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Pediatrics 2006;118:408-414
DOI: 10.1542/peds.2005-3134

This information is current as of August 1, 2006

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Characterization of Dermatoglyphics in PHOX2B-Confirmed Congenital Central Hypoventilation Syndrome

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Individuals with congenital central hypoventilation syndrome have characteristic variants in the PHOX2B gene (primarily polyalanine expansion mutations). The PHOX2B gene acts as a transcriptional activator in the promotion of pan-neuronal differentiation in the autonomic nervous system during early embryologic development, with a primary role in the sympathetic noradrenergic phenotype in vertebrates. Because sympathetic innervation has been hypothesized to affect the development of dermatoglyphic pattern types, we hypothesized that individuals with PHOX2B-confirmed congenital central hypoventilation syndrome would have characteristic dermatoglyphic patterning and that the dermatoglyphic phenotype would be related to the disease-defining PHOX2B genotype.

METHODS. Dermatoglyphic pattern type frequency, left/right symmetry, and genotype/phenotype correlation were assessed for 33 individuals with PHOX2B-confirmed congenital central hypoventilation syndrome and compared with published control data.

RESULTS. Dermatoglyphic pattern type frequencies were altered in congenital central hypoventilation syndrome cases versus controls. In particular, there was an increase of arches in females and ulnar loops in males, with the largest differences for the left hand and for individuals with both congenital central hypoventilation syndrome and Hirschsprung disease. Dissimilarity scores between the congenital central hypoventilation syndrome and congenital central hypoventilation syndrome + Hirschsprung disease cases were not significantly different, nor were dissimilarity scores between all of the female and all of the male cases. No significant association was found between the number of polyalanine repeats in the PHOX2B genotypic category and dermatoglyphic pattern frequencies in the congenital central hypoventilation syndrome study groups.
CONCLUSIONS. These results represent the first report describing specific dermatoglyphic patterning in congenital central hypoventilation syndrome and suggest a relationship between \( \text{PHOX2B} \) and the expression of dermatoglyphic pattern types. An expanded congenital central hypoventilation syndrome data set to include the full spectrum of \( \text{PHOX2B} \) mutations is necessary to further delineate the role of \( \text{PHOX2B} \) in dermatoglyphic patterning.

CHILDREN WITH CONGENITAL central hypoventilation syndrome (CCHS) characteristically present in the neonatal period with alveolar hypoventilation “in the absence of primary neuromuscular, lung, or cardiac disease, or an identifiable brainstem lesion.” They demonstrate attenuated/absent responses to hypoxemia and hypercarbia, and related evidence of autonomic nervous system (ANS) dysfunction/dysregulation that may include Hirschsprung disease (HD) and/or tumors of neural crest origin. Children with CCHS are heterozygous for a polyalanine expansion mutation in the paired-like homeobox (PHOX)2B gene, although a subset of patients has unique mutations in \( \text{PHOX2B} \). Recently, a characteristic facial phenotype in CCHS has been described, with a pattern compatible with the developmental expression of \( \text{PHOX2B} \). Long thought to be a rare disorder, CCHS is being diagnosed with increased frequency, since genetic testing for the \( \text{PHOX2B} \) mutation became clinically available in 2003. As a result, general pediatricians may be caring for affected children in their practice.

The \( \text{PHOX2B} \) gene encodes a highly conserved homeobox domain transcription factor with an early embryologic action as a transcriptional activator in the promotion of pan-neuronal differentiation in the ANS and a separate role wherein it represses expression of inhibitors of neurogenesis. \( \text{PHOX2B} \) is considered to regulate the sympathetic noradrenergic phenotype in vertebrates. Sympathetic innervation has been hypothesized to affect the development of dermatoglyphic pattern types in primates, including humans, with dermatoglyphics defined as the study of the morphology and distribution of ridged skin patterns on the palmar surface of the hands and feet. We sought to more fully characterize the phenotype of CCHS by evaluating dermatoglyphics, an accessible phenotypic measure of embryologic development. We hypothesized that individuals with \( \text{PHOX2B} \)-confirmed CCHS would have characteristic dermatoglyphic patterning and that these pattern differences would vary with the clinical severity of CCHS (characterized by the presence or absence of HD) and the disease-defining \( \text{PHOX2B} \) genotype.

METHODS

Study Subjects

Diagnosis of CCHS was based on the American Thoracic Society Statement on CCHS and confirmed with \( \text{PHOX2B} \) genotyping (patent pending). Dermatoglyphic prints from 33 white individuals with \( \text{PHOX2B} \)-confirmed CCHS (all heterozygous for a polyalanine expansion mutation in \( \text{PHOX2B} \)) were analyzed, including 28 cases of isolated CCHS (14 females) and 5 cases with both CCHS and HD (2 females). CCHS subject age range was 3.0 to 20.75 years (mean: 13.6 ± 4.9 years). \( \text{PHOX2B} \) expansion mutations ranged from 25–33 repeats (mean: 27 ± 2 repeats). Control data were obtained from a published data set including 720 white children aged 7 years. This control data set was designed with the intent to provide a comparison sample for investigators studying dermatoglyphics in individuals with disease or congenital anomalies. Because fingerprints do not change during postnatal life, ages did not need to be matched. The study was approved by Rush University Medical Center and University of Pittsburgh institutional review boards. Informed consent and Health Insurance Portability and Accountability Act authorization were obtained from subjects and/or their parents or legal guardians.

Printing Technique and Dermatoglyphic Protocol

Fingerprints were obtained using a standard inkless technique using INFA-PRINT Inkless Imprint Wipes (Kansas City, MO). Three trained raters (E. S. T., N. M. S., D. E. W-M.) independently categorized the prints from 33 white individuals with CCHS and HD (2 females). CCHS subject age range was 3.0 to 20.75 years (mean: 13.6 ± 4.9 years). \( \text{PHOX2B} \) expansion mutations ranged from 25–33 repeats (mean: 27 ± 2 repeats). Control data were obtained from a published data set including 720 white children aged 7 years. This control data set was designed with the intent to provide a comparison sample for investigators studying dermatoglyphics in individuals with disease or congenital anomalies. Because fingerprints do not change during postnatal life, ages did not need to be matched. The study was approved by Rush University Medical Center and University of Pittsburgh institutional review boards. Informed consent and Health Insurance Portability and Accountability Act authorization were obtained from subjects and/or their parents or legal guardians.

Statistical Analysis

\( \chi^2 \) analysis was used to compare pattern frequencies for cases versus published control data, grouped by CCHS.

FIGURE 1

This figure provides representative examples of dermatoglyphic patterns. These are from a right hand with the radial side of each print being to the left and the ulnar side to the right. A, Arch; B, Ulnar loop; C, Radial loop; D, Whorl.
status (all CCHS, isolated CCHS, or CCHS + HD), then stratified for gender and hand (left or right). Asymmetry was measured by dissimilarity scores, which were calculated by comparing prints on the paired homologous fingers of the left and right hands (eg, left index finger compared with right index finger). Paired fingers with dissimilar dermatoglyphic pattern types were given a score of 1, whereas paired fingers with the same pattern types were given a score of 0. Scores were then summed across all 5 finger pairs, thus, dissimilarity scores may range from 0 (having no dissimilarity) to 5 (having all 5 pairs of fingers dissimilar). The results were compared using the Wilcoxon-Mann-Whitney test. In addition, PHOX2B repeat number was compared with frequency of pattern type using linear regression with the continuous repeat number and logistic regression with repeat number divided into 2 categories: <29 repeats and ≥30 repeats. Dissimilarity scores were also compared between the 2 categories of PHOX2B repeat number using a Wilcoxon-Mann-Whitney test. Results were considered significant if $P < .05$.

**RESULTS**

**Dermatoglyphic Results**

Pattern frequencies in CCHS cases and controls are provided in Table 1. Pattern frequencies in the text and table are shown as percentages of the total number of digits evaluated in each group. Gender differences in pattern frequency for cases, as well as arch positivity results, are provided below. Control values for arch positivity/multiple arches are unavailable, thus, no comparisons to controls could be made.

**All CCHS Cases**

Female cases had a higher arch frequency versus male cases (10.8 vs 3.6; $P = .01$) and a higher left-hand arch frequency versus male cases (14.1 vs 3.6; $P = .02$). Arch positivity (the presence of ≥1 digital arch) was seen in 30% of cases, with 60% of the arch-positive cases being female. Multiple arches (≥4, no case had 3 arches) were identified in 12.1% of cases, with 75% of these being female.

**Isolated CCHS**

Arch positivity was seen in 25% of cases, with 57.1% of the arch-positive cases being female. Multiple arches were identified in 7.1% of cases, with 50% of these being female.

**CCHS + HD**

Female cases had a higher arch frequency versus male cases (both hands: 40.0 vs 0, $P = .002$; left hand: 40.0 vs 0, $P = .025$; right hand: 40.0 vs 0, $P = .025$). Arch positivity was seen in 60% of cases, with 66.7% of the arch-positive cases being female. Multiple arches were identified in 40% of cases, with 100% of these being female.

**Dissimilarity Scores**

Dissimilarity scores between the CCHS and CCHS + HD cases were not different (1.11 and 0.75, respectively), nor were dissimilarity scores between all of the female cases and all of the male cases (mean: 1.0 and 1.13, respectively). Control values for dissimilarity scores are unavailable, thus, no comparisons to controls could be made.

**Genotype/Phenotype Correlation**

No significant association was found by linear regression or by logistic regression between the PHOX2B genotypic category (<29 polyalanine repeats versus ≥30 polyalanine repeats on the affected allele) and dermatoglyphic pattern frequencies in the CCHS study groups (all CCHS cases, isolated CCHS, and CCHS + HD).

**DISCUSSION**

These results represent the first report describing dermatoglyphics in individuals with PHOX2B-confirmed CCHS. Pattern type frequencies were altered in CCHS cases versus controls. In particular, there was an increase in arch and ulnar loop frequencies (typically seen in female and male cases, respectively), with the largest differences seen in the left hand and in the individuals with CCHS + HD. Dissimilarity scores as a proxy for asymmetry did not differ among the CCHS study groups or by PHOX2B genotypic category (<29 polyalanine repeats or ≥30 polyalanine repeats). Likewise, no significant association was found between the PHOX2B genotypic category and dermatoglyphic pattern frequencies.

Dermatoglyphics have been studied in children with isolated constipation and isolated HD, and both symptoms compatible with ANS dysregulation/dysfunction and both often reported among children with CCHS. Gottlieb and Schuster reported arch positivity in 53% of patients and ≥4 arches in 27% of patients with early onset constipation (<10 years of age) (vs 13% and 2% of controls, respectively). Staiano et al demonstrated arch positivity in 38% of patients with constipation (vs 11% of controls) but no relationship between HD and digital arches. Drongowski and Coran identified arch positivity in 33% of cases with functional chronic constipation, 32% of cases with anatomic chronic constipation (including HD), and 30% of control cases with inguinal hernia. Jackson et al demonstrated arch positivity in 13% of constipated cases (vs 7% of controls). Goshima et al demonstrated arch positivity in 28% of constipated patients (vs 24% of controls). The published results describing arch positivity in constipated patients are in keeping with our current results in children with CCHS. The published results describing arch positivity in patients with HD, however, are distinctly different from
our findings in children with CCHS. These differences may be because of an intrinsic difference in the etiology and genetic basis of idiopathic HD versus syndromic HD.27 Taken together, these findings extend the understanding of a relationship between dermatoglyphic patterning and functional/anatomic bowel disease, conditions that fall within the rubric of ANS dysregulation and will be encountered by the general care pediatrician.

The embryologic timing of the ridge pattern formation, between weeks 10 and 24 postfertilization, is associated with the type of dermatoglyphic pattern development. Early ridge formation is associated with whorls, late formation with arches, and intermediate formation with loops. Clinical syndromes that have arrested embryologic development and decreased developmental maturation tend to have more arches and fewer whorls.28 For example, an increase in arch and ulnar loop frequency and a decrease in whorl frequency have been reported in nonsyndromic female Filipinos with cleft lip and/or cleft palate.29 Likewise, an increased incidence of arches30,31 and cleft lip and/or cleft palate32 has been reported in fetal hydantoin syndrome. Interestingly, female white sudden infant death syndrome (SIDS) victims have an increased arch frequency compared with the same control population we used.33 Furthermore, male SIDS infants with dysmorphic features

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*P* values are based on a Bonferroni correction and are a case/control comparison of frequencies. Total indicates female and male cases combined; Both, left and right hand combined.

a P < .01.
b P < .001.
or anatomic anomalies presented with more ulnar loops and fewer whorls, not dissimilar to the most affected cases with CCHS + HD in our study. Recognizing that children with CCHS have ANS dysregulation and that infants who have succumbed to SIDS also have ANS dysregulation, the finding of altered dermatoglyphic patterning in CCHS and SIDS supports a relationship between the developing systems that regulate dermatoglyphics and altered embryologic development of the ANS. These interrelationships indicate that the study of dermatoglyphics provides an accessible means by which the pediatrician can probe the origin of complex diseases.

Although dermatoglyphic formation has been associated with many factors, including skeletal growth, and volar pad topography, most interesting for the current study is that dermatoglyphic fingerprint patterns have been associated with the sympathetic innervation of the hand. We anticipate that the PHOX2B gene, as a regulator of the sympathetic noradrenergic phenotype in vertebrates, has a role in the determination of dermatoglyphic patterning, just as it has a role in the embryologic development of the enteric nervous system. This possibility is supported by our previous observation that 43% of children with CCHS have severe constipation, 21% of children with CCHS have HD, and our current finding of an increased arch and ulnar loop frequency that is highest among children with PHOX2B-confirmed CCHS + HD. Our results here provide tentative support for the hypothesis that polyalanine expansion mutations in PHOX2B impact dermatoglyphic pattern formation, in addition to gut motility.

Also of interest is the noted gender difference in the pattern frequency analysis. These differences are notable in light of the well-recognized male predominance of isolated HD. Recently, a common noncoding RET variant mutation within a conserved enhancer-like sequence has been identified as a contributing factor to the differences in susceptibility to HD by gender. Most likely, the gender differences in frequency distribution of dermatoglyphics in CCHS are a result of the multifactorial inheritance of dermatoglyphic patterns, similar to HD. This is a more likely explanation for gender variation than a direct influence of the PHOX2B mutation, because we are unaware of other identified gender differences in the CCHS phenotype.

We have identified 2 potential limitations of this study. First, we relied on the published control data set including 720 white children aged 7 years (360 females) rather than recruit individual age-matched controls. This technique was used because it represents a better approximation of the population norms than a smaller set of matched controls. Furthermore, dermatoglyphic patterns do not change during an individual’s postnatal life, unlike other phenotypic features, such as facial characteristics, which have the potential to change with increasing age. Because of the data set used, we were not able to compare ≥1 or ≥3 to 4 arches with controls, which would have been useful in comparing our results with existing literature. Likewise, dermatoglyphic raters were not blinded to case versus control group, although it should be noted that the raters were blinded within CCHS clinical grouping. The second limitation is the small sample size of CCHS subjects. This may have reduced the ability to generalize our findings, but also may have contributed to the lack of significance when evaluated by PHOX2B genotype. In particular, the limited number of cases with higher numbers of polyalanine repeats (only 5 cases with 30 to 33 repeats) may have precluded detection of a significant correlation between the number of polyalanine repeats and frequencies of dermatoglyphic patterns.

CONCLUSIONS

Dermatoglyphic pattern frequency is clearly altered in CCHS cases versus controls, but the role of PHOX2B and the implication of the frequency differences are still to be determined. Based on these results, an increased sample size, including children with PHOX2B-confirmed CCHS unique mutations and a broad array of the common polyalanine expansion mutations, should be studied to fully understand the genotype/phenotype correlation in CCHS. Children with other disorders of neural crest origin, such as HD and neuroblastoma, should be studied to elucidate the relationship between these other disorders and an accessible phenotypic measure of the embryological neural crest. It would also be worthwhile to evaluate dermatoglyphics of parents and siblings of individuals with CCHS to look for an absence of familial tendencies, thus supporting a causative effect of the PHOX2B mutation on the dermatoglyphic pattern frequencies. In so doing, the dermatoglyphic phenotype of CCHS will be further characterized, and the contribution of PHOX2B to both dermatoglyphic patterning and CCHS will be better understood.

ACKNOWLEDGMENTS

This work was supported by Rush University Dean’s Office Summer Research Fellowship and Sigma Xi Outstanding Rush Medical College Student Research Award (E. S. Todd), Spastic Paralysis and Allied Diseases of the Central Nervous System Research Foundation of the Illinois-Eastern Iowa District Kiwanis International (E. M. Berry-Kravis), and National Institutes of Health/National Institute of Dental and Craniofacial Research grants R01-DE016148 and P50-DE016215 (M. L. Marzita).

We thank Kelly Dearing Roollen and Indentiseal/Infra-Print for their gracious donation of the inkless fingerprinting materials to make this study possible. We also thank Foster Lewin for the preparation of the DNA.

Downloaded from www.pediatrics.org by on August 1, 2006
Chinton Desai and Ronak Lahkia who assisted with PCR assays, and the children with CCHS who graciously shared their DNA and their fingerprints.

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