Review article :

Review On Clinical And Molecular Genetics Of Autosomal Recessive Intellectual Disability

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Abstract

Intellectual disability (ID) is a relatively common phenotype with multiple etiologies. Recent progress in the genetics of ID greatly expanded our understanding of the biological defects underlying this clinical entity. While most published cohort genetic studies on ID revealed the important contribution of de novo (germline or postzygotic) variants, we focused in this study of autosomal recessive ID (ARID), that account for most of the molecular bases in ID cases in inbred populations. We discussed the current state of ARID from a clinical, molecular and genetics standpoints.

Keywords:

Autosomal Recessive, Intellectual Disability, ARID, Positional Mapping, Whole-exome Sequencing.

الملخص

الإعاقة الذهنية أو التأخير العقلي هو خلل طبي شائع نسبيًا مع عدة أسباب له. و قد أدى التقدم الأخير في علم الوراثة السريرية إلى توسيع فهمنا للبيولوجية الكامنة وراء هذاالخلل الطبي. حيث كشفت معظم الدراسات الجينية و الوراثية المتعلقه بداراسات التأخير العقلي على أن أحد أكبر الأسباب المؤدية الي التأخير العقلي هو الطفرات و التغيرات الوراثية التي تحدث في الشخص المصاب و لا تكون في الغالب مورثة من أحد الأبوين أو تنتنقل بالصفحة السائدة. في هذا البحث نقوم بالتركيز على النوع الآخر من الطفرات الوراثية التي تنتقل بالصفحة المتنحية من الناحية السريرية و الجزيئية

INTRODUCTION

Genetic defects are the predominant cause of Autosomal Recessive Intellectual Disability (ARID). There are two large defined groups of genetic causes of ARID, syndromic and non-syndromic. In syndromic disorders, the involvement of the neurological system is complicated by the involvement of additional systems. However, in non-syndromic disorders usually the involvement is isolated i.e., only cognitive impairment. There are more than 800 syndromes with ARID manifestation are listed in the Online Mendelian Inheritance in Man Database (https://www.omim.org/), including rare syndromes with known underlying genetic defects. Common genetic

syndromes frequently encountered in the clinical setting not essentially autosomal recessive include Down syndrome, Fragile X syndrome, Tuberos Sclerosis, Rett syndrome, and Angelman syndrome, with a wide range of phenotypes including neuropsychiatric symptoms, intellectual disabilities, autism spectrum disorder, epilepsy, and structural brain abnormalities.

Non-syndromic intellectual disability (ID) comprises patients with isolated involvement of the neurodevelopment. Some of these disorders are idiopathic, with no identified genetic cause. Most of the ARID disorders have very strong evidence of heritability, whether through recurrence of similar cases in multiplex families, shared genetic defects found in a large cohort of patients, or the application of twin studies to understand the impact of genetics and environmental influences supporting the hypothesis of an unidentified genetic cause.

ARID disorders are caused by abnormalities in brain development due to germline diseases that cause DNA variations and include certain psychiatric disorders as well[1,2]. Affecting an estimated 15% of the population, Neuro Developmental Disorders (NDD) and in part ARID are a major economic and clinical burden (National Institute of Mental Health Statistics). Clinically, ARID are characterized by a wide range of neurobehavioral signs and symptoms, such as mood disorders, (including major depressive disorder and bipolar affective disorder) schizophrenia; autism spectrum disorder (ASD); and attention-deficit hyperactive disorder (ADHD). Diagnostic criteria display significant overlap, making clinical variation difficult to distinguish. Around 30–43% of NDDs are thought to have an underlying genetic defect [1, 2] however, the pathophysiology of the development of psychiatric disorders as part of ARID remain unknown and involve complex interactions among genes and environmental factors. The genes reported as more frequent in ARID include VPS13B, ASPM, POLG, MUT, GLDC, CEP290, SMPD1, SPG11, LAMA2 and GALT, however, other studies in ARID[3,4,5,6,7,8] failed to identify particular disorders more common and recurrent as cause of ARID. Most likely population specific, for example ADAT3 is considered as one of the most common causes of ARID in Saudi Arabia, other disorders like Cohen syndrome OMIM # 216550 Mental retardation, autosomal recessive 15 OMIM # 614202 Spastic paraplegia 50, autosomal recessive # 612936 are reported more frequently in different studies [8]. Recent advancement in genetic studies, biological functions analysis and the role of altered genes in ARID provide opportunities to discover the etiologies

and risk factors of the medical, clinical and psychiatric features of ARID.

Almost all types of gene alteration are linked to ID, including chromosomal structural aberrations and single gene defects with all modes of inheritance (autosomal recessive, autosomal dominant, X-linked and mitochondrial) (Figure 1). De-novo and somatic DNA variations and a combination of common single-nucleotide polymorphisms (SNP) predispose higher risk of developing ID and sometimes can present as ARID.

Advancement in molecular testing and diagnostic technologies have helped to reveal underlying biological defects, yielding insights into the role of altered genes and the interactions among multiple pathways that allow for better focus on drug development and enable personalized medical care. This article focuses on one mode of inheritance i.e.; autosomal recessive that can cause ID and neurodevelopmental disorders (NDD).

ARID IN CHROMOSOMAL AND STRUCTURAL ABERRATIONS

In 1956, the human diploid chromosome number was established as 46 9, and between 1960s and 1970s banding techniques were introduced that allowed the identification of chromosomal abnormalities. Karyotype testing was first used to identify chromosomal aberrations in patients with ID. Down Syndrome, or Trisomy 21, is the most recognizable example of chromosomal aneuploidy, accompanied by 19% prevalence of Autism Spectrum Disorder (ASD) [10]. Copy Number Variants (CNV) inherited as autosomal dominant or de-novo and rarely results from homozygous loss of both copies of the two alleles and run in the family in as autosomal recessive mode of inheritance. However, CNV considered as one of the major causes of ASD, molecular testing for CNV is first-tier genetic testing for cases with ASD or non-specific ASD; diagnostic yield in such cases reaches as far as up to 10% regardless the mode of inheritance. Furthermore, CNV contribute to many causes of other NDD which could present as ARID and by unmasking of a recessive allele that would normally not be expressed.

Table 1: list of signs and symptoms of Inborn Errors of Metabolism that trigger further analysis

- Microcephaly
- Dermatologic changes (skin rash)
- Cyclic vomiting
- Developmental regression
- Seizures, hypotonia, dystonia
- Gastrointestinal dysfunction
- Lethargy
- Neurodegeneration
- Failure to thrive
- Hyperammonemia
- Lactic acidosis
- Homocystinuria
- Acid/base disturbances
- Anemia
- Elevated liver enzyme
- Elevated creatine kinase

- Flagged results in newborn screening
- Abnormal acylcarnitine profile
- Abnormal organic acids in urine

ARID

Known syndromic disorders are believed to comprise around 10–15% cases of NDD. However, the total number of autosomal recessive genes causing NDDs is unknown, in one review study the percentage of ARID among all NDD is around 57% [11].

Ethnicity could be an attribute factor relating ARID to particular causes. For example, 3.6% of cases were attributable to ARID in patients of European ancestry where consanguineous marriages are less than 5% compared to 31% of cases in countries with high rates of consanguinity. Several studies reported hit high rates of ARID among NDDs cases i.e.; 30-40% [12, 13, 14]. Populations with many consanguineous marriages having an estimated 81% of patients with ARID, carry causative point mutations in autosomal recessive diseases, and 8% of patients in X-linked disorders. Whereas, fragile X syndrome accounts for only 1% in non-consanguineous offsprings[3]. The differences in the numbers could be attributed to ethnicity and consanguinity when compared, to an estimated 10% of all diagnosable ID cases were in an outbred population 8. In ARID, not all variants are homozygous. Atudy about the rate of compound heterozygous in German population revealed as leading cause to of ARID as high as 14%.

NDDs due to de novo variant is estimated as 1:213. However, autosomal recessive NDDs in offspring of marriages is estimated to be four to eight times higher than de-novo variants, and first cousin marriages is around two times higher than the de-novo variants making it as 1:147 [6, 15].

Based on SysID database https://sysid.cmbi.umcn.nl/ around 702 genes are linked to ARID (last accessed in August 2010). However, by calculating ion the size and the known genes of chromosome X lading to NDDs and comparing this number with the size of the autosomes, the estimated number of genes would be 2500 – 3000 8. Furthermore, approximately, half of ARID are not yet identified, and of the cases of ID not diagnosed yet, and suspected to be ARID are15–20% [8, 16].

Some of ARID classification can be based on the underlying pathology as they might share as ciliopathies or based on single clinical presentation like microcephaly or can be included under clinically well studied group of disorders, like inborn errors of metabolism, and the molecular defect like disorders affecting tRNA modification.

Large family structure and consanguinity helps in identification of novel single genes or variants in ARID disorders. For

example, the well-known gene ADAT3, related to intellectual disability, has been described in many individuals from Saudi families with the homozygous founder variant c.382G>A p. (Val128Met). These individuals often have cognitive impairment, microcephaly, epilepsy, nonspecific brain abnormalities, and dysmorphic facial features. ADAT3-related intellectual disability is now a recognizable cause of ID in Saudi Arabia [17,18]. Another founder variant, in C12orf57 in the methionine ATG–starting codon of the gene (c.1A>G: p. Met1?), causes Temtamy syndrome, a form of ID. It is characterized by epilepsy, causes ocular involvement, and dysgenesis of the corpus callosum, discovered after studies done in multiplex families [19]. Studying consanguineous families has expanded the knowledge of tRNA modification in ARID disorders. For example, WDR4 has been identified as distinct form of primordial dwarfism (OMIM #618346) associated with microcephaly, agenesis of the corpus callosum, simplified gyration, and severe encephalopathy with seizures. The disease-causing variant in WDR4 that impairs tRNA m (7)G46 methylation was identified by studying two consanguineous families and comparing the human variant with the corresponding ortholog yeast variant. The disease-causing variant significantly reduces the m(7)G46 methylation of specific tRNA species, providing a potential mechanism for the primordial dwarfism associated with low level of m(7)G46 modification causes a growth-deficiency phenotype in yeast [20]. Another form of ARID- and tRNA-related disorders most commonly derives from defects in RNA pseudouridylation. Pseudouridine synthases are encoded by 13 genes in humans, and several genes linked to ARID. Defects in PUS1, PUS3, and PUS7 impact the post-transcriptional modification of tRNA.

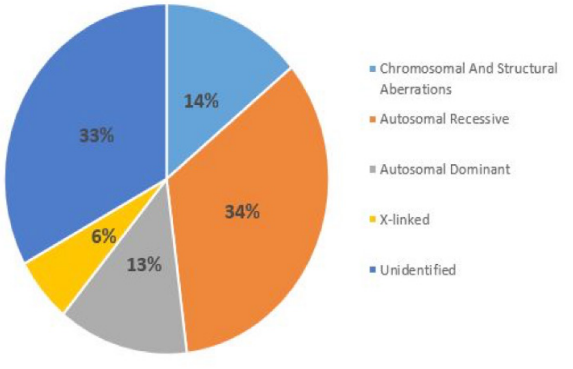
while, the impact of PUS7 was discovered by studying two consanguineous families [21,22]. CTU2-related DREAM-PL (dysmorphic facies, renal agenesis, ambiguous genitalia, microcephaly, polydactyly, and lissencephaly) , was recently described as impacting the post-transcriptional modification of tRNA and was found in a multiethnic groups [23]. Finally, truncating disease-causing variants in ALKBH8 leads to ARID by impacting tRNA post-transcriptional modification. This is an expansive list of genes related to ARID syndromes and with variants linked to tRNA modification defects.

Other presentations, like microcephaly or autosomal recessive primary microcephaly (MCPH), are another common form of ARID. Microcephaly is classified into congenital, progressive, non-syndromic, and microcephaly with normal brain archi-

tecture. The majority (60%) of causes of microcephaly are genetic, with established disease phenotypes in humans; 24% are found in known MCPH genes and around 15% are in novel or candidate genes [24]. Primary cilia are essential for the normal development of neurons and cortical migration. Ciliopathies, another group of ARID, results in variation in genes encoding defective proteins and abnormal function of cilia, constellation of features, including intellectual disability, skeletal, cerebral, renal, and liver dysfunction. Bardet–Biedl syndromes account for 30% of all cases with ciliopathies followed by Meckel syndrome, Joubert syndrome, and short-rib thoracic dysplasia in the Saudi population.[25].

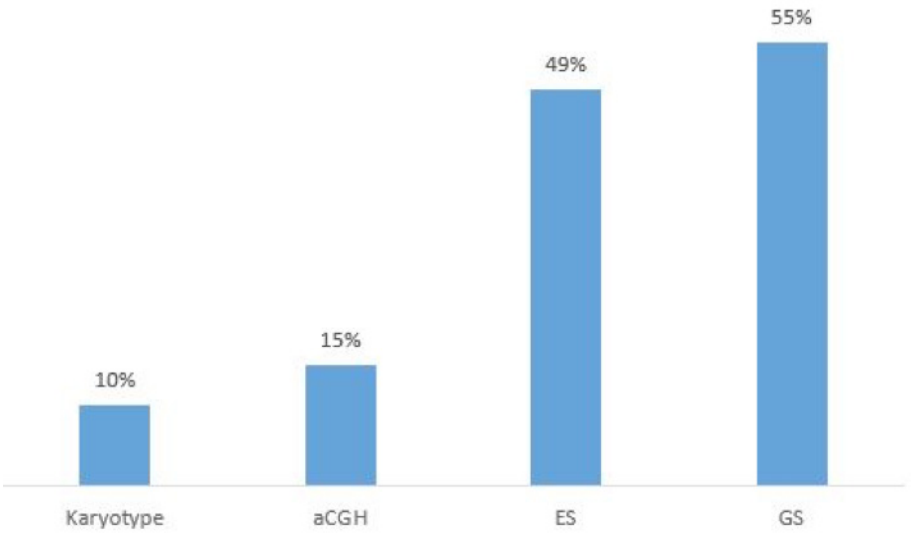
Inborn error of metabolism is another example of disorder that can presents as ID disorder and mostly inherited as an autosomal recessive disorder. Metabolic disorders can affect the central nervous system (CNS) and may presents at any age. Clinical presentation can resemble neuropsychiatric syndromes, depression or psychosis can be the presenting symptoms and can leads to significant morbidity and mortality. Metabolic disruption can lead to chronic or acute illness of the CNS, including maple syrup urine disease, urea cycle disorders, phenylketonuria, acute intermittent porphyria, Wilson's disease, and disorders of homocysteine metabolism. Metabolic disruption can also affect neurodevelopmental processes. Examples include many disorders present in the early stage of life such as neuronal ceroid lipofuscinosis, alpha mannosidosis, metachromatic leukodystrophy,adrenoleukodystrophy, Niemann–Pick type C, and GM2 gangliosidosis [26]. An important consideration for metabolic disorders is availability of treatment, an estimated 1 in 20 psychiatric disorders result from treatable metabolic disorders [27]. The estimated percentage of metabolic disorders results in ARID is 1% provided that all investigations are done, and this number is based on cases detected by newborn screening [28].

Figure 1: Distribution of NDDs by mode of inheritance. Unidentified are patient with NDDs clinical manifestation. However, with unknown underlying mode of inheritance.



Clinical signs and symptoms that should prompt further metabolic investigation and workup in any patients presenting with neuropsychiatric disorder include microcephaly, acid/base disturbances, anemia, dermatologic changes, cyclic vomiting,

Average hit rate of molecular testing on NDDs based on testing method. aCGH: array-based comparative genomic hybridization, ES: exome sequencing, GS: genome sequencing.



developmental regression, seizures, hypotonia, dystonia, gastrointestinal dysfunction, hyperammonemia, lactic acidosis, lethargy, neurodegeneration, and failure to thrive (Table 1).

MITOCHONDRIAL DEFECTS (MD) AND ARID

ARID are common presentation in MD. The nuclear coding gene POLG1 encodes the mitochondrial DNA polymerase which replicates and repairs mtDNA. Damage to POLG1 can result in neurological or hepatic dysfunction, as affected individuals will have depleted mtDNA content in tissues. POLG1-related disorder can manifest in the heterozygous or homozygous state and hence can cause disorders in the autosomal recessive or autosomal dominant modes of inheritance. Autosomal-recessive disorders causing variation in POLG1 lead to many distinct neurologic features, including developmental delay, generalized anxiety, and obsessive–compulsive spectrum disorder. Both dementia and depression have been described, usually beginning with gradual declines in visual, attention, and abstraction capabilities [29]. Autosomal dominant–related POLG1 clinical presentation could include idiopathic Parkinsons, male infertility, and progressive external ophthalmoplegia [29].

Diagnostic evaluation of individuals with suspected mitochondrial disorder related to ARID or mtDNA requires multisystem evaluation, including brain imaging, cardiac, and ophthalmologic evaluation, alongside audiology and clinical genetic testing. Blood testing should include liver enzymes, creatine kinase, ammonia, lactate and acylcarnitine profile, urinalysis for

organic acids, and CSF lactate, pyruvate, and CSF amino acids analysis.

TREATMENT

Early identification of disorders can prevent disease sequalae. Several ARID disorders result from defects in enzyme pathway metabolism or inborn error of metabolism. In one study around 3% of treatable inborn error of metabolism were missed despite the biochemical marker of ARID, elaborate about the importance of genetic testing in such cases when treatment is available [8].

CONSLUSION

ID is a common phenotype with multiple etiologies. However, in population with high rate of consanguineous marriages the autosomal recessive disorders account for most cases with ID, understanding the major causes is first step toward providing management, intervention and eventually prevention of the disorder.

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