Increased Prevalence of Left-Handedness in Hemifacial Microsomia

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Abstract: Ten percent of people are left handed, but a higher frequency has been associated with certain craniofacial malformations, such as cleft lip and unilateral coronal synostosis. The purpose of this study was to determine the frequency of left-handedness in patients with hemifacial microsomia (HFM). Patients with HFM were identified in our craniofacial database. Normal controls were recruited by local pediatricians. Data gathered included age, sex, and handedness (determined by writing and/or drawing); the orbit, mandible, ear, nerve, and soft tissue (OMENS)–plus score and side of involvement were tabulated for patients with HFM. Hand preference was compared between the groups using χ^2 analysis; possible correlations were analyzed between handedness and age, sex, the OMENS score, extracraniofacial findings, and side of involvement. One hundred seventy-eight patients with HFM were identified; 92 (51%) were excluded. Of the 86 included, 48% were boys (n = 47) and the mean age at inquiry was 13.5 years. Predominant side of involvement was right in 49% (n = 42) and left in 38% (n = 33). Eleven patients (13%) had severe involvement of both sides. Expanded-spectrum HFM was documented in 41% of patients. Ninety-six children were in the control group; 44% were boys (n = 42), and the mean age was 10 years. The difference in age between the groups was significant ($P < 0.05$), but sex differences were not. Patients with HFM were more likely to be left handed for writing compared with the control group (26% vs. 11%; $P < 0.05$). The frequency was higher, 36%, in those with bilateral involvement ($P > 0.05$). There was no correlation with predominant side or OMENS score. This study confirms that this disorder affects cerebral lateralization.

Key Words: Hemifacial microsomia, craniofacial microsoma, handedness, laterality

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The body plan for humans is essentially symmetric around the midaxis. Nevertheless, asymmetric arrangement of organs in the thoracoabdominal cavities indicates that cellular functions become unequal early in development. Cellular symmetry persists throughout the gastrula stage and, thereafter, differential cascades of gene expression break the otherwise symmetrical internal structure.[1] Animal models have provided some insight into the molecular and developmental mechanisms by which right-left symmetry is altered.[1,2] Nevertheless, investigators are still unclear why these structural asymmetries occur in a nonrandom, or unequal, distribution. Nonrandom laterality is seen in the human brain, face, heart, great vessels, lungs, liver, gallbladder, biliary tract, gastrointestinal tract, spleen, and male genitalia.[3,4] All but 0.01% of humans exhibit the same asymmetric arrangement of their internal organs (situs or situs solitus).[5,6] Nevertheless, in extremely rare instances, the standard body plan is inexplicably altered. One in 50,000 persons, the laterality of the internal organs, is reversed (situs inversus)[7–9] or somewhat randomly arranged (situs ambiguous).[3,10,11]

Even more perplexing is the observation that certain malformations of symmetric bilateral structures occur in greater proportions on one side: For example, there is greater right-sided involvement in Poland anomaly, unilateral coronal synostosis, pulmonary agenesis, inguinal hernia, and radial and fibular aplasia[12–16] and left-sided preponderance in unilateral cleft lip, agenesis of the maxillary lateral incisor, Romberg disease, renal agenesis, supernumerary nipples, postaxial polydactyly, and congenital dislocation of the hip.[15,17–23] These observations argue that subtle temporal or structural differences exist between the sides of the body during early development, although the specific causes have not been determined.

In addition to nonrandom anatomic asymmetry, humans can also exhibit various forms of nonrandom functional laterality. The most highly investigated type of functional laterality is hand preference. More than 90% of humans are right handed, and this strong bias seems to be conserved in all ethnic populations.[24,25] Other forms of nonrandom functional laterality include speech and language,[26] eye and ear preference,[27–29] and footedness.[30] Right eye dominance occurs in 65% to 77% of people.[31,32] Most persons are also right ear dominant and recognize auditory stimuli for a longer duration on the right side.[33] Some investigators believe that this represents a specialized auricular function rather than true dominance.[34] Footedness lateralizes to the right side in more than two thirds of the population; this proportion is stable in professional soccer players despite the emphasis on the superiority of 2-footed players.[35,36]

The relationships between anatomic (or pathoanatomic) and functional lateralities have also been widely explored. There is a strong correlation between structural and functional lateralities in lower vertebrates, for example, in zebrafish;[37,38] however, this relationship does not hold true for humans. The best example of this is situs inversus. Despite the reversed laterality of internal organs, these subjects demonstrate similar distribution of dichotic listening, language dominance, and hand preference as the general population.[5,24,39,40] Perhaps because of the contemporaneous development[41] or close anatomic proximity of the face and the cranial vault, investigations relating craniofacial and functional asymmetries have yielded more interesting results. Several reports have associated handedness with increased contralateral hemifacial width. For example, left-handers have increased right craniofacial width.[33,42–44] Magnetic resonance imaging data have shown that left- and right-handed people have larger right and left cerebral hemispheres, respectively.[45,46] Even pathoanatomic asymmetry, such as cleft lip, has been found to correlate with hand preference,[41,47–50] although this relationship is inconsistently found.[51,52]

We recently demonstrated a significant increase in left-handedness in patients with unilateral coronal synostosis compared with a control group of healthy children (30.2% vs. 11.4%).[53] Left-handedness was 2-fold more likely than normal (20.4%) when the fusion was on the right and 4-fold more likely when there was a left-sided fusion (44.4%). Although lateralization of cerebral function was clearly affected in this population, we were unable to assign the leftward shift to intrinsic (inherent cerebral development) or extrinsic (pressure from abnormal cranial shape) influences.

To further investigate a possible association between abnormal craniofacial development and alterations in laterality of cerebral function (exhibited by handedness), we chose hemifacial microsomia (HFM) for several reasons. First, this malformation has no apparent genetic basis. Therefore, any effects on functional laterality are less likely to have a defined molecular etiology. Second, cranial shape and volume are relatively unaffected in this disorder. This reduces the possibility that externally applied force, such as caused by craniosynostosis, could affect cerebral function or form. Lastly, facial involvement in hemifacial microsomia is more pervasive than in cleft lip and palate. Hence, we would anticipate a stronger association between craniofacial maldevelopment and handedness in this anomaly than has been suggested for cleft lip.

METHODS

After obtaining approval from our institutional review board, we identified all patients with the condition diagnosed as HFM seen at our craniofacial unit since 1985. Healthy children were recruited by local pediatricians as a control group. Data collected for all patients included age, sex, and handedness, as determined by the preferred hand for writing and/or drawing. To reduce the likelihood of ambiguous handedness or uncertainty, children who were under 3 years of age or those in whom the parents were uncertain of which hand they preferred were excluded.

In the HFM group, additional data were collected, including the side(s) of involvement; total orbit, mandible, ear, nerve, and soft tissue (OMENS) score;[54] and the presence of expanded-spectrum anomalies.[55] Hand preference was compared between the study and control groups using χ^2 analysis. Further statistical analysis was done to identify possible correlations between handedness and age, sex, OMENS score, extracraniofacial anomalies, and side of predominant involvement.

RESULTS

A total of 178 patients with HFM were identified; 92 patients (51%) were lost to follow-up or did not meet the inclusion criteria. Of the 86 patients included in the study, 48% were boys ($n = 47$) and the mean age at inquiry was 13.5 years (range, 4–45 y; SD, 9.3). The sides of predominant involvement were the right in 49% ($n = 42$) and the left in 38% ($n = 33$). Thirteen percent ($n = 11$) had almost equal bilateral involvement. Mean OMENS scores were 5.7 for those with predominantly unilateral hypoplasia (range, 2–13; SD, 2.8) and 8.6 for those with bilateral hypoplasia (range, 6–13; SD, 2.7); this difference was significant ($P < 0.05$). Extracranial manifestations were documented in 41% of study patients. There were 96 children in the control group: 44% were boys ($n = 42$), and the mean age was 10 years (range, 3–17 y; SD, 3.5). The difference in age between the groups was significant ($P = 0.000$), but sex differences were not.

Twenty-six percent (22/86) of all the study group patients were left-hand dominant for writing compared with only 11% (11/86) for the control group; this difference was significant ($P = 0.025$). Thirty-six percent (4/11) of patients with bilateral facial hypoplasia were left-hand dominant for writing. This difference was significantly different than the control group ($P = 0.03$) but not different than the predominantly unilateral group. There were no significant differences between right- and left-handed persons in the study group with respect to age, sex, OMENS score, or expanded-spectrum findings. However, for patients with bilateral involvement, the side most affected was almost uniformly predictive of hand preference. In this group, 4 of 5 patients with left-predominant involvement were left handed, whereas all 6 patients with right-predominant findings were right handed.

DISCUSSION

This study revealed a significant shift to left-hand preference in patients with HFM. Although handedness is only 1 measure of cerebral functional laterality, this finding further emphasizes that the developmental abnormality that causes HFM is not isolated to the face. Extracraniofacial anomalies of the cardiac, skeletal, genitourinary, gastrointestinal, and central nervous systems have been reported in up to 18% of patients with HFM.[55] Thus, the term craniofacial microsomia may be more accurate than the more commonly used HFM.[56]

Our results also invite further discussion of the 2 major etiological theories of HFM. The first theory states that it is caused by a vascular disruption in the first or second pharyngeal arches. This hypothesis is supported by an animal model in which a similar phenotype could be produced by drug-induced vascular insult.[57] Furthermore, human epidemiological studies have suggested that maternal exposure to vasogenic drugs during pregnancy increases the risk of having a child with HFM.[58] It is possible that a focal or regional vascular event in the upper pharyngeal arches could also involve the developing cerebrum. There are a number of studies that have suggested an increased incidence of left-handedness in children and infants with various neurologic conditions. This pathologic left-handedness has been described in children with brain injury from infection or trauma,[59] epilepsy,[60] low birth weight,[61] prematurity,[62,63] and right congenital hemiplegia (left hemispheric insult).[64] Lateralized neurologic problems, such as epilepsy and hemiparesis, have been reported in patients with HFM.[54] Nevertheless, none of our patients had these findings.

Most people are left hemispheric dominant for speech, language, and motor functions,[65,66] whereas the right hemisphere is usually dominant for abstract functions such as self-awareness, self-recognition, and empathy.[67,68] Accordingly, damage to the left hemisphere typically causes greater functional consequences than a similar injury to the right hemisphere.[69] If HFM were caused by a unilateral vasculopathic event, the incidence of left-handedness should be markedly higher in patients with right-sided involvement. We found that there was no correlation between the side of facial involvement and hand preference except in those patients with nearly symmetric bilateral involvement. Unfortunately, the number was too small in this group to draw any meaningful conclusions.

The second major etiopathologic theory for HFM implicates abnormal proliferation or migration of neural crest cells.[69,70] These multipotent cells are unique to vertebrate development and help to orchestrate growth of the craniofacial skeleton, muscles, cranial nerves,[71,72] heart, great vessels,[73–75] peripheral nerves, and gastrointestinal innervation.[76] The abnormal division, migration, or induction of neural crest cells could easily account for the extracranial anomalies (eg, cardiac, skeletal, and central nervous system) reported in HFM.[55] Cephalic neural crest cells also help coordinate the formation of the forebrain and midbrain.[77,78] Thus, the facial anomalies and altered cerebral functional laterality (ie, increased left-handedness) observed in our patients with HFM may have the same pathogenic basis. Interestingly, increased apoptosis of cranial neural crest cells is caused by mutations in the *TCOF1* gene, which is implicated in the pathogenesis of the Treacher Collins syndrome, the other major disorder of the first and second pharyngeal arches.[71]

The possible evolutionary advantage of structural or behavioral asymmetry is debated. Nearly all vertebrates have structural asymmetries, and many species exhibit specific types of nonrandom activity or behavior.[79–81] Some lower vertebrates, for example, fish, reptiles, and amphibians, evidence lateralized responses to predators and during mating.[82] Toads and certain species of fish react faster to a stimulus presented on 1 side.[80] Lower mammals, such as mice, chicks, cats, and dogs, also exhibit specific behaviors that clearly indicate cerebral lateralization.[81,83] For example, many bird and mammal species have a preferred limb for feeding or digging, although the bias for one limb over the other is relatively weak compared to human hand preference.[84–90] Even chimpanzees and great apes, which seem to favor using their right hand for a relatively wide range of activities, have a smaller population bias for this trait than humans.[91,92] In all of these animal comparisons, it is still debated whether task-specific paw preferences or other types of lateralized behavior commonly seen in other animals are functionally analogous to human handedness.[81]

Humans exhibit a wide range of lateralized behaviors, although none as strongly directional, strictly conserved, or as heavily studied as handedness. Human population bias for right-hand dominance has been noted throughout recorded history.[93] Despite the attention it has received, the physiologic and evolutionary bases for the strong hand bias in humans remain unclear.[80–82] Numerous investigations suggest that right-handed people have greater anatomic and functional asymmetries (ie, specialization) of their cerebral hemispheres[46,94–99] and less interhemispheric connectivity (greater independence?) than left-handed persons.[99–104] In theory, greater cerebral "division of labor," as seen in right-handed persons, could reduce neural redundancy and allow more complex cognitive processing.[105,106] Some researchers have speculated that the development of functional hemispheric specialization may be the basis for man's intellectual superiority over other animals.[80,81]

Limitations of this study warrant discussion. First, hand preference is only 1 aspect of human nonrandom functional laterality. Therefore, the significant shift in handedness we found in our patients with HFM may not be representative of abnormalities in other types of cerebral specialization. Furthermore, our findings cannot be expanded to more general measures of cerebral function, such as intelligence. Additional cognitive testing or supplemental imaging with functional or diffusion tensor magnetic resonance imaging would provide more insight. A second possible criticism of this investigation is determination of handedness solely on the basis of writing. Some investigators have suggested that because writing is learned, this measure may be influenced by cultural norms. More complicated indicators of handedness, such as the Edinburgh Handedness Inventory, have been widely used.[33,43,107–109] These questionnaires also have been criticized because they rely on the examinee's recollection of hand preference and have shown inconsistent results when compared with direct observations.[25] Other methods include pooling tasks, such as writing, throwing, handling a tool, so on, to produce a composite of hand preference.[110] In these methods, people who consistently use their right hand are considered right handed and all others are non–right handed. It is unclear if this diversity of tasks adds clarity because nearly all manual functions, except writing, can be learned equally well with either hand.[25,111] Corey et al[112] showed that it is writing, not other measures of hand performance, that most strongly correlates with scores on broader handedness inventories. The distribution of handedness in our control group supports the reliability of using writing as a measure of handedness because it was nearly identical to the findings in other studies using more complex measures.

REFERENCES

1. Cooke J. Developmental mechanisms and evolutionary origin of vertebrate left-right asymmetries. *Biol Rev* 2004;79:377–407
2. Hamada H, Meno C, Watanabe D, et al. Establishment of vertebrate right-left asymmetry. *Nat Rev Genet* 2002;3:103–113
3. Aylsworth AS. Clinical aspects of defects in the determination of laterality. *Am J Med Genet* 2001;101:345–355
4. Gorlin RJ. Asymmetry. *Am J Med Genet* 2001;101:290–291
5. Tanaka S, Kanzaki R, Yoshibayashi M, et al. Dichotic listening in patients with situs inversus: brain asymmetry and situs asymmetry. *Neuropsychologia* 1999;37:869–874
6. Tubbs RS, Wellons JC, Salter G, et al. Intracranial anatomic asymmetry in situs inversus totalis. *Anat Embryol (Berl)* 2003;206: 199–202
7. Uragoda CG. Dextrocardia and situs inversus in Sri Lanka. *Trop Geogr Med* 1977;29:14–18
8. Stoler J, Holmes L. A case of agnathia, situs inversus, and a normal central nervous system. *Teratology* 1992;213–216
9. Casey B. Two rights make a wrong: human left-right malformations. *Hum Mol Genet* 1998;7:1565–1571
10. Opitz JM. Editorial comment on the paper by de la Monte and Hutchins on familial polyasplenia. *Am J Med Genet* 1985;21:175–176
11. Splitt MP, Burn J, Goodship J. Defects in the determination of left-right asymmetry. *J Med Genet* 1996;33:498–503
12. Kato K. Congenital absence of the radius. *J Bone Joint Surg* 1924; 6:589–626
13. Aitken GT. Amputation as a treatment for certain lower-extremity congenital abnormalities. *J Bone Joint Surg* 1959;41-A: 1267–1285
14. Gunnlaugsson GH, Dawson B, Lynn HB. Treatment of inguinal hernia in infants and children: experience with contralateral exploration. *Mayo Clin Proc* 1967;42:129–136
15. Schnall BS, Smith DW. Nonrandom laterality of malformations in paired structures. *J Pediatr* 1974;85:509–511
16. Cohen MM Jr, Rollnick BR, Kaye CL. Oculoauriculovertebral spectrum: an updated critique. *Cleft Palate J* 1989;26:276–286
17. Collins DC. Congenital unilateral renal agenesis. *Ann Surg* 1932;95: 715–726
18. Landauer W. Supernumerary nipples, congenital hemihypertrophy and congenital hemiatrophy. *Hum Biol* 1939;11:447–472
19. Ingalls TH, Taube IE, Klingberg MA. Cleft lip and cleft palate: epidemiologic considerations. *Plast Reconstr Surg* 1964;34:1–10
20. Gregersen HN. Congenital dislocation of the hip. *Acta Orthop Scand* 1969;40:53–61
21. Tolarova MI. A study of the incidence, sex-ratio, laterality and clinical severity in 2,660 probands with facial cleft in Czechoslovakia. *Acta Chir Plast* 1987;29:77–87
22. Jensen BL, Kreiborg S, Dahl E, et al. Cleft lip and palate in Denmark, 1976–1981: epidemiology, variability, and early somatic development. *Cleft Palate J* 1988;25:258–269
23. Cohen MM Jr. Asymmetry: molecular, biologic, embryopathic, and clinical perspectives. *Am J Med Genet* 2001;101:292–314
24. McManus IC, Martin N, Stubbings GF, et al. Handedness and situs inversus in primary ciliary dyskinesia. *Proc R Soc Lond* 2004;271: 2579–2582
25. Perelle IB, Ehrman L. On the other hand. *Behav Genet* 2005;35: 343–350

26. Broca P. Remarques sur le siege de la faculte du langage articule. *Bull Soc Anth* 1861;6:330–357
27. Ward WD. Hearing of naval aircraft maintenance personnel. *J Acoustical Soc Am* 1957;29:1289–1301
28. Chatrian GE, Wirch AL, Edward KH, et al. Cochlear summating potential to broadband clicks detected from the human external auditory meatus, a study of subjects with normal hearing for age. *Ear Hear* 1985;6:130–138
29. Porac C, Coren S. Sighting dominance and egocentric localization. *Vision Res* 1986;1709–1713
30. Porac C, Coren S. *Lateral Preferences and Human Behavior*. New York, NY: Springer-Verlag, 1981
31. Annett M, Turner A. Laterality and the growth of intellectual abilities. *Br J Educ Psychol* 1974;44:37–46
32. Reiss M, Reiss G. Ocular dominance: some family data. *Laterality* 1997;2:7–15
33. Dane S, Gumustekin K, Polat P, et al. Relations among hand preference, craniofacial asymmetry, and ear advantage in young subjects. *Percept Mot Skill* 2002;95:416–422
34. Job A, Grateau P, Picard J. Intrinsic differences in hearing performances between ears revealed by the asymmetrical shooting posture in the army. *Hear Res* 1998;122:119–124
35. Carey DP, Smith G, Smith DT, et al. Footedness in world soccer: an analysis of France '98. *J Sports Sci* 2001;19:855–864
36. Martin WLB, Machado AH. Deriving estimates of contralateral footedness from prevalence rates in samples of Brazilian and non-Brazilian right- and left-handers. *Laterality* 2005;10:353–368
37. Concha ML, Wilson SW. Asymmetry in the epithalamus of vertebrates. *J Anat* 2001;199:63–84
38. Barth KA, Miklosi A, Watkins J, et al. *fsi* Zebrafish show concordant reversal of laterality of viscera, neuroanatomy, and a subset of behavioral responses. *Curr Biol* 2005;15:844–850
39. Matsumoto T, Kuriya N, Akagi T, et al. Handedness and laterality of the viscera. *Neurology* 1997;49:1751
40. Kennedy DN, O'Craven KM, Ticho BS, et al. Structural and functional brain asymmetries in human situs inversus totalis. *Neurology* 1999;53: 1260–1265
41. Wentzlaff KA, Cooper ME, Yang P, et al. Association between non–right-handedness and cleft lip with or without cleft palate in a Chinese population. *J Craniofac Genet Dev Biol* 1997;17:141–147
42. Keles P, Diyarbakirli S, Tan M, et al. Facial asymmetry in right- and left-handed men and women. *Int J Neurosci* 1997;91:147–160
43. Dane S, Ersoz M, Gumustekin K, et al. Handedness differences in width of right and left craniofacial regions in young healthy adults. *Percept Mot Skills* 2004;98:1261–1264
44. Hardie S, Hancock P, Rodway P, et al. The enigma of facial asymmetry: is there a gender-specific pattern of facedness? *Laterality* 2005;10:295–304
45. Geschwind DH, Miller BL, DeCarli C, et al. Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. *Proc Natl Acad Sci U S A* 2002;99:3176–3181
46. Hervé PY, Mazoyer B, Crivello F, et al. Finger tapping, handedness and grey matter amount in the Rolando's genu area. *Neuroimage* 2005;25:1133–1145
47. Tisserand M. Dominance laterale et bec de lievre. *Arch Fr Pediatr* 1944;2:166–167
48. Rintala AE. Relationship between side of the cleft and handedness of the patient. *Cleft Palate J* 1985;22:34–37
49. Yorita GJ, Melnick M. Cleft lip and handedness: a study of laterality. *Am J Med Genet* 1988;31:273–280
50. Daskalogiannakis J, Kuntz KL, Chudley AE, et al. Unilateral cleft lip with or without cleft palate and handedness: is there an association? *Cleft Palate Craniofac J* 1998;35:46–51
51. Fraser FC, Rex A. Excess of parental non–right-handedness in children with right-sided cleft lip: a preliminary report. *J Craniofac Genet Dev Biol* 1985;1S:85–88
52. Jeffery SLA, Boorman JG. Left or right hand dominance in children with cleft lip and palate. *Br J Plast Surg* 2000;50:477–478
53. Oh AK, Mulliken JB, LaBrie RA, et al. Increased incidence of left-handedness in patients with unilateral coronal synostosis. *Cleft Palate Craniofac J.* In press.
54. Vento AR, LaBrie RA, Mulliken JB. The O.M.E.N.S. classification of hemifacial microsomia. *Cleft Palate Craniofac J* 1991;28:68–77
55. Horgan JE, Padwa BL, LaBrie RA, et al. OMENS-Plus: analysis of craniofacial and extracraniofacial anomalies in hemifacial microsomia. *Cleft Palate Craniofac J* 1995:32:405–410
56. McCarthy JG, Grayson BH, Coccaro PJ, et al. Craniofacial microsomia. In: McCarthy JG, ed. *Plastic Surgery.* Philadelphia, PA: WB Saunders Co, 1990:3054
57. Postwillo D. The pathogenesis of first and second branchial arch syndrome. *Oral Surg* 1973;35:302–328
58. Werler MM, Sheehan JE, Hayes C, et al. Vasoactive exposures, vascular events, and hemifacal microsomia. *Birth Defect Res* 2004;70:389–395
59. Miller JW, Jayadev S, Dodrill CB, et al. Gender differences in handedness and speech lateralization related to early neurologic insults. *Neurology* 2005:65:1974–1975
60. Silva DA, Satz P. Pathological left-handedness: evaluation of a model. *Brain Lang* 1979;7:8–16
61. O'Callaghan MJ, Burns YR, Mohay HA, et al. The prevalence and origins of left hand preference in high risk infants, and its implications for intellectual, motor and behavioural performance at four and six years. *Cortex* 1993;29:617–627
62. Ross G, Lipper EG, Auld PA. Hand preference of four-year-old children: its relationship to premature birth and neurodevelopmental outcome. *Dev Med Child Neurol* 1987;29:615–622
63. Ross G, Lipper E, Auld PA. Hand preference, prematurity, and development outcome at school age. *Neuropsychologia* 1992;30: 483–494
64. Carlsson G, Hugdahl K, Uvebrant P, et al. Pathological left-handedness revisited: dichotic listening in children with left vs. right congenital hemiplegia. *Neuropsychologia* 1992;30:471–481
65. Warrington EK, Pratt RTC. Language laterality in left-handers assessed by unilateral E.C.T. *Neuropsychologia* 1973;11:423–428
66. McManus IC. The inheritance of left-handedness. In: Wolpert L, ed. *Biological Asymmetry and Handedness, Ciba. Foundation Symposium No. 162*. New York, NY: John Wiley and Sons. 1991:P251–P281
67. Keenan JP, Rubio J, Racioppi C, et al. The right hemisphere and the dark side of consciousness. *Cortex* 2005;41:695–704
68. Keenan JP, Nelson A, O'Connor M, et al. Self-recognition and the right hemisphere. *Nature* 2001;409:305
69. Gut M, Urbanik A, Forsberg L, et al. Brain correlates of right-handedness. *Acta Neurobiol Exp* 2007;67:43–51
70. Johnston MC. Embryology of the head and neck. In: McCarthy JG, ed. *Plastic Surgery.* Philadelphia, PA: WB Saunders, Co, 1990:2491–2492
71. Dixon J, Jones NC, Sandell LL, et al. Tcof1/Treacle is required for neural crest cell formation and proliferation deficiencies that cause craniofacial abnormalities. *Proc Natl Acad Sci U S A* 2006;103: 13403–13408
72. Rinon A, Lazar S, Marshall H, et al. Cranial neural crest cells regulate head muscle patterning and differentiation during vertebrate embryogenesis. *Development* 2007;306:3065–3075
73. High F, Epstein JA. Signalling pathways regulating cardiac neural crest migration and differentiation. *Novartis Found Symp* 2007;238: 152–161
74. Snider P, Olaopa M, Firulli AB, et al. Cardiovascular development and the colonizing cardiac neural crest lineage. *ScientificWorldJournal* 2007;3:1090–1113
75. Langenberg T, Kahana A, Wszalek JA, et al. The eye organizes neural crest migration. *Dev Dyn* 2008;237:1645–1652
76. Simpson MJ, Zhang DC, Mariani M, et al. Cell proliferation drives neural crest cell invasion of the intestine. *Dev Biol* 2007;15:553–568
77. Creuzet SE, Martinez S, LeDouarin NM. The cephalic neural crest exerts a critical effect on forebrain and midbrain development. *Proc Natl Acad Sci U S A* 2006;103:14033–14038
78. LeDourin NM, Brito JM, Creuzet S. Role of neural crest in face and brain development. *Brain Res Rev* 2007;55:237–247
79. Vallortigara G, Rogers LJ. Survival with an asymmetrical brain:

advantages and disadvantages of cerebral lateralization. *Behav Brain Sci* 2005;28:575–633
80. Vallortigara G. The evolutionary psychology of left and right: costs and benefits of lateralization. *Dev Psychobiol* 2006;48: 418–427
81. Corballis MC. Of mice and men- and lopsided birds. *Cortex* 2008; 44:3–7
82. Bisazza A, Rogers LJ, Vallortigara G. The origins of cerebral asymmetry: a review of evidence of behavior and brain lateralization in fish, reptiles, and amphibians. *Neurosci Behavior Rev* 1998;22: 411–426
83. Walker SF. Lateralization of functions in the vertebrate brain: a review. *Br J Psychol* 1980;71:329–367
84. Fabre-Thorpe M, Fagot J, Lorincz E, et al Laterality in cats: paw preference and performance in a visuomotor activity. *Cortex* 1993;29: 15–24
85. Tan U. Paw preferences in dogs. *Int J Neurosci* 1987;32:825–829
86. Biddle FG, Coffaro CM, Ziehr JE, et al. Genetic variation in paw preference (handedness) in the mouse. *Genome* 1993;36:935–943
87. Waters NS, Denenberg VH. Analysis of two measures of paw preference in a large population of inbred mice. *Behav Brain Res* 1994;63:195–204
88. Bulman-Fleming MB, Bryden MP, Rogers TT. Mouse paw preference: effects and variations in testing protocol. *Behav Brain Res* 1997;86: 79–87
89. Wells DL. Lateralised behavior in the domestic dog, *Canis familiaris*. *Behav Processes* 2003;61:27–35
90. Guven M, Elalmis DD, Binokay S, et al. Population-level right-paw preference in rats assessed by a new computerized food-reaching test. *Int J Neurosci* 2003;113:1675–1689
91. Hopkins WD, Leavens DA. Hand use and gestural communication in chimpanzees (*Pan troglodytes*). *J Comp Psychol* 1998;112: 95–99
92. Hopkins WD. Comparative and familial analysis of handedness in great apes. *Psychol Bull* 2006;132:538–559
93. Coren S, Porac C. Fifty centuries of right-handedness: the historical record. *Science* 1977;198:631–632
94. Steinmetz H, Volkmann J, Jancke L, et al. Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers. *Ann Neurol* 1991;29:315–319
95. Kertesz A, Polk M, Black SE, et al. Anatomical asymmetries and functional laterality. *Brain* 1992;115:589–605
96. Foundas AL, Leonard CM, Heilman KM. Morphologic cerebral asymmetries and handedness. The pars triangularis and planum temporale. *Arch Neurol* 1995;52:501–508
97. Evitar Z, Hellige J, Zaidel E. Individual differences in lateralization: effects of gender and handedness. *Neuropsychology* 1997;11: 562–576
98. Büchel C, Raedler T, Sommer M, et al. White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cerebr Cortex* 2004;14: 945–951
99. Cherubin N, Brinkman C. Hemispheric interactions are different in left-handed individuals. *Neuropsychology* 2006;20:700–707
100. Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. *Brain* 1989;112:799–835
101. Habib M, Gayraud D, Oliva A, et al. Effects of handedness and sex on the morphology of the corpus callosum: a study with brain magnetic resonance imaging. *Brain Cogn* 1991;16:41–61
102. Moffat SD, Hampson E, Lee DH. Morphology of the planum temporale and corpus callosum in left handers with evidence of left and right hemispheric speech representation. *Brain* 1998;121: 2369–2379
103. Hoffman L, Polich J. P300, handedness, and corpus callosal size: gender, modality, and task. *Int J Psychophysiol* 1999;31:163–174
104. Westerhausen R, Kreuder F, Dos Santos Sequeira S, et al. Effects of handedness and gender on macro- and microstructure of the corpus callosum and its subregions: a combined high-resolution and diffusion-tensor MRI study. *Brain Res Cogn Brain Res* 2004;21: 418–426
105. Vallortigara G, Rogers LJ, Bisazza A. Possible evolutionary origins of cognitive brain lateralization. *Brain Res Brain Res Rev* 1999;30: 164–175
106. Yoshizaki K, Weissman DH, Banich MT. A hemispheric division of labor aids mental rotation. *Neuropsychology* 2007;21:326–336
107. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113
108. Dayi E, Gungormus M, Okuyan M, et al. Predictability of hand skill and cognitive abilities from craniofacial width in right- and left-handed men and women: relation of skeletal structure to cerebral function. *Intern J Neurosci* 2002;112:383–412
109. Dane S, Gumustekin K, Yazici AT, et al. Correlation between hand preference and intraocular pressure from right- and left-eyes in right- and left-handers. *Vision Res* 2003;43:405–408
110. Rife DC. Handedness, with special reference to twins. *Genetics* 1940; 25:178–186
111. Perelle IB, Ehrman L, Manowitz JW. Human handedness: the influence of learning. *Percept Motor Skill* 1981;53:976–977
112. Corey DM, Hurley MM, Foundas AL. Right and left handedness defined: a multivariate approach using hand preference and hand performance measures. *Neuropsychiatry Neuropsychol Behav Neurol* 2001;14:144–152