## Fluid-dynamical basis of the embryonic development of left–right asymmetry in vertebrates

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The bilaterally symmetric external appearance of vertebrates is deceptive, for beneath the skin asymmetry reigns. Magnificent experimental work in developmental biology has recently shown that fluid flow driven by rotating cilia in the node, a structure present in the early stages of growth of vertebrate embryos, is responsible for determining the normal development of the left-right axis, with the heart on the left of the body, the liver on the right, and so  $on^{1-8}$ . This confirms a hypothesis of Afzelius<sup>9</sup>, who first surmised that the movement of cilia might be crucial in this symmetry breaking. The rôle of physics, in particular of fluid dynamics, in the process, is one of the important questions that remain to be answered<sup>10</sup>. We show with an analysis of the fluid dynamics of the nodal flow in the developing vertebrate embryo that the leftward flow that has been experimentally observed may be produced by the monocilia driving it being tilted toward the posterior. We propose a model for morphogen transport and mixing in the nodal flow, and discuss how this might initiate the development of left-right asymmetry in vertebrates.

<sup>1</sup> S. Nonaka, Y. Tanaka, Y. Okada, S. Takeda, A. Harada, Y. Kanai, M. Kido, and N. Hirokawa. Randomization of left–right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein. *Cell*, 95:829–837, 1998. See erratum *ibid* 99: 117, 1999.

- <sup>2</sup> Y. Okada, S. Nonaka, Y. Tanaka, Y. Saijoh, H. Hamada, and N. Hi-rokawa. Abnormal nodal flow precedes situs inversus in *iv* and *inv* mice. *Mol. Cell*, 4:459–468, 1999.
- <sup>3</sup> B. A. Afzelius. Asymmetry of cilia of mice and men. *Int. J. Dev. Biol.*, 43:283–286, 1999.
- <sup>4</sup> J. Capdevila, K. J. Vogan, C. J. Tabin, and J. C. Izpisúa Belmonte. Mechanisms of left–right determination in vertebrates. *Cell*, 101:9–21, 2000.
- <sup>5</sup> D. M. Supp, S. S. Potter, and M. Brueckner. Molecular motors: the driving force behind mammalian left–right development. *Trends in Cell Biol.*, 10:41–45, 2000.
- <sup>6</sup> J. J. Essner, K. J. Vogan, M. K. Wagner, C. J. Tabin, H. J. Yost, and M. Brueckner. Conserved function for embryonic nodal cilia. *Nature*, 418:37–38, 2002.
- <sup>7</sup> S. Nonaka, H. Shiratori, Y. Saijoh, and N. Hirokawa. Determination of left–right patterning of the mouse embryo by artificial nodal flow. *Nature*, 418:96–99, 2002.
- <sup>8</sup> H. Hamada, C. Meno, D. Watanabe, and Y. Saijoh. Establishment of vertebrate left–right asymmetry. *Nature Rev. Genetics*, 3:103– 113, 2002.
- <sup>9</sup> B. A. Afzelius. A human syndrome caused by immotile cilia. *Science*, 193:317–319, 1976.
- <sup>10</sup> C. D. Stern. Fluid flow and broken symmetry. *Nature*, 418:29–30, 2002.