International Journal of Genetics and Genomics
2026, Vol. 14, No. 2, pp. 45–49
https://doi.org/10.11648/j.ijgg.20261402.11

Research Article

Factors Responsible for the Diagnostic Odyssey and Counseling for Children with Intellectual Disability

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Abstract

Intellectual disability (ID), a widely prevalent condition is a neurodevelopmental condition which encompasses diverse causes, both genetic and non-genetic. They most commonly show symptoms of delayed milestones, limited motor skills, unwarranted emotional changes, difficulty in learning new skills and poor memory. Genetic causes usually accounting up to 50%, most frequently includes chromosomal (structural and numerical), monogenic and de novo variants. Advancements in genetic testing options have enabled early diagnosis, minimizing complications and preventing further hereditary transmission. Genetic tests, such as karyotyping, chromosomal microarray (CMA), Next-Generation Sequencing (NGS) and various molecular assays like Multiplex Ligation-dependent Probe Amplification (MLPA), Methylation Specific polymerase chain reaction (MS-PCR) are available in contemporary healthcare settings for timely diagnosis. This study focuses on individuals with Intellectual disability (ID), who require support for diagnosis and rehabilitation and are visiting the National Institute for the Empowerment of Persons with Intellectual Disabilities (NIEPID) for therapy and are referred for genetic testing and genetic counseling. The paper also analyzes the reasons for diagnostic delays and gaps in genetic counseling, affecting the treatment and management. It also advocates for collective efforts to enhance awareness, potentially reduce costs and improve accessibility for testing, paving the way for a future grounded in precise management and preventative medicine.

Keywords

Developmental Delay, Karyotyping, Chromosomal Microarray, Ngs, Genetic Testing

1. Introduction

Intellectual disability (ID) is a neurodevelopmental disorder characterized by significant limitations in both intellectual functioning and adaptive behavior [1]. In children, it may present as delayed milestones, limited motor skills, unwarranted emotional changes, difficulty in learning new skills and poor memory [2]. Individuals who progress into adulthood with ID show characteristics of the causative disease and lower adaptive skills, higher incidence of psychiatric illnesses and poor choices in health behavior [3, 4]. ID estimates in India range between 1-3.2% with a male to female ratio of 1.6: 1 [6, 7]. The clear etiology of ID is not known but is dived into genetic and environmental causes [8]. Many studies have identified various causes for ID, of which genetic causes account to upto

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Received: 6 March 2026; **Accepted:** 19 March 2026; **Published:** 29 April 2026

50% [9]. The heterogeneous nature of ID makes it challenging to identify the underlying causes, but with advancements in testing options and relatively lower testing costs, early diagnosis of genetic diseases is possible to prevent the complications and their inheritance in future generations. Several tests including Newborn Screening, karyotyping, Chromosomal Microarray (CMA), Multiplex ligation-dependent probe amplification (MLPA), Methylation Specific Polymerase Chain Reaction (MS-PCR) and next-generation sequencing (NGS) are currently available for identifying the cause of ID. However, multiple studies have shown that many children with ID reach adulthood without proper diagnosis despite evidence proving that early intervention can reduce complications [5]. The Diagnostic Odyssey, which is the period between the first detection of symptoms to the point of final diagnosis, is often prolonged due to delay in testing or incorrect and unnecessary testing.

In this paper, we tried to identify the most appropriate diagnostic tests for the children with ID and analyzed the possible reasons responsible for the delay in diagnosis and counseling in a low resource country like India, with a varied range of socio-cultural issues and different levels of literacy.

2. Methodology

The study included pediatric cases referred to the Department of Genetics and Molecular Medicine, Kamineni Hospitals, Hyderabad, and to the Genetics Counseling unit of the National Institute for Empowerment of Persons with Intellectual Disabilities (NIEPID). The inclusion criteria encompassed cases with delayed milestones, neurobehavioral symptoms, low IQ with or without seizures. All the cases were assessed by a Genetic Counselor in a face to face interview with parent/gaurdian, who then documented demographic details, clinical and family history along with investigations carried out, previous visits to other centers or doctors and the current concerns of the families. A 3-generation pedigree was collected from each of them. Appropriate genetic diagnostic tests were recommended and reasons for acceptance or rejection were noted.

3. Results

The data was collected from 200 ID pediatric patients. Out of these, 125 (62.5%) were males and 75 (37.5%) were females. Their age range was 6 months to 18 years and maximum patients 114/200 (57%) were in the age group of 2-5 years Table 1. A total of 50/200 (25%) cases had a diagnosis, this included 22/50 (44%) of males and 28/50 (56%) of females. Among the diagnosed children that underwent the recommended genetic tests, a total of 44 were under the age of 5 years, 4 between 5 - 10 years of age and 2 children were above 10 years age Table 1.

Table 1. *Age and gender distribution in the tests performed.*

Age (in years)	Number	Diagnosed	Males	Males Tested	Females	Females Tested
<1	5 (2.5%)	1 (20.0%)	4 (3.2%)	1 (25.0%)	1 (1.3%)	0
1-2	63 (31.5%)	28 (44.4%)	38 (30.4%)	12 (31.6%)	25 (33.3%)	16 (64.0%)
2-5	114 (57%)	15 (13.15%)	76 (60.8%)	6 (7.9%)	38 (50.6%)	9 (23.7%)
6-10	13 (6.5%)	4 (30.76%)	6 (4.8%)	2 (33.3%)	7 (9.3%)	2 (28.6%)
>10	5 (2.5%)	2 (40%)	1 (0.8%)	1 (100%)	4 (5.3%)	1 (25%)
	200	50 (25.0%)		22 (44%)		28 (56%)

The most common referral reasons for evaluation included delayed milestones, behavioral issues with or without delayed speech, seizures and syndromic features Figure 1.

A total of 160 cases were recommended some form of genetic testing, it was observed that the uptake for karyotyping was highest (8/8), while the most frequently advised test was NGS based exome sequencing, the other tests were recommended less frequently Table 2. The uptake for CMA and MLPA was about the same, while that of NGS was 21.5% Table 2. NGS uptake was higher in older age group (> 6 years) followed by children below 1 year Table 3.

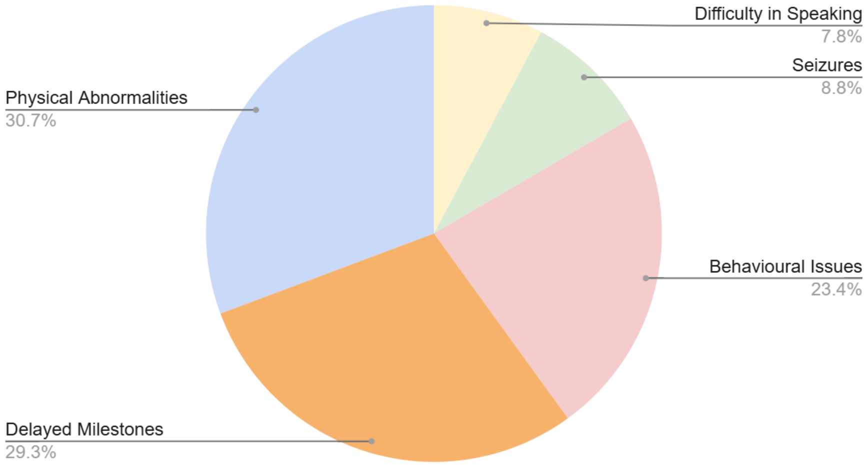

Figure 1. *Percentages of different neurological symptoms.*

Table 2. *Data showing different types of genetic tests carried out.*

Genetic test	Referred	Tested	Diagnosed	Undiagnosed
Karyotype	08	08 (100%)	08	0
MS-PCR	22	0 (0%)	0	22
NGS	93	20 (21.5%)	18	74
CMA	27	03 (11.1%)	01	26
MLPA	10	01 (10%)	01	09

Table 3. *Percentages of NGS done in different age categories.*

Age in years	Referred for NGS	Tested	Diagnosed	Undiagnosed
<1	8	5 (62.5%)	5	3
1-2	25	6 (24%)	6	19
2-5	55	5 (9.1%)	4	51
6-10	4	3 (75%)	3	1
>10	1	1 (100%)	1	0

All the cases diagnosed with karyotyping were those of Trisomy 21, CMA helped diagnose one case of Phelan-McDermid Syndrome (22q13.3 del), one was diagnosed as Guillian Barre based on antibodies and NGS diagnosed 18 cases.

4. Discussion

Intellectual disability, whether evident from birth or symptoms emerging progressively may be more widespread in our country than currently acknowledged. Fortunately, contemporary multispecialty hospitals and institutions offer various genetic tests capable of diagnosing the disorders. These tests, complementing clinical assessments, provide more precise diagnoses leading to appropriate management and counseling. In addition, advances in prenatal testing can offer preventive measures within the family [9-15].

Despite these advancements, only 25% of cases had a diagnosis, this is partly because of a low uptake of recommended tests except karyotyping, which clearly indicates that the cost of the tests was a prohibiting factor. The fact that MS-PCR test was not taken up may be because that it is not offered by most labs in India despite being a relatively cheaper test, effort has to be made in indicating to labs that this test needs to be included and clinicians made aware of its availability.

Common presenting symptoms included developmental delay, dysmorphology and neurobehavioral issues. Notably, cases with behavioral issues were less likely to undergo genetic testing. Gender disparity was negligible among tested children, and those below 5 years of age were more frequently brought in for testing, as compared to older children (>6 years), this may be because most of the families opt for testing when their reproductive life is not complete and are taking decisions about subsequent pregnancies. Testing rates significantly decreased among children older than 10, possibly due to previous exhaustive testing attempts and inconclusive results or the parents have decided not to plan further pregnancies.

The reasons for diagnostic delay apparent from face to face interview indicated: (i) lack of knowledge regarding appropriate testing amongst clinicians (ii) late referral to a Genetic counselor or Clinical Geneticist (iii) Genetic test costs not covered in government programs for individuals belonging to low socio-economic groups (iv) unavailability of genetic tests or atleast facility of sample collection within the same institution (ie NIEPID). Results from this analysis advocates for collective efforts to enhance awareness regarding the role of genetics in ID, increase the number of trained/certified genetic counselors who can be hired by organizations dealing with ID like NIEPID, pediatric hospitals, Neurological clinics, special schools and primary health centers. Government should potentially subsidize/reduce costs and improve accessibility for genetic testing, paving the way for a future grounded in precise management and preventative medicine.

Abbreviations

NIEPID	National Institute for the Empowerment of Persons with Intellectual Disabilities
ID	Intellectual Disability
NGS	Next Generation Sequencing
CMA	Chromosomal Microarray
MLPA	Multiple Ligation-dependent Probe Amplification

Acknowledgments

National Institute for the Empowerment of Persons with Intellectual Disabilities, Manovikasnagar, Secunderabad, Telangana India is acknowledged for allowing to include patients referred here for the study.

Author Contributions

Sreelatha Komandur: Conceptualization, Resources
Beulah Thullimelli: Resources
Aashna Nanda: Resources
Namratha Gangidi: Resources
Venkatesh Pochaboina: Resources
Shyamson Kandula: Resources
Qurratulain Hasan: Conceptualization, Resources

Conflicts of Interest

The study has no conflict of interest.

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