Genetics of intellectual disability
H Hilger Ropers

Early onset intellectual disability (ID) is one of the largest unsolved problems of health care. Yet, it has received very little public attention in the past because many health care professionals do not perceive it as a health condition but as a social or educational issue. In severe ID, cytogenetically visible chromosomal abnormalities like trisomy 21 continue to be common, but since the introduction of array CGH, it is becoming clear that submicroscopic deletions and duplications are equally frequent, yet previously overlooked causes of ID. Until recently, the search for gene defects causing ID has focused on the X-chromosome. So far, >80 genes have been implicated in X-linked ID, largely owing to coordinated efforts of international consortia, and mutations in these genes account for >50% of the families with this condition. Autosomal forms, either due to dominant de novo mutations or to recessive gene defects, are presumably (far) more common than X-linked ones, and their molecular elucidation is a new challenge for research in this field. As recently shown, autosomal recessive ID (ARID) is extremely heterogeneous, and common forms are unlikely to exist. Ongoing studies into the function of ID genes are shedding more light on the pathogenesis of this disorder, and there is reason to believe that at least some genetic forms of ID may be amenable to drug treatment.

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Introduction

Early onset intellectual disability (ID), or ‘mental retardation’ (MR),\(^1\) has been defined as ‘a significantly reduced ability to understand new or complex information, to learn new skills (…), with a reduced ability to cope independently (…), which started before adulthood, with a lasting effect on development’ [1]. To diagnose ID and to assess its severity, standardized IQ tests such as the Wechsler Adult Intelligence Scales (WAIS) and the Wechsler Intelligence Scales for Children (WISC) are being used, although these tests were not primarily devised for this purpose (see [2\(^\ast\)] and references therein). In Western countries, the prevalence of ID (IQ < 70) is 1.5–2%, and 0.3–0.5% are severely impaired, with IQs of <50 [3]. As documented by various studies (e.g. [4–7]), the prevalence of ID tends to be even higher in developing countries. This observation has been ascribed to a variety of non-genetic factors such as malnutrition, cultural deprivation and poor health care. In several of these studies, parental consanguinity was identified as another important etiologic factor, which is supported by the finding that inbreeding is associated with reduced cognitive performance [8]. Despite the enormous socio-economic costs of ID, which exceed those related to dementia [9,10], ID has received very little public attention in the past, partly because many health care professionals, NGOs and parent organizations do not perceive it as a health condition but as a social or educational issue [2\(^\ast\)].

It is generally assumed that mild forms of ID represent the lower end of the normal IQ distribution, which results from the interaction of many genes and non-genetic factors. By contrast, severe forms are thought to be due to catastrophic events, such as perinatal asphyxia and prenatal infections, or more often, specific genetic causes including chromosomal abnormalities or defects of single genes. During the past decade, significant progress has been made in the elucidation of genetic factors underlying severe ID. Cytogenetically visible chromosomal aberrations account for almost 15% of all cases [3]. Deletions and duplications that are too small to be detectable by conventional karyotyping seem to be equally important, previously overlooked causes of ID, as discussed below. X-linked gene defects are thought to be responsible for ~10% of the ID found in males, which means that there must be other factors to explain why cognitive impairment is far more common in males than females [11] (see also Skuse [12] and Nguyen and Disoteche [13]). The cause of ID is still unknown in up to 60% of the cases [14\(^\ast\)]. This leaves ample room for autosomal gene defects, either novel mutations giving rise to isolated cases with dominant forms of ID, or recessive forms, most of which will also appear as sporadic cases in the small families that are characteristic of industrialized countries.

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\(^1\) As discussed by Salvador-Carulla and Bertelli [2\(^\ast\)], this term should no longer be used.
Chromosomal aberrations and ID

Despite widespread prenatal diagnosis in older mothers, Down syndrome (trisomy 21) remains the most important single cause of ID [15,16]. Other numerical and structural aberrations are far less common, but taken together, cytogenetically visible chromosomal aberrations are found in one out of seven individuals with severe cognitive impairment [3]. After the recent introduction of high-resolution array CGH it has become apparent that small deletions and duplications are an equally important cause of ID. Using a BAC array that was designed to detect copy number variants (CNVs) in 130 genomic regions known to be flanked by low-copy repeats (LCRs), Sharp et al. [17] identified pathogenic rearrangements in 16 (or 5.5%) out of 290 patients with ID. In the largest cohort of patients with ‘idiopathic’ ID screened to date for copy number variants with whole genome tiling path BAC arrays, de Vries et al. [18] found apparently causative de novo deletions or duplications ranging in size between 100 kb and several megabases in almost 15% of their patients. Three quarters of these CNVs had not been reported before and were not flanked by LCRs, suggesting that recurrent genomic disorders that are due to nonallelic homologous recombination account only for a minority of cases. Non-homologous end joining and more recently, homologous recombination account only for a minority of recurrent genomic disorders that are due to nonallelic homologous recombination. The most common duplication encompasses the 1p36.1 region that is found in ~1% of the patients with ‘idiopathic’ ID [31].

Array CGH has also been instrumental in delineating the functional defect causing ID in several of these disorders, including CHARGE, ‘Peters plus’ and Pitt-Hopkins syndrome that could be ascribed to defects of specific genes (reviewed in [32]). Similarly, loss of one copy of the MAPT gene seems to be responsible for the developmental delay seen in patients with 17q21.31 microdeletions [17,33,34], and mutations causing loss or gain of TBX1 activity have been shown to mimic the common 22q11.2 deletion or duplication syndromes [35]. Previously, mutation screening had revealed that haplinsufficiency of the RAI1 gene is sufficient to explain the characteristic features of Smith-Magenis syndrome [36], and the same holds true for the UBE3A gene and Angelman syndrome [37]. Thus, CNVs provide new and exciting opportunities for identifying gene defects that are associated with ID, and they promise to shed more light on the pathogenesis of this heterogeneous condition.

Moderate to severe ID is found in about 3% of all patients carrying de novo balanced chromosome rearrangements [38], and as discussed in more detail elsewhere [32], systematic breakpoint mapping in such patients has led to the identification of numerous (candidate) genes for ID. Recently, efficient methods involving chromosome sorting and high-resolution array CGH [39] or next-generation sequencing [40] have been developed, which greatly facilitate the molecular characterization of breakpoint regions and the identification of truncated genes. At the same time, several studies have shown that before such investigations, it is important to rule out submicroscopic deletions or duplications in the entire genome, which have been observed in a proportion of these cases, particularly in severely affected patients with congenital abnormalities [41,42].

X-chromosomal forms of ID

X-linked forms of ID (XLID) are easily identifiable because of their characteristic inheritance pattern. The human X-chromosome carries only about 4% of the protein-coding genes in the human genome, but X-chromosomal defects are thought to account for 8–12% of the ID seen in males (e.g. see [11]). This has rendered the X-chromosome an attractive target for research into the molecular causes of ID. To date, >80 genes for X-linked ID have been identified, the vast majority during the past decade as a result of systematic studies that became possible after the collection of large cohorts of families by international consortia. Mutations in ~30 of these genes have been found in non-syndromic, or ‘pure’ forms of XLID, where ID is the only clinical abnormality, and mutations in these genes may account for >50% of such cases. However, many of these genes have also been implicated in syndromic XLID, and clinical separation of these two forms is difficult. As more patients with defects in the same gene are being found, it will become easier to recognize specific clinical patterns, and consequently, the proportion of non-syndromic cases is likely to decrease.

Recent efforts to screen most of the ~900 annotated X-chromosomal genes in ~250 XLID families have led to the identification of two or several protein-truncating mutations in eight novel genes, as well as a plethora of sequence variants with as yet unclear clinical significance [43]. So far, potentially relevant sequence changes were only found in a minority of these families (personal communication from M Stratton, Hinxton, on behalf of the IGOLD Consortium). There are various explanations for this, including the possibility that relevant mutations were missed by exon sequencing, such as mutations in non-coding sequences or small submicroscopic duplications. The most common duplication encompasses...
the MECP2 gene; it is found in about 1% of males with moderate to severe XLID [44]. Apparently pathogenic CNVs that are larger than 100 kb have been found in 5% of >400 families of the European MRX Consortium [45,46] (G Froyen, Leuven, personal communication), indicating that such changes are not common enough to account for the ‘missing’ mutations in the IGOLD study. Another possibility is that some of the smaller families of this study do not have X-linked ID, which is certainly also true for other cohorts.

Since the previous review on X-linked MR, which appeared in this journal two years ago [47], 16 additional genes have been implicated in XLID. These are listed in Table 1. Large-scale mutation screening is beginning to shed light on the relative frequency of these defects. After the Fragile X syndrome, which may account for 25% of all families with XLID [48], ARX mutations rank second, giving rise to non-syndromic XLID and to a variety of syndromic forms in >5% of the families ([49], see also [50] and references therein). CUL4B, JARID1C and SLC6A8 mutations are all relatively frequent, each accounting for 2–3% of the families, whereas defects of all other known XLID genes seem to be significantly less common, in the 1% range or (far) below. These are raw estimates based on the number of mutations reported and the number of families screened, and they are biased in various ways, for example, because of varying ‘contamination’ of the relevant cohorts with syndromic forms of ID, which is certainly also true for other cohorts.

Table 1. Large-scale mutation screening is beginning to shed light on the relative frequency of these defects. After the Fragile X syndrome, which may account for 25% of all families with XLID [48], ARX mutations rank second, giving rise to non-syndromic XLID and to a variety of syndromic forms in >5% of the families ([49], see also [50] and references therein). CUL4B, JARID1C and SLC6A8 mutations are all relatively frequent, each accounting for 2–3% of the families, whereas defects of all other known XLID genes seem to be significantly less common, in the 1% range or (far) below. These are raw estimates based on the number of mutations reported and the number of families screened, and they are biased in various ways, for example, because of varying ‘contamination’ of the relevant cohorts with syndromic forms of ID, which is certainly also true for other cohorts.

Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>OMIM</th>
<th>Function</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCCS</td>
<td>300056</td>
<td>Links heme group to cytochrome c in mitochondria</td>
<td>[120]</td>
</tr>
<tr>
<td>FANCB</td>
<td>300315</td>
<td>DNA repair, removal of DNA crosslinks</td>
<td>[121]</td>
</tr>
<tr>
<td>AP1S2</td>
<td>300629</td>
<td>Coated vesicle protein, required for synaptic development and function</td>
<td>[122]</td>
</tr>
<tr>
<td>SMC1A (SMC1L1)</td>
<td>300040</td>
<td>Belongs to cohesion complex, essential for correct mitotic chromosome segregation</td>
<td>[123], [124]</td>
</tr>
<tr>
<td>HUWE1</td>
<td>300697</td>
<td>E3 ubiquitin-protein ligase, mediates proteasomal degradation of target proteins</td>
<td>[125]</td>
</tr>
<tr>
<td>PORCN</td>
<td>300651</td>
<td>Endoplasmic reticulum transmembrane protein, processing of wingless proteins</td>
<td>[126], [127]</td>
</tr>
<tr>
<td>MED12</td>
<td>300188</td>
<td>Transcriptional coactivator, subunit of TRAP and ARC/DRIP complexes</td>
<td>[128], [129]</td>
</tr>
<tr>
<td>BRWD3</td>
<td>300553</td>
<td>Required for JAK/STAT signalling, cellular proliferation?</td>
<td>[130]</td>
</tr>
<tr>
<td>SRPX2</td>
<td>300642</td>
<td>Brain-expressed membrane protein</td>
<td>[131]</td>
</tr>
<tr>
<td>NXF5</td>
<td>300319</td>
<td>Export of mRNA from the nucleus to the cytoplasm</td>
<td>[46]</td>
</tr>
<tr>
<td>UBE2A</td>
<td>312180</td>
<td>E2 ubiquitin-protein ligase, required for post-replicative DNA damage repair</td>
<td>[132]</td>
</tr>
<tr>
<td>UPF3B</td>
<td>300298</td>
<td>Nuclear export and surveillance of mRNA</td>
<td>[43]</td>
</tr>
<tr>
<td>NDPF1</td>
<td>300078</td>
<td>Essential component of complex I of the respiratory chain</td>
<td>[130]</td>
</tr>
<tr>
<td>RPL17</td>
<td>312173</td>
<td>Structural constituent of ribosome; protein biosynthesis</td>
<td>[134]</td>
</tr>
<tr>
<td>SLC9A6</td>
<td>300231</td>
<td>Exchange of protons for Na(+) and K(+) across the mitochondrial inner membrane.</td>
<td>[135]</td>
</tr>
<tr>
<td>ARHGEF9</td>
<td>300429</td>
<td>GDP-GTP exchange factor GTPase Cdc42, targets gephyrin to synapses</td>
<td>[136]</td>
</tr>
</tbody>
</table>

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The strategy of choice for elucidating the molecular defects underlying ARID is homozygosity mapping in large consanguineous families, followed by mutation screening of candidate genes [57–59]. Recently, this strategy has been employed to identify several gene defects underlying autosomal recessive microcephaly and other syndromic forms of ARID [60–64]. By analogy with XLID, non-syndromic forms of ARID are thought to be more common than syndromic forms. Until 2007, however, very few loci and no more than three genes for non-syndromic ARID had been identified [65–67], because in industrialized countries, large families and parental consanguinity are rare.

In the only systematic effort so far to map and identify genes for non-syndromic ARID, Najmabadi et al. [68**] have performed homozygosity mapping in 78 consanguineous Iranian families with at least two intellectually disabled children. These studies showed that ARID is extremely heterogeneous, and they ruled out the
existence of common gene defects that account for more than a few percent of the patients. At the same time, these studies identified eight novel loci for non-syndromic ARID, including a complex deletion of the GRIK2 gene, which encodes the ionotropic glutamate receptor GLUR6 [69]. Continuation of these studies has revealed nine additional *bona fide* loci for non-syndromic ARID (Najmabadi, Kuss, Garshasbi, Kahrizi, Tzschach, Ropers and co-workers, unpublished). Including loci and genes identified by other groups ([70] and see below), this brings the total number of ARID loci to 22. The vast majority of these linkage intervals do not overlap, thereby confirming previous evidence that non-syndromic ARID is highly heterogeneous.

Recently, a protein-truncating mutation and a complex deletion involving the TUSC3 gene have been identified in a French and an Iranian family [71,72]. This renders TUSC3 the only ARID gene for which more than one mutation has been detected. An inactivating mutation in the FTO gene, previously implicated in obesity [73,74] has been described as another cause of ARID [75]. Thus, six genes for non-syndromic ARID have been identified to date, but in view of the growing interest in this previously neglected condition, it is safe to predict that their number will soon explode. Array-based SNP typing has paved the way for high-throughput homozygosity mapping in large consanguineous families with recessive disorders, and novel methods are being developed, which will greatly accelerate mutation screening and gene finding (see below).

**Function of ID genes—loose ends are beginning to meet**

Until recently, the function of most ID genes has remained largely obscure, but during the past two years, remarkable progress has been made in this field. Fragile X syndrome, the most common heritable form of ID that is caused by loss of function of the RNA-binding FMR1 protein FMRP, is thought to result from upregulation of group1 metabotropic glutamate receptor (mGluR) signalling [76]. Numerous recent studies have shed more light on the role of FMRP at the synapse and in dendritic mRNA transport. For example, it was shown that enhanced mGluR signalling leads to excessive internalization of AMPA receptors [77]. FMRP interactions with the postsynaptic scaffolding protein Homer are necessary for mGluR-induced long-term depression and translational activation [78], and FMRP controls the stability of mRNA encoding PSD-95, a key molecule regulating synaptic signalling and learning [79]. FMRP was shown to directly interact with the neurospecific kinesin KIF3C and to link this transport molecule with dendritic RNA granules [80]. Finally, Narayanan et al. [81] showed that upregulation of phosphatase 2A (PP2A) is responsible for rapid FMRP dephosphorylation after immediate group 1 mGluR stimulation, whereas extended mGlu activation results in mTOR-mediated PP2A suppression (for a recent synopsis, see Ronesi and Huber [82**]).

The ARX gene, implicated in cortical development and various forms of XLID, codes for a transcriptional repressor and activator in brain development (reviewed by Geicz et al. [49] and Friocourt et al. [83]), which has recently been shown to bind to TLE1 and other Groucho/transducin-linke enhancer of split proteins [84]. JARID1C, another common XLID gene [85,86] with a role in transcriptional regulation and chromatin remodelling, has been found to encode a histone H3 lysine 4 (H3K4) demethylase, which reverses trimethylated H3K4 to dimethylated and monomethylated products [87*], and to form a complex with the transcriptional repressor REST [88] and several other chromatin-modifying enzymes [89*].

PRSS12, the first gene implicated in non-syndromic autosomal recessive ID (NS-ARID), encodes the neuronal serine protease neurotrypsin [65]. Recently, Reif et al. [90*] showed that this protein specifically cleaves agrin, which is involved in the formation of filopodia on neuronal axons and dendrites [91,92]. Agrin cleavage generates an inactivating ligand of the Na+/K+-ATPase at CNS synapses, previously identified as the neuronal receptor for agrin [93]. These and recent studies on the expression of neurotrypsin in live hippocampal neurons [94] argue for an essential role of this protein in activity-dependent synapse remodelling.

CC2D1A, the third gene implicated in NS-ARID [67], codes for Freud-1, a neuronal calcium-regulated repressor of the serotonin (5HT1A) receptor [95*]. Recent studies have revealed that Freud-1 also binds to an intronic repressor element in the dopamine receptor D2 gene [96*]. Both receptors function as pre-synaptic autoreceptors regulating the neurotransmission of serotonin and dopamine, respectively, and have a role in memory and behaviour (see also Basel-Vanagaite et al. [97]). Previously, CC2D1A has been identified as an activator of NF-κB [98]. Because the NF-κB pathway is important for neural plasticity and memory, this finding may also explain why CC2D1A is indispensable for normal brain function in humans.

As the number of known ID genes increases and their function is elucidated, directly interacting genes are being discovered, and pathways are beginning to emerge. For example, several regulators and effectors of Rho GTPases that control the actin cytoskeleton and neurite outgrowth have been implicated in ID (reviewed by Ramakers [99]). More recently, it has been shown that genes involved in protein glycosylation are often mutated in (mostly syndromic forms of) ID (e.g. see Kornak et al. [100] and review by Zeevaert et al. [101]). Defects involving kinetochore proteins and other mechanisms interfering with normal
mitotic chromosome segregation are often found in ID associated with microcephaly [102–105]; and another, presumably very large group of ID genes is involved in transcriptional regulation and chromatin (re-)modelling, as exemplified by MECP2 (reviewed by Villard [106]) and JARID1C. As pointed out by Laumonnier et al. [107], many of the presently known genes for X-linked ID encode synapse proteins; therefore, genes coding for synapse proteins are also excellent candidates for the more numerous autosomal forms of ID.

Genes encoding synaptic proteins such as neuroligins 3 and 4 have not only been implicated in ID but also in autism [107,108]. De novo deletions encompassing neuroligin 1 (NRXN1), which bind neuroligins, have been identified as another cause of autism [109]. Moreover, common and rare sequence variants in another member of the neuroligin superfamily, the contactin-associated protein-like 2 (CNTNAP2), have been identified as risk factors for autism [110,111,112]. It is of note that NRXN1, and the directly interacting synaptic protein APBA2, have also been implicated in schizophrenia [113], suggesting that many forms of ID, autism and schizophrenia are functionally related, with synaptic dysfunction as a common denominator.

Outlook
Using commercially available next-generation sequencing systems, re-sequencing of >30 megabases of genomic DNA has become possible in a single experiment (reviewed by Bentley [114]), and oligonucleotide arrays have been employed for the quantitative isolation of DNA from defined genomic intervals [115,116]. Combination of these methods should greatly speed up the search for mutations in large deletion or linkage intervals, which is currently the rate-limiting step in the identification of novel ID genes, and render mutation detection in non-coding sequences economically feasible. Only about 1.2% of the human genome codes for protein, but 2.5–5% are subject to purifying selection (see Ponting and Lunter [117]); therefore, it is entirely possible that a significant proportion of the genetic variation causing or predisposing for disease involves non-coding sequences.

However, recognizing clinically relevant changes, for example, CNVs or single nucleotide exchanges, in a sea of functionally neutral sequence variants, will be a considerable challenge, which can only be met by studying very large cohorts of clinically well-characterized patients. The advent of the ‘$1000$ genome’, which may be only a few years off, will revolutionize genotype–phenotype comparisons in man, but at the same time, it will greatly aggravate the problem of how to make sense of all this genetic variation. Still, there is no doubt that whole genome sequencing will be a major asset for the identification of disease genes, and it will have almost immediate consequences for the diagnosis and prevention of ID and other genetic disorders. Even with the existing next-generation sequencing technology, it should be entirely feasible to develop a diagnostic test for mutations in all known ID genes. This will be particularly important for non-syndromic forms of ID, which cannot be distinguished clinically. In the long run, whole genome sequencing may become the method of choice for assessing all known genetic risks in a single experiment.

Ongoing studies to elucidate the function of ID genes are shedding more light on the pathogenetic mechanisms underlying disorders of brain development and function. Numerous of these studies have revealed relatively minor histologic changes, including subtle alterations of dendrite spacing and morphology. In parallel, confocal time-lapse and confocal imaging has revealed a remarkable structural plasticity of the brain, including dendrite and synapse formation and maintenance (see Ropers [47] and references therein). Together, these findings suggest that at least some of the genetic forms of ID may be amenable to drug treatment, possibly even after birth. Recent animal studies (see Dölen et al. [118] and references therein) have raised hopes that eventually, drug treatment may become available even for the Fragile X syndrome, the most common hereditary form of ID (see Bear et al. [119]).

Acknowledgements
I am grateful to Alan Bittles for alerting me to literature about parental consanguinity and ID; to Mike Stratton and the IGOLD Consortium for unpublished information concerning their large-scale mutation screening in XLID families; to Guy Froyen for unpublished data on the frequency of clinically relevant CNVs in XLID families; to Reinhard Ullmann, Andreas Kuss, Andreas Tzschach, Vera Kalscheuer, and Lars Jensen for critically reading this manuscript; and last but not least, to Gabriele Eder who assisted me with its preparation in various ways. This work was supported by the Innovations Fund of the Max Planck Society and the Deutsche Forschungsgemeinschaft (through SFB577).

References and recommended reading
Papers of particular interest, published within the period of the review, have been highlighted as:

● of special interest
●● of outstanding interest


The authors point out that despite its enormous socio-economic importance, intellectual disability (ID) is still a disregarded topic in medicine, and why this has to change.


The authors show that state-of-the-art cytogenetic and clinical examination of patients with developmental delay or ID yields a specific diagnosis in no more than 40% of the cases.


These papers indicate that both in Australia and in Chile, the prevalence of Down syndrome (DS) has been remarkably stable during the past decades and that DS remains a major cause of ID.


These papers indicate that both in Australia and in Chile, the prevalence of Down syndrome (DS) has been remarkably stable during the past decades and that DS remains a major cause of ID.


These authors show that roughly 75% of the de novo CNVs found in patients with ID are not recurrent and not flanked by low-copy repeats (LCRs).


Studying non-recurrent CNVs involving the PLP1 locus in patients with Pelizaeus–Merzbacher disease, authors conclude that such rearrangements are due to a mechanism involving replication fork stalling and template switching.


These papers describe recurrent CNVs on chromosome 16p that are associated with autism, ID and related disorders.


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Authors conclude that 1q36 microdeletions occur in ~1% of the patients with idiopathic ID.


The author points out that the complexity of ID and other common disorders is primarily due to genetic heterogeneity. Therefore, association studies have yielded very few major risk factors for common diseases, and other strategies are required for their elucidation.


35. Torres-LuÁn L, Rosell J, Morla M, Vidal-Pou C, Garcia-Algas F, de la Fuente MA, Juan M, Tubau A, Bachiller D, Bernues M et al.: Mutations in TBX1 genotype the 22q11.2 deletion and...


39. Gribble SM, Kalaitzopoulos D, Burford DC, Prigmore E, Selzer RR, Ropers HH:


41. Gribble SM, Prigmore E, Burford DC, Porter KM, Ng BL, Gecz J, Cloosterman D, Partington M:


The articles of Iwase et al. [87] and Tahiliani et al. [89] show that the JARID1C gene, previously implicated in X-linked ID, encodes a histone H3 lysine 4 demethylase and links it to the transcriptional repressor REST.


Reif et al. have identified the proteoglycan agrin as a specific substrate of the serine protease neurotrypsin, previously implicated in a form of ARID. This means that neurotrypsin mutations interfere with the inactivation of the Na+/K+-ATPase at CNS synapses.


