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Personalised medicine for developmental disorders

PERSPECTIVES

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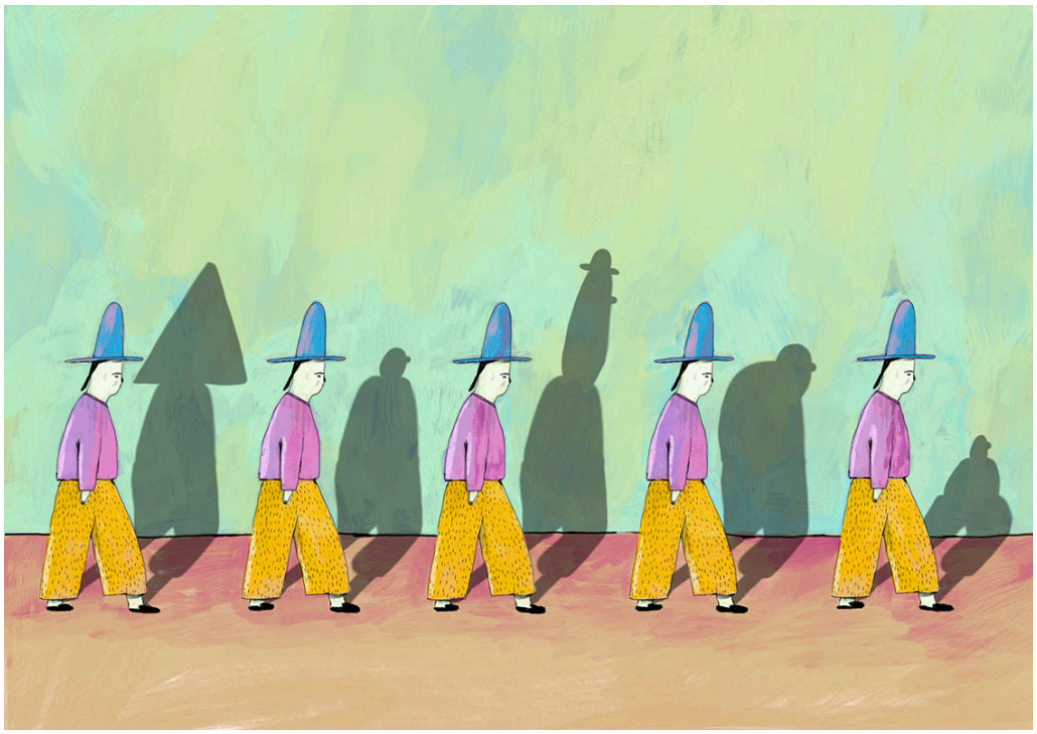

Illustration: Skinkeape

Personalised medicine refers to a type of medical care in which treatments are tailored to the biological characteristics of the individual patient. This is not a new concept; however, modern gene sequencing technologies have provided new opportunities for diagnostic practice and individualised care. Today,

comprehensive genetic testing is often carried out at an early stage in the clinical investigation of a child with a developmental delay (1). Hence, more individuals are being diagnosed with rare genetic disorders, but genetic testing alone is not enough to ensure personalised treatment for these children.

Paradigm shift

Next-generation sequencing technologies have significantly improved the diagnostic yield for rare disorders and shortened the time to receive an accurate molecular diagnosis. An increasing number of genes and genetic variants associated with various congenital and developmental disorders are being identified, allowing more individuals to receive a causal explanation for their condition (1, 2). Many parents find this beneficial.

> ***«An increasing number of genes and genetic variants associated with various congenital and developmental disorders are being identified»***

Rare genetic variants associated with cognitive developmental disorders often occur *de novo*, meaning that the genetic variant causing the disorder is not present in the parents' DNA (1, 2). *De novo* variants can be identified by trio sequencing (comparing the genomic sequence of the child with the parents' sequences) (2). Several large studies, including the British DDD project (Deciphering Developmental Disorders), have contributed to diagnostic advances in rare developmental disorders (2).

Genetic syndrome and behavioural phenotype

A genetic syndrome is defined as a recognisable pattern of various developmental features that are attributed to the same underlying genetic factor (3). These features are often organ-specific symptoms and findings such as characteristic skin lesions and epilepsy in tuberous sclerosis; however, a genetic syndrome can also be associated with specific cognitive and behavioural characteristics or a risk of mental disorders (4). Some examples of these include deficits in working memory (especially for language) in Down syndrome, an apparently cheerful personality in Angelman syndrome, an increased risk of developing schizophrenia in 22q11.2 deletion syndrome, bipolarity and regression in Phelan-McDermid syndrome (deletion 22q13.3/*SHANK3*) and development of behavioural disorders in Rubinstein-Taybi syndrome (4–7).

In English literature, the term 'behavioural phenotypes' is used to describe observable behavioural characteristics that are more common in individuals with a specific genetic syndrome than in others (4). Nevertheless, there is no

clear distinction between somatic and behavioural characteristics in these syndromes, since somatic problems, mental disorders and cognitive difficulties can all affect behaviour (4).

Diagnostic overshadowing

Knowledge of behavioural phenotypes in an individual can be helpful to better understand and identify appropriate treatment and care. People with an intellectual disability are at an increased risk of physical and mental health disorders but often struggle to communicate what is bothering them. This can lead to other conditions being overlooked, and these individuals may actually receive less help than others because their intellectual disability is the sole focus (4). Diagnostic overshadowing means that comorbidities are overlooked because the symptoms are attributed solely to the underlying disorder (8). There is a real risk that severe and treatable conditions may be missed and that people with an intellectual disability may actually die from causes that could potentially have been treated (9).

> ***«Diagnostic overshadowing means that comorbidities are overlooked because the symptoms are attributed solely to the underlying disorder»***

Pain occurring in a person with major communication problems can manifest as challenging behaviour and must not be misinterpreted as a mental health problem. Pain is associated with both aggression and self-injurious behaviour and occurs frequently in certain genetic syndromes (10). The characteristics of self-injurious behaviour, such as topography and age of onset vary among the syndromes and therefore require different treatment strategies. Knowledge of what can cause pain is crucial. The link between gastroesophageal reflux and self-injurious behaviour in Cornelia de Lange syndrome is a classic example (4), and European guidelines state that gastroesophageal reflux and constipation should be suspected in cases of behavioural changes in people with Phelan-McDermid syndrome (11). Certain syndromes may be associated with altered sensory perceptions. Many individuals with Williams syndrome (deletion 7q11.23) may have increased sensitivity to auditory stimuli, while impaired perception of painful stimuli has been reported among those with Cornelia de Lange syndrome, Angelman syndrome, Prader-Willi syndrome and Phelan-McDermid syndrome (4, 5). If pain perception is impaired, it is conceivable that the risk of diagnostic overshadowing will be even greater.

Different phenotypes

Individuals diagnosed with the same genetic disorder may have different phenotypes. The new genetic era has shown that once a genetic basis of a syndrome has been recognised, individuals with milder or distinct phenotypes with the same molecular basis are also diagnosed (1).

DiGeorge syndrome was originally described as a triad of immunodeficiency, hypocalcaemia and heart malformations, but it is now well-known that the syndrome is associated with a wide range of symptoms and signs that can manifest at different times in life (7). The syndrome is now referred to as 22q11.2 deletion syndrome, in which a small part of one chromosome 22 is missing and the deletion involves several genes.

Conditions that only affect a single gene can also be associated with different phenotypes. Various mutations in the *SCN1A* gene are associated with a clinical spectrum ranging from Dravet syndrome, which is a severe form of epilepsy, to familial hemiplegic migraine. Even within a family where everyone has the same mutation, the phenotype can vary between Dravet syndrome, mild epilepsy and no impairment (12, 13).

> ***«Since the characteristics of individuals diagnosed with the same genetic syndrome may differ, accurate clinical and functional assessments are necessary»***

Since the characteristics of individuals diagnosed with the same genetic syndrome may differ, accurate clinical and functional assessments are necessary. Today, children can be diagnosed with a genetic disorder before being diagnosed with intellectual disability or autism, while on the other hand many adults with an intellectual disability have not been offered genetic testing. To avoid diagnostic overshadowing, it is crucial that the assessment does not stop after a genetic diagnosis has been identified. In a report by the Norwegian Broadcasting Corporation (NRK), a mother of a child with a rare diagnosis described the diagnosis of intellectual disability as follows: 'It was almost a relief to get this diagnosis because it makes it easier to explain to people what's wrong with her' (14).

Autism and genetic syndromes

Some rare syndromes are characterised by the large number of individuals with the syndrome who also meet the criteria for an autism spectrum disorder. Autism is characterised by difficulties with communication and social interaction, as well as repetitive and stereotypical behaviour (15). There is an increased prevalence rate of autism in some genetic syndromes; fragile X syndrome and tuberous sclerosis being the most well-known (15, 16). Individuals with these syndromes can have different degrees of intellectual disability, and it is estimated that approximately 30 % of men with fragile X syndrome and 36 % of people with tuberous sclerosis also meet the criteria for an autism spectrum disorder (8, 16). The risk is highest amongst those with the most severe intellectual disabilities, but the prevalence of autism in tuberous sclerosis is also higher among those with normal cognitive levels (16). It was long believed that everyone with Down syndrome was sociable and outgoing and thus almost protected against autism, but it is now known that autism in Down syndrome is not uncommon (16).

The cause of autism is largely genetic, but people with autism are a highly heterogeneous group, and different people have different genetic makeup (15, 17). Diagnosing autism in addition to a genetic syndrome is useful because people with autism have special educational needs (16). Moreover, communication difficulties in autism increase the risk of diagnostic overshadowing, causing physical or mental health problems to be overlooked.

Structure and predictability, language and communication support, and help with social interaction are core educational principles for individuals with autism. Advances in medical technology are leading to the continual discovery of more genetic variants associated with autism (18); however, there is no evidence of 'autism-specific' genes (17). Genes associated with autism are also associated with intellectual disability or other neurodevelopmental disorders.

Brain development and formation of neural connections start in the womb, while the symptoms that define autism become apparent during the first two years of life. Genetics, brain development, neural connections, and the functional impairments that define autism are descriptions at different levels. Among those with average or above average intelligence, the genetic risk for autism is typically due to the sum of effects of several common genetic variants, whereas in others the genetic cause of autism is explained by the effect of a single rare genetic variant.

Summary

Today, many children with congenital and developmental disorders can receive a genetic diagnosis early in the diagnostic process. Rare genetic variants causing autism often occur *de novo*, meaning that they are not found in the parents' DNA. Moreover, there can be considerable phenotypic variability among individuals with the same genetic diagnosis. Genetic testing is therefore not sufficient to provide personalised treatment. Genetic testing must be supplemented with detailed assessment in various areas, including physical health, cognition, social interaction and communication.

Individuals with an intellectual disability are at an increased risk of physical and mental health problems but may struggle to convey what is bothering them. Knowledge of genetics and the behavioural phenotype associated with a genetic syndrome can be useful in the assessment process and reduce the risk of diagnostic overshadowing.

The autism diagnosis is made on the basis of observed behaviour, and individuals with autism constitute a highly heterogeneous group with various genetic causes. The rare variants in genes associated with autism are also associated with intellectual disability or other neurodevelopmental disorders.

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