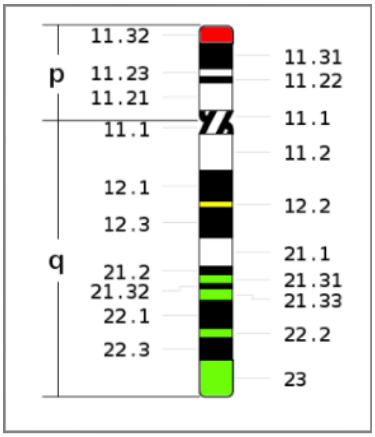
Pitt-Hopkins Syndrome

Pitt-Hopkins Syndrome (PHS) is a neurodevelopmental disorder characterized by intellectual disability, lack of speech, abnormal breathing, and facial dysmorphisms. First described in 1978, PHS results from the deletion or malfunction of the transcription factor 4 (TCF4) gene located on chromosome 18q21.



This malfunction may be caused by point mutations in the TCF4 gene and by deletions of this chromosomal segment. Approximately 50% of patients have mutations and 50% have deletions [1]. Deletions may affect the whole TCF4 gene (sometimes with the loss of the neighboring genes) or only several segments (exons) of this gene. For patients who lost only several exons it was shown that deletions of the first 8 exons (as well as deletions in this part of the gene) produce less severe manifestations than patients who lost exons 9-20 (or have mutations in this part of the gene)[2]. TCF4 plays a crucial role in the early development of the brain. Its lack of function results in the intellectual disability and motor delays often seen in patients.

PHS is present in about 1:34,000-1:41,000 births[3]. Currently, there are believed to be fewer than 500 confirmed cases worldwide[1]. It is believed, however, that the condition is underdiagnosed due to its strong similarity to other known genetic syndromes such as Mowat-Wilson, Angelman, Rett, and Joubert syndromes[4].

PHS is characterized by intellectual disability, severe developmental delay, abnormal breathing, facial dysmorphism, musculoskeletal anomalies and possible seizures.

Patients always present severe developmental delays that can often be noticed within the first year of life. Those with PHS frequently have problems with their verbal memory as well as their language development. Language acquisition is

virtually absent in most individuals with only very few (6%) being able to use short sentences[5]. These language skills will remain constant throughout most of life. Motor skills, on the other hand, may improve throughout childhood and into adulthood[4].

Intellectual disability is seen among all individuals with PHS. Individuals tend to have a happy disposition and will often participate in stereotypes (78%) that include flapping, hand-wringing, and rocking back and forth. Some individuals are also given an autism spectrum diagnosis[1].

Epilepsy is reported in up to 50% of PHS patients. The seizures themselves range in their type as well as their overall severity. These seizures can begin as early as the first year of life or as late as early adulthood[5].

Many PHS patients will have abnormal breathing patterns (48%). This includes sudden attacks of hyperventilation that may or may not be followed with a period of no breathing. The typical onset is between ages 3 to 7 years[1]. These fits can be brought on by excessive excitement, stress, or anxiety but may also occur without a definitive cause. Although these periods may be troublesome to witness, they are most likely unharmful to the patient[5].

There are several facial dysmorphisms which are distinctive to PHS. Features present in PHS patients includes eyebrows that are thin and widely spaced, enophthalmos, a marked fronto-nasal angle, a broad and prominent nasal bridge with flared nostrils, a short philtrum, a wide mouth with a thick and protruding upper lip and an everted lower lip, widely spaced teeth, possible prognathism, and thick helices[6]. These facial dysmorphisms are used when determining a diagnosis and differentiating a PHS diagnosis from other genetic syndromes with similar phenotypes[5]. Of course, only molecular cytogenetics and/or whole exome sequencing may provide a final diagnosis.

Patients with PHS often demonstrate various musculoskeletal anomalies. These deformities are often mild in nature and include clubbed feet with overriding toes, toe brachydactyly, limited thumb movement, long and slender fingers, clubbed fingers, and a single palmar crease[6]. PHS patients are also likely to have vision problems including myopia and hypermetropia (64%) as well as strabismus (44%) and nystagmus (14%)[5].

Constipation as well as gastroesophageal reflux are both common in children and adult patients.

There are no current treatments for individuals with PHS. Professionals recommend clinical management of symptoms as they arise and surveillance for common comorbidities. It is recommended that individuals be evaluated for constipation, myopia, strabismus, spells of abnormal breathing, seizures, and sleep disturbances. Patients should also seek treatment from speech, physical and occupational therapists in order to manage developmental delays as they arise[1]. This will require lifelong medical care from a multidisciplinary team.

REFERENCES

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