



MOLECULAR GENETICS OF INTELLECTUAL DISABILITY WITH SPECIAL EMPHASIS ON THE IDIOPATHIC TYPE

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Abstract- Intellectual disability (ID), a phenomenon characterized by significantly subaverage intellectual functioning with deficits in adaptive behavior, such as daily-living skills, social skills and communication, is of common occurrence throughout the world. Depending on the diagnostic methods used, 2-85 individuals per 1000 are diagnosed with ID. Extraordinarily heterogeneous causes like environmental, chromosomal and/or genetic defects have been found to be associated with ID. Among these, genetic abnormalities are frequently encountered in connection with ID and therefore, unraveling the genetic causes of ID is one of the greatest challenges for molecular geneticists. Recent advances in high resolution comparative genomic hybridization and annotation of genomic sequence have helped in identifying cryptic changes and different syndromes not known earlier. Further, several novel X-linked and autosomal genes, that may lead to ID, have been identified by molecular genetic approaches and the process is still going on. In this review, an attempt has been made to compile recent advances in the molecular genetics of ID and in discovering new genetic conditions that may give rise to nonsyndromic ID or idiopathic ID (IID). From the evidences obtained, genetics of IID turned out to be remarkably complex. It may be inferred that the molecular mechanism behind IID is far from understanding till date and is likely to remain a challenge for clinicians and scientists for years to come.

Keywords- intellectual disability, nonsyndromic, idiopathic, genetics

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Introduction

Intellectual Disability (ID), the most common form of cognitive impairment, is a circumstance, a reality, a symptom, a source of pain and incomprehension to many families. The American Association of Intellectual and Developmental Disability (AAIDD; earlier known as AAMR) defines ID as a disability characterized by significant limitations both in intellectual functioning and adaptive behavior, which covers day to day social and practical skills, originating before the age of 18 [1]. This definition is widely accepted and emphasizes on social and environmental effects rather than the state of the individual.

The term "ID" (more frequently defined as mental retardation or MR) is highly controversial; arguments mainly deal with conceptual approaches as well as phenotypes associated with the disorder. Based on the traditional approaches, which mainly define the basis of medical or statistical model of definition, ID is considered as a state of a person with limitations in adaptive and communication skills. Characteristic symptoms are identified by the medical model, while the statistical model mainly categorizes by the intelligence

quotient (IQ) of an individual [2]. Since there is no standardized method for determination of social adaptive behavior under different socioeconomic and cultural environments, IQ forms the sole criterion for classifying ID rather than adaptive behavior [2]. On the basis of IQ, the Diagnostic and Statistical Manual for Mental Disorders-IV-TR (DSM-IV-TR) [3] categorizes five different levels of ID: borderline (IQ 67-83), mild (IQ 50-66), moderate (IQ 33-49), severe (IQ 16-32), and profound (IQ<16). Due to concern about the over or misidentification of ID, particularly in minority populations, borderline classification was eliminated from the interpretation of significant, subaverage, general intellectual functioning and the upper range of IQ was changed from <85 to $\leq 70-75$.

On the bases of presenting symptoms, ID can be grouped into two major subclasses i.e. syndromic (S) and non-syndromic (NS) [4]. Syndromic ID cases are characterized by certain definite clinical, radiological, metabolic or biological features while in NS-ID, cognitive impairment is the major manifestation. However, it has been a challenge to rule out the presence of neurological anomalies and psychiatric disorders in these patients, as they may be less appar-

ent, or difficult to diagnose. Additionally, symptoms of some syndromes may be so subtle that they are extremely difficult to diagnose unless the features are looked for specifically in the context of a known genetic defect previously associated with these features [5]. Thus the distinction between S-ID and NS-ID is often blurred, though being often used for clinical studies. With advancement in detection, the barrier between syndromic and non-syndromic ID has decreased considerably [6,7].

Prevalence of ID

By definition, incidence of ID is estimated around 1-3% in some countries and regions [8]. However, worldwide prevalence of ID is 2-85 per 1000 individuals [9]. Worldwide prevalence of mild and moderate ID is 0.9-2.7% and 0.3-0.4% respectively in the total population [10]. The combined prevalence of intellectual and developmental disabilities is 14.9 per 1000 in the United States [11] while, in India, the national prevalence rate for ID is currently 1.4-25.3 per 1000 [12]. This wide variation could be due to variations in classification systems as well as survey of hospital-based population rather than an entire population [2]. Despite the universal occurrence, incidence of ID especially the mild cases, is much higher in the developing countries as compared to the developed countries [13,14]; however, recorded prevalence rate could be apparently low due to higher infant mortality [13]. It has been suggested that this discrepancy is likely due to various external factors like age, sex, socioeconomic status and ethnicity which may indirectly influence the estimation process [9,14,15].

Studies have shown a male preponderance for all types of ID; males being 1.6-1.7 times more vulnerable compared to females [3,8,16]. Especially studies on mild ID have shown a higher prevalence among the male population (male: female ratio 1.9) [2]. Maternal factors like smoking have also been found to be responsible for gender biasness of ID [17]. Epidemiological investigations have also revealed that low birth weight associated with low IQ is often predominant in male individuals rather than females [18]. Moreover, low birth weight in association with higher mortality rate is also higher in boys (22%) as compared to girls (15%) [19]. These observations suggest that gender variation could be one of the primary influencing factors for the observed difference in frequency of ID in epidemiological studies.

Pathophysiology of ID

ID has been defined as a manifestation of a group of disorders of the central nervous system (CNS) controlled primarily by cortical structures including the hippocampus and the medial temporal cortex [10]. Most individuals with significant cognitive impairment have no discernible structural abnormalities of the brain [10]. CNS malformations, a visual correlate of the disorder, are diagnosed in only 10-15% of cases; the most common malformations consisting of neural tube defects, hydranencephaly, and microcephaly [10]. Indeed, in many cases, ID is part of a complex syndrome comprising of developmental brain abnormalities such as microcephaly, lissencephaly, neuronal heterotopia, agenesis, polymicrogyria and schizencephaly, which result in a cerebral cortex that lacks the normal pattern of organization [4]. ID, in these cases is most likely to be a secondary symptom, and factors required for normal development of the CNS become primary [4]. In contrast, conditions in which ID is associated with an apparent normal brain structure and

architecture, subtle neuronal or more specifically glial cell functional, morphological or cell-cell interaction and connection abnormalities are likely to be the bases for the disorder [4].

Initially, two major groups of genes were identified: (i) genes involved in ID with brain developmental abnormalities; (ii) those involved in ID with no specific brain abnormality, with an update concerning recessive autosomal ID genes [4]. Although it has many weaknesses, this subdivision allowed to highlight genes implicated in potential common genetic and functional pathways and provides the basis and framework for understanding the physiopathological and biological mechanisms underlying ID [20,21]. However, understanding the biology of ID is complicated by the underlying cognitive impairment [4] and extraordinary heterogeneity of genetic disorders associated with it [20]. Dysfunction of proteins might lead to defects in synaptic structure or function and neuronal connectivity via deregulation of specific pathways and cellular processes thereby hampering ability of the brain to process information [4]. Based on this hypothesis, it can be speculated that in some forms of ID, deficient proteins act during the postnatal stages of active learning periods and the resulting deficits may be prevented or improved to a certain extent if early postnatal diagnosis and appropriate therapeutic approaches are implemented [4]. Therapeutic interventions like behavioral and cognitive therapies can help ID patients to reach their maximum potential [21,22].

Advancements in Determining the Genetic Origin of ID

ID is caused in many cases by rare, highly-penetrant loss-of-function mutations affecting a set of identified genes [4,20,23]. Lehrke [24] first suggested that such 'mental retardation genes', especially X-linked ones, might exhibit variants affecting 'intelligence' (defined in terms of IQ) in nonclinical populations. However, this prediction was based on early studies showing an excess of male individuals over females with ID, a wider distribution of IQ in males, and segregation patterns of ID within families. It has since been reiterated by other authors as more evidence on the genetic bases of cognitive abilities and intellectual disability has become available [7,25-34]. The most common genetic bases identified are (i) chromosomal abnormalities including aneuploidies, microdeletion, duplication and rearrangements that result mainly into deleterious gene dosage effect, (ii) deregulations of genetic or genomic imprintations, (iii) monogenic causes or dysfunctions of single genes and (iv) polygenic or multi gene defects. The precise cause for the disorder, with moderate to severe ID, is found in only 50% of cases; in the mild ID category, much lower proportion reveal any specific cause [4]. In about 40-60% of cases the exact cause remains unknown and these cases are generally identified as unexplained cases of ID, NS-ID and/or Idiopathic ID (IID) [35-38].

Genetic causes of ID are thought to be present in 25-50% of cases, although this number increases proportionally with severity [8] of the disorder. Among the known causes, Down syndrome and Fragile X syndrome are the two largest individual contributors. Several hundred other genetic disorders, mostly very rare, have also been found to be associated with ID [39,40] and it is reasonable to suppose that a considerable proportion of cases of unknown etiology (IID) also have a genetic origin [41] and the real challenge is to estimate that proportion. An institution based survey on 262 moder-

ate ID individuals revealed genetic defects may account for over half of IID where the IQ is less than 50 [42]. Though the investigators were unable to estimate such figures for ID individuals having 50 to 70 IQ score, there were indications that single gene conditions and chromosomal abnormalities may be more frequent than previously assumed.

Inherited Cases of ID

ID associated monogenic disorders account for only a small proportion and exhibit autosomal recessive, autosomal dominant or X-linked inheritance patterns [43]. However, progress in delineating the genetic basis of inherited forms of ID is at present largely restricted to the X-linked ID (XLID, also known as XLMR), because only X-linked recessive disease is compatible with the occurrence of affected members in multiple generations. XLID is important because it is common and genes identified in association with XLID have a major impact on the rapid development of cognitive abilities during human growth [44]. Overall, XLID occurs approximately in 1 per 5,000 live births [45] and frequency is estimated to be 1.8 in 1,000 males with a carrier frequency of 2.4 in 1,000 females [46]. Earlier, Inlow and Restifo [20] presented a status report on autosomal and X-linked monogenic causes of ID through careful search for 'MR' entries in the literature and in the Online Mendelian Inheritance in Man (OMIM) database. They identified more than 1237 entries for MR and recorded 282 MR genes. Most of the monogenic ID are syndromic and is often associated with abnormal expression of genes located in the X chromosome resulting in higher prevalence in the male population [4]. Recent advances in genetic linkage analysis techniques in families with multiple affected members have revealed more than 50 candidate genes along the X chromosome for ID [4]. Till date, about 140 different XLID syndromes have been identified and 66 of them are associated with allelic variation (Ropers and Hamel 2005). A recent update on XLID genes by Chiurazzi, et al. [38] listed 215 X-linked ID conditions including 98 syndromes and 51 neuromuscular conditions, and 66 nonspecific (MRX) forms. Linkage analyses have revealed heterogeneous distribution pattern of XLID genes in affected families [31]. Many of these proteins played important roles in regulating synaptic activities by controlling Rho-GTPase and NMDA receptor signaling pathways in the physiopathology of ID [4]. ID resulting from mutations in genes encoding transcription factors and cofactors, partners of signal transduction cascades, as well as chromatin remodeling proteins, also represent a major group in this category of X-linked genes [4]. However the actual roles of a few XLID genes are still uncertain [38].

Inheritance pattern of fragile-X syndrome, a syndromic XLID [31], is the true documentation of X-linked disorder where males are mostly affected [47]. Majority of fragile-X syndrome, designated as FRAXA, is caused by a fragile site at Xq27.3 and is associated with severe to moderate ID. Positional cloning of the *FMR1* gene in association with FRAXA revealed expansion of CGG repeat along with extensive methylation which prevents expression of the gene.

Compared with genes on the X chromosome, very few autosomal genes have been studied in ID [7]. The autosomal ID genes identified are primarily involved in syndromal and metabolic conditions [4,7] and only a few are involved in unexplained cases of ID (NS-ID and/or IID) [Table-1]. Identification of autosomal genes associated

with ID has been very difficult primarily because of the lack of large families for linkage analysis [5]. In addition, recognition of ID-causing gene mutations in candidate genes has been difficult because of enormous genetic heterogeneity and rarity of mutations in any individual gene in the ID population. However, despite all these difficulties number of autosomal genes associated with NS-ID is growing rapidly [4].

Single gene disorders, that affect metabolic pathways, form another major group of autosomal dominant or recessive ID. Among them, the mostly studied is ID due to phenylketonuria caused by an autosomal recessive mutation in the phenylalanine hydroxylase gene located at 12q24.1 [48].

Quantitative Analysis in ID

The extent to which IQ can be genetically determined for ID has been a subject of strong debate, but the fact that genes play some part cannot be ignored. Chromosomal mapping of loci that determine genetic variability under multifactorial conditions [49] could also be used for localizing the genetic basis of ID and attempts have already begun to map the loci determining quantitative trait loci (QTL) in IQ [34]. However, QTL mapping may not be successful under genetically heterogeneous conditions; for example, in case of severe ID. Assuming that the approach does work and localization becomes possible, the question would be whether genes that determine variation in IQ overlap with the genes already implicated in ID. So far, work has been concentrated on the molecular pathology to identify mutations that disrupt gene function [Table-1]. QTL mapping might localize DNA variants that do not inactivate genes but alter their function in a much less dramatic way. Possibly the same pathways could allow both types of variation, in which case combination of QTL mapping and molecular pathology screening would be ideally placed to identify genes that are responsible for ID.

Identification of NS-ID or IID

Over the past 15 years, many single candidate genes have been identified in association with NS-ID or IID. Many of these genes are also identified as causal factors for syndromic ID and other neurodevelopmental disorders like autism [7]. However, in spite of the recent developments in molecular genetic studies, cause for IID still remains unknown in majority of the cases. Percentage of syndromes mapped or characterized at the molecular level is still small and molecular mapping or cloning approaches, to substantially reduce the number of IID cases, are yet to be achieved. Characterization of these sporadic cases of ID with a genetic origin might seem a harder task than linkage analysis [43]. It is thought that rare variants are likely responsible for most of these cases and this has been the focus of genetics of IID for some time, although linkage and association studies are still used to identify polymorphisms that potentially contribute to the phenotype (e.g. *SNAP25* [50]; *MAOA* [51]; *DRD4*, *DAT1*, *COMT* [52]). It is likely that many rare variants across many genes result in the same phenotype.

IID refers to individuals who show no evidence of gross chromosomal defects or single-gene anomalies. It is sometimes considered as representing the lower end of IQ distribution [41]. IQ scores have been shown to have an average weighted correlation of 0.86 for monozygotic twins and 0.61 for dizygotic twins and an average

correlation between first-degree relatives of 0.4, suggesting an overall heritability of 50% [53]. Therefore, etiology of IID is usually explained in terms of the 'polygenic multifactorial model' [43]. The main difficulty is that only few studies provide sufficiently precise estimate on the likely role of genes and environment in determining IID. However, recent studies have shown higher rates of chromosomal abnormalities and this raises the possibility that a proportion of individuals with IID may have undetected or unknown chromosomal aberrations or single-gene defects [54-56]. Examples of some of the very rare ID cases those were previously known as idiopathic or had no known cause but later revealed presence of chromosomal aberrations/rearrangements are Williams syndrome [57], Rubinstein-Taybi syndrome [58], Di-George syndrome [59], XY_{xq} syndrome [60], Smith-Magenis syndrome [61] and mental retardation microdeletion syndrome [62].

Chromosomal rearrangements involving the terminal or subtelomeric regions of chromosomes have been suggested to contribute to about 6% of IID [54]. Since small rearrangements (of the order of 1-2 megabases (Mb) of DNA) are undetectable even at the highest resolution of chromosome analysis, it is likely that such sub-microscopic chromosomal rearrangements are present in a proportion of individuals with IID. In addition to subtelomeric rearrangements, interstitial rearrangements have been implicated in a number of ID syndromes, including Di-George (22q11 deletion), Williams-Beuren (7q11.2 deletion) and Smith-Magenis (17p11.2 deletion) and are diagnosed mainly by molecular cytogenetic approaches. Moreover, recent diagnostic studies using chromosome specific [63] or genomewide microarray-CGH [64] have shown that interstitial chromosomal deletions or duplications may also account for a significant proportion of IID. Further advances in molecular genetics may find IID to be an etiologically heterogeneous group with some individuals showing retardation secondary to specific genetic causes while others are influenced by environmental effects or due to multifactorial causes [43].

Importance of Molecular Genetics in ID

The Human Genome Project (HGP) has been successful in opening the floodgates upon a wealth of genomic information. Grueling research since then has led scientists to identify innumerable genetic factors which contribute to a wide range of psychiatric and neurobehavioral disorders. Studies have shown that a gene may contribute to susceptibility or resistance towards a disease while also affecting its severity or progression [4]. However, molecular genetics will not provide a simple gene-based classification of psychiatric illness [65,66]. Rather, there is a complex relationship between genotype and phenotype that involves multiple genes and environmental factors, together with stochastic variation [4]. Nonetheless, we can expect molecular genetic findings to play an important role in helping to delineate the relationship between specific biological pathways/systems/networks and broad patterns, or domains, of psychopathology [67]. A precedent for such insights from genetic studies is already emerging from Genome Wide Association Studies (GWASs) in other areas of medicine that have revealed unforeseen biological relationships among different autoimmune diseases [68]. Genetic findings, which cannot be expected to map cleanly onto current descriptive psychiatric diagnostic categories, will be a guide to the biological processes and systems that are most important in the expression of the clinical phenotypes of

psychiatry [69]. Based on these fundamental ideas, present day biomedical research is designed to understand the genetic bases of diseases that will help in revolutionizing diagnosis, treatment and prevention of ID [Fig-1]. Undoubtedly new technologies will play a major part in speeding up the whole process on different levels: linkage analysis (automated genotyping, SNP analysis); candidate gene identification (by using GWAS approach), characterization (based on finished or a draft human genome sequence) and expression analysis (ESTs, SAGE, cDNA microarrays); and high-throughput mutation detection technology (DNA chips for known and new mutations, direct candidate gene mutation screen). Application of forward genetics techniques (search for interacting proteins, pathways) will add yet another dimension to the scheme. With this knowledge, resources and technologies, identification of both X-linked and autosomal genes involved in aspects of cognitive function and understanding of its molecular basis will make a giant leap forward.

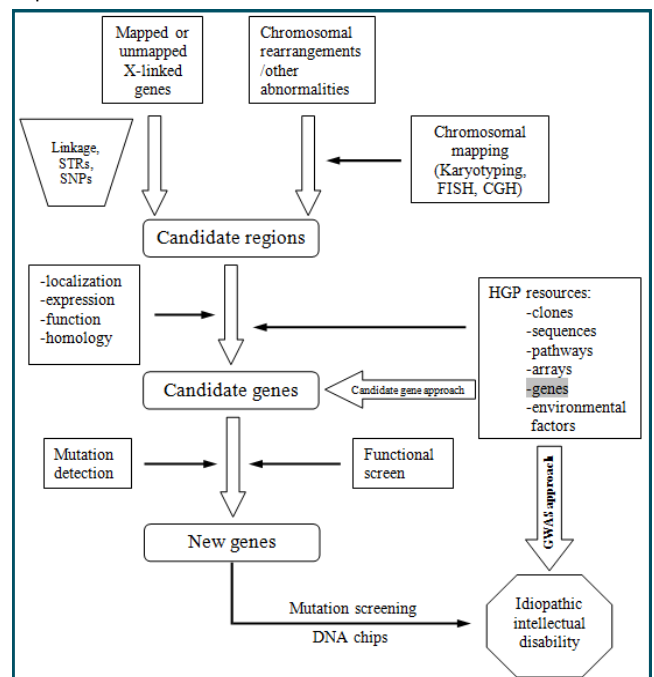


Fig. 1- A flow diagram of current approaches and resources available for mapping and identification of genetic bases of IID based on the approaches described by Gecz and Mulley [28] for X-linked ID.

Relevance of Studying Molecular Genetics in II

Diagnosis of ID done solely by psychometric evaluation based on presenting symptoms and status of cognition (DSM-IV) may not be always of great help to find a better remedy in the form of medical, educational and treatment needs. It fails to look into the genetic status that varies from individual to individual, and therefore, an individuals' response to a given therapy. Work on monogenic causes of ID, like XLID genes, that follow Mendelian pattern of inheritance has been overtly thriving. Mapping and cloning of genes and their disease causing variations have been successfully carried out. However, in case of NS-ID or IID, explorations for disease-causing genes have been very unrewarding [43]. Susceptibility in this case is probably caused by multiple genes of relatively small effect or by a combination of genetic and environmental factors, thus presenting substantial challenges for the genetic inquest [43].

Genetic defects may account for over half of IID where IQ is less than 50 [42]. There are currently three major areas of development in this field. First, there has been progress in delineating the genetic determinants of ID, which promises to reduce the number of cases classified as IID. Second, the molecular basis of a number of syndromes associated with ID has been described, thus beginning to explore pathogenesis of the condition. Third, researchers are now attempting to analyze molecular forms of ID that has a polygenic component.

Identification of the biological causes of IID is necessary to understand cognition and intellect [70]. Because IID presents with intellectual impairment as the major feature, genes that cause it are likely to be related to the processes of learning and memory. These processes are fundamental to our understanding of the formation of normal intellectual capabilities, and in particular how intellect develops from a neurological perspective. Additionally, finding genes that cause IID might help us to decipher relevant pathways that are involved in neurological development. Understanding these pathways may aid us in treating or relieving symptoms of IID in certain cases. Knowledge of pathways involved in IID will also make it easier to select candidate genes to analyze in research and clinically based studies. Understanding the genetics of a complex disorder like IID is also relevant to genetic counseling in families with affected individuals, particularly where consanguinity is involved [71].

Molecular Testing and Candidate Gene Approaches in IID

Molecular genetic studies worldwide (cytogenetic, linkage and association analysis) have nevertheless identified a number of chromosomal regions or candidate gene polymorphisms that confer susceptibility to several psychiatric and neurobehavioral phenotypes associated with ID. On the other hand, these studies directly in association with IID are scanty. We have explored several candidate genes involved in dopaminergic, noradrenergic, serotonergic and folate metabolism pathways in association with IID. A summary of several putative chromosomal regions and/or candidate genes identified in the etiology of NS-ID and/or IID (including our findings), have been provided in [Table-1]. Emphasis has been given mainly to the autosomal genes studied till now, since information about X-linked genes had already been discussed earlier in many literatures [4,20,27,28,31,33,44,46,72,73] and newly invented XLID gene variants are coming out now-a-days in a regular intervals [74].

Typical genetic mapping strategies like linkage and association analysis are frequently used to find candidate genes in IID [52,75-79]. Recently Rafiq, et al. [80] mapped three novel gene loci on chromosome 2 and 9 for NS-autosomal recessive ID in families undergoing consanguineous marriages (MR2, MR6, MR7, MR8, MR9 and MR11) by linkage analysis. Almost all of the genes identified for autosomal recessive IID thus far have been identified through microarray technology combined with homozygosity mapping using large consanguineous families [81-84]. In these studies, large multiplex families were recruited and detailed demographic data were collected. Affected family members were typically assessed for additional clinical phenotypes that may suggest S-ID and were screened for more commonly known causes such as fragile-X mutations and gross chromosomal anomalies. DNA from

peripheral blood of affected family members, along with one or two unaffected family members, was analyzed using either by traditional PCR-RFLP and sequencing technique or by modern microarray technology and analysis software. This method allowed a fast screening of individual genotypes and identification of regions in the genome that are homozygous for the same alleles among all affected individuals.

However, these approaches have been unsuccessful for autosomal dominant IID cases due to genetic heterogeneity and lack of suitable multiplex families, as procreation of affected individuals is unlikely. Thus, autosomal dominant IID is likely to be sporadic, resulting from de novo mutations [7]. Sequencing candidate genes could be another approach for identifying autosomal dominant causes of IID [85-88]. While this approach can be effective, it may also require much work and will frequently be unsuccessful if the level of genetic heterogeneity is as high as anticipated. However, as our knowledge of biological pathways involved in ID grows, our ability to select probable candidates will increase and this strategy may become more plausible. Additionally, with improved technology such as 'Next Generation Sequencing' techniques, sequencing entire exomes for causes of ID will become a less laborious and more productive screening method.

Characterization of chromosomal aberrations (gross chromosomal abnormalities and subtelomeric rearrangements like CNVs) by breakpoint analysis has long been used as a method to identify both autosomal dominant and recessive disease causing genes. Determining the exact location of the breakpoints and study of disrupted genes has led to the discovery of several candidate genes for autosomal dominant IID [89-91].

There is a belief that once disease susceptibility genes are identified, the next step will be to study the phenotypic contribution of these genes in the etiology of the disorder. This will open avenues for exploring pharmacogenetic interactions for better therapeutic intercession, and further, will offer a foundation for improved diagnostic categorization, case management and genetic counseling.

Importance of Genetics in Clinical Evaluation of ID and IID

The genetics of ID and especially IID is one of the most complex fields of human genetics. The combination of etiological heterogeneity, the small numbers of individuals with the same disorder and the unexpected complexity of the genetic basis of ID (such as in case of Fragile X, Angelman and Prader-willi syndromes) [92-94] have slowed down the progress. One of the lessons that emerges is the need for obsessional clinical and molecular genetic investigation of individual families. The discovery of new syndromes and the characterization of critical chromosomal regions for particular disorders have only come about because of attention to rare cases which appeared to be exceptions to general rules such as patients with the phenotype of Prader-Willi syndrome/Angelman syndrome but no obvious deletion provided evidence for genomic imprinting [94, 95]; rare families where sporadic disorders were present in more than one family member have provided important gene localizing information [e.g., reference no. 127 in table 1 and 80].

The phenotypic heterogeneity of ID deserves more clinical interest than it currently receives for another reason. 'Pure' ID is very rare (severe cases) and it is frequently accompanied by other behavior-

al abnormalities and psychiatric disorders [96]. As compared to the general population, ID individuals were reported to have five times higher emotional and behavioral problems (Rutter, et al. 1976). The frequency of DSM-IV co-morbid disorders was also reported to be very high in ID children than normal children [98]. In many instances this has been correctly attributed to environmental influences but in some syndromes specific behavioral patterns appear genetically determined [99]. These behavioral phenotypes may provide a way of characterizing the genetic basis of behavior as was demonstrated in the family where ID and impulsive aggression with other severe behavioral problems were attributed to mutations in the genes like *MAOA*, *COMT*, *DRD4* and *DAT1* [51,52,100-102]. Therefore, an initial clinical observation that a behavioral abnormality showed a pattern of X-linked/autosomal inheritance in these cases made the molecular genetic discovery possible. Further advancements in this field attributable to clinical skills are expected. [Fig-2] describes a widely accepted way to the optimal clinical genetic evaluation or diagnosis of child with ID [103,104] which ultimately would help the clinicians for designing possible therapeutic approach while treating ID child. This approach was slightly modified from that suggested by American Association of Pediatrics (AAP) Committee on Genetics [104], based on the recent developments in molecular genetic studies reported in association with ID [Table-1].

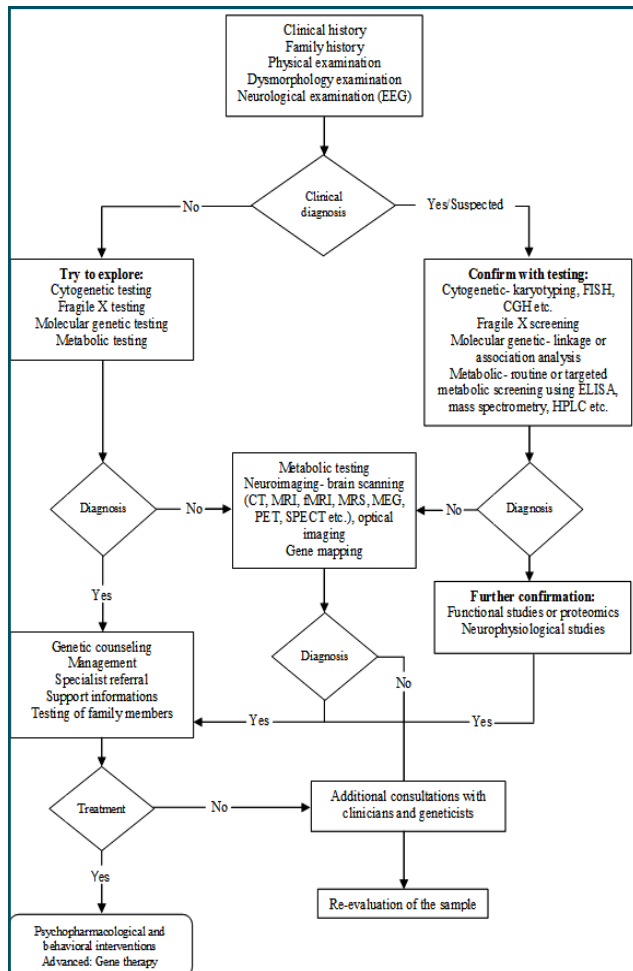


Fig. 2- Approach to the clinical genetic evaluation for ID patients based on description by the AAP Committee on Genetics [104].

Recent Developments and Future Challenges

The genetic complexity or heterogeneity underlying cognitive function seems to be enormous. There will always be the need to develop new approaches with improved molecular tools and techniques to move from detection of only X-linked genes that affect the extreme phenotype for cognitive function to autosomal genes that modulate fine tuning of cognitive function within the major range of variations. Therefore, it would be a challenge for future to decipher this complexity underlying cognitive function in ID. Scientists and clinicians in this field from different countries are actually trying to apply new technologies for large scale expression analysis, such as serial analysis of gene expression (SAGE), cDNA microarrays, RNA differential display and associated informatics [105,106], to organize and analyze the experimental data into meaningful patterns/pathways that might help to realize the ultimate goal of determination of genes associated with ID (both X-linked and autosomal). In this way the beginning of understanding of function in global terms might be achievable. We may envisage that based on the growing understanding of X-linked ID pathology. In near future, forward genetic approaches [107] will start to play an increasingly important role in identification and characterization of genes that may be associated with ID. Moreover, preliminary studies on transgenic animal models such as that of the *fmr1*, *fmr2* mice models of Fragile X syndrome [108,109], Ts65Dn mouse model of Down syndrome [110] and CBP +/- mice model for cognitive deficit [111] are encouraging and demonstrate the use of animal transgenics in understanding principles and mechanisms of human learning and memory. Now the intriguing question of what makes us different from our closest mammal and especially primate relatives, the quality (new function) or the quantity (new genes), or both, resurfaces.

Another way of thinking in this area is a 'synapse-based' hypothesis or 'synaptic plasticity' for the pathogeny of several forms of ID. Cerebral cortex and hippocampus regions of brain play important role in memory, attention, cognitive functions like perceptual awareness, thought, language, and consciousness and reward related behaviors. Studying the underlying mechanisms that co-operate to achieve synaptic plasticity, including changes in the quantity of neurotransmitters released into a synapse and changes in how effectively cells respond to those neurotransmitters in these regions of brain is very important to understand the complexity of ID. Since memories are postulated to be represented by vastly interconnected networks of synapses in the brain, synaptic plasticity is one of the important neurochemical fundamentals of learning and memory [112]. McBride, et al. [113] showed that synaptic plasticity can be rescued using a pharmacological approach of applying mGluR antagonists that can courtship behavior and mushroom body defects in a *Drosophila* model of fragile X syndrome. Another example suggesting that cognitive deficits could, to a certain extent, be partially reversible is provided through the autosomal form of inborn errors of creatine biosynthesis that corresponds to guanidinoacetate methyltransferase (GAMT) deficiency [114]. In this metabolic disorder with ID, cognitive impairment could be improved by arginine restriction and ornithine/creatine supplementation [115]. Although therapeutic possibilities in human remain very rare, these examples emphasize the necessity of establishing accurate diagnosis that could lead to preventive and therapeutic actions.

Table 1- Summary of putative chromosomal regions and/or candidate genes identified in association with Nonsyndromic (NS) and/or Idiopathic ID (IID) through molecular genetic studies.

Candidate genes	OMIM reference	Locus	Phenotypic expression	Disorders	Mutation type	Literature references
IL1RAPL1	300206	Xp22.1-p21.3	X-linked recessive type 21/34	NS-ID	A stop mutation (C-A) in exon 11	[121]
IL1RAPL1	300206	Xp22.1-p21.3	X-linked recessive type 21/34	NS-ID	A stop mutation (1460G-A) in exon 10	[122]
IL1RAPL1	300206	Xp22.1-p21.3	X-linked recessive type 21/34	NS-ID	A deletion of exons 2, 3, 4 and 5	[123]
IL1RAPL2	300277	Xq22.2-q22.3	X-linked recessive	NS-ID	Five SNPs (rs5962434, rs5916817, rs3764765, rs5962298 and rs9887672)	[124]
IQSEC2	300522	Xp11.22, Xp11.3-q21.1	X-linked type1/18	NS-ID	Four different hemizygous variants (2587C-T transition in exon 8, 2402A-C transversion in exon 6, 2273G-A transition in exon 5, 1075C-T transition in exon 4)	[125]
MAOA	309850	Xp11.23	X-linked recessive	ID, IID and associated behavioral problems	A truncating point mutation (rs72554632) in exon 8	[100,101]
MAOA	309850	Xp11.23	X-linked recessive	ID, IID and associated behavioral problems	A 30bp Promoter u VNTR	[51,77, 102,126]
MAOA	309850	Xp11.23	X-linked recessive	ID, IID and associated behavioral problems	A silent mutation (rs6323) in exon 8	[102]
UPF3B	300298	Xq25-q26	X-linked recessive type 14	S-ID	Hemizygous 4-bp deletion (674delGAAA) in exon 7, 2-bp deletion (867delAG) in exon 9 and 1288C-T transition in exon 10 (R430X)	[127]
UPF3B	300298	Xq25-q26	X-linked recessive type 14	NS-ID	A missense 478T-G transversion in exon 5 (Y160D)	[127]
UPF3B	300298	Xq25-q26	X-linked recessive type 62	Nonspecific ID	One nonsense mutation in exon 10 (c.1081C>T/p.Arg36)	[128]
Other X-linked genes	-	X	-	NS-ID	-	[7]
ADA	608958	20q12-q13.11	Autosomal recessive	Mild IID	One functional SNP (G>A) at nucleotide 22 of exon 1	[129]
CACNG2	602911	22q13.1	-	NS-ID	One denovo missense variant (c.427G>C/p.Val143Leu)	[85]
CALL, ITPR1 and AD7c-NTP	607416, 147265, 607413	3p26.1	Autosomal recessive	NS-ID	Subtelomeric deletions	[130]
CBRN	609262	3p26.2	Autosomal recessive type 2	NS-ID	One homozygous SNP (rs121918368) at exon 11	[131]
CBS	613381	21q22.3	Autosomal recessive	IID with nutritional deficiency	A double mutation T833C/844ins68 and a 31 bp VNTR that spans the exon 13-intron 13 boundary	[79,132, 133]
CC2D1A	610055	19p13.12	Autosomal recessive type 3	NS-ID	Chromosomal deletion from intron 13 to 16	[134,135]
CDH15	114019	16q24.3	Autosomal dominant type 3	NS-ID	One chromosomal translocation t(11;16)(q24.2;q24) and four missense variants (SNPs)	[91]
COMT	116790	22q11.21	Autosomal codominant	ID, IID and related behavioral problems	Functional SNPs: rs4680 in exon 4 and rs165599 in 3'-UTR.	[52,136, 137]
DIO2	601413	14q24.2-q24.3	Autosomal dominant	Definite ID and borderline ID	Three SNPs: rs225014 in exon 2, and rs225012 and rs225010 in intron 1.	[75]
DRD4	126452	11p15.5	Autosomal dominant	IID and related behavioral problems	A 48bp VNTR in exon 3 and a functional SNP (rs1800955) in the promoter region	[52]
DOCK8	611432	9p24.3	Autosomal dominant type 2	NS-ID	Chromosomal deletion (230 kb in subtelomeric 9p) and translocation t(X;9)(q13.1;p24)	[90]
EPB41L1	602879	20q11.2-q12	-	NS-ID	One denovo missense variant (c.2560C>T/p.Pro854Ser)	[86]
GRIK2	138244	6q21	Autosomal recessive type 6	NS-ID	120-kb deletion removing exons 7 and 8 with an inversion of approximately 80 kb including exons 9, 10, and 11, in combination with a deletion of approximately 20 kb of intron 11	[138]
GRIN1	138249	9q34.3	Autosomal dominant	NS-ID	One denovo missense variant (c.1984G>A/p.Glu662Lys) and one 3bp chromosomal duplication (c.1679_1681dup/p.Ser560dup)	[138]
KIF1A	601255	2q37	Autosomal dominant	NS-ID	One denovo missense variant (c.296C>T/p.Thr99Met)	[138]
KIRREL3	607761	11q24.2	Autosomal dominant type 4	NS-ID	One chromosomal translocation t(11;16)(q24.2;q24) and three missense variants (SNPs)	[91]
MBD5	611472	2q23.1	Autosomal dominant type 1	NS-ID	200-kb deletion that removed 1 noncoding exon and the first 7 coding exons and 4 missense variants	[89]
MTHFR	607093	1p36.3	Autosomal recessive	IID with nutritional deficiency	Two functional SNPs: rs1801133 at exon 4 and rs1801131 at exon 7	[78,139, 140]
PRSS12	606709	4q26	Autosomal recessive type 1	NS-ID	4bp deletion in exon 7	[141]
POU1F1	173110	3p11	Autosomal dominant and/or recessive	IID	Three SNPs: rs4988463 and rs4988464 are in the 3'-UTR, whereas rs300977 is in intron 1	[76]
SHANK2	603290	11q13.3-q13.4	Autosomal dominant	NS-ID	CNV deletion (120bp deletion of exon 7), 6bp duplication and 6 missense variants	[142]
SHANK3	606230	22q13.3	Autosomal recessive	NS-ID	Truncating and/or splicing variant (c.601-1G>A) in intron 5	[138]
SLC6A3	126455	5p15.3	-	IID and related behavioral problems	A 40bp VNTR in 3'-UTR and a 30 bp VNTR in intron 8 region.	[52]

Table 1- Continue

Candidate genes	OMIM reference	Locus	Phenotypic expression	Disorders	Mutation type	Literature references
SLC26A4	605646	7q31	Autosomal recessive	Definite ID and borderline ID	Six SNPs (rs6970857, rs2395911, rs1858929, rs1858930, rs982663 and rs2712218) at 3'-UTR, a tag SNP rs2248465, rs17154282 at 5'-UTR and two nsSNPs: rs17154335 at exon 17 and rs17154353 at exon 19.	[143]
SLC6A4	182138	17q11.1-q12	Autosomal dominant	IID and related behavioral problems	Two VNTRs in the promoter (5-HTTLPR) and intron 2 regions (STin2)	[102]
SOBP	613667	6q21	Autosomal recessive	S-ID and NS-ID	A homozygous 1981C-T transition in exon 6	[84]
STXBP1	602926	9q34.11	Autosomal dominant	IID	One nonsense variant (rs121918321) in exon 14 and a splicing mutation (c.169+1G>A) in intron 3	[85,87]
SYNGAP1	603384	6p21.32	Autosomal dominant type 5	NS-ID	Two nonsense variants (rs121918315 and rs121918316) and a 1 bp deletion (c.2438delT/p.Leu813ArgfsX23)	[85,88]
SYNGAP1	603384	6p21.32	Autosomal dominant type 5	NS-ID	Two denovo out-of-frame deletions (c.2677delC/p.Q893RfsX184 and c.321_324delGAAG/p. K108VfsX25) and a splicing mutation (c.2294 + 1G>A) in exon 13	[86]
Trp53	191170	17p13.1	Autosomal dominant	NS-ID	One functional SNP (Arg72Pro) in exon 4	[144]
TRAPPC9	611966	8q24.3	Autosomal recessive type 13	NS-ID	Two homozygous truncating variants (1423C-T and 1129C-T) in exon 7	[83]
TRAPPC9	611966	8q24.3	Autosomal recessive type 13	NS-ID	One nonsense variant (1422C-T) and a 4bp deletion (2311delTGTT) in exon 7	[145]
TRAPPC9	611966	8q24.3	Autosomal recessive type 13	NS-ID	A nonsense variant (1708C-T) in exon 9	[146]
TTR	176300	18q12.1	Autosomal dominant	Definite ID and borderline ID	Eight SNPs: rs723744 at intron 1, rs1803082, rs11541793, rs11541785, rs1804118, rs2276382, rs11541782, rs11541798 at exon 4	[147]
TUSC3	601385	8p22	Autosomal recessive type 7	NS-ID	A homozygous 120- to 150-kb deletion on chromosome 8p22 including the exon 1	[81]
TUSC3	601385	8p22	Autosomal recessive type 7	NS-ID	A homozygous, truncating 1-bp insertion (787insC) in exon 6	[82]

The recent remarkable progress in the field of ID is suggesting that defects in synaptogenesis and synaptic activities as well as their plasticity, especially in postnatal stage during learning and acquisition of intellectual performances and emotional behavior, are perhaps crucial cellular processes that underlie cognitive impairment resulting from mutations in some ID-related genes most of which are X-linked. The importance of the functions of these gene products in synapse had been broadly discussed in the review article of Chelly, et al. [4].

Finally the most challenging part of this subject is to deal with the sporadic cases of ID. Assessing cognitive function is complex in these individuals and performances can be subject to profound social and environmental factors which made the things more complicated. Proper genetic counseling followed by molecular genetics approaches may be the only way we can deal with this challenge. However, recently very few studies are available in ascertaining the genetic bases of unexplained or idiopathic cases of ID [Table-1]. Now-a-days microarray-based copy number variation (CNV) analysis to identify submicroscopic chromosomal deletions and duplications has found its way into routine clinical practice, predominantly for the diagnosis of patients with IID [116]. Recently these CNVs were also identified in ADHD children from UK having ID as a comorbid feature [117].

In providing the insights of evolutionary genomics of human ID, recently Crespi, et al. [118] emphasized that candidates for genes subject to loss-of-function or other mutations may, in some cases, be better-recognized though tests for recent adaptive evolution, given that such tests are strongly indicative of functional differences between specific haplotypes or alleles. They also showed genes involved in the DNA repair and Rho-GTPase pathways may represent especially strong candidates for involvement in IID.

Deary, et al. [119] described the process of integration of evolutionary tools and perspectives into studies dissecting the genetic bases of human intellectual capabilities which might accelerate progress into understanding both the evolution of human intelligence and the causes of variation in intellectual abilities within extant populations.

Conclusions

It is clear that further research is needed to identify desired health outcomes across the lifespan for persons with ID [120]. In the present review a summary of relevant and current research and health care achievements pertaining to individuals with ID, specifically IID was discussed. Research accomplishments have moved this field forward in many positive directions, however there is much to be done to promote the optimal quality of life and health status for ID and IID individuals. The field of genetics or in wide term genomics and proteomics will greatly enhance our knowledge on the causes of intellectual disabilities. Next challenge would be to ensure that this disenfranchised population has affordable access to healthcare that embodies best practices and evidence-based care. It is indeed inspiring to notice that the field of ID related research is gaining importance in spite of several shortcomings and in near future we may be able to find out a definite genetic basis for most of these conditions.

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