Case Report

PHOX2B Mutation–confirmed Congenital Central Hypoventilation Syndrome

Presentation in Adulthood

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Congenital central hypoventilation syndrome (CCHS) typically presents in the newborn period. A case series of five adults is presented, each heterozygous for a documented polyalanine expansion mutation in the *PHOX2B* gene and evidence of nocturnal alveolar hypoventilation. All cases had symptoms in childhood, but survived to adulthood without ventilatory support. After identification of physiologic compromise, artificial ventilation was initiated. These adults have the mildest of the CCHS-related *PHOX2B* polyalanine expansion mutations, coding for only five extra alanines; three of the adults have affected offspring. Report of these cases should lead to a more rapid identification of CCHS presenting in adulthood.

Keywords: congenital central hypoventilation syndrome; *PHOX2B* gene

This case series demonstrates that adults may present with a *PHOX2B* mutation–confirmed late-onset form of congenital central hypoventilation syndrome (CCHS), having survived childhood without artificial ventilatory support. All cases had apparent symptoms, though often mild, in childhood. It is hoped that increased awareness of this condition among adult-medicine physicians across a number of specialties will lead to earlier clinical and genetic diagnosis and treatment of unexplained cases of hypoventilation in adulthood.

CCHS (MIM number: 209880) is a disorder of respiratory control with related autonomic nervous system dysregulation/dysfunction (ANSD) (1). The most commonly cited associations include Hirschsprung disease and/or tumors of neural crest origin (neuroblastoma, ganglioneuroblastoma, ganglioneuroma), reported in approximately 20 and 6% of CCHS cases, respectively (1). Other symptoms of diffuse ANSD are seen frequently in CCHS and include decreased heart rate variability, attenuated heart rate response to exercise, severe constipation, esophageal dysmotility/dysphagia, decreased perception of discomfort, pupillary abnormalities, decreased perception of anxiety, sporadic profuse sweating, and decreased basal body temperature (1).

PHOX2B, located on chromosome 4p12 and coding for a highly conserved transcription factor known to play a key role in the development of ANS reflex circuits in mice (2), is the disease-defining gene for CCHS (2–7). Approximately 92% of individuals with CCHS are heterozygous for a polyalanine repeat expansion mutation involving the second polyalanine repeat sequence in exon 3 of the *PHOX2B* gene (2–7). Expansions are in-frame and range from 15 to 39 nucleotide insertions, resulting in expansion of the normal 20-repeat polyalanine tract to 25 to 33 alanine repeats to produce genotypes of 20/25 to 20/33 (the normal genotype would be referred to as 20/20) (3, 5, 6). The remaining 8% of patients with the CCHS phenotype have unique mutations in the *PHOX2B* gene (2–7). More than 90% of *PHOX2B* expansion mutations occur *de novo* in CCHS probands, with up to 10% of unaffected parents showing somatic mosaicism for the expansion mutation seen in her/his child (3). In these families, as well as in offspring of a proband with *PHOX2B* mutation–confirmed CCHS, the mutation and the phenotype are inherited as an autosomal dominant trait (3). Polyalanine expansion size has been associated with severity of autonomic dysfunction (number of ANSD symptoms) (3, 5), increased R-R interval on Holter monitoring (8), and severity of ventilatory dependence (3, 5).

Although individuals with CCHS typically present in the newborn period (1), we recently described an individual who presented in adulthood (9). Just as with the newborns, the adult was diagnosed in the absence of primary lung, cardiac, or neuromuscular disease, or an identifiable brainstem lesion that could account for the alveolar hypoventilation. The diagnosis in the reported adult was expedited because of prior diagnosis of CCHS in his daughter, and by application of the clinically available *PHOX2B* test for the CCHS-related polyalanine expansion mutation. We subsequently identified four more adult cases presenting after age 21, all of whom survived into adulthood without artificial ventilatory support until the time of diagnosis, and all with a documented polyalanine expansion mutation in the *PHOX2B* gene (genotype 20/25 in all cases, meaning one normal allele with 20 alanine repeats and one mutated expanded allele with 25 alanine repeats). The purpose of this report is to review the medical history and clinical presentation of these five adult cases to more clearly characterize the adult presentation of CCHS and to alert the adult practitioner to the possibility of CCHS presenting in adulthood.

(*Received in original form May 4, 2006; accepted in final form July 27, 2006*)

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Am J Respir Crit Care Med Vol 174. pp 923–927, 2006
Originally Published in Press as DOI: 10.1164/rccm.200605-607CR on July 27, 2006
Internet address: www.atsjournals.org

METHODS

Case Identification and Case Report Preparation

All cases were identified by positive test results for the CCHS-related *PHOX2B* polyalanine expansion mutation through the CCHS Center and Molecular Diagnostics Laboratory at Rush University Medical Center (Chicago, IL). Cases 1 and 2 had been published as unexplained alveolar hypoventilation, so *PHOX2B* testing was sought to clarify the diagnosis. Cases 3 and 4 were referred for clinical recommendations and genetic testing. Case 5 was identified after enrollment in the Rush University CCHS Center research program. All described cases consented to inclusion in the institutional review board–approved CCHS/*PHOX2B* research project.

Medical records from each proband were collected and reviewed by two authors (D.E.W.-M. and N.A.A.). One to two investigators familiar with each case were invited to prepare a case report based on the medical records and clinical evaluation. Additional testing or records were requested on a case-by-case basis in an aim for uniform clinical assessment. The case report format was standardized and prepared to convey the available test results, with areas of overlap and variance (D.E.W.-M. and N.A.A.).

Genetic Testing: DNA Preparation

Blood (3–10 ml) was obtained by venipuncture and collected into an ethylenediaminetetraacetic acid (EDTA) tube from CCHS cases. Genomic DNA was isolated using a Puregene reagent kit (Gentra, Minneapolis, MN) according to the manufacturer's instructions. DNA samples were saved in Tris-EDTA hydration buffer at −80°C before genotyping.

Genotyping of *PHOX2B* Polyalanine Repeat Sequence

The *PHOX2B* exon 3 region coding for the polyalanine repeat was amplified with primer pair 5′-CCAGGTCCCAATCCCAAC-3′ (forward) and 5′-GAGCCCAGCCTTGTCCAG-3′ (reverse) in a Perkin Elmer 9600 thermal cycler (Applied Biosystems, Foster City, CA). The PCR reactions were performed using 0.25 units AmpliTaq Gold polymerase (Applied Biosystems) in a total volume of 25 μl containing 50 ng genomic DNA, 0.3 μM primers, 2.5 mM $MgCl_2$, and 0.2 mM dNTPs with 70% 7-deazaGTP, 0.2 μCi of [^{32}P]dCTP (Perkin Elmer/NEN Life Sciences, Boston, MA), and 10% glycerol. The amplification was performed with an initial denaturation at 95°C for 10 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 57°C for 30 s and extension at 72°C for 30 s. Final extension was at 72°C for 10 min. The PCR products (232 bp for normal 20-repeat allele) were subjected to electrophoresis on a 6% denaturing polyacrylamide gel, and visualized by autoradiography. Allele repeat number was determined by comparison of bands to known size standards for which the repeat number had been determined by sequence analysis. This assay was developed at Rush Children's Hospital (patent pending, property of Chicago Community Trust). For further detail regarding methodology, the reader is referred to Reference 3.

CASES

Case 1

Case 1 (Adelaide, Australia) presented to the emergency department (ED) at age 22 with symptoms of a minor upper respiratory tract infection. An arterial blood gas measurement, taken because of an unexpectedly low pulse oximetry reading, revealed a P_{O_2} of 36 mm Hg, a P_{CO_2} of 63 mm Hg, an HCO_3 of 37 mmol/L, and a pH of 7.42 while awake breathing room air. The admission hematocrit was 55% and the echocardiogram revealed right heart dilatation. Pulmonary function testing, complete neurologic examination, and muscle biopsy were normal. Magnetic resonance imaging (MRI) of the brain/brainstem was normal. Body mass index (BMI) was 28. Holter recording revealed sinus rhythm with a rate of 29 to 122 beats/min with occasional ventricular ectopic beats. One hundred eighteen sinus pauses were noted, exclusively during wakefulness, and all were asymptomatic, with the longest R-R interval measured at 8.4 s. Polysomnography (PSG) revealed severe hypoxemia (nadir Sp_{O_2}, 71%) and hypercarbia (peak transcutaneous CO_2 [$TcpCO_2$], 82 mm Hg) in non-REM sleep. No REM sleep was documented on the first or subsequent PSGs. Voluntary breath-hold lasted more than 2 min despite hemoglobin desaturation to 65%, without any perception of dyspnea. Nasal mask bilevel positive airway pressure was initiated with confirmed compliance, but with further deterioration in arterial blood gases. Subsequently, almitrine bismesylate (Vectarion; Servier, Gidy, France) was initiated (50 mg twice daily), producing a sustained improvement in P_{CO_2} measurements (decline from 80 to 49 mm Hg over 6 mo without any change in bilevel ventilation compliance or body weight). Case 1 is now 35 yr old and he remains adequately ventilated during sleep with bilevel nasal mask positive pressure, although almitrine therapy has been complicated by a nonprogressive peripheral neuropathy requiring a dosage reduction. There has been no recurrence of seizures previously noted in childhood since he has been adequately oxygenated and ventilated. His hypoventilation remains during sleep only, with normal P_{CO_2} documented while awake. Case 1 is heterozygous for the *PHOX2B* polyalanine expansion mutation, with genotype 20/25. This case was described in the literature several years ago (10) as having unexplained respiratory failure.

Evidence for apparent symptoms before adulthood and evidence for chronicity. Past medical history for Case 1 was pertinent, indicating symptoms apparent before adulthood. These included prolonged and unexplained apneas after general anesthesia at age 8 yr, extraordinary breath-holding and underwater swimming capabilities as a child, and frequent seizures as a child and young adult that were unresponsive to medication. Evidence for chronicity of the respiratory failure was apparent: chronic compensated respiratory acidosis, polycythemia, and right heart dilatation noted on echocardiography. The patient has subnormal intellect and has not been able to sustain employment.

Case 2

Case 2 (Freiburg, Germany) presented to the ED at age 22 with symptoms of daytime sleepiness. An arterial blood gas measurement, taken because the patient was noted to be cyanotic, revealed a P_{O_2} of 56 mm Hg, a P_{CO_2} of 60 mm Hg, an HCO_3 of 30 mmol/L, and a pH of 7.32 while awake. The admission hematocrit was 77% and the echocardiogram revealed right ventricular hypertrophy. Pulmonary function testing was normal, and there was no clinical evidence of neuromuscular disease. MRI of the brain/brainstem revealed bilateral cerebral parenchymal lesions of the occipital region and basal ganglia, but no brainstem abnormality. BMI was 23.8. PSG revealed central hypopneas and apnea with severe hypoxemia (nadir Sp_{O_2}, 40%) and hypercarbia ($TcpCO_2$ peak, 72 mm Hg) in non-REM sleep. Only 8 min of REM sleep was documented. He had an attenuated ventilatory response to 0.08 $F_{I_{CO_2}}$ rebreathing while awake (minute ventilation increased from 16 to 34 L/min and $P_{0.1}$ increased from 0.21 to 0.38 kPa, whereas Pa_{CO_2} increased from 32 to 52 mm Hg and pH decreased from 7.48 to 7.34). Nasal mask bilevel positive airway pressure ventilation was initiated with confirmed compliance. There has been no report of seizures. Case 2 is now 30 yr old and he remains adequately ventilated during sleep. His hypoventilation remains during sleep only, with normal P_{CO_2} documented while awake and normal hematocrit levels. Case 2 is heterozygous for the *PHOX2B* polyalanine expansion mutation, with genotype 20/25. This case was described in the literature several years ago (11) as having unexplained respiratory failure.

Evidence for apparent symptoms before adulthood and evidence for chronicity. Past medical history for Case 2 was pertinent, indicating symptoms apparent before adulthood. These included repeated episodes of cyanosis in childhood, with requirement

for mechanical ventilation at 5 wk of age, and extraordinary underwater swimming capabilities as a child, often requiring rescue for severe cyanosis but without breathlessness. Evidence for chronicity of the respiratory failure was apparent: polycythemia and right ventricular hypertrophy on echocardiography. The patient has significant cognitive impairment (attended a special school) and has not been able to sustain employment.

Case 3

Case 3 (Nashville, TN) presented to the ED at age 27 after being found at home by her husband subsequent to a probable epileptic seizure. She was confused and poorly arousable, and had delivered her second child just 8 d previously. In the ED, she experienced two additional epileptic seizures that did not initially respond to lorazepam. Subsequent to the administration of the lorazepam, she developed apnea and required intubation. Her seizures responded to fosphenytoin. A brain MRI done on admission suggested a small right occipital stroke anterior and adjacent to the right lateral ventricle, without evidence of venous thrombosis or other abnormalities. A follow-up brain MRI with magnetic resonance angiography done several days later was normal. She was subsequently extubated, and she returned to her baseline mental state before discharge. Because of her persistent fatigue, overnight home pulse oximetry was evaluated 4 mo later and revealed severe hypoxemia (nadir Sp_{O_2} values of 60%). Pulmonary function testing and complete neurologic examination were normal. BMI was 24. An urgent PSG confirmed severe hypoxemia (Sp_{O_2} nadir, 52%) with minimal sleep-disordered breathing (apnea–hypopnea index of 3.2 events/h with subtle hypopneas and hypoxemia out of proportion to events). Daytime oximetry was normal (99%), as was Pco_2 measurement. Nasal mask bilevel positive airway pressure was initiated with confirmed compliance. Case 3 is now 28 yr old, and she remains adequately ventilated during sleep. Her hypoventilation remains during sleep only, with normal Pco_2 documented while awake and normal hematocrit levels. She has two children with CCHS: a 6-yr-old boy and a 5-mo-old girl. Her son presented at 3 mo of age and her daughter presented at 1 mo of age. Both require nocturnal mechanical ventilation via tracheostomy. The son has severe neurologic impairment. Case 3 and both of her children with CCHS are heterozygous for the *PHOX2B* polyalanine expansion mutation, all with genotype 20/25.

Evidence for apparent symptoms before adulthood and evidence for chronicity. Past medical history for Case 3 was pertinent, indicating symptoms apparent before adulthood. These included severe breath-holding episodes as a child. There was no evidence for chronicity of the respiratory failure.

Case 4

Case 4 (Denver, CO) had a PSG performed 6 mo before his presentation to the ED at age 35. That PSG revealed 46 obstructive events (38 hypopneas, 8 apneas), 16 central apneas, and an apnea–hypopnea index of 77 events/h, with an Sp_{O_2} nadir of 65% in room air and 80% with supplemental oxygen. No REM sleep was noted on this or subsequent PSGs. He temporarily responded to nasal mask bilevel positive airway pressure ventilation with supplemental oxygen during sleep, but within 6 mo he was referred for uvulopalatopharyngoplasty because he was not tolerating the bilevel ventilation. Forty-eight hours after discharge for the surgical intervention, he presented to the ED with intermittent confusion, difficulty staying awake, and respiratory failure. An arterial blood gas, taken because of altered mental status and severe headache, revealed a Po_2 of 78 mm Hg, a Pco_2 of 68 mm Hg, an HCO_3 of 36 mmol/L, and a pH of 7.30 while breathing 2 L of oxygen awake. The admission hematocrit was 63%; hemoglobin was 20.2 g/dl; body temperature was 35.5°C; chest X-ray revealed cardiomegaly; and ECG revealed right axis deviation, enlargement, and right ventricular hypertrophy. Neurologic examination and lumbar puncture were both unremarkable. There was no clinical evidence of neuromuscular disease. MRI of the brain/brainstem and computed tomography scan were normal; BMI was 27. He required intubation and mechanical ventilation, followed by a tracheostomy; however, mechanical ventilation was discontinued as he had weaned appropriately during the day without hypercapnia. The morning after discontinuation of mechanical ventilation, an arterial blood gas measurement revealed a Pco_2 of 129 mm Hg and a pH of 7.03. Bilevel ventilation was recommenced with good effect, and the daytime Pco_2 normalized. There has been no subsequent report of seizures. Because of his daughter's diagnosis of CCHS 3 yr before, and documentation that the child is heterozygous for the CCHS-related *PHOX2B* polyalanine expansion mutation, *PHOX2B* analysis was performed on DNA from Case 4, and demonstrated the identical mutation seen in the 4-yr-old daughter. A 2-yr-old daughter, who also has alveolar hypoventilation, was heterozygous for the mutation as well (all three have a genotype of 20/25). The older daughter presented at 9 mo of age and the younger daughter presented at 2 mo of age. The older daughter requires nocturnal mechanical ventilation via tracheostomy and the younger daughter receives 2 L/min nasal cannulae oxygen during sleep. This case was described in the literature as the first adult to present with a *PHOX2B* mutation and the CCHS phenotype (9)

Evidence for apparent symptoms before adulthood and evidence for chronicity. Past medical history for Case 4 was pertinent, indicating symptoms apparent before adulthood. These included childhood apnea with cyanosis while asleep, use of Dexadrine to "stay on task," symptoms compatible with ANSD (low body temperature, postural hypotension, pinpoint pupils minimally reactive to light, no shortness of breath despite markedly increased carbon dioxide levels), and awakening with headaches and periods of disorientation for several years. Evidence for chronicity of the respiratory failure was apparent: chronic compensated respiratory acidosis, polycythemia, and right heart dilation at diagnosis.

Case 5

Case 5 (Manchester, UK) presented to medical attention at age 36 yr after her children with the clinical CCHS phenotype were recruited into a research study and *PHOX2B* testing was performed on probands and parents. Case 5 was identified because she had the *PHOX2B* polyalanine expansion mutation characteristic of CCHS. Pulmonary function testing was normal, and there was no clinical evidence of neuromuscular disease. MRI of the brain/brainstem was normal, and BMI was 23. PSG was performed and revealed alveolar hypoventilation with hypoxemia (nadir Sp_{O_2}, 76%) and hypercarbia (peak $TcpCO_2$, 60 mm Hg) during sleep. Her hematocrit, echocardiogram, and daytime Pco_2 remain normal (Pco_2, 36 mm Hg). Because of an increasing seizure frequency, unresponsiveness to medication, and concern that nocturnal hypoxemia was a trigger, Case 5 was convinced to initiate nasal mask bilevel positive airway pressure ventilation. There has been no subsequent report of seizures. Case 5 is now 38 yr old and she remains adequately ventilated during sleep with bilevel nasal mask positive-pressure ventilation. Her hypoventilation remains during sleep only, with normal Pco_2 documented while awake and normal hematocrit. Case 5 and both of her children with CCHS are heterozygous for the *PHOX2B* polyalanine expansion mutation, all with genotype 20/25.

Evidence for apparent symptoms before adulthood and evidence for chronicity. Past medical history for Case 5 was pertinent, indicating symptoms apparent before adulthood. These included what were labeled as petit mal epilepsy in childhood (with prolonged "staring spells" and normal EEG) and delayed arousal (6 h) with anesthetic. She has had two recent further seizures involving tongue biting, neither witnessed, both occurring in the setting of upper respiratory tract infection and again with normal subsequent EEG. At other times, she has had "staring spells." During one of these episodes, her oxygen saturation was noted to be 85%, raising the possibility that the seizures are related to physiologic compromise.

DISCUSSION

This report of five adults with *PHOX2B* mutation–confirmed CCHS indicates that individuals with the shortest of the *PHOX2B* polyalanine expansion mutations known to cause CCHS can survive into adulthood without manifesting the early respiratory failure classically associated with the CCHS phenotype. Although these cases were not diagnosed until adulthood, it is apparent that these adults had subtle symptoms indicative of CCHS during childhood and even adulthood, including unexplained "epilepsy" resistant to anticonvulsants and with a normal EEG, cyanotic apnea spells, and the ability to breath-hold for prolonged periods. Likewise, many of these adults had laboratory evidence for chronicity of symptoms, including hypercarbia, polycythemia, and right heart changes. Furthermore, two of the cases presented with significant cognitive impairment, suggesting the possibility that these adults suffered neurocognitively from sequelae of the hypoxemia and hypercarbia. Taken together, these cases indicate that there are likely other adults with yet undiagnosed CCHS. These adults may present to the sleep laboratory, epilepsy clinic, pulmonary clinic, emergency room, or the intensive care unit. Because most emergency room physicians and adult intensivists will not be familiar with CCHS, the diagnosis of CCHS will depend on a heightened level of suspicion and on careful medical history for diseases among offspring. It will be essential to assess hemoglobin saturation and, ideally, end tidal carbon dioxide levels before administering drugs that depress ventilation. It is hoped that increased awareness and the clinically available genetic testing for CCHS might lead to earlier diagnosis, earlier therapeutic intervention, and avoidance of inadvertent respiratory depression.

The 25-repeat polyalanine expansion mutation in *PHOX2B* is the smallest expansion known to cause CCHS. The results presented here indicate that individuals with the 25-repeat expansion in their mutated allele (20/25 genotype) can show variable penetrance. Specifically, the described adults did not present until between age 22 and 36 yr. Some of the children with CCHS born to these adults also had a delayed age at presentation, although all within the first year of life. Because no mutations larger than 25 repeats have been identified in adult-onset cases, it appears that longer expansions containing 26 to 33 alanine repeats (genotypes 20/26 to 20/33) cause typical CCHS and are not associated with variable penetrance or adult-onset presentations. As such, cellular impairment in PHOX2B transcriptional activity (12, 13), mislocalization of PHOX2B to the cell cytoplasm (normally present only in the nucleus) (12), and a tendency to PHOX2B protein misfolding with multimer formation (13) have been found to be increasingly severe with increasing repeat size for polyalanine repeat mutations. PHOX2B-containing cellular aggregates are identifiable only for mutations larger than 25 repeats (13). Thus, the relatively milder cellular defects associated with the small 25-repeat expansion mutations may not always reach a threshold required for clinical disease or may have milder phenotypic consequences. Although repeat expansions larger than 25 repeats always cause CCHS evident in infancy, repeat expansions smaller than 25 repeats have not been identified in association with CCHS, and it is likely that such small expansions do not impair function of *PHOX2B* enough to cause disease. The variable clinical penetrance associated with the 25-repeat mutation thus reflects the molecular effect of this mutation, which operates near the threshold of *PHOX2B* impairment necessary to result in disease.

Three of the adults described in this report have two affected children each, consistent with the expected autosomal dominant inheritance pattern for CCHS (3). Given the possibility of incomplete and variable penetrance and subtle to moderate clinical symptoms in adults carrying the 25-repeat mutation, it would be advised that parents of any CCHS proband with a 25-repeat mutation have *PHOX2B* testing performed, both for counseling regarding recurrence of the condition in future children and because the parent carrier may have undiagnosed symptoms of alveolar hypoventilation requiring evaluation and intervention. There is a range of presentation associated with the 25-repeat expansion mutation, which extends from the newborn period to adulthood, raising the possibility that some individuals may remain asymptomatic throughout life. The explanation for this is not clear but most likely involves genetic modifiers or environmental cofactors acting in concert with a level of *PHOX2B* impairment balanced at the threshold for disease, such that an acute stressor or even aging could result in decompensation and symptomatic presentation.

In summary, we believe there are likely to be many other adults with the *PHOX2B* 20/25 genotype who are yet to be diagnosed with CCHS. Through increased awareness, the diagnosis of these adults and of parents of children with the 20/25 genotype can be expedited. Through prompt intervention with noninvasive nasal mask ventilation during sleep, and comprehensive follow-up as provided to children with CCHS, further physiologic compromise can be prevented.

***Conflict of Interest Statement*:** N.A.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.D.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.L.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.T. has received a research grant from Pfizer for a clinical trial to be conducted on the early diagnosis of chronic obstructive pulmonary disease, and has also received $3,500 for lectures at meetings sponsored by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca, Pfizer). W.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.M.B.-K. donated the patent for the *PHOX2B* assay to the Chicago Community Trust and has not received any income from this patent. D.E.W.-M. donated the patent for the *PHOX2B* assay to the Chicago Community Trust and has not received any income from this patent.

***Acknowledgment*:** The authors thank Dr. Kay Metcalfe and Dr. Ian Ballin for their involvement in Case 5, and all unnamed physicians who helped to identify the five cases.

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