Diagnosis of intellectual disability/global developmental delay via genetic analysis in a central region of China

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Abstract

Background: Advanced technology has become a valuable tool in etiological studies of intellectual disability/global developmental delay (ID/GDD). The present study investigated the role of genetic analysis to confirm the etiology in ID/GDD patients where the cause of the disease was uncertain in central China.

Methods: We evaluated 1051 ID/GDD children aged 6 months to 18 years from March 2009 to April 2017. Data concerning basic clinical manifestations were collected, and the method of etiology confirmation was recorded. Genome-wide copy number variations (CNVs) detection and high-throughput sequencing of exons in the targeted regions was performed to identify genetically-based etiologies. We compared the incidence of different methods used to confirm ID/GDD etiology among groups with differing degrees of ID/GDD using the Chi-square or Fisher exact probability test.

Results: We recruited 1051 children with mild (367, 34.9%), moderate (301, 28.6%), severe (310, 29.5%), and profoundly severe (73, 6.9%) ID/GDD. The main causes of ID/GDD in the children assessed were perinatal factors, such as acquired brain injury, as well as single gene imbalance and chromosomal gene mutation. We identified karyotype and/or CNVs variation in 46/96 (47.9%) of cases in severe ID/GDD patients, which was significantly higher than those with mild and moderate ID/GDD of 34/96 (35.4%) and 15/96 (15.6%), respectively. A total of 331/536 (61.8%) patients with clear etiology have undergone genetic analysis while 262/515 (50.9%) patients with unclear etiology have undergone genetic analysis ($\chi^2 = 12.645$, $P < 0.001$). Gene structure variation via karyotype analysis and CNV detection increased the proportion of children with confirmed etiology from 51.0% to 56.3%, and second-generation high-throughput sequencing dramatically increased this to 78.9%. Ten novel mutations were detected, recessive mutations in X-linked genes (ATPase copper transporting alpha and bromodomain and WD repeat domain containing 3) and dominant de novo heterozygous mutations in X-linked genes (cyclin-dependent kinase like 5, protocadherin 19, IQ motif and Sec7 domain 2, and methyl-CpG binding protein 2) were reported in the study.

Conclusions: The present study indicates that genetic analysis is an effective method to increase the proportion of confirmed etiology in ID/GDD children and is highly recommended, especially in ID/GDD children with uncertain etiology.

Keywords: Intellectual disability; Global developmental delay; Children; Gene analysis; Etiology

Introduction

Intellectual disability (ID), also known as mental retardation, is a disorder including both intellectual and adaptive functioning deficits in conceptual, social, and practical domains. Deficits in intellectual functions, such as reasoning, problem-solving, planning, abstract thinking, judgment, academic learning and learning from experience, and practical understanding have been confirmed.[1-3] The term global developmental delay (GDD) is usually reserved for younger children (ie, typically less than 5 years of age) and refers to a subset of developmental disabilities defined as a significant delay in two or more developmental domains. ID/GDD is currently the primary global cause of disability, and a confirmed etiologic diagnosis is beneficial for information regarding treatment, symptom management, and surveillance for known complications.[4-5] Chromosomal microarray analysis has been reported as a useful tool in etiological confirmation. However, a consensus on targeted high-throughput sequencing in the evaluation of ID/GDD children remains unresolved.

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Because various genetic and environmental factors are involved in disease development, a definitive etiological diagnosis of ID/GDD while still in the early stages of manifestation can improve treatment efficacy and life quality. \(^\text{[6-8]}\) Most severely affected children can be identified before 2 years old, while some mildly affected children are only diagnosed at school-age due to less apparent manifestations such as stunted growth and poor gross motor skills. Advances in ID/GDD diagnosis and treatment using medical genetics evaluations have reported by the American Academy of Pediatrics since their original report in 2006.\(^\text{[4,5,9,10]}\) Although several hundred genes have been confirmed as the cause of monogenic forms of ID/GDD, evidence to support the use of high-throughput methods as tools for the regular clinical detection remains uncertain.

We conducted a retrospective study of the etiological characteristics of 1051 children with ID/GDD. We investigated the current proportion of advanced genetic technologies used in ID/GDD etiological confirmation and explored the causes of developmental disorders in central Chinese ID/GDD populations. This information could provide evidence for improving pregnancy care and high-risk maternal labor monitoring as well as highlight the importance of genetic analysis to optimize the ID/GDD diagnosis process.

**Methods**

**Ethical approval**

The study was approved by the Institutional Research Ethics Committee of Xiangya Hospital, Central South University (No. 201703238). ID/GDD patients were included in ID/GDD project of our hospital and entered into the project database; informed consents were signed by guardians of each child and obtained as soon as the diagnosis of ID/GDD was made. All methods in this study were performed in accordance with relevant guidelines and regulations.

**Patients and diagnostic criteria**

We recruited 1051 ID/GDD children aged 6 months to 18 years from Xiangya Hospital, Central South University, China, from March 2009 to April 2017. The identified children were diagnosed by experienced pediatric neurologists according to the American Association of Mental Retardation and the Diagnostic and Statistical Manual of Mental Disorders.\(^\text{[11]}\) The ID/GDD severity was classified according to intelligence quotient (IQ) scores: mild (IQ of 55–70), moderate (IQ of 40–54), severe (IQ of 25–39), or profoundly severe (IQ of less than 25).

**Test scales used for children of different ages**

The standardized intelligence tests used in children less than 3.5 years old were the Gesell Developmental Schedules or the Bayley Scales of Infant Development (second edition). The Wechsler Preschool and Primary Scale of Intelligence (fourth edition) was used in children aged 3 to 7 years, and the Wechsler Intelligence Scales for Children (fourth edition) in those aged 7 to 16 years. A children’s neuropsychological development scale was also used for patients aged 0 to 6 years and the Raven test in children aged 7 to 18 years.

**Data collection and clinical examinations**

Details concerning basic clinical information, clinical manifestations including head circumference and routine physical examination, laboratory analysis of body fluid, medical history, family history, and social and family environment were collected. Screening for inherited metabolic disorders included urine organic acid analysis using gas chromatography-mass spectrometry, acylcarnitine analysis, and the detection of amino acid levels in the blood by tandem mass spectrometry. Neuroimaging examination included cerebral X-rays, computed tomography, brain magnetic resonance imaging, and electroencephalography (EEG). Karyotype analysis, genome-wide copy number variation (CNV) detection, and second-generation sequencing, including targeted genomic capture and massively parallel sequencing, mitochondrial gene testing, and whole exon sequencing (WES), were performed according to the manufacturer’s protocols. Genomic DNA was isolated from peripheral blood leukocytes (AUI802; Bioteke, Beijing, China). Target enrichment and amplification were performed with the SureDesign target enrichment kit (Agilent, Santa Clara, CA, USA) according to the manufacturer’s instructions. The Illumina HiSeq 2500 platform (Illumina Inc., San Diego, CA, USA) was used to sequence the exons from the targeted regions. The mutations were further confirmed by Sanger sequencing. Co-separation analysis among families was performed for detected mutations.

**Procedure of etiology confirmation for ID/GDD**

In Phase I, we classified the patients according to the method used to identify their ID/GDD etiology. This included metabolic disease screening in patients exhibiting abnormal muscular tension, hepatomegaly, or regression; neuroimaging in those with an abnormal perinatal history, abnormal head circumference, intracranial infection, or intracranial trauma; EEG in those with seizure or autism; and karyotype analysis in those with dysmorphic features. In any case, where the ID/GDD etiology remained unclear following the above-mentioned tests, we performed karyotype analysis and genome-wide CNV detection. In Phase II, any remaining ID/GDD cases of unknown etiology underwent metabolic disease screening. In Phase III, we performed targeted genomic capture and massively parallel sequencing, mitochondrial gene testing, and WES in any cases whose etiology still remained unconfirmed following the metabolic screening in Phase II to explore the definitive causes of ID/GDD [Figure 1].\(^\text{[12]}\)

**Statistical analysis**

Normality of the data distribution for our study with sample size ≥50 was detected by the Kolmogorov-Smirnov test. Normally distributed data were described as the mean...
standard deviation, and data with non-normal distributions were described as the median (percentile value). Categorical variables were expressed as count and percentage and were compared by the Fisher exact probability tests. Statistical analysis was performed using SPSS Statistics software, (version 22.0, SPSS Inc., Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.
Language development retardation was the most common clinical manifestation of mild ID/GDD and was noted in 306 (83.5%) of the study subjects followed by moderate clinical manifestation of mild ID/GDD and was most common in children with severe ID/GDD. The most common clinical manifestations in children with severe ID/GDD were a prominent speech delay followed by gross motor delay since birth and dysmorphic features. We identified karyotype and/or CNVs variation in 46/96 (47.9%) of cases in severe ID/GDD patients, which was significantly higher than those with mild and moderate ID/GDD of 34 (35.4%) and 15 (15.6%) [Table 2].

Cerebral imaging revealed 211 patients with abnormal signs including encephalomalacia foci and ventricular system expansion followed by brain dysplasia, hydrocephalus, brain atrophy, and abnormal signals in brain white matter in both mild and severe cases of ID/GDD. Additionally, absenceism of the corpus callosum and gyrus deformity was mainly identified in children with severe ID/GDD.

**Genetic analysis improved etiological diagnostic yield in ID/GDD patients**

After the examinations of Phase I, a definitive ID/GDD etiology was identified in 536 of the 1051 cases (51.0%). We evaluated 798 patients during Phase II, of which a definitive etiology was confirmed in 56.3%, with 253 (24.1%) of ID/GDD patients who did not undergo genome-wide CNV detection due to economic reasons. There were 679 patients who underwent all three phases of the diagnostic process, of which a definitive etiology was identified in 536 cases (78.9%). However, the ID/GDD etiology in 143 patients still remained unidentified [Table 3].

The number of patients who underwent genetic analysis was higher in those with a definitive etiology than those with an unclear etiology, 331/536 (61.8%) patients with clear etiology have performed genetic analysis while 262/515 (50.9%) patients with unclear etiology have genetic analysis ($\chi^2 = 12.645$, $P < 0.001$); [Table 4]. Of the 536 patients with a definitive diagnosis, genetic analysis was not performed in 205 cases, where the etiology was identified as an acquired factor. However, in the 515 patients with unclear etiology, 253 did not undergo genome-wide CNV detection following routine examination due to the expense involved. Abnormal karyotype in 45, X and 47, XY, +21 were main disorders found in ten patients with mild and moderate ID/GDD of 34 (35.4%) and 15 (15.6%) [Table 2].

Remarkably, 87 ID/GDD cases were associated with pathogenic or likely pathogenic variants based on the results of targeted genomic capture and massively parallel sequencing. The diagnostic rate of targeted genomic capture based on a custom probe library containing 3994 to 4678 genes reported to be associated with a monogenic disorder was 30.9%. The positive rate of targeted genomic capture based on a custom probe library containing 118 genes reported to be associated with leukencephalopathies was 47.1% and that based on a custom probe library containing 308 genes reported to be associated with epilepsy was 33.8%. The positive rate of mitochondrial gene sequencing was 6.4%. Of the 98 cases where WES was performed, 12 ID/GDD children were identified with pathogenic or likely pathogenic gene variants.

### Table 1: Clinical characteristic of the 1051 patients and number of patients finishing metabolic screening and genetic analyses.

| Characteristics                          | Number of patients (%) |
|------------------------------------------|------------------------|
| **Sex**                                  |                        |
| Male                                     | 685 (65.2)             |
| Female                                   | 366 (34.8)             |
| **Age**                                  |                        |
| <1 year                                  | 280 (26.6)             |
| ≥1, ≤3 years                             | 316 (30.1)             |
| >3, ≤6 years                             | 237 (22.5)             |
| >6, ≤18 years                            | 218 (20.7)             |
| **Severity**                             |                        |
| Mild                                     | 367 (34.9)             |
| Moderate                                 | 301 (28.6)             |
| Severe                                   | 310 (29.5)             |
| Profound severe                          | 73 (6.9)               |
| **Auxiliary examinations**               |                        |
| Neuroimaging                             | 831                    |
| EEG                                      | 573                    |
| GC/MS (analysis of organic acid in the urine) | 570              |
| Karyotype analysis and/or                | 535                    |
| Genome-wide CNVs detection               |                        |
| Targeted gene sequencing                 | 207                    |
| Mitochondrial DNA sequencing             | 74                     |
| Whole exon sequencing                    | 98                     |

Data are presented as $n$ (%) or $n$. CNVs: Copy number variations; EEG: Electroencephalography; GC/MS: Gas chromatography-mass spectrometer.

### Results

**General information and clinical manifestations of ID/GDD patients**

We recruited 1051 children with ID/GDD, including 685 males (65.2%) and 366 females (34.8%). As many as 596 ID children were under 3 years old, accounting for 56.7%, in which patients under 1-year-old accounted for 26.6% and patients between 1 and 3 years old for 30.1%, 237 cases (22.5%) ranging from 3 years 1 month to 6 years old to 6 years 1 month to 18 years old. ID/GDD was mild in 367 (34.9%), moderate in 301 (28.6%), severe in 310 (29.5%), and profoundly severe in 73 (6.9%) cases [Table 1].

Language development retardation was the most common clinical manifestation of mild ID/GDD and was noted in 306 (83.5%) of the study subjects followed by learning disabilities in 271 cases (73.8%) and fine motor retardation in 267 cases (72.8%). Hyperactivity, convulsions, and deficits in emotional behavior were also observed. The most common clinical manifestations in children with severe ID/GDD were a prominent speech delay followed by gross motor delay since birth and dysmorphic features. We identified karyotype and/or CNVs variation in 46/96 (47.9%) of cases in severe ID/GDD patients, which was significantly higher than those with mild and moderate ID/GDD of 34 (35.4%) and 15 (15.6%) [Table 2].
Concrete etiological spectrum of ID/GDD patients

The ID/GDD etiology was identified as inherited metabolic diseases in eight children, comprising two cases of glutaric aciduria type 1, two cases of glutaric aciduria type 2, one case of ornithine ammonia methyltransferase deficiency, one case of pyruvate carboxykinase deficiency, one case of very long-chain acyl-CoA dehydrogenase deficiency, and one case of malonyl-CoA decarboxylase deficiency. This was followed by Angelman and Prader-Willi syndrome and 1p36 monosomy syndrome.

There were 87 ID/GDD cases associated with pathogenic or likely pathogenic variants based on the results of targeted genomic capture and massively parallel sequencing. Ten novel mutations were detected in our study. Compound heterozygous mutations in autosomal recessive genes (tripeptidyl peptidase 1, phosphoenolpyruvate carboxykinase 2 [PCK2], solute carrier family 25 member 19, NADH:ubiquinone oxidoreductase core subunit S3, solute carrier family 12 member 3, phospholipase A2 group VI, PCK2, alanyl-tRNA synthetase 2, phosphomannomutase 2, aldehyde dehydrogenase 7 family member A1, N-sulfoglucosamine sulfohydrolase, and dual oxidase maturation factor 2) and homozygous mutations in autosomal recessive genes (dolichol kinase, arylsulfatase A, electron transfer flavoprotein dehydrogenase, and ceroid-lipofuscinosis, neuronal 6), de novo heterozygous mutations in autosomal dominant genes (hyperpolarization activated cyclic nucleotide gated potassium channel 1, sodium voltage-gated channel alpha subunit 5, potassium voltage-gated channel subfamily Q member 2, potassium sodium-activated channel subfamily T member 1, sodium channel, voltage-gated, type VIII, alpha, DEP domain deletion syndrome).

Of the 535 ID/GDD cases where karyotype analysis and CNV detection was performed, an abnormal karyotype was observed in 25 cases [Table 1]. Of them, microdeletion syndrome accounted for 32.3%, microduplication syndrome for 23.0%, and 24.6% were cases of combined microdeletion and microduplication. Known syndromes were identified in 45.1% (32/71) of cases, including 1q42-q44 microdeletion syndrome, Angelman syndrome, Prader-Willi syndrome, 1p36 monosomy syndrome, Wolf-Hirschhorn syndrome, cri-du-chat syndrome, Williams-Beuren syndrome, 9p syndrome, lissencephaly, Smith-Magenis syndrome, Sotos syndrome, 17p12 microduplication syndrome, 22q11.21 microdeletion syndrome, and 22q13 microdeletion syndrome, among others. The highest detection rate was observed for 1q42-q44 microdeletion syndrome.
Table 4: Genetic analysis differed in ID/GDD patients with/without clear etiology.

| Item                        | Patients with clear etiology (n = 536) | Patients with unclear etiology (n = 515) | Total (n = 1051) | χ²    | P     |
|-----------------------------|----------------------------------------|------------------------------------------|-----------------|-------|-------|
| Genetic analysis            |                                        |                                          |                 |       |       |
|                             | 331 (61.8)                             | 262 (50.9)                               | 593 (56.4)      | 12.645| <0.001|
| Non-genetic analysis        | 205 (38.2)                             | 253 (49.1)                               | 458 (43.6)      |       |       |

Data are presented as n (%). *Comparison of genetic analysis between patients with clear etiology and patients without unclear etiology. ID/GDD: Intellectual disability/global developmental delay.

Discussion

ID/GDD is a developmental disorder with an incidence rate of 1% to 3%, affecting an estimated 150 million children globally. This study suggests that genetic testing is an effective approach for etiological confirmation in children with ID/GDD. Gene structure variation via karyotype analysis and CNV detection as well as second-generation high-throughput sequencing increased the proportion of definitive etiological confirmation from 56.2% to 78.9%, respectively. Although no novel mutations were identified, recessive mutations in X-linked genes (ATP7A, bromodomain and WD repeat domain containing 3 (BRWD3)) and dominant de novo heterozygous mutations in X-linked genes (cyclin-dependent kinase 5 (CDK5), protocadherin 19 (PCDH19), IQ motif and Sec7 domain 2 (IQSEC2), and methyl-CpG binding protein 2 (MECP2)) were also detected [Table S3, http://links.lww.com/CM9/A50].

Although mild IDs present with atypical symptoms, language impairment is usually the primary symptom of mild ID/GDD in children. Common signs of severe ID/GDD children include abnormal facial dysmorphic features, congenital malformation, obesity, short stature, and microcephaly. The etiology of ID/GDD in children with severe facial dysmorphic features, obvious deformity, and microcephaly may be associated with the pathogenesis of diseases. A genetic etiology is common in severe mental disorders, and severe malformations can significantly limit intelligence. Approximately, 11.6% (122/1051) of the ID/GDD children were affected by prenatal factors, suggesting that these are one of the most critical non-genetic factors. Therefore, it is hoped that all the prenatal factors inducing ID/GDD can be prevented or controlled in the future. With the development of neonatal-related technologies, the survival rate of high-risk infants has significantly increased, with a corresponding increase in the incidence of ID/GDD children. This was reflected in our study results, where the incidence of ID/GDD was higher than that of a similar study in India. Therefore, improved pregnancy care and high-risk maternal labor monitoring, improved delivery technology, a reduction in pre-term birth and low birth weight, and timely prevention and treatment of neonatal asphyxia and intracranial hemorrhage are essential measures to reduce ID/GDD children.

Congenital cerebral malformations are another major pathogenesis factor of ID/GDD. In our study, 39 cases (3.7%) demonstrated obvious cerebral malformation such as absent corpus callosum and ventricular system expansion. Van Karnebeek et al. found that the rate of ID/GDD etiology identification by brain imaging examination alone was very low. However, another study demonstrated a three-fold higher positive rate of etiological identification via brain imaging in some children with concomitant symptoms such as microcephaly, macrocephaly, local movement disorders, and depigmented macules.

In this study, inherited metabolic disease accounted for 0.8% (8/1051) of ID/GDD etiology, which is close to the figure of 0.2% to 8.4% reported previously in 2005. Metabolic disorders such as disorders of creatine metabolism, Sanfilippo disease type B, congenital disorders of glycosylation, adenylosuccinate lyase deficiency, etc, may have an ID/GDD phenotype, and these disorders should be investigated in children less than 2 to 3 years old or presenting with regression, ataxia, etc. Since the implementation of neonatal screening in China and the improvement of screening technology, more children with the inherited metabolic disease are receiving a timely diagnosis and appropriate treatment to avoid developing ID/GDD.

Genetic factors are an important cause of ID/GDD and have been reported to account for two-thirds of the ID/GDD population. In this study, chromosomal abnormalities, inherited metabolic disease, and single gene disorders were identified as genetic causes of ID/GDD. However, this is lower than similar studies in developed countries, suggesting that the awareness of the genetic disease and detection methods require improvement. Chromosomal abnormalities, including abnormal karyotypes and CNVs, are the most common genetic risk factors of ID/GDD. Chromosomal microarray analysis with a high resolution (minimum resolution of approximately 100 kb) within the scope of whole genome CNV detection at the sub-microscopic level has become the first-tier genetic testing method for intelligence obstacles, achieving a positive rate of 15% to 20%. In this study, we identified the presence of pathogenic CNVs in 16.9% of the 420 children with ID/GDD who underwent genomic CNV analysis, which is consistent with the previous report mentioned above.
Since 2010, the rapid identification of new genes has dramatically increased the diagnostic yield of genetic tests for ID/GDD. To date, more than 800 genes are known to dramatically increase the diagnostic yield of genetic tests since 2010. The rapid identification of new genes has dramatically increased the diagnostic yield of genetic tests for ID/GDD. The power of exome sequencing to define an etiology has been published following studies of small patient populations. The additional diagnostic yield rate varies from 25% to 32.5%, [10-28,29] In this study, 87 cases of ID/GDD were associated with pathogenic or likely pathogenic variants based on the results of targeted genomic capture and massively parallel sequencing. The diagnostic yield of targeted genomic capture based on a custom probe library containing 3994 to 4678 genes reported to be associated with monogenic disorder-related genes was 30.9%. A custom probe library could be designed individually according to the clinical demand. The determination of a specific genetic diagnosis is hugely beneficial to the patient’s family, relieving their uncertainty, ending their quest for a diagnosis, and identifying specific therapeutic interventions. Additionally, genetic counseling for recurrence risks, future reproductive planning, and prenatal diagnosis can be implemented to prevent the recurrence of a disabling disorder.

In addition to the above biological factors, non-biological factors such as the social, psychological, and cultural background as well as economic status account for a fraction of ID/GDD cases. In this study, non-biological factors were attributed to unknown reasons, as there are no practical criteria to determine them.

There are still several limitations in this study: first, this is a single-center research, the inference for other ID/GDD patients was limited. Multi-centers researches are recommended in the further investigation; second, small size sample for an epidemiology study. We will keep collecting information and gather more comprehensive suggestions about Chinese ID/GDD patient etiology combination; finally, even with these limitations, our result still provides etiological characteristics about ID/GDD children in central China, and further proved genetic analysis was benefit for early diagnosis of ID/GDD.

In conclusion, we report the etiological characteristics of ID/GDD children in a central region of China. Perinatal factors are one of the most important, which are of vital significance in the intervention and prognosis improvement of ID/GDD patients and their quality of life. Advances in genetic analysis have enabled the early diagnosis of ID/GDD.

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Conflicts of interest
None.

References
1. Michelson DJ, Shevell M, Sherr EH, Moeschler JB, Groisman AL, Ashwal S. Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2011;77:1629–1635. doi: 10.1212/WNL.0b013e3182343896.
2. Mauk PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies. Res Dev Disabil 2011;32:419–436. doi: 10.1016/j.ridd.2010.12.018.
3. Leonard H, Wen X. The epidemiology of mental retardation: challenges and opportunities in the new millennium. Ment Retard Dev Disabil Res Rev 2002;8:117–134. doi: 10.1002/mrdd.10031.
4. Moeschler JB, Shevell M. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics 2006;117:2304–2316. doi: 10.1542/peds.2006-1006.
5. Moeschler JB, Shevell M. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics 2014;134:e903–e918. doi: 10.1542/peds.2014-1839.
6. Eaton J, McCay L, Semrau M, Chatterjee S, Raingana F, Araya R, et al. Scale up of services for mental health in low-income and middle-income countries. Lancet 2011;378:1592–1603. doi: 10.1016/S0140-6736(11)60891-x.
7. Turey P, Raymond FL, O’Meara E, Sedges K, Teague J, Butler A, et al. Mutations in CUL4B, which encodes a ubiquitin E3 ligase subunit, cause an X-linked mental retardation syndrome associated with aggressive outbursts, seizures, relative macrocephaly, central obesity, hypogonadism, pes cavus, and tremor. Am J Hum Genet 2010;86:345–352. doi: 10.1016/j.ajhg.2010.01.017.
8. Kieling C, Baker-Henningham H, Belfer M, Conti G, Ertom I, Omobodun O, et al. Child and adolescent mental health worldwide: evidence for action. Lancet 2011;378:1515–1525. doi: 10.1016/S0140-6736(11)60827-1.
9. Nguyen DP, Klein B, Meyer D, Austin DW, Abbott JAM. The Diagnostic Validity and Reliability of an Internet-Based Clinical Assessment Program for Mental Disorders. J Med Internet Res 2015;17:e218. doi: 10.2196/jmir.4195.
10. Redin C, Gerard B, Lauer J, Herenger Y, Muller J, Quattori A, et al. Efficient strategy for the molecular diagnosis of intellectual disability using targeted high-throughput sequencing 2014;51:724–736. doi: 10.1136/jmedgenet-2014-102554.
11. Rauch A, Hoyer J, Gurt S, Zweier C, Kraus C, Becker C, et al. Diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation. Am J Med Genet Part A 2006;140:2063–2074. doi: 10.1002/ajmg.a.31416.
12. Richards S, Aziz N, Bale S, Bik D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–425. doi: 10.1038/gim.2015.30.
13. Dua T, Barbui C, Clark N, Fleischmann A, Pozynik V, van Ommeren M, et al. Evidence-based guidelines for mental, neurological, and substance use disorders in low- and middle-income countries: summary of WHO recommendations. PLoS Med 2011;8:e1001122. doi: 10.1371/journal.pmed.1001122.
14. Johnson CP, Walker WO Jr, Palomo-Gonzalez SA, Curry CJ. Mental retardation: diagnosis, management, and family support: Curr Prob Pediatr Adolesc Health Care 2006;36:126–165. doi: 10.1016/j.cppeds.2005.11.005.
15. Aggarwal S, Bogula VR, Mandal K, Kumar R, Phadke SR. Aetiology spectrum of mental retardation & developmental delay in India. Indian J Med Res 2012;136:436–444.
16. van Karnebeek CD, Janseweijer MC, Leenders AG, Offerma M, Hennekam RC. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Hum Genet 2005;13:6–25. doi: 10.1038/sj.ejhg.5201279.
17. Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic yield of subspecialists’ evaluation of young children with global developmental delay. J Pediatr 2000;136:593–597. doi: 10.1016/s0022-3476(00)00735-8.
18. van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. Mol Genet Metab 2012;105:368–381. doi: 10.1016/j.ymgme.2011.11.191.
19. Mefford HC, Batshaw ML, Hoffman EP. Genomics, intellectual
disability, and autism. New Engl J Med 2012;366:733–743. doi:
10.1056/NEJMra1114194.
20. Flore LA, Milunsky JM. Updates in the genetic evaluation of the child
with global developmental delay or intellectual disability. Sem Pediatr
Neurol 2012;19:173–180. doi: 10.1016/j.spen.2012.09.004.
21. de Ligt J, Willemsen MH, van Bon BW, Kleefstra T, Yntema HG,
Kroes T, et al. Diagnostic exome sequencing in persons with severe
intellectual disability. New Engl J Med 2012;367:1921–1929. doi:
10.1056/NEJMoa1206524.
22. Kaufman L, Ayub M, Vincent JB. The genetic basis of non-syndromic
intellectual disability: a review. J Neurodev Disord 2010;2:182–209.
doi: 10.1007/s11689-010-9053-2.
23. Gijsbers AC, Lew JY, Bosch CA, Schuurs-Hoeijmakers JH, van
Haeringen A, den Hollander NS, et al. A new diagnostic workflow for
patients with mental retardation and/or multiple congenital abnor-
malities: test arrays first. Eur J Hum Genet 2009;17:1394–1402. doi:
10.1038/ejhg.2009.74.
24. Morrow EM. Genomic copy number variation in disorders of
cognitive development. J Am Acad Child Adolesc Psychiatry
2010;49:1091–1104. doi: 10.1016/j.jaac.2010.08.009.
25. Schaaf CP, Wisniewska J, Beaudet AL. Copy number and SNP
arrays in clinical diagnostics. Ann Rev Genomics Hum Genet
2011;12:25–51. doi: 10.1146/annurev-genom-092010-110715.
26. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR,
Carter NP, et al. Consensus statement: chromosomal microarray is a
first-tier clinical diagnostic test for individuals with developmental
disabilities or congenital anomalies. Am J Hum Genet 2010;86:749–
764. doi: 10.1016/j.ajhg.2010.04.006.
27. Chiurazzi P, Pirozzi F. Advances in understanding - genetic basis of
intellectual disability. F1000Res 2016;5. doi: 10.12688/F1000res.
search.7134.1.
28. Thevenon J, Duffourd Y, Masurel-Paulet A, Lefebvre M, Feillet F, El
Chehadeh-Djebbar S, et al. Diagnostic odyssey in severe neuro-
developmental disorders: toward clinical whole-exome sequencing as
a first-line diagnostic test. Clin Genet 2016;89:700–707. doi:
10.1111/cge.12732.
29. Gilissen C, Hehir-Kwa JY, Thung DT, van de Vorst M, van Bon BW,
Willemsen MH, et al. Genome sequencing identifies major causes of
severe intellectual disability. Nature 2014;511:344–347. doi:
10.1038/nature13394.

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CM9.000000000000295.