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SHORT ARTICLE


# Genetic diseases with impaired central respiratory control

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## Abstract

Respiration is controlled by the complex orchestration of central nervous system centers, peripheral chemoreceptors and muscles of respiration and is shaped by complex ontogenetic factors. Genetic defects can interfere with these factors, leading to the development of disorders of central control of breathing. Here, we briefly discuss the most important of these rare genetic syndromes: congenital central hypoventilation syndrome (CCHS), Rett's syndrome (RTT), Prader-Willi syndrome (PWS) and Joubert syndrome. All these conditions are severe neurodevelopmental pathologies that can also involve other organs and systems and have specific genetic backgrounds that if correctly identified can enable better prognostic counseling of patients and/or caregivers. Treatment of disordered breathing is often necessary to counteract the life-threatening problems typical of CCHS and those that complicate the clinical course of RTT, PWS and Joubert syndrome.

**Keywords:** Genetic diseases, CCHS, RTT, PWS, Joubert syndrome

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## Introduction

### Central and peripheral control of respiration

Respiration is a vital function controlled by the complex orchestration of central nervous system centers, peripheral chemoreceptors and muscles of respiration (**Fig. 1**). The central nervous system centers initiate and regulate breathing and are located in the brainstem (medulla and pons). Medullary centers include two clusters of neurons: the ventral respiratory group (VRG) and the dorsal respiratory group (DRG) (1). The VRG includes the pre-Bötzinger complex, considered the pacemaker of respiration, due to its ability to generate and maintain inspiration (2), and the Bötzinger complex, containing predominantly expiratory neurons. The DRG contains mainly inspiratory neurons. The respiratory centers in the pons include the Kolliker-Fuse nucleus, important in the regulation of the inspiratory-expiratory phase transition and control of upper airway patency, and the parabrachial complex, a vital component of the pontine pneumotaxic center (3).

In order to adapt respiration to variable metabolic demand, the respiratory centers receive feedback from the central and peripheral chemoreceptors, the baroreceptor and vagal afferents from the lungs (**Fig. 2**) (4). The central chemoreceptors are pH sensitive and monitor cerebrospinal fluid gas content. When pH decreases the central chemoreceptors stimulate the respiratory centers to increase the inspiratory rate. Peripheral chemoreceptors in the aortic arch and carotid arteries monitor blood chemistry and stimulate the respiratory centers when pH or $pCO_2$ increase or $pO_2$ decreases in the blood. Mechanoreceptors in the lungs and airways signal the respiratory centers to stop stimulation of the inspiratory muscles, allowing expiration to begin (inflation reflex).

This system is also shaped by complex ontogenetic factors which may be influenced by genetic defects, leading to disorders of central respiratory control. These disorders usually become evident soon after birth or in childhood. Here we briefly discuss some genetic syndromes that affect central control of breathing including: congenital central

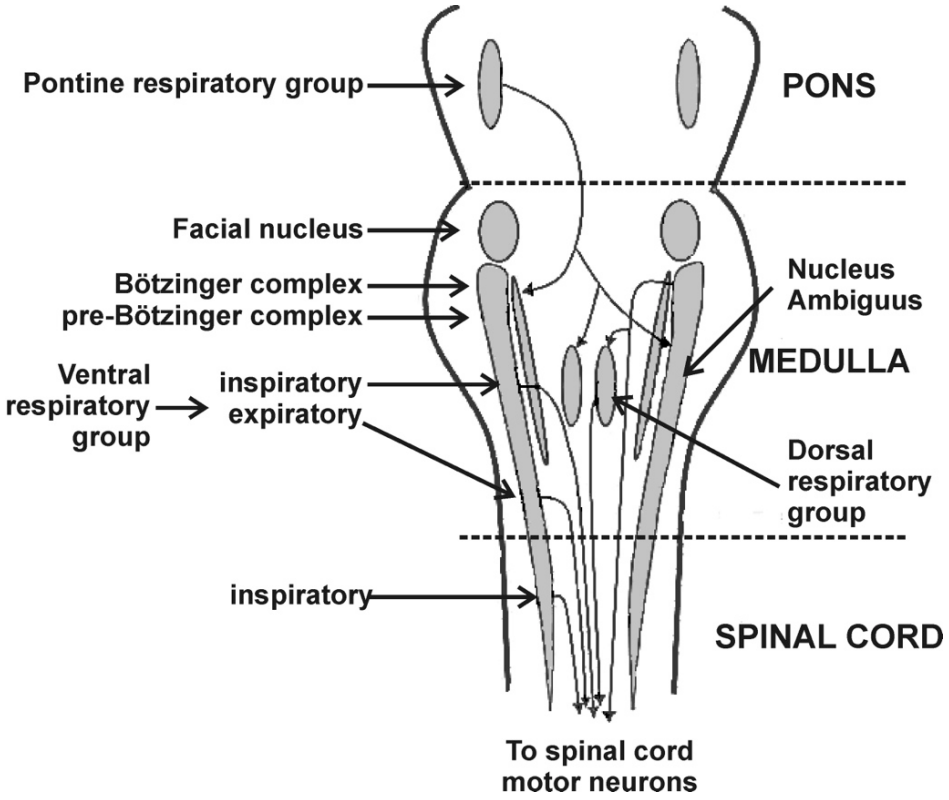


**Figure 1.** Brainstem centers that control breathing.

hypoventilation syndrome (CCHS), Rett's syndrome (RTT), Prader-Willi syndrome (PWS) and Joubert syndrome.

**Congenital central hypoventilation syndrome (CCHS)**

Congenital central hypoventilation syndrome is a rare disorder of regulation of respiratory and autonomic function, typically evident in newborns, but occasionally with later onset in toddlers, children and adults. The hallmark of the disease is central respiratory dysregulation (5), characterized by hypoxemia and hypercapnia during sleep, secondary to abnormal central integration of chemoreceptor signals (6, 7). In severe cases of CCHS, hypoventilation occurs in waking state as well as sleep.

Several other organs and systems may be involved. Heart signs include: alterations of heart rate variability; blood pressure values that decrease during wakefulness and increase during sleep, indicating attenuation of the normal sleep-related fall in blood pressure (8); increased risk of prolonged sinus pauses (cardiac pacemaker) in some genetic subtypes (9); incapacity to elevate blood pressure sufficiently on standing and head-up tilt positions and absence of standing-related blood

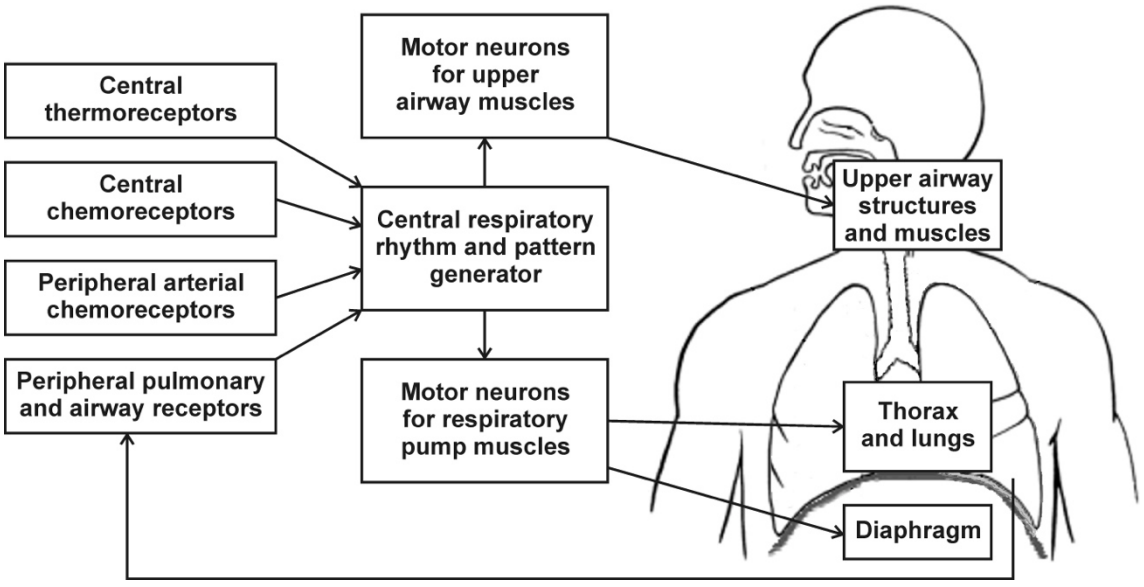


**Figure 2.** Overview of breathing control.

pressure overshoot; abnormal dermatoglyphics and/or facies (10); Hirschsprung disease in 16-20% of patients (11); severe constipation (12); abnormal esophageal motility/dysphagia; tumors originating from the neural crest (neuroblastoma, ganglioneuroblastoma and ganglioneuroma)(11-13); pupil and accommodation abnormalities (14); decreased perception of anxiety (15); lack of normal ventilatory and arousal responses to hypercarbia and hypoxemia and reduced breath-to-breath variability (5).

Congenital central hypoventilation syndrome is diagnosed on the basis of clinical findings of alveolar hypoventilation and autonomic nervous system disorders in the absence of other pulmonary, cardiac or neuromuscular diseases, or a brain stem lesion that could account for the breathing disorder. The clinical diagnosis is confirmed by identification of a pathogenic mutation in the PHOX2B gene.

Congenital central hypoventilation syndrome has autosomal dominant inheritance that often occurs *de novo*. Most mutations (90%) cause expansion of the 20-residue polyalanine region. The higher the number of polyalanine repeats (20/27-20/33) the more severe the symptoms (hypoventilation during wakefulness and sleep), while patients with fewer polyalanine repeats (20/24-20/25) usually have nocturnal symptoms only, or late onset presentation (16). The other 10% of patients are usually heterozygous for a non-polyalanine repeat mutation in the PHOX2B gene or have a different mutation. These patients are at higher risk of severe Hirshsprung's disease and neural tumors (17). Parents of patients with a known pathogenic PHOX2B mutation should be tested to determine their risk for later-onset CCHS or mosaicism.

Treatment involves ventilator support with or without tracheostomy. Non-invasive ventilation has been used in patients who need ventilatory support only during sleep. Diaphragm pacing is a treatment option for patients who need treatment during the day as well (18). Superimposed illnesses may complicate the needs of all CCHS patients, including those requiring treatment only during sleep, making intensive care necessary. Prevention of secondary complications is extremely important and surveillance should be regular and frequent, at least yearly (every 6 months until age 3 years).

**Rett syndrome (RTT)**

Rett syndrome is a serious genetic disorder first described by Andreas Rett in 1966 (18). It manifests in early childhood and is almost exclusive to girls. The vast majority of cases of RTT are due to *de novo* mutations in the MECP2 gene; more than 200 have been identified worldwide. The symptoms and their severity vary depending on the mutation. For example, the MeCP2 mutation called "R133C" causes rather mild effects. In missense mutations, the symptoms are less serious than those resulting from lack of a protein or the production of a much smaller protein. Respiratory defects are associated with mutations that interrupt the protein, while scoliosis is associated with missense mutations. Since these are conclusions from analyzing a large number of patients, it is still difficult to predict the severity of a case on the basis of the mutation identified. We also do not know if other factors (environment) can modify the effect of a specific mutation.

The severity of symptoms can be affected by inactivation of the X chromosome on which the gene is located. If mutation of the MECP2 gene inactivates the X chromosome in a girl with RTT, fewer cells have malfunctioning protein and symptoms should be less severe. Conversely, if the X chromosome is inactivated with the copy of the intact MECP2 gene, cells with altered protein are a majority and symptoms can be expected to be more severe. In any case, the clinical picture is influenced above all by how the X chromosome is inactivated in brain cells (19).

The CDKL5 gene is also found on the X chromosome. More than 150 mutations in this gene have been identified. In this case, RTT takes the form of the so-called "Hanefeld variant", characterized by early onset of seizures. A third gene was recently associated with a form of early-onset RTT, namely FOXG1 on chromosome 14. Mutations in this gene are involved in several cases of congenital RTT (20).

The prevalence of RTT is approximately 1 in 10,000 female births (21). Diagnostic criteria include a period of normal psychomotor development in the first 6-18 months of life followed by a period of regression (not due to brain injury, neurometabolic disease or severe infection), in which girls lose already acquired hand skills and language abilities and show attitudes of isolation and social closure. In this period, they begin to manifest a movement disorder characterized by repetitive hand movements resembling hand-washing, clapping or wringing. These stereotyped movements are another distinctive feature of the disease (22).

In the regression phase, or shortly thereafter, walking problems occur and development slows down. The disease then stabilizes, but over the years there is a complex set of multisystem symptoms that make the life of patients and their families particularly difficult.

Breathing disturbances are another characteristic of RTT and include various breathing patterns that range from deep breathing, hyperventilation, rapid shallow breathing, hypoventilation, central apneas, apneustic breathing, Biot's breathing, periodic breathing and breath holding (23-26). In one study, up to 93% of RTT patients showed periods of hypoventilation alternating with irregular breathing or hyperventilation. This pattern was more prominent during wakefulness (26). A study of 47 patients showed that breathing patterns were also disturbed during sleep (25). Age seems to be crucial and while the predominant rhythm in the youngest is protracted inspiration (including apneusis), in older subjects prolonged breath holds can often be terminated by the Valsalva maneuver (27).

Cardiac vagal tone seems very low, associated with low baroreflex sensitivity; this leads to unbalanced sympathetic effects on blood pressure and heart rate which bounce between extremes during breathing dysrhythmia (28).

Some authors report paroxysmal slow waves in EEGs, especially in drowsy states or sleep and lower amplitude during waking hyperventilation (15). However, epileptiform activity,

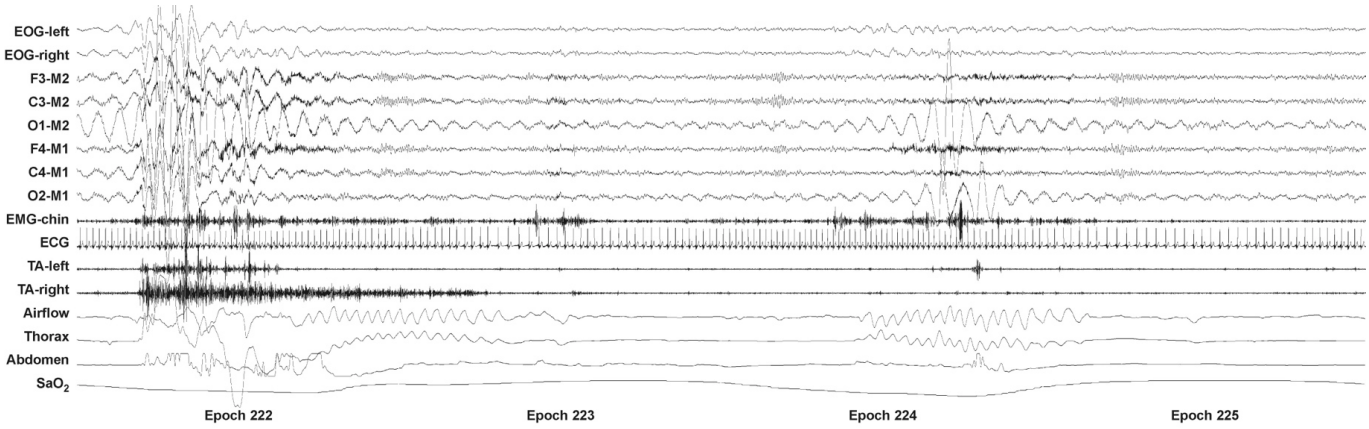


**Figure 3.** Two-minute polysomnogram period showing episodes of hyperpnea followed by apnea and oxygen desaturation in a patient with Joubert syndrome.

when present, does not seem strictly correlated with hyperventilation.

On the whole, RTT patients show evident difficulty in terminating inspiration (16,17), suggesting brainstem dysfunction, possibly mediated by serotoninergic neurons and consistent with an increased density of serotonin receptors, as a consequence of attempts to compensate.

Although diagnostic possibilities have greatly improved, RTT is incurable. Major symptoms, such as seizures, nutritional and gastrointestinal problems can only be alleviated. Surgery can be performed for scoliosis and tendon retraction. Rehabilitation is therefore crucial for motor and cognitive symptoms: physiotherapy, cognitive therapy, speech therapy, music therapy, hypnotherapy and communication can help reduce stereotyped movements, increase skills and improve quality of life.

**Prader-Willi syndrome (PWS)**

Prader-Willi syndrome is a genetic disorder, in most cases (approximately 75%) related to a deletion of the paternal proximal long arm of chromosome 15 (15q11-13). The other cases are caused by both chromosomes 15 originating from the mother (maternal disomy). PWS affects 1 in 10,000-20,000 children; boys and girls have similar prevalence. Diagnosis is often made at birth as infants have hypogonadism, hypotonia and feeding difficulties. After infancy, toddlers and school-age children develop hyperphagia and rapid weight gain. Older children can have delayed puberty and sleep disorders (29-32).

Infants with PWS show hypothalamic dysfunction, brainstem immaturity and abnormal chemosensitivity to $CO_2$ and $O_2$ resulting in abnormal breathing patterns. Gozal et al. (33) studied 17 adults with PWS and demonstrated that patients with PWS did not increase minute ventilation when breathing 15% $CO_2$. When controls breathed 100% oxygen they decreased minute ventilation, whereas patients with PWS showed a paradoxical increase. The authors postulated a defective peripheral chemoreceptor ventilatory response or defective afferent pathways (33).

Patients with PWS have also shown abnormal arousal and respiratory response to hypoxia. There is less hypoxia induced tachycardia and arousals in PWS patients than in controls (34). Sleep studies in infants have shown an increased prevalence of central central apnea and hypoventilation. Central apnea is thought to be secondary to deletions in genes involved in neuromodulation of the pre-Bötzinger nucleus. Oxygen administered to infants with PWS improves the central apnea index and stabilizes breathing patterns (35). Older children also have obstructive sleep apnea due to obesity, hypotonia, micrognathia and small nasal and oral pharynx (36). Excessive daytime sleepiness and narcolepsy-like symptoms due to hypothalamic dysfunction are also seen in these patients (38-40).

More than 50% of patients with PWS have growth hormone (GH) deficiency (29-41). Although GH supplementation improves height, body composition and developmental milestones, its effects on the control of breathing in PWS are not completely understood (42).

**Joubert syndrome**

Joubert syndrome is a rare disorder of autosomal recessive inheritance found in 1:80,000 live births. At least 10 different genes are affected, including NPHP1, AHI1 and CEP290. These genes encode proteins involved in neural cell migration, renal tubules and retinal primary cilia. Symptoms include hypotonia, retinal dysplasia, renal disease, nystagmus, ataxia, mental retardation, polydactyly, thyroid dysfunction and congenital hepatic fibrosis (43, 44).

Affected children have agenesis of the cerebellar vermis and failure of decussation in the superior cerebellar peduncles and pyramidal tracts, showing as the characteristic *molar tooth* MRI sign. The molar tooth sign is formed by deepening of the interpeduncular fossa with elongation of the superior cerebellar peduncles and hypoplasia of the vermis (45). These brainstem abnormalities are thought to affect the pontine respiratory centers, resulting in the typical breathing pattern seen in these patients. A a period of fast breathing (tachypnea) is usually followed by a pause (central apnea) (**Fig. 3**) (46, 47). Prolonged apneas can be life threatening, particularly in in-

fants, and treatment may be needed (48). Treatment of these breathing patterns with assisted ventilation has not been thoroughly studied, but isolated case reports have shown various degrees of success (46).

## Conclusion

All the conditions described above are severe neurodevelopmental pathologies which can also involve other organs and systems. They have specific genetic backgrounds, which if correctly identified, can enable better prognostic counseling of patients and/or caregivers. Treatment of disordered breathing is often necessary, for example to counteract the life-threatening problems typical of CCHS that can also complicate the clinical course of RTT, PWS and Joubert syndrome.

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