TABLE 1. Imprinting Disorders Associated With Global Developmental Delay and Intellectual Disability		
Disorder	**Genetic Etiology**	**Clinical Features**
Angelman syndrome	Abnormal methylation at 15q11.2-q13 (including UBE3A gene) – maternally imprinted	Feeding difficulties, progressive microcephaly, seizures, ataxia/tremulousness, epilepsy behavioral peculiarities (happy disposition, fascination with water), variable developmental delay/intellectual disability[13]
Prader-Willi syndrome	Abnormal methylation of 15q11.2-q13 – paternally imprinted	Severe feeding difficulties in infancy followed by obesity in childhood, severe hypotonia, hypogonadism, short stature, behavioral abnormalities, global developmental delay/intellectual disability[14]
Temple syndrome	Abnormal methylation of 14q32.2 – paternally imprinted	Intrauterine growth restriction, short stature, feeding difficulties in infancy followed by obesity later in childhood, precocious puberty, hypotonia, variable developmental delay/intellectual disability[15]

have reproductive implications for the child him- or herself when they are of reproductive age, as having a genetic diagnosis can help inform their own reproductive decisions. It can directly impact treatment (ie, inborn errors of metabolism) or identify as candidates for future treatments (eg, gene therapy); reduce further unnecessary diagnostic testing; allow access to developmental therapies/services, appropriate disease-specific support networks, or clinical trials; and provide positive psychological impact on parents/caregivers.[16]

The diagnostic yield of genetic testing is influenced by the severity of GDD/ID. In severe ID, as defined in DSM-5, a genetic etiology may be discovered in approximately 80% of cases, whereas in mild ID, the diagnostic yield is closer to 20%.[17] The genetic diagnostic yield is also increased if there are dysmorphic features, congenital anomalies, or neurological comorbidities. The genetic evaluation of GDD and ID requires a thoughtful and systematic evaluation. This evaluation includes a detailed medical history, family history, clinical examination, and use of corollary investigations such as neuroimaging, vision assessment, and hearing assessment.

GDD/ID can be divided into syndromic and nonsyndromic forms. Syndromic refers to clinical features beyond GDD/ID that may suggest a specific disorder or category of disorders, whereas nonsyndromic GDD/ID lacks such features.[18] Up to two-thirds of GDD/ID is considered nonsyndromic.

If the patient has features suggestive of a syndromic form of GDD/ID, when possible, a phenotype-driven diagnostic approach is useful to make the clinical diagnosis or to refer for more targeted genetic testing to improve testing accuracy as well as to save cost and time. When a specific diagnosis is not suspected, or in cases of nonsyndromic GDD/ID, an agnostic, or "hypothesis-free," approach may be utilized.

PHENOTYPE-DRIVEN APPROACH TO DIAGNOSTIC EVALUATION

Following history and examination, the etiology of GDD/ID can be established in up to 17.2% to 34.2% of cases.[19]

Medical History

The evaluation includes taking a full developmental history, including gross motor, fine motor, language, social-emotional, and self-help skills. Developmental delay isolated to the motor domains may suggest a central (eg, brain) or peripheral (eg, neuromuscular) disorder. Abnormalities in language and social domains raises concern for autism spectrum disorder (ASD). Although the genetic etiologies of ASD may overlap with those associated with GDD/ID, the genetic diagnostic approach to ASD will not be covered further in this review.

It is useful to establish the trajectory of the individual's development to assess whether there is developmental regression. Developmental regression may suggest a neurodegenerative disorder or acquired process necessitating a prompt urgent referral to a neurologist and/or geneticist. The diagnostic evaluation for developmental regression will not be covered in this review.

Comorbid behavioral abnormalities are important to elicit in the child with GDD/ID and can suggest a specific diagnosis. For example, severe self-injurious behaviors can be seen in Lesch-Nyhan syndrome and Cornelia-de-Lange syndrome.[20,21] Some genetic disorders are associated with unique behavioral peculiarities, such as fascination with water or crinkly items in Angelman syndrome, skin picking and hyperphagia in Prader-Willi syndrome, midline stereotypies and intense eye contact in Rett syndrome, and episodic hyperventilation and breath-holding in Pitt-Hopkins syndrome.[13,14,22,23]

In addition to the developmental history, it is useful to establish whether there are any additional health concerns. It is often these features that can allow for the differential diagnosis to be narrowed based on phenotype. Additional health concerns can include other neurological symptoms (eg, seizures, movement disorder, weakness, nystagmus, hypotonia, spasticity, dystonia, hyperreflexia, ataxia, focal neurological findings); vision loss; hearing loss; feeding difficulties; organomegaly; and abnormalities of the gastrointestinal, dermatologic, dental, respiratory, cardiovascular, musculoskeletal, or endocrine systems. Occasionally, history of an unusual odor may prompt evaluation for an