SRIWIJAYA JOURNAL OF MEDICINE

Genetic Conditions Associated with Intellectual Disability in Indonesian Population: A Review

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Abstract

Intellectual disability (ID) brings challenges to the affected individuals, their families, and the community at large. It is a multifactorial condition with many contributing factors, namely genetics. This review aims to briefly provide several related genetic conditions for ID in the Indonesian population. Literature studies search relevant articles using PubMed and Google Scholar using the terms 'intellectual disability', 'genetics', 'Indonesian population'. In Indonesia, the prevalence of children with ID is 1–3%, with 62,011 school-aged children affected with Intellectual Disability. Genetics plays a role in around 25–50% of cases. ID in the Indonesian population is associated with several genetic disorders, namely Duchenne muscular dystrophy (DMD), autism spectrum disorder (ASD), fragile X syndrome (FXS), Down syndrome (DS), Apert syndrome, and subtelomeric chromosomal rearrangements. There is limited research on genetics related to intellectual disability in Indonesia, implying further research is needed.

Keywords: Intellectual Disability, Indonesia, Indonesian Population, Genetics, Genetic Factors

1. Introduction

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) lists three main criteria for intellectual disability: 1) A general mental impairment that affects adaptive functioning in three areas, including conceptual, social, and practical skills, 2) occur before the age of 18 and 3) have an IQ below 70.[1] This restriction can be seen in a variety of areas, including communication, self-care, self-government, and effective academic skill, to name a few.[2]

In addition to intellectual impairment, a developmental condition known as global developmental delay affects children under the age of five (60 months) (GDD). Patients with GDD will display ID after developing.[3] A meta-analysis determined that 10.37/1000 people worldwide had ID.[4] As a result, intellectual impairment affects children with ID, their families, and society as a whole in terms of public health, social welfare, and education. ID is more prevalent in low-income countries due to higher rates of anoxia, birth trauma, and newborn brain infection.[5]

ID can be present alone (non-syndromic ID, NSID), or it can be accompanied by other morphological anomalies, multisystemic disorders, epilepsy, autism, or other neuropsychiatric and/or neurobehavioral issues, as well as neuromuscular features like ataxia, spastic paraplegia, sensory or motor neuropathy, and muscular dystrophy.[6]

A key instrument for assessing intellectual functioning, or the brain's potential for learning, thinking, problem-

solving, and other cognitive processes, is the intelligence quotient test (IQ test). The Wechsler Intelligence Scale for Children (WICS) exam and the VABS are used to evaluate intelligence (Vineland Adaptive Behavior Scale).[7] A test result of less than or equal to 70 or more than 75 reveals intellectual functioning limitations. IQ testing became the method of classifying individuals and defining groupings.[1] ID is classified as mild (IQ 50-55 to 70), moderate (IQ 35-49 to 50-55), severe retardation (IQ 25--20 to 35-40), or profound retardation according to IQ tests (IQ below 20).[5,8]

2. Etiology and epidemiology of ID

Prenatal, perinatal, and postnatal variables can all be contributing factors in the etiology of intellectual impairment. Chromosome abnormalities, teratogenic factors, environmental factors (such as the transfer of illnesses including syphilis, HIV, rubella, toxoplasmosis, and CMV from mother to kid), and genetic mutations are examples of prenatal risk factors. Prematurity and hypoxia during pregnancy are postnatal variables, whereas sepsis, meningitis, encephalitis, and many multifactorial causes are perinatal ones.[5,9] These elements significantly contribute to the occurrence of moderate types of ID.[1] Genetic causes such as chromosomal structural abnormalities, chromosome aneusomies, genomic disorders, and monogenic illnesses account for around 65% of cases of moderate- to severe ID.[4,5]

Around 2%–3% of people in the general population have an ID. There are now 1396 genes associated with an intellectual impairment that has been investigated by various researchers, according to studies.[10,11] A single genetic abnormality, such as the deletion or mutation of a single gene, can be one of the genetic causes (SYN1, POLR3B, SLC5A2; SYNGAP1, DYRK1A, SCN2). More severe types of ID may also be triggered by structural defects, chromosomal deletion, aneusomies, and inversion. These genes have some involvement in the calcium signaling system. Ten calcium channel genes, including CACNA1A, CACNA1C, CACNA1I, CACNA1H, CACNA1D, CACNA2D1, CACNA2D2, CACNA1E, CACNA1F, and CACNA1G, were discovered to be related with ID in the previous study.[4]

ID is separated into two categories: syndromic ID and nonsyndromic ID, depending on how the symptoms manifest. Non-syndromic ID has no phenotypic alterations and no accompanying organ system defects; the sole clinical symptom is a cognitive deficiency. Three inheritance patterns are possible: X-linked mode, autosomal recessive mode, and autosomal dominant mode. Growth alterations, neuromuscular changes, metabolic illnesses, and phenotypic dysmorphic (craniofacial, skeletal) are all associated with syndromic ID. This review was restricted to neurological disorders such as Down syndrome, Fragile X syndrome, Duchenne muscular dystrophy, Apert syndrome, and subtelomeric chromosomal rearrangements.[1,3,5]

One to three percent of children has intellectual impairments, which means that out of every 1000 persons in Indonesia, 30 have intellectual disabilities. According to Riskesdas' 2013 data, there were 62,011 school-aged children with intellectual disabilities.[10,12] There are 38,545 children with intellectual impairments enrolled in special schools in Indonesia, according to the Ministry of Health.[13] A complete individual and family medical history, supported by head to toe physical examination, and a detailed evaluation of the child's developmental status are pivotal for the diagnosis. Understanding how ID is defined and categorized is crucial for diagnosing the condition.[5]

2.1. Fragile X Syndrome (FXS)

FXS is an X-linked recessive disease in which the disease is inherited from the carrier mother. The frequency of occurrence of FXS in

the world is approximately 1:4000 male births and causes intellectual disability in about 1 in 8000 females.[5,14] The typical features of fragile X syndrome include an elongated face, large ears, a raised palate, joint hypermobility, and macroorchidism. Intellectual disability, speech delays, language disorders, poor eye contact, sleep disturbances, seizures, and even obsessive-compulsive disorder are all serious complaints.[15]

FXS is more common among Indonesia's population of intellectually disabled people (0.9-1.9%), while Autism is more common (6.15%).[16] A high prevalence of ID of about 45% was discovered during screening on the island of Java, which is connected to the origin of genetic clusters. The FXS gene causes the trinucleotide cytosine-guanine-guanine (CGG) repeat to expand in the 5' region, which causes FXS (FMR1).

In a 1995 study, the first screening for FXS in Indonesia was discovered in ID children of Javanese descent attending special needs schools. when the child has two brothers who also share the same phenotype.[16]

There are several non-pharmacological and pharmaceutical treatments for fragile X syndrome. Occupational therapy, speech, and language therapy, cognitive behavior therapy (CBT), music therapy, exercise, applied behavior therapy (ABA), and physical therapy are examples of non-pharmacologic therapy. Pharmacological therapy is recommended, which includes sertraline, methylphenidate, clonidine, guanfacine, risperidone, aripiprazole, and melatonin, to decrease psychiatric symptoms.[15]

2.2. Duchenne Muscular Dystrophy (DMD)

Duchenne muscular dystrophy is an X-linked recessive progressive muscular disease characterized by developmental delays due to a mutation in the DMD gene encoding dystrophin protein. The incidence rate is 1: 3,500 male births. Girls do not show dystrophic symptoms even if they are heterozygous carriers of a mutant allele on one of their X chromosomes. In each generation, only boys experience dystrophy. If the X chromosome genotype is homozygous, girls can develop dystrophy. This happens when the mother is a carrier and the father has DMD. Patients with DMD experience skeletal muscle weakness accompanied by increased blood levels of muscle enzymes and creatine kinase (CK) enzymes. 2/3 of DMD carriers have elevated blood levels of CK, even if they present as clinically healthy. This condition is used to identify carriers of a heterozygous genotype early on.[17]

The mutated gene is located on chromosome Xp21. The gene has 79 exons, where mutations and deletions can happen anywhere. The protein is called dystrophin.[14] Its function is linking between the internal cytoskeleton and extracellular matrix protein that helps stabilize the contraction of muscle.[7] Dystrophin is important for brain development and function. The intact dystrophin protein (Dp427) and other shorter isoforms (Dp260, Dp140, Dp116, Dp71) are expressed particulary in muscle, heart, and brain tissues. The incidence of cognitive impairment was higher in the deletions of exons 45-52, affecting the Dp140 and Dp71 isoforms, implying the signifcance of these isoforms in cognitive and brain function.[7] Patients lacking Dp140 and/or Dp71 have a particularly high incidence of neuro-developmental disorders. Brain tissue is also attacked so that the level of intelligence (IQ) decreased by about 20 points.[17]

In DMD patients, the prevalence of developing intellectual disability ranges from 19 to 35%.[18] Children with DMD are more likely to have intellectual disabilities (30%) than the general population, where the prevalence is only 1%. Boys with DMD have a high-risk factor for intellectual disability. The risk seems to rise with gene mutations at the 3' end (Dp71 disruption).[7] Genetic testing for

the dystrophin gene mutation establishes the diagnosis.[14]

2.3. Autism Spectrum Disorder (ASD)

Research from the Centers for Disease Control and Prevention (CDC) in the United States shows that 1 in 3 children aged 8 years with ASD suffers from ID.[3] The onset of ASD is in infancy and preschool years. ASD is seen in approximately 1% of the population with fairly equal prevalence rates among all racial and ethnic groups. From 1/5000 in 1975 to 1/44 in 2021, the prevalence of diagnosed ASD has greatly increased, but the reason for this increase is still unidentified.[3] Boys are diagnosed much more frequently than girls (4.3:1 ratio), but girls with the disorder typically experience more severe symptoms and intellectual impairment.[14] A small amount studies have investigated that ID children with comorbid ASD had more severe intellectual disability than children with ID alone. Research conducted in China in 2021 found that the prevalence of ASD with GDD was around 62.3% of 521 children in China. GDD children with ASD are more likely to have poor gross motor impairment than GDD without ASD.[3]

There are twenty genes related with the non-specific ID, while 40 genes are known to be responsible for specific genetic conditions. SHANK2, CNTNAP2, RELN, CHD8, NLGN3, NLGN4X, and PTCHD1 are the genes known to be related with ASD.[19,20]

A child with ASD, DMD, mild intellectual disability, and a history of febrile seizures was the subject of a case report by Simone et al. in 2021. This child also had a large deletion in the proximal region of the dystrophin gene. Nevertheless, other literature reveals that the symptoms of ASD do not appear to be significantly associated with specific dystrophin isoform mutations.[21,22]

2.4. Down syndrome

In liveborn infants, DS is the most prevalent abnormality of chromosomal number. While the exact numbers for Indonesia are still unknown, it occurs in about 1 out of every 700 births. However, a study from the University of Indonesia suggests that 300,000 children with SD are born annually.[8] There were 0.21% disabled DS in Indonesia as of 2018.[23]

Almost all patients with DS have an intellectual disability.[14] Trisomy-21 was detected by chromosomal analysis in 95% of Down syndrome cases, while mosaics and translocations were found in the remaining 5%. Genes that Affect Down Syndrome According to the gene imbalance theory, individuals with Down syndrome have more copies of the gene on HSA21, which results in higher levels of gene expression. According to this theory, a particular gene or region of a gene may control particular phenotypes associated with Down syndrome.[24,25] The DYRK1A gene, which is found in the DS critical region on chromosome 21, has also been linked to Down syndrome.[26]

According to WHO (World Health Organization) data there are 8 million cases of Down syndrome worldwide, 300,000 of which are in Indonesia. The incidence in Indonesia is increasing every year. Excess chromosome 21 in Down syndrome causes overexpression of certain proteins. So Down syndrome can manifest in certain clinical situations.[27]

2.5. Subtelomeric Chromosomal Rearrangements

Intellectual disability (ID) and malformation syndromes are frequently correlated with unbalanced subtelomeric chromosomal rearrangements. In ID populations, the prevalence of these rearrangements has been estimated to be 5-9%. Subtelomeric rearrangements were discovered to be a significant cause of ID in several studies, with an estimated prevalence

of 5-9% of cases in various populations. They were also found to be associated with mild to severe phenotypic abnormalities.

According to research by Mundhir et al., there are 16 cases of this phenotype in Indonesia. The result was a detection rate of 3.7% (16/436), of which 31% (5/16) had a complex rearrangement or unbalanced translocation, 44% (7/16) had a simple deletion, and 25% (4/16) had a simple duplication. Additionally, in 3% (16/527) of the cohort's cases, subtelomeric rearrangements played a genetic role in the development of ID. Nine different subtelomeric regions were involved in the deletions, including complex rearrangements (2q, 4p, 8p, 9p, 10p, 12p, 18p, X/Yp, X/Yq), while eight subtelomeric regions were involved in the duplications, including complex rearrangements (4p, 9p, 9q, 11p, 12q, 15q11, 22p, X/Yp).[28]

2.6. Apert Syndrome

Apert syndrome is associated with other systemic malformations, including intellectual disability. Apert syndrome is characterized by the presence of multi-suture craniosynostosis, midface retrusion, and syndactyly of the hands with the fusion of the second through fourth nails. The majority of those who are affected also have involvement of the sagittal and lambdoid sutures in addition to having coronal craniosynostosis in almost all cases. A subset of those with Apert syndrome have cleft palates, and the midface is underdeveloped and retruded.[29]

A case report was found of an Indonesian man with Apert syndrome with a c.755C>G (p.Ser252Trp) mutation in the FGFR2 gene. Direct sequencing was used to perform molecular genetic analysis on FGFR2, specifically targeting exon 7. c.755C>G, a missense mutation that converts a serine into a tryptophan, was found in this patient.[21]

3. Evaluating and Testing

The clinical geneticist is helpful in the assessment of individuals with intellectual disabilities and in considering whether to conduct additional genetic testing. Physical examination and the gathering of family history data are both included in the evaluation process. Congenital abnormalities, somatometric measurements, and behavioral assessments should be the main emphasis of the physical examination. Neuroimaging tests - MRI (magnetic resonance imaging) should be carried out in all individuals with neurological complaints, such as epilepsy and macro/microcephaly - to assess any brain anomalies. There should be tests performed for metabolic diseases and their symptoms. Many years ago, cytogenetic testing was typically used as the initial investigation when examining a patient with ID, whether or not they had dysmorphic traits (GTG-banding).[5,30]

The cytogenetic examination of the metaphase karyotype is still used to detect trisomy 21, all other aneuploidies, and balanced translocations. Cytogenetic analysis is the process of looking at the 46 chromosomes, commonly referred to as karyotypes, and how they are generally arranged. White blood cells normally have the most chromosomes, which are counted to see whether they are normal. Deletions or duplications in the chromosome structure are also examined.[2]

Prenatal diagnosis can also be accomplished using several molecular assays, including fluorescent in situ hybridization (FISH), quantitative fluorescence PCR (QF-PCR), and MLPA multiplex probe ligation assay (MLPA). The most often used method of nuclear interphase is the FISH technique, either specific HSA21 or all HSA21. Another technique that is often used in many nations is QFPCR, which uses polymorphic DNA (microsatellite) tags on HSA21 to identify the presence of three distinct alleles. This

approach depends on the availability of DNA and informative tags. The difficulty with conventional procedures may be lessened by a quick diagnosis employing PCR-based techniques and polymorphism STR markers. With only two markers, the STR sign technique can identify trisomy in 86.67% of instances. In addition, MLPA, a technique for relative quantification in DNA, which was initially introduced in 2002, can be used to determine the copy number of DNA sequences. A few benefits of MLPA are its effectiveness, simplicity, and quick (2-4 days) diagnosis time. It also comes at a low price.

MLPA is not capable of identifying an insufficient placenta. The present approach, known as "paralogous sequence quantification" (PSQ), counts the number of HSA-21 copies using paralogous sequences. PSQ is a PCR-based technique that uses paralogous genes to identify target chromosomes in abnormally high numbers. Examining parallelly sequenced clonally amplified DNA is known as next-generation sequencing (NGS). Each sequence read serves as a "sequence tag," identifying a sample of clonal DNA or a single DNA molecule, and this offers quantitative information.[2]

4. Conclusion

Intellectual disability (ID) is described as delayed mental and cognitive maturation that occurs before the age of 18. 1-3% of all children in Indonesia are said to have intellectual impairments. The genetic causes of instances with moderate-to-severe ID include chromosome structural abnormalities, chromosome aneusomies, genomic disorders, and monogenic diseases. Using information from the Ministry of Health and other Indonesian periodicals, we were able to identify all of the review-related genes for ID in the Indonesian population. The ID-related genes in the Indonesian population are associated with ASD, DMD, FXS, DS, Apert syndrome, and subtelomeric chromosomal rearrangements. Data on the prevalence of genetic disorders associated with intellectual disability in Indonesia do not describe the actual incidence because there are only a few studies investigating genetic disorders related to intellectual disability. There is not much research on genetics related to intellectual disability in Indonesia, implying further research is needed.

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