

CLINICAL QUIZ (p122) ANSWER

What is the diagnosis ?

This child presented with neonatal hypotonia, feeding difficulties, cryptorchidism, speech and motor delay, fair complexion, small hands and feet, and facial dysmorphic features such as narrow bifrontal diameter and almond shaped eyes. All these clinical features are compatible with Prader-Willi syndrome (PWS).

Methylation-specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) analysis was performed in this child that showed hypermethylation and heterozygous deletion of *SNRPN* locus in 15q11-q13 region (also known as the Prader-Willi syndrome/Angelman syndrome region, or PWS/AS region). This test confirmed the deletion of the paternally inherited *SNRPN* allele, thus substantiating the diagnosis of PWS.

What is Prader-Willi syndrome?

Prader-Willi syndrome is a neurodevelopmental disorder which is caused by an absence or disruption of the expression of paternal alleles of *SNRPN* locus imprinted genes in the PWS/AS region. The prevalence of PWS was found to be 1 in every 15000 to 30000 live births.¹

What are the clinical features and diagnosis of Prader-Willi syndrome?

Clinical manifestations of PWS change significantly with age.² In infants and young children, PWS is characterised by neonatal hypotonia and feeding difficulties which may lead to failure to thrive. When patients grow older, their appetite will increase dramatically and remarkable food-seeking behaviours can be observed. Without food intake restriction, patients would easily become obese and the risk of comorbidities such as type 2 diabetes and cardiovascular diseases would rise. Besides abnormal appetite and weight gain, hypogonadism, global developmental delay, mental retardation, short stature, growth hormone deficiency, sleep apnoea, behavioural and psychological problems such as psychosis and autism are commonly observed in patients of PWS.³⁻⁵

Consensus diagnostic criteria of PWS have been established in 1993 and the scoring system is summarised in Table 1. For the full list of diagnostic criteria, one can refer to *Prader-Willi syndrome: Consensus Diagnosis Criteria* by Holm et al.

What are the genetic mechanisms that lead to PWS?

Three different genetic mechanisms that lead to abnormal expression of paternal alleles in the PWS/AS region, would result in PWS phenotype. Among them, deletions in paternal alleles of 15q11.2-q13 region accounts for around 70-75% of all PWS cases. Other mechanisms include maternal uniparental disomy of chromosome 15 (i.e. both copies of chromosome 15 are maternally inherited, without paternal contribution) (25%), and imprinting defects (1%).⁶

The exact pathophysiology of PWS is not yet fully understood. It involves multiple imprinted genes that lie within the PWS region in 15q11.2-q13. In a healthy individual, the maternal alleles of some genes in the PWS region are silenced by specific methylation patterns so that the expressed genes in this region are always from paternal origin. However, in PWS patients, the lack of functional paternal alleles leads to a deficiency of their protein products, which brings about various clinical features of PWS.⁶ For instance, the loss of function of *MAGEL2* gene,

Table 1 Scoring system for diagnosis of PWS³

| Categories | Diagnostic criteria |
|--|---|
| Major criteria (1 point each) | |
| Neurological | <ul style="list-style-type: none"> • Neonatal and infantile hypotonia with poor suck • Hyperphagia |
| Craniofacial | <ul style="list-style-type: none"> • 3 or more of the followings: <ol style="list-style-type: none"> 1) Dolichocephaly in infancy 2) Narrow face/narrow bifrontal diameter 3) Almond-shaped eyes 4) Small mouth with thin upper lip 5) Down-turned corners of the mouth |
| Oral/gastrointestinal Gonadal | <ul style="list-style-type: none"> • Feeding problems in infancy, requiring special feeding techniques • Hypogonadism, with any of the following features: <ol style="list-style-type: none"> 1) Genital hypoplasia (e.g. cryptorchidism, small penis/testes, hypoplasia of scrotum or labia minora/clitoris) 2) Delayed/incomplete gonadal maturation with delayed signs of puberty after the age of 16 |
| Genetic | <ul style="list-style-type: none"> • Deletion/other molecular abnormality of the PWS/AS region (15q11-q13) |
| Others | <ul style="list-style-type: none"> • Excessive weight gain between the ages of 1 and 6 • Global developmental delay with mental retardation |
| Minor criteria (0.5 point each) | |
| Psychological/ behavioural | <ul style="list-style-type: none"> • 5 or more of the followings: <ol style="list-style-type: none"> 1) Temper tantrums 2) Violence and obsessive/compulsive behaviour 3) Personality-wise: <ol style="list-style-type: none"> a) Argumentative b) Oppositional c) Rigid d) Manipulative e) Possessive f) Stubborn 4) Behaviour-wise: <ol style="list-style-type: none"> a) Perseverating b) Stealing c) Lying |
| Ophthalmological | <ul style="list-style-type: none"> • Skin picking |
| Respiratory | <ul style="list-style-type: none"> • Esotropia/myopia |
| Oral | <ul style="list-style-type: none"> • Sleep apnoea/other forms of sleep disturbance • Viscous saliva with crusting corners of the mouth • Articulation disorder |
| Dermatological | <ul style="list-style-type: none"> • Hypopigmentation |
| Others | <ul style="list-style-type: none"> • Limited foetal movement, infantile lethargy/weak cry • Short stature before the age of 15 • Small hands/feet • Narrow hands with straight ulnar border |
| Supportive features (0 point) | |
| Neurological | <ul style="list-style-type: none"> • High pain threshold • Reduced vomiting • Temperature instability/abnormal temperature sensation • Normal neuromuscular examinations |
| Musculoskeletal | <ul style="list-style-type: none"> • Scoliosis/kyphosis • Osteoporosis |
| Gonadal | <ul style="list-style-type: none"> • Early adrenarche |
| Others | <ul style="list-style-type: none"> • Proficiency with jigsaw puzzles |

* Diagnostic scoring system:

0-3 years of age: 5 points or more are required, 4 of which should be from major features;

3 years of age or older: 8 points or more are required, 5 of which should be from major features.

* Clinical features presented in our patient are shown in bold.

* Our proband scored 5.5 points according to this scoring system, supporting the diagnosis of PWS.

which is normally highly expressed in the areas of brain that control appetite, can cause dopaminergic dysfunction and hypothalamic leptin insensitivity. It is thus suggested that this gene may be associated with hyperphagia and food-seeking behaviours in PWS.^{2,7} Table 2 summarises other major candidate genes of PWS and their functions.

The phenotypic manifestations of PWS patients can be correlated to their pathogenic molecular subtype. Generally, patients with deletion mutation have the most prominent clinical features. These patients are more prone to the presentation of neonatal feeding difficulties, hypopigmentation, hypogonadism, small hands and feet, sleep disturbance, articulation defects and more prominent behavioural problems. The average IQ and birthweight of the deletion type are also found to be lower than other PWS patients. All these genotype-phenotype correlation are important for prognosis counselling.^{12,13}

Table 2 Major candidate genes of PWS and their functions

| Gene | Functions and the consequence of deficient expression |
|---------------------------------|---|
| <i>SNURF-SNRPN</i> ⁸ | Responsible for postnatal neural development; Deficient expression in brain can impair neurite outgrowth, neuron migration and development of dendrites and may be related to autism spectrum disorders. |
| <i>OCA2</i> ⁹ | Associated with hypopigmentation in PWS |
| <i>NECDIN</i> ¹⁰ | Crucial for neurite outgrowth and early neural development |
| <i>MKRN3</i> ¹¹ | Associated with inherited central precocious puberty |

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