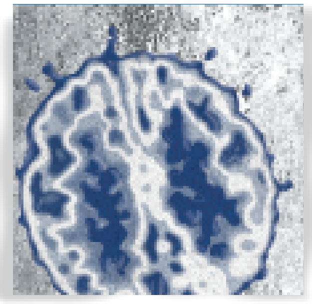
Genetic basis of cognitive disability

Jonathan Flint, MRCPsych



The importance of genetic influences on cognitive disability has been recognized for a long time, but molecular analysis has only recently begun to yield insights into the pathogenesis of this common and disabling condition. The availability of genome sequences has enabled the characterization of the chromosomal deletions and trisomies that result in cognitive disability, and mutations in rare single-gene conditions are being discovered. The molecular pathology of cognitive disability is turning out to be as heterogeneous as the condition itself, with unexpected complexities even in apparently simple gene-deletion syndromes. One remarkable finding from studies on X-linked mental retardation is that mutations in different small guanosine triphosphate (GTP)–binding proteins result in cognitive disability without other somatic features. Advances are also being made in cognitive disability with polygenic origins, such as dyslexia and autism. However, the genetic basis of mild intellectual disability has yet to be satisfactorily explained.

Cognitive disability, or mental retardation (MR), is a common condition, affecting about 3% of the population,[1,2] and is associated with a series of social and medical handicaps. Yet we have almost no effective treatment and little to offer beyond support to carers and psychological or pharmacological intervention for any comorbid behavioral disorder. The size of the problem is matched only by our ignorance as to its causes. There can be little doubt that cognitive disability is extremely heterogeneous, encompassing a gamut of both social and biological conditions, yet, in an age when we have the draft sequence of the human genome, it is disappointing that we still know so little about the genetic abnormalities that result in MR. Genetic abnormalities, as we explain below, are without doubt a major contributor to moderate and severe cognitive disability, but despite recent advances in uncovering the molecular basis of some forms of MR, our understanding of the pathogenesis of the condition is still limited. Consequently, the chances of improving care are also limited; inadequate understanding of the origins of cognitive disability remains a major challenge for medical practice.

The extent to which genes are involved

The causes of cognitive disability vary with the severity of the condition: moderate-to-severe intellectual disability (defined as an intelligence quotient [IQ] score less than 50) is much more likely to be due to a single pathological cause (genetic or environmental) than mild MR (defined as an IQ score between 50 and 70), which is often thought to be multifactorial in origin. Chromosomal and genetic disorders account for 30% to 40% of moderate-to-severe MR; environmental insults explain a further 10% to 30%, and the cause is unknown in about 40% of cases.[3-7] Genetic and environmental causes explain, in roughly equal proportions, about 30% of mild intellectual disability; an etiological diagnosis is not obtained in the remaining 70% of cases.[8-13]

Table I summarizes data from epidemiological studies of low IQ, following the convention of separating mild disability from moderate to severe. Overall, the results reveal a distinction between the two groups. While controversy has long surrounded the extent to which genetic

Author affiliations: Department of Psychiatry, Oxford University, Oxford, UK

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Address for correspondence: Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK
(e-mail: jf@molbiol.ox.ac.uk)

Selected abbreviations and acronyms

AS	*Angelman syndrome*
ATRX	*alpha-thalassemia X-linked mental retardation syndrome*
CLS	*Coffin-Lowry syndrome*
CREB	*cyclic adenosine monophosphate response element–binding protein*
CTAF	*conotruncal anomaly face syndrome*
DGS	*DiGeorge syndrome*
GAP	*GTPase-activating protein*
GDI	*guanosine nucleotide dissociation inhibitor*
GDP	*guanosine diphosphate*
GTP	*guanosine triphosphate*
GTPase	*guanosine triphosphatase*
MAPK	*mitogen-activated protein kinase*
MR	*mental retardation*
NF1	*neurofibromatosis type 1*
PWS	*Prader-Willi syndrome*
snoRNA	*small nucleolar RNA*
VCFS	*velocardiofacial syndrome*
XLMR	*X-linked mental retardation*

variation contributes to variation in intellectual function, there is now little doubt that moderate-to-severe intellectual disability is due primarily to chromosomal and genetic abnormalities. The largest individual contributors are Down's syndrome, chromosomal rearrangements, and X-linked mental retardation (XLMR) *(Table I)*. Small chromosomal rearrangements, affecting the ends (telomeres) of chromosomes have emerged as a common cause in cases until recently regarded as idiopathic,[14] and it is likely that a considerable proportion of cases of unknown etiology will also be found to have a genetic origin.

The picture is less clear for IQ scores between 50 and 70. The importance of polygenic influences is inferred from the results of twin, family, and adoption studies for normal IQ measures, and rarely from direct investigation of families with low IQ; studies evaluating biological and environmental risk factors in this group are singularly lacking, but there are indications that single-gene conditions and chromosomal abnormalities may be more frequent than previously assumed.

Table II presents data on the genetic basis of conditions for which there is evidence that mutations give rise directly to intellectual disability. The table lists conditions where the genetic effects on intellectual function are thought to be relatively immediate, that is to say where no obvious developmental abnormality of the brain or progressive destruction of neuronal tissue results in cognitive impairment. The conditions are discussed in more detail in the following sections.

Cause	IQ less than 50	IQ between 50 and 70
Genetic	47	10
Down's syndrome	33	5
Autosomal aneuploidy	2	1
Sex chromosome aneuploidy	<1	1
Subtelomeric rearrangements	3	<1
Fragile X	2	<1
Single-gene disorder	6	2
Environmental	19	10
Prenatal	4	3
Perinatal	10	4
Postnatal	5	3
Unknown	34	80

Table I. The causes of intellectual disability. IQ, intelligence quotient.

When we consider the pathogenesis of intellectual disability, it is important to bear in mind that the phenotype involves multiple domains of intellectual functioning, often broadly divided into verbal and performance skills, but also encompassing capacities such as memory and attention, where performance is not traditionally seen as central to intellectual ability. Unfortunately, we do not know whether the domains that psychologists recognize correspond to the way genes operate, whether, for instance, verbal and performance skills can be separated at a genetic level.

Information is lacking about genetic influences on the domains of both normal and abnormal intellectual functioning. Studies of the heritability of intelligence, a measure of the extent to which genes contribute to the variation in intellectual functioning in the population, have mostly been carried out on overall measures of cognitive function, such as IQ, although more recent work on speech and language development is beginning to indicate that genetic effects that have more specific influences can be identified.[15,16] Similarly, there have been few detailed psychometric investigations of people with intellectual disability due to a specific genetic lesion, so we do not know whether cognitive functioning is abnormal over all domains or whether there are discrete abnormalities. In fact, as discussed later, there is some evidence in favor of the latter hypothesis.

Genetic mapping techniques and molecular cloning have made it possible to investigate disorders where the relationship between intellectual disability and genetic defect might be immediate. These are conditions where there are no noticeable alterations in brain structures and the cause of cognitive impairment is difficult to find. In general, this distinction is reflected in the division of MR into syndromic and nonsyndromic conditions. In syndromic MR, the phenotype includes additional physical abnormalities (such as facial dysmorphism or minor abnormalities of the hands and feet), while in nonsyndromic MR the only abnormality is cognitive impairment.

It might appear that genetic lesions are directly responsible for intellectual disability more commonly in nonsyndromic than in syndromic conditions, but it should be borne in mind that, without an understanding of the pathogenesis, this is only an assumption. For example, phenotypes vary considerably and mutations in the same gene may give rise to both syndromic and nonsyndromic intellectual disability: mutations in *RSK2* give rise to Coffin-Lowry syndrome (CLS) and to nonspecific intellectual disability,[17] and mutations in different parts of the *ATRX* gene produce either syndromic or nonsyndromic MR.[18] Nevertheless, some remarkable advances in X-linked nonsyndromic intellectual disability are uncovering genes that act directly on cognition, probably through central nervous system (CNS) development.

Syndromic intellectual disability

Mendelian disorders

Almost all recognized Mendelian intellectual disability is X-linked. This is because X-linked recessive disease is compatible with the occurrence of affected members in multiple generations; it is therefore both recognizable as an inherited condition and amenable to genetic mapping. X-linked intellectual disability (ie, XLMR) is common: the frequency is estimated to be 1.8 in 1000 males with a carrier frequency of 2.4 in 1000 females.[19] The number of recognized conditions continues to increase: currently 210 have been described, 126 mapped, and 32 cloned.[20]

Fragile X syndrome is the commonest form of XLMR, with a prevalence of approximately 1 in 5000 males and causes intellectual disability in about 1 in 8000 females.[21] Affected individuals have a folate-sensitive fragile site in the region Xq27.3, associated with an expansion of a trinucleotide repeat (CGG) in the 5'-noncoding region of a gene that encodes an RNA binding protein termed FMR1.

Despite being one of the early triumphs of positional cloning, the function of FMR1, and in particular how its deficiency gives rise to intellectual disability, is still not understood. In the normal brain, the FMR protein is found in nearly all neurones.[22] It can bind RNA, including its own transcript, and it has been postulated that the FMR protein has a role in the machinery of translation and, as it shuttles between nucleus and cytoplasm, that it may be involved in mRNA export.[23] One explanation for the effect of the gene on brain function is that it plays a role in the maturation and pruning of dendritic spines during brain development.[24]

Mutations in factors that regulate gene expression are emerging as an important genetic cause of intellectual disability. Two syndromic conditions have been found in which the gene acts as a transcriptional regulator through its effect on chromatin. In Rett's syndrome, a progressive neurological disorder that affects females almost exclusively, mutations have been found in methyl-CpG-binding protein 2 (MeCP2).[25] MeCP2 selectively binds CpG dinucleotides in the mammalian genome and mediates transcriptional repression through interaction with histone deacetylase and the corepressor SIN3A. In the alpha-thalassemia X-linked mental retardation syndrome (ATRX), mutations in *ATRX* give rise to characteristic developmental abnormalities including severe MR, facial dysmorphism, urogenital abnormalities, and alpha-thalassemia. The gene contains sequence motifs that indicate that it belongs to a group of proteins that to bind to chromatin.[26] At a molecular level, the mutation has effects on the pattern of genomic methylation, consistent with the role of *ATRX* in chromatin remodeling.[27] The pleiotropic effects of mutations in *MECP2* and *ATRX* could result from the regulated expression of a restricted class of genes.

Investigation of a syndromic MR condition, CLS, has led to the discovery of the involvement of another signaling pathway in cognitive impairment, namely the MAPK-activated signaling pathway (MAPK for mitogen-activated protein kinase). CLS is characterized by severe psychomotor retardation, facial and digital phys-

Disorder	Genetic abnormality	Chromosomal region	Gene and/or product	Function
● Nonspecific intellectual disability				
XLMR	Single gene mutation	Xp	*IL1RACPL*	IL-1–signaling pathway
XLMR	Single gene mutation	Xp	*TM4SF2*	Interaction with beta-1 integrins
XLMR	Single gene mutation	Xq	*Rho-GAP* (*OPHN1*)	Rho-GTPase cycle
XLMR	Single gene mutation	Xq	*PAK3*	Rho-GTPase cycle
XLMR	Single gene mutation	Xq	*GDI1*	Rab-GTPase cycle
XLMR	Single gene mutation	Xq	*ARHGEF6*	Rho-GTPase cycle
XLMR	Single gene mutation	Xq	*FMR2*	Unknown
● Syndromic intellectual disability (mutations in a single gene)				
Fragile X (FRAXA)	Single gene mutation	Xq	*FMR1*	Unknown
ATRX syndrome	Single gene mutation	Xq	*ATRX*	Abnormal methylation-transcriptional regulator
Duchenne muscular dystrophy	Single gene mutation	Xp	Dystrophin	Cytoskeletal component
Rett's syndrome	Single gene mutation	Xq	Methyl-CpG-binding protein 2	Abnormal methylation-transcriptional regulator
Coffin-Lowry syndrome	Single gene mutation	Xp	*RSK2*	Ras–MAPK-signaling pathway
● Syndromic intellectual disability (segmental aneusomy)				
Rubinstein-Taybi syndrome	Single gene mutation	16p	*CBP*	Transcriptional coactivator
Williams' syndrome	Segmental monosomy	7q	*LIM1* kinase	Synapse formation and maintenance?
Turner's syndrome	Segmental monsomy	X	Multiple genes?	Unknown
Prader-Willi syndrome	Segmental monosomy/ parent-of-origin imprint	15q	Multiple genes?	Unknown
Angelman syndrome	Single gene mutation/ parent-of-origin imprint	15q	*UBE3A*	Ubiquitin-mediated protein degradation
DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes	Segmental monosomy	22q	Multiple genes?	Transcriptional regulators?
Down's syndrome	Segmental trisomy	21q	?Minibrain	
● Complex disorders				
IQ	Quantitative trait locus	?4p	Unknown	
Autism	Quantitative trait locus	?1p, ?4p, ?6q, ?7q, ?13q, ?15q, /16p,	Unknown	

Table II. The genetic basis of conditions for which there is evidence that mutations give rise directly to intellectual disability. ATRX, alpha-thalassemia X-linked mental retardation syndrome; XLMR, X-linked mental retardation; IL-1, interleukin-1; IQ, intelligence quotient; MAPK, mitogen-activated protein kinase.

ical anomalies, and progressive skeletal deformation. The disorder was mapped by linkage to the region Xp22.2 and mutations discovered in a positional candidate gene *RSK2* (also known as *RPS6KA3*).[28] RSK2 mediates growth factor induction of cyclic adenosine monophosphate response element–binding protein (CREB) phosphorylation, as part of a signaling pathway whereby Ras-MAPK and Ras signals are transmitted to the nucleus to activate gene expression. Remarkably, mutations in *RSK2* give rise to nonsyndromic MR: patients in an XLMR family with neither facial, digital, nor skeletal anomalies compatible with CLS, but with mild MR, have been found to have a mutation in exon 14 of the gene, resulting in a conservative amino acid change.[17] The pathogenesis remains obscure.

Segmental aneusomy syndromes

A number of genetic conditions associated with intellectual disability have been found to be due to small chromosomal deletions or duplications (typically less than 5 megabases) and are known as segmental aneusomy syndromes *(see Table II)*.[29] The small size of some of the regions has enabled a search for dosage-sensitive genes. However, in order to prove that a deleted gene is indeed dosage-sensitive, it has been necessary to find families with point mutations in the gene that segregate with intellectual disability. This has been achieved with Rubinstein-Taybi syndrome (characterized by abnormal craniofacial features, broad thumbs, and intellectual disability), which can arise from monosomy of a small region in 16p13.3.[30] The responsible gene expresses the CREB-binding protein (CBP).[31]

Unfortunately, this approach has not been so successful for other segmental aneusomies. Williams-Beuren syndrome is a neurodevelopmental disorder characterized by congenital heart disease, infantile hypercalcemia, dysmorphic facial features, and cognitive disability. It is due to haploinsufficiency of genes in the region 7q11.[32] It is known that mutations affecting the elastin gene give rise to the supravalvular aortic stenosis, but there are still at least 15 candidate genes that could be involved in the unusual cognitive profile of the syndrome. These include a number of transcriptional regulators, such as Williams' syndrome transcription factor, which contains a plant homeodomain (PHD), LIMK1, which contains one PHD motif followed by a bromodomain, and the *WBSCR14/WS-bHLH* gene, which encodes a basic-helix–loop–helix leucine zipper, characteristic of a subclass of transcription factors.[33]

Two clinically distinct disorders, Prader-Willi and Angelman syndromes (PWS and AS), arise from abnormalities of a small region in 15q11-q13.[34] These syndromes have characteristic and distinct neurobehavioral profiles: in AS the retardation is severe (very few affected individuals can talk) and there is ataxia, seizures, abnormal EEG, microcephaly, facial dysmorphism, hyperactivity, and paroxysmal laughter. By contrast, in PWS, the MR may be only mild; there is a characteristic facial appearance and a specific behavioral abnormality, ie, hyperphagia resulting in severe obesity.

Despite the phenotypic differences, the basic defect is the same in the two disorders: a failure of parent-of-origin–specific gene expression. If both copies of chromosome 15 derive from the mother then the individual will have PWS; if both are from the father then the phenotype is AS. The basic defect is not simply a dosage effect; it turns out that about a quarter of cases of PWS are not due to a deletion but to the inheritance of two maternal copies of chromosome 15 (rather than the usual situation of one maternal and one paternal). Conversely, two paternal copies of chromosome 15 result in AS. The chromosomal region is said to bear a parent-of-origin imprint, of which the molecular signature is a difference in DNA methylation.[35] Mutations in a ubiquitin protein ligase gene (*UBE3A*) have been found in a few rare families with AS.[36] The gene product is part of a widely used ubiquitin-mediated protein degradation pathway.

PWS is probably not the result of a defect in a single gene. Seven genes (and candidate genes) have been identified in the PWS region, all of which appear to be brain specific.[29] It is not known if the phenotype is due to an abnormality in a single gene. However, there is now some evidence to suggest that abnormal RNA editing, due to misregulation of guide RNAs, mediates the defect in PWS.

The nucleolus contains a large number of small RNAs, termed small nucleolar RNAs (snoRNAs); the majority of these snoRNAs function in the posttranscriptional modification of rRNA nucleotides. However, it is now clear that the action of methylation guide snoRNAs goes beyond the field of ribosome biogenesis. Recently, three brain-specific snoRNAs, which are subject to genomic imprinting in mice and humans, have been discovered within the 15q11 critical region for PWS and AS.[37] Unusually, they do not have appropriate antisense elements, so their function is not clear, but one has a similarity to the mRNA encoded by the gene for the serotonin receptor–2C. The sequence matches a conserved region subject to both alternative splicing and adenosine-to-inosine editing.[38] Because of the known involvement of serotonin in appetite control and cognition, this finding raises the intriguing possibility that the defect in PWS involves a defect in serotonin neurotransmission.

Similar problems beset attempts to understand how deletions in the region 22q11 give rise to cognitive disabilities.[39] DiGeorge (DGS), velocardiofacial (VCFS), and conotruncal anomaly face (CTAF) syndromes are different phenotypic manifestations of deletions within 22q11. Both DGS and VCFS are associated with intellectual disability; additionally psychosis is found in some patients with VCFS. The region most consistently contains at least 14 genes. Cloning and sequencing of the entire region has not identified any obvious candidates for the cognitive defect and it now seems likely that the syndromes arise from combined monosomy of more than one gene.

Aneuploidy

Given the difficulties encountered in investigating the segmental aneusomies, then trying to identify specific genes responsible for the abnormalities found in aneuplodies, where there is an abnormality in the number of a whole chromosome, might seem impossible. However comparison between individuals with partial aneuploidy of a chromosome has allowed the definition of critical regions in both Down's syndrome (trisomy 21)[40,41] and Turner syndrome (XO).[42]

Candidate genes for some of the somatic features of Turner syndrome have been proposed: *SHOX/PHOG* encodes a homeodomain protein that may explain the short stature,[43,44] while *RPS4Y* encodes an isoform of a ribosomal small subunit protein.[45,46] Identification of genes for features other than short stature has been problematic. There are no candidates for the unusual cognitive profile. However, there is one report that Turner syndrome patients with a paternally derived X chromosome have superior verbal abilities and skills involved in social interactions.[47,48]

In work on Down's syndrome, attention has been focused on the region 21q22.2 as a potential site for dosage-sensitive genes that affect learning and behavior. On the basis of transgenic mouse experiments, a homologue of the *Drosophila* gene *minibrain* has been identified as a candidate.[49,50] The gene encodes a tyrosine/serine kinase expressed in developing neuroblasts and a human gene lies in the Down's syndrome–critical chromosomal region 21q22. However, as with the segmental aneusomies, there is a proliferation of Down's syndrome critical region (*DSCR*) genes; as yet no definitive evidence of their role in intellectual disability has been provided.

Nonsyndromic intellectual disability

Perhaps the most striking finding to emerge from the study of nonsyndromic XLMR is the discovery of mutations in genes affecting different components of the Rho-signaling pathway *(Table II)*.[51] Two genes, oligophrenin-1 (*OPHN1*) and *ARHGEF6*, directly affect the Rho-activation cycle. *OPHN1* encodes a Rho-GAP protein (GAP for GTPase [guanosine triphosphatase]–activating protein) that stimulates the intrinsic GTPase activity of Rho, Rac, and Cdc42.[52] *ARHGEF6* encodes a small cytoplasmic protein, homologous to proteins that activate Rho-GTPases by exchanging guanosine diphosphate (GDP) for guanosine triphosphate (GTP).[53] A third gene found to be mutated in XLMR families is *PAK3*.[54] *PAK3* may well be a downstream effector of the Rho-GTPases Rac and Cdc42 putting the message forward to the actin cytoskeleton[55] and to transcriptional activation.

A subfamily of Rab-GTPases is also implicated in MR.[56] Guanosine nucleotide dissociation inhibitor–1 (GDI1) inhibits GDP dissociation from Rab3a by binding to GDP-bound Rab proteins and appears to be crucial in maintaining the balance between the GTP- and GDP-bound forms of Rab3. Rab3a is a small GTP-binding protein that functions in the recruitment of synaptic vesicles for exocytosis[57,58] and is essential for long-term potentiation (LTP) in hippocampal neurons.[59] All Rab proteins are hydrophobic by nature and need GDI to mediate membrane attachment and retrieval.[60,61] Rab exists exclusively as a soluble complex with GDI in the cytoplasm, where it forms a reservoir to deliver Rab to the membrane during assembly of a transport vesicle.

How might the biology of the small GTP-binding proteins explain human cognitive function? One possibility is that mutations disrupt the normal development of axonal connections.[62-64] This would fit with the known cell biology of the Rho-GTPases.[65] Growth cones of developing axons find their way through the brain by sampling molecular signals, helped by GTPases.[66] Whereas Cdc42 and Rac1 are involved in the formation of lamellipodia and filopodia,[67] inhibition of Rho, Rac, and Cdc42 also reduces dendrite formation.[68] Cognitive dysfunction could therefore be due to a failure to establish correct neuronal connections during CNS development.

A second possibility is that synaptic function is compromised. This view is supported by what is known about the function of Rab3a in exocytosis.[69] Synaptic vesicles contain Rab3a, the most abundant Rab protein in the brain and, in one model, exocytosis leads to the dissociation of Rab3a from the vesicle.[58] Since Rab3a-deficient mice have no fundamental deficits in synaptic vesicle exocytosis,[57] the protein is not essential to the process, but is required to maintain a normal reserve of synaptic vesicles. The GDI1 mutation, by disrupting Rab3a traffic, is expected to alter neurotransmitter release, which might, in turn, account for the intellectual impairment.

Why is the effect of the mutation specific? Both the developmental and synaptic transmission account of Rho-GTPase involvement must explain why only neurones involved in cognitive systems are disrupted. One likely explanation is that the mutations only partly disrupt the brain system on which they operate, but it could also be that compensatory mechanisms, effective in other cell types, fail when it comes to neuronal processes involved in cognitive processing.

Interestingly, there is also evidence that the cognitive defects associated with neurofibromatosis type 1 (NF1) derive from an effect on the Ras pathway. NF1 is a common familial tumor syndrome with an incidence of 1 in 3500. It is a Mendelian autosomal dominant trait primarily affecting brain and skin. Some 30% to 65% of the affected children have learning difficulties, but only 4% to 8% have MR.[70,71] The NF1 gene, neurofibromin, has a GAP-related domain linking it to signal transduction pathways.[72] Molecular investigation of a family with NF1 identified a mutation that disabled the Ras-GTPase–activating function.[73] Affected children had an IQ range of 80 to 89 and impairment in both language and motor development, indicating that the GAP of neurofibromin is critical to the development of these functions.

The function of other nonsyndromic XLMR genes is less clear *(Table II)*. *TM4SF2* encodes a member of a group of proteins that complex with integrins, proteins that function as αβ-heterodimers mediating adhesive interactions with the extracellular matrix and also acting to transduce signaling. Evidence for the role of integrins in human cognition came from the isolation of a mutation in *TM4SF2* in a patient with nonsyndromic XLMR.[74] Analysis of the expression pattern of *TM4SF2* using mRNA in situ hybridization on mouse brain sections revealed that it is ubiquitously expressed early in brain development.

IL1RAPL (interleukin-1 [IL-1] receptor accessory protein–like) has, as its name suggests, homology to IL-1 receptor accessory protein. The function of the *FMR2* gene, associated with mild intellectual disability gene, is also unknown: it encodes a nuclear protein that may regulate transcription and available data indicate that it functions at the cell surface. The *IL1RAPL* gene was identified by analyzing overlapping microdeletions in Xp22.1-21.3 associated with nonspecific MR. Using DNA sequence from this region, a gene was found with a weak homology to interleukin-1 receptor accessory protein. Nonoverlapping deletions encompassing the *IL1RAPL* gene were found[75] and a point mutation in this gene was discovered segregating with MR in an unrelated family. The nonsense mutation introduces a premature stop codon that leads to a barely detectable level of *IL1RAPL* transcript. The expression pattern of *IL1RAPL* mRNA on mouse brains is also consistent with a role in learning in memory, as it is present in the granular layer of the dentate gyrus and the pyramidal layer of the hippocampus.

Examples of autosomal single-gene defects resulting in intellectual disability are very rare. However, there is one good example of a four-generation family with a speech and language disorder that, remarkably, segregates as an autosomal dominant condition.[76] The speech and language difficulties are part of a broader syndrome that includes a lower than average IQ; affected members also have a pronounced impairment in articulation.[77] The gene has been mapped to the chromosomal region 7q,[78] a region also implicated in studies of autism, a polygenic condition, one characteristic of which is abnormal speech development.[79] Molecular characterization of this unusual Mendelian disorder could well provide new insights into the biology of language development.

Polygenic effects on intellectual disability

There are a small number of rare developmental disorders that result in intellectual disability and are thought to have a polygenic basis. Among these, autism (a condition marked by abnormal language and social development, together with obessional behavior) is known to have an extremely high heritability (over 90%).[80] The difficulties besetting attempts to identify the predisposing loci are common to all attempts to dissect the genetic basis of complex, polygenic phenotypes, with different studies reporting different findings *(Table II)*.[79,81] At present, there is some replicated evidence pointing to a locus on chromosomal region 7q.[82] Mapping the loci determining quantitative variation in IQ has yet to yield convincing results. There has been more success mapping the genes that influence a specific intellectual function, namely reading. A locus at 6p21.3 is one of the few replicated findings in behavioral genetics, with a number of studies reporting that the locus is relatively specific for reading disability.[83-87]

Assuming that the approach does work and that localizations for polygenic variation in intellectual disability are found, we are faced with the question of whether genes that determine variation overlap with the mutations described above. Conceivably, the same pathways are involved, in which case the combination of mapping and molecular pathology screening would be ideally placed to identify the many genes that are responsible for intellectual disability. ❑

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Bases genéticas de la incapacidad cognitiva

Desde hace bastante tiempo se ha reconocido la influencia genética en la incapacidad cognitiva, pero sólo recientemente el análisis molecular ha comenzado a producir conocimientos acerca de la patogénesis de esta común e incapacitante enfermedad. La disponibilidad de las secuencias del genoma ha permitido la caracterización de las supresiones y trisomías cromosómicas que llevan a una incapacidad cognitiva y se han descubierto mutaciones en las raras condiciones de gen único. La patología molecular de la incapacidad cognitiva está resultando ser tan heterogénea como la condición misma de la incapacidad, con complejidades insospechadas en síndromes aparentemente simples de supresión de genes. Un hallazgo notable de los estudios de retardo mental relacionado con el cromosoma X es que las mutaciones en diferentes proteínas pequeñas unidas a guanosina - trifosfato (GTP) se traducen en incapacidad cognitiva sin otras características somáticas. También se están realizando avances en la incapacidad cognitiva con orígenes poligénicos como la dislexia y el autismo. Sin embargo, las bases genéticas de la incapacidad intelectual leve aún deben ser explicadas satisfactoriamente.

Bases génétiques du déficit cognitif

Si l'importance de la génétique dans les déficits cognitifs est connue depuis longtemps, ce n'est que depuis peu que l'analyse moléculaire est en mesure de fournir un nouvel éclairage sur la pathogenèse de ces états tant courants qu'invalidants. Grâce aux séquences génomiques disponibles dans les bases de données on a pu caractériser des délétions chromosomiques et des trisomies à l'origine de déficits cognitifs, tandis que des mutations monogéniques dans certaines formes rares sont en cours de découverte. De fait, la pathologie moléculaire du déficit cognitif s'avère aussi hétérogène que le déficit lui-même, présentant des complexités inattendues, même dans certains syndromes de délétion génique apparemment simples. Des études portant sur le retard mental lié au chromosome X ont permis la découverte remarquable de mutations sur différentes petites protéines liantes de la guanosine triphosphate (GTP) qui entraînent un déficit cognitif en l'absence de tout autre expression somatique. Des progrès sont également en cours dans l'exploration des déficits cognitifs d'origine polygénique comme la dyslexie et l'autisme. Il n'en reste pas moins qu'en dépit de ces acquisitions récentes, les bases génétiques du déficit cognitif léger attendent toujours une explication satisfaisante.

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