damage has diminished significantly in recent years due to improving standards of long-term care for CCHS patients. Poignantly, although consistently managed patients thrive and mature normally, “children receiving suboptimal and inconsistent management were left with significant disabilities, and achievement of lesser accomplishments...” (8). Thus, genotype–phenotype, age, gender, and management status of subjects must be carefully considered when interpreting data from CCHS patients. Singular approaches to research on diseases of autonomic dysregulation risk obscuring their complexity and variability while precluding personalized treatment.

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Response to Latorraca and Palli

doi:10.1038/pr.2012.98

To the Editor: In their letter to the editor (1), Latorraca and Palli raise questions about the article titled “Progressive gray matter changes in patients with congenital central hypoventilation syndrome” (2). Specifically, Latorraca and Palli suggest that we neglected critical aspects of congenital central hypoventilation syndrome (CCHS) diagnosis and patient management in this study.

The first concern was related to genetic assessment of the CCHS subjects. The study used high-resolution T1-weighted magnetic resonance images to assess gray matter changes in CCHS subjects after a 4-y interval from initial scans, and evaluated those changes with voxel-based-morphometry procedures. All CCHS subjects were diagnosed based on American Thoracic Society 1999 criteria (3), since only limited *PHOX2B* mutation information was available at study design (2002 to 2003). The characteristics are well known to any CCHS researcher; all subjects showed early onset of the condition, hypoventilation during sleep, ventilatory insensitivity to hypercapnia and hypoxia, and severe autonomic characteristics, typically including failed temperature regulation, recurrent syncope, and frequently, asymmetric parasympathetic signs. However, we realize the importance of genetic evaluation for the syndrome, and have specifically emphasized that necessity elsewhere (4). We made repeated efforts to gather additional genetic information from our CCHS subjects, but to no avail, despite the obvious

medical benefits. The reasons for declining a request varied, but included statements often found in response to testing for other life-threatening diseases, and included parental refusal. We had genetic information from a limited number of CCHS subjects (two positive (20/27 and 20/25 polyalanine expansions), one negative, and four untested); based on other published studies, from 62 to 97% of CCHS subjects show *PHOX2B* mutations (5,6), and we believe that the majority of our CCHS subjects also have such mutations, along with the primary CCHS characteristics described above. However, a small proportion of CCHS subjects in the literature shows an absence of *PHOX2B* mutation, despite presence of characteristics positive for the syndrome (5). Although handicapped by largely absent specific genetic information, we used the obvious clinical presentation here.

We did raise several study limitations in the article, including limited numbers, the proportion of male subjects, and slightly variable MRI procedures between the 4-y intervals. However, those issues should not significantly affect the findings. Subject relocation, especially of controls, reduced numbers, but the design using CCHS and control subjects as their own controls was necessary to control for normal regional gray matter changes over time, and to substantially assist statistical assessment.

The second major concern of Latorraca and Palli is the suggestion that we fail to consider the potential for ventilatory mismanagement as contributing to the enhanced injury during the 4-y scanning interval. However, we indeed raised the issue that the progression of injury develops from hypoxic exposure rather than consequences of *PHOX2B* mutation (page 4, lines 8–25). The parents of our subjects were extremely motivated, as evidenced by their willingness to transport their charges for scanning across the continent, and were very much aware of the

dangers of hypoventilation. Moreover, we also outlined (page 4, lines 8–25) how the enhanced injury could also develop, not from ventilatory aspects, but from consequences of impaired perfusion from a compromised vascular system, another characteristic of CCHS, and frequently overlooked as a source of neural injury. We earlier demonstrated damage to the raphe system, mediator of selected vascular processes (7) and likely contributor to the specific impairment of blood vessels supplying the brainstem (8). We also found damage in autonomic regulatory sites of insular cortex, hypothalamus, and deep cerebellar nuclei (9–11), all of which can affect cerebral perfusion. Such perfusion impairment is unlikely to exist without continuing consequences to glia, neurons, and fibers. Despite aggressive attention to ventilatory issues of CCHS, little attention is paid to intervention for support of the brain vasculature; the only current intervention for cardiovascular aspects of CCHS is pacemaker implantation against asystole, which does little for integrity of cerebral vessels. Other interventions, including pharmacologic or other protection for neurons and glia may be necessary. The collective findings of injury progression in this sample, together with the unique brain structural alterations in CCHS, suggest that interventions may be more complex than just diligent ventilatory support, and may require active study and treatments for a compromised cerebrovascular system.

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