyltransferase	Immunodeficiency, centromeric instability and facial dysmorphisms syndrome
	<i>MECP2</i>	Xq28	Methyl DNA-binding protein	Rett syndrome
Histone modifications	<i>CREBBP</i>	16p13.3	Histone acetyltransferase	Rubinstein-Taybi syndrome
	<i>EHMT1</i>	9q34.3	Histone methyltransferase	Kleefstra syndrome
	<i>HUWE1</i>	Xp11.2	Histone ubiquitin ligase	Non-syndromic XLID
	<i>MED12</i>	Xq13	Histone methyltransferase binding protein, histone phosphorylation activator	Optiz-Kaveggia syndrome; Lujan-Fryns syndrome
	<i>PHF8</i>	Xp11.2	Histone demethylase	Siderius XLID syndrome
	<i>RPS6KA3</i>	Xp22.2-22.1	Kinase-histone phosphorylation	Coffin-Lowry syndrome; XLID
	<i>JARID1C</i>	Xp11.22-21	Histone demethylase	X-linked intellectual disability
DNA/Chromatin binding	<i>BRWD3</i>	Xq13	Chromatin binding protein (putative)	Non-syndromic XLID with macrocephaly
	<i>PHF6</i>	Xq26.3	Chromatin binding protein (putative)	Borjeson-Forssman-Lehmann syndrome
	<i>ZNF41</i>	Xp22.1	DNA-binding protein	Non-syndromic XLID
	<i>ZNF81</i>	Xp221-p11	DNA-binding protein	Non-syndromic XLID
	<i>ZNF674</i>	Xp11	DNA-binding protein	Non-syndromic XLID
	<i>ZNF711</i>	Xq21.1	DNA-binding protein	Non-syndromic XLID

Table 4. Examples of transcription regulators genes known to be associated with intellectual disability. XLID, X-linked intellectual disability.

For instance, the NF1 protein - associated with intellectual disability in neurofibromatosis type I (OMIM 162200), and the RSK2 protein - associated with Coffin-Lowry syndrome (OMIM 303600), act upon MAPK/ERK signalling. Whereas NF1 regulates MAP/ERK by targeting Ras, RSK2 (ribosomal protein S6 serine/threonine kinase) intervenes downstream in the Ras/ERK cascade and is involved in transcription activation through chromatin remodelling (Shalin et al., 2006). Other intellectual disability-associated genes can act in the

opposite direction. MeCP2 (methyl-CpG-binding protein 2, Rett syndrome), CDKL5 (cycling dependent kinase 5, Rett-like syndrome), ZNF41 (zinc finger protein 41, non-syndromic intellectual disability) and XNP (helicase 2, ATRX syndrome) proteins are involved in processes that repress transcription (Vaillend et al., 2008). MeCP2 and CDKL5 can both interact and mediate the silencing of specific genes through binding to methylated DNA, while ZNF41 contains a transcriptional repressor domain. Mutations in some RNA binding proteins are also known to account for some forms of intellectual disability. The most widely studied case is the FMRP protein, coded by *FMR1*, causative of Fragile X syndrome (Heulens and Kooy, 2011). FMRP is an RNA binding protein that associates with many mRNAs, some of which encode proteins important for neuronal development and plasticity. FMRP controls activity-dependent dendritic mRNA localization and translational efficiency of dendritic mRNAs in response to stimulation of metabotropic glutamate receptors (mGluRs) (Antar et al., 2004).

Other molecules that are potential candidates for involvement in the pathology of intellectual disability are miRNAs, small non-coding RNA molecules (~21 bp) encoded in the genome that regulate gene expression by binding to the 3'UTR of specific target mRNAs (Corbin et al., 2009). Many of these miRNAs are expressed in the brain and seem to be essential for neuronal cell development, intervening in processes such as neurite outgrowth, synaptic development and neuronal plasticity. For example, miRNA miR132 has been shown to influence the Rac1-PAK-mediated spinogenesis and influence dendritic growth in hippocampal neurons (Hansen et al., 2010). Additionally, miR132 was also shown to regulate expression of *MECP2*, the gene responsible for Rett syndrome (OMIM 312750). Further data from miR132 overexpressing transgenic mice, confirmed decreased MeCP2 protein expression and showed significant deficits in novel object recognition (Li et al., 2008). It has been proposed that miR132 is a regulatory miRNA in neurons and may contribute not only for the cognitive defect in Rett syndrome, but also for a larger set of intellectual disability related disorders. As our current knowledge of the role that these processes play in synaptic plasticity and cognitive processes increases, so we will better understand the importance of signalling components, transcription factors and chromatin regulation processes in intellectual disability.

8. From human genetics to animal models and new therapeutic perspectives

For some intellectual disability disorders the current state of knowledge on the underlying genetics and pathophysiology of the disease has already allowed the conception and development of some therapeutic approaches. These initial clinical results are very encouraging and the cases described below are good examples of how basic science, cell and animal model research can lead to the treatment of human diseases which were thought to be untreatable not many years ago.

8.1 Rett syndrome

Rett syndrome (RTT) is a neurodevelopmental disease associated with abnormalities in brain size, branching and synaptic morphology, neurotransmitter receptors and gene expression (Johnston et al., 2001). Clinically it is characterized by intellectual disability associated with other neurological features, breathing and cardiac function abnormalities, as well as growth impairment (Weaving et al., 2005). Rett syndrome presents an X-linked

recessive mode of inheritance and an estimated incidence of 1:10000-1:15000 female births. It is mostly a sporadic condition, resulting from *de novo* mutations in the *MECP2* gene. Duplications in *MECP2* have also been reported in patients with diverse clinical presentation (Chahrour and Zoghbi, 2007). MeCP2 (methyl-CpG-binding protein 2) is a ubiquitously expressed transcription factor that binds methylated DNA. Although MeCP2 was first characterized as a transcription repressor, it has been found that the majority of MeCP2-regulated genes are actually activated in the presence of this protein (Chahrour et al., 2008). With regard to links to cognition, MeCP2 has been shown to bind the transcriptional activator CREB1, known to be involved in learning and memory (Carlezon et al., 2005), and to repress the expression of *BDNF*, involved in synaptic transmission and plasticity (Chen et al., 2003). To allow a better understanding of the function of MeCP2 in brain development and consequently increase the knowledge of the pathophysiology of Rett syndrome, several disease mouse models have been generated. In general, these mouse models are able to recreate many physiological and neurological features of Rett syndrome (Calfa et al., 2011), and a number of therapeutic approaches have already been tested. Of notice, treatment of the Jaenisch mouse model with an active peptide fragment of Insulin-like Growth Factor 1 (IGF-1) extended the life span, improved locomotor function, ameliorated breathing patterns and reduced irregularities in heart rate of the animals (Tropea et al., 2009). IGF-1 activates pathways common to those induced by *BDNF* (Zheng and Quirion, 2004), and a clinical trial using IGF-1 in humans has already been initiated (NCT01253317). Direct modulation of BDNF levels with CX546, an ampakine drug, was also successful in restoring normal breathing parameters in *Mecp2* null mice (Ogier et al., 2007). With regard to BDNF and neuronal function, application of exogenous BDNF was able to rescue *Mecp2* mice-associated synaptic pathology, described as increased amplitude of spontaneous miniature and evoked excitatory postsynaptic currents in nucleus tractus solitarius neurons (Kline et al., 2010). In addition, treatment of *Mecp2*(stop/y) mice with the NMDA receptor blocker memantine was able to partially restore short-term synaptic plasticity (Weng et al., 2011). Another therapeutic approach being tested in humans involves treatment with desipramine (NCT00990691), a selective inhibitor of norepinephrin transport shown to improve breathing and survival in *Mecp2*-deficient mice (Roux et al., 2007).

8.2 Fragile X

Fragile X is the most common form of inherited intellectual disability with an estimated frequency of 1:2500-1:4000. It exhibits an X-linked recessive mode of inheritance and the clinical presentation includes mild to moderate intellectual disability, developmental delay, very defined dysmorphic characteristics, hyperactivity, hypersensitivity to stimuli, mood instability and autism (Hagerman, 2008). The Fragile X syndrome is caused by the expansion of the trinucleotide repeat (CGG) in the promoter of the *FMR1* gene to >200 repeats. This mutation results in the methylation and silencing of *FMR1* and consequent absence of FMRP protein. FMRP is a multifunctional RNA binding protein thought to play an important role in synaptic formation and plasticity through the down regulation of the transport and translation of a wide subset of protein coding mRNA (>500 targets have been identified) at the dendrites (Berry-Kravis et al., 2011). This regulatory action is mainly dependent on activation by mGluR (group 1 metabotropic glutamate receptors) (Antar et al., 2004). Several studies using animal models have shown that deregulated expression of FMRP targets at the dendrites results in enhanced mGluR-activated hippocampal and

cerebellar long term depression (LTD), impaired long term potentiation (LTP) at the hippocampus and cortex, and abnormal dendritic spine morphology (Berry-Kravis et al., 2011). As such, group I mGluR signalling is thought to play a central role in the pathophysiology of Fragile X and is a major target for therapeutic intervention. Studies using *Drosophila* and mouse models of Fragile X have been very successful in demonstrating the efficacy of mGluR antagonists in the recovery of disease phenotypes even in adult animals (Yan et al., 2005; McBride et al., 2005). Another effective approach seems to be the modulation of the excitatory pathway through the GABAergic inhibitory pathways (Chang et al., 2008). While the impact of similar therapeutic strategies in human patients is still unknown, translation of these findings to the human context has begun and many clinical trials have been initiated that anticipate the possibility of effective treatments for X Fragile syndrome (<http://clinicaltrials.gov/>).

8.3 Down syndrome

Down syndrome (trisomy 21) is the most common single cause of intellectual disability, with an estimated prevalence of 1:750-1:800 (Hassold et al., 1996). In addition to mental impairment, Down syndrome patients may present other phenotypic characteristics such as the easily recognizable facial appearance, congenital malformations, hearing loss and early onset Alzheimer's disease (Epstein, 2001). Hypothetically, the additional copy of human chromosome 21 (Hsa21) should lead to an increased expression of many Hsa21 genes, resulting in the clinical phenotype associated with Down syndrome. However, not all of the more than 400 genes contained in the Hsa21 chromosome are bound to be dosage-sensitive (Gardiner and Costa, 2006). Identification of which specific genes are dosage-sensitive and responsible for the Down syndrome phenotype is being accomplished either through genomic association studies which try to draw genotype-phenotype correlations using patients with partial trisomy or other Hsa21 rearrangements (Lyle et al., 2009), and also through studies using animal models. Some prime candidates for trisomy 21 associated intellectual disability are *DYRK1A*, *GIRK2*, *SYNJ1* and *SIM2*, which in several mouse models have been shown to be associated with learning and memory defects. Of notice, *DYRK1A* is a kinase which is involved in the phosphorylation of some synaptic proteins and many other kinases, known to play a role in intercellular signalling, endocytosis and cell cycle (Wiseman et al., 2009). In fact, gene therapy applied to the *TgDyrk1A* mouse model has shown that normalization of *Dyrk1A* gene expression was able to attenuate behavioural phenotypes, restore motor-coordination and improve sensorimotor gating (Ortiz-Abalia et al., 2008). Moreover, modulation of *DYRK1A* activity with the use of epigallocatechin gallate (EGCG), found in great amounts in green tea leaves, has proved successful in reverting *DYRK1A*-induced synaptic vesicle endocytosis defects in cultured hippocampal neurons (Kim et al., 2010) and rescuing the major phenotypic features of *DYRK1A* transgenic mice (Guedj et al., 2009). Following these positive outcomes, a human clinical trial has been recently completed, although no results have been published so far (NCT01394796). A more recent mouse model, *TgRCAN1*, also highlighted the impact of the overexpression of *DSCR1* (*RCAN1*), a functional inhibitor of calcineurin, in visuo-spatial learning and memory tasks similar to those present in Down syndrome affected persons (Dierssen et al., 2011). Other studies exploring the hypothesis of high levels of inhibition being involved in Down syndrome cognitive dysfunction also revealed promising results. Prolonged treatments with GABAA receptor antagonists, picrotoxin and pentylentetrazole, resulted in a persistent

recovery of behaviour and cognitive deficits in adult Ts65Dn animals (Fernandez et al., 2007; Rueda et al., 2008).

8.4 Tuberous sclerosis

Tuberous sclerosis (TSC) is a multi-system disorder that causes benign tumours called hamartomas in the central nervous system and many other organs. Clinical manifestations include developmental delay, mental retardation, autism and epilepsy among other neurological problems. Tuberous sclerosis presents an autosomal dominant mode of inheritance and is estimated to affect 1:6000 individuals worldwide (Crino et al., 2006). As such, due to its severe clinical presentation, most cases arise from *de novo* mutations. The genetic basis for the disease has been linked to mutations in the *TSC1* and *TSC2* genes, coding for hamartin and tuberin respectively (Dabora et al., 2001). Initial studies in *Drosophila* provided the first links of the TSC1/TSC2 complex to the PI3K-Akt-mTOR-S6K pathway and further studies on mammalian systems eventually demonstrated that TSC1/TSC2 function as GTPase activating protein against Rheb – a Ras-like small GTPase, which in turn regulates TOR signaling in nutrient-stimulated cell growth (Pan et al., 2004). mTOR (mammalian target of rapamycin) is a serine/threonine protein kinase and a major regulator of cell growth and proliferation, cell motility, cell survival, protein synthesis, and transcription (Hay and Sonenberg, 2004). This suggested a possible therapeutic approach through the inhibition of mTOR. Several mouse models have been described that are able to reproduce, at least partially, the tuberous sclerosis phenotype (Ess, 2010). Recent publications using these animal models have provided promising data in support of the use of mTOR inhibition as a therapeutic strategy. The use of mTORC1 inhibitor rapamycin has successfully prevented epilepsy and premature death of *Tsc1^{GFAP}* mice, homozygous for conditional knockout in astrocytes (Zeng et al., 2008). Similar effects were reported for the *Tsc1^{Synapsin}* conditional knockout, which presents inactivation of *Tsc1* in post-mitotic neurons, with near resolution of cell size defects and increased survival (Meikle et al., 2008). With regard to learning abnormalities, rapamycin was able to normalize impaired LTP and spatial learning in the *Tsc2^{+/-}* heterozygous knockout mice (Ehninger et al., 2008). These positive results prompted researchers to suggest the use of rapamycin for treatment of tuberous sclerosis patients. As of now, several reports have been published that describe the regression of subependymal giant cell astrocytomas induced by mTOR inhibitors rapamycin and everolimus (RAD001) (Franz et al., 2006; Micozkadioglu et al., 2010; Birca et al., 2010; Krueger et al., 2010). No data has been published with regards to cognitive deficits so far. However, several clinical trials are undergoing that should provide a more complete evaluation of the efficacy of mTOR inhibitor treatment for tuberous sclerosis complex.

9. Genetic diagnosis of intellectual disability in the clinical context: costs vs. benefits; New challenges

A child with intellectual disability should be offered the best diagnostic evaluation available in order to improve the health and well-being of that child and his/her family. An adequate and precise diagnosis can be used by the family in obtaining information about a prognosis, recurrence risks and available therapy. In addition, it will provide an answer and appeasement to the common uncertainty and fear shared by many parents as to the origin of the disease (Barr and Millar, 2003). From a clinical perspective, establishing a diagnosis will

allow a better understanding of the prognosis and future needs, improvement of the response by medical and educational services by passing on the patients to an appropriated specialist and also to make future reproductive decisions based on appropriate estimated recurrence rate. At a scientific level, a specific diagnosis may provide potential insight into disease mechanisms and eventual development of therapeutic interventions.

Currently, the extensive genetic heterogeneity of intellectual disability hampers the accurate diagnosis with classic technologies. New benefits and also challenges to the diagnosis field come from the advent of technologies such as high resolution aCGH and, most importantly, next generation sequencing. The application of these new technologies to clinical diagnosis is still limited, mostly due to the prohibitive costs they still imply when considering their application to full-scale diagnosis. This will likely change in the short term, as there is a huge effort from biotech companies to deliver the so called “\$1000 genome” in the scope of 1-2 years, and to scale the cost down even further as technology matures. This should allow a much higher rate of detection at a fraction of the price it now costs to cover all diagnostic hypothesis through classical techniques (e.g. regular karyotype analysis plus a customized FISH, such as subtelomeric FISH). The advent of aCGH and massive parallel sequencing is also changing current clinical diagnosis approaches. As these methodologies become more efficient in the identification of the genetic alterations underlying intellectual disability, clinical practice is being compelled to move to a new paradigm of “genotype-first”, followed by a more detailed clinical characterization as more patients with the same alteration are discovered. The exception will be cases in which the clinical phenotype is so well defined and evident, e.g. in some cases of syndromic intellectual disability, that this alone will give a clear indication of the underlying genetic cause.

Perhaps the biggest challenge of all is implementation - how these technologies will be applied to the clinical procedure. In order for these to be applied to clinical genetic diagnosis, several practical and ethical issues must be overcome. There is the need for national and international regulatory bodies to produce technical guidelines and procedures to allow the integration to diagnostics. With regard to massive parallel sequencing, and from a technical perspective, these should provide recommendations for sequence depth and coverage requirements, quality metrics, and additional validation procedures. The creation of extensive databases of genetic variance for healthy and disease individuals must also be fostered, as this will be required for correct interpretation of data, specially concerning new variants, and must take into account the natural occurring variances found in regional or ethnic groups. The ethical challenges brought by these technical advancements are perhaps even more controversial. Complete genome data, and even only exome data, will contain thorough information unrelated to the disease being tested. These may contain the carrier status or indicate the presence of high risk variants regarding other diseases. So there must be a responsible management on if, what and how this information will be returned to the patients, and on the psychological consequences of having knowledge of such data (Sharp, 2011). Other, more practical concerns, regard the ownership, storage and access to the data, especially considering future unanticipated applications. Another aspect that should be taken into account are cases where no conclusion can be drawn at the moment of analysis. Considering the rate at which the biological processes underlying intellectual disability are being unravelled, and new intellectual disability or modifier genes are being discovered, these negative cases should be kept “on hold” and re-

evaluated in light of this new flow of information. This will likely require more integration between research and diagnostic laboratories to tackle these new evidences. In the years ahead of us, we will certainly see massive parallel sequencing acquiring the “first-tier test” position in clinical diagnosis.

10. References

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