

cians and AMA members supported the public insurance option and the expansion of Medicare,<sup>1</sup> the AMA opposed Medicare expansions and proposed coverage of the uninsured primarily through private means.<sup>2,3</sup> We conducted a national survey of physicians to determine whether the AMA represented the views of physicians in the insurance expansion debate and to understand who the AMA represented.

We surveyed 5157 physicians using data from the AMA Physician Masterfile.<sup>1</sup> Respondents were asked to indicate their support for the public insurance option or expansion of health insurance through private means, and their support for a proposal that would allow adults 55 to 64 years of age to buy into Medicare. We considered a physician as endorsing the AMA's platform if he or she agreed with private expansions only and opposed the expansion of Medicare. Using multivariate logistic-regression analysis, we determined the profile of physicians most likely to endorse the AMA's platform. Details of the study have been described previously.<sup>1</sup>

The response rate was 43.2%. Respondents were less likely to be female and were older on average by 1 year as compared with nonrespondents. There were no significant differences in responses based on specialty, practice type, or geographic location of practice. Only 12.5% of all physicians responding, and 14.2% of AMA members, supported the AMA's viewpoint on coverage expansions (Table 1). Support for the AMA's platform was highest among doctors of osteopathy (16.5%), physicians whose income was based on billing (16.1%), and physicians in rural practices (16.0%) and lowest among women (7.9%).

Multivariate analysis revealed that those less likely to support the AMA position were older

physicians (adjusted odds ratio, 0.72; 95% confidence interval [CI], 0.54 to 0.96), female physicians (adjusted odds ratio, 0.53; 95% CI, 0.36 to 0.77), and physicians living in the Northeast. Support for the AMA position was more likely among nonmedical and nonsurgical specialists (adjusted odds ratio, 1.52; 95% CI, 1.03 to 2.24) and among practice owners (adjusted odds ratio, 1.43; 95% CI, 1.01 to 2.03).

A large majority of physicians, including AMA members, supported proposals for health insurance expansion that were opposed by the AMA. Physicians whose positions were consistent with those of the AMA were more likely to be younger, male, practice owners, and in nonmedical and nonsurgical specialties such as anesthesiology, pathology, or radiology. Although the AMA is the most visible organization representing physicians, it did not represent the majority of physicians' views on coverage expansions in recent reform efforts.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## VANGL2 Mutations in Human Cranial Neural-Tube Defects

**TO THE EDITOR:** Mutations in more than 200 genes are known to cause neural-tube defects in mice; less is known about the genetic cause of neural-tube defects in humans.<sup>1</sup> Kibar and colleagues<sup>2</sup> hypothesized that human neural-tube defects are caused by mutations in *VANGL1* and

*VANGL2*, genes that affect planar cell polarity and cause neural-tube defects in mice. They identified mutations in *VANGL1* but not in *VANGL2* in humans.<sup>2</sup> We hypothesized that mutations in *VANGL2* are lethal to the fetus, and therefore we sequenced *VANGL2* in 163 stillborn or miscarried

Han Chinese fetuses with neural-tube defects (Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org) and 508 apparently unrelated healthy Han Chinese infants. We obtained written informed consent from the parents and collected and analyzed samples with the approval of the institutional review board of Fudan University.

We identified three novel missense mutations in *VANGL2*. All were heterozygous in fetuses with a cranial neural-tube defect: S84F (737C→T), R353C (1543C→T), and F437S (1796T→C). R353C was detected in a male fetus at 21 weeks' gestation. This fetus had anencephaly with occipital and cervical spina bifida. F437S was detected in a male fetus at 24 weeks' gestation with anencephaly, and S84F was detected in a female fetus at 22 weeks' gestation with holoprosencephaly. All three mutations affect conserved residues in *VANGL2* proteins across species (see the Figure in the Supplementary Appendix) and were absent in controls. The prevalence of other variants was similar among cases and controls (Table 2 in the Supplementary Appendix).

R353 and F437 are located in the cytoplasmic domain, adjacent to the carboxy-terminal PDZ-binding domain. The mutations R353C and F437S are predicted to affect protein structure, and both affect residues that are highly conserved across species (see the Figure in the Supplementary Appendix). Similarly positioned mutations (D255E and S464N) of *Vangl2* in mice have been shown to affect *Vangl2* function, and they are predicted to disrupt interactions with the cytoplasmic protein, disheveled (Dvl).<sup>3,4</sup> S84F predicts the substitution of a serine residue at position 84 (which is highly conserved across species) with a phenylalanine residue (see the Figure in the Supplementary Appendix). Its association with holoprosencephaly is uncertain.

Using a yeast two-hybrid system, we tested the ability of *VANGL2* mutants (carrying either the R353C or the F437S mutation) to bind Dvl. All constructs were stably expressed at similar levels (Fig. 1A). F437S completely abrogated interaction with Dvl, whereas R353C diminished but did not abolish this interaction (Fig. 1B, 1C, and 1D). In contrast, and serving as a positive control, was the interaction between nonmutant *VANGL2* and Dvl.

**Figure 1 (next page). Interaction between Human *VANGL2* Variants and Disheveled Proteins in a Yeast Two-Hybrid System.**

Panel A shows an immunoblot of the wild-type and mutant cytoplasmic domain of *VANGL2* (positions 239–522) expressed in yeast cells. We used a monoclonal antibody directed against a *c-myc* epitope that was engineered at the N-terminal of *VANGL2*. The mutant D255E and S464N variants are loss-of-function negative controls. We detected N-terminal segments of disheveled (Dvl) (positions 1–404 of Dvl1-5, positions 1–418 of Dvl2-5, and positions 1–395 of Dvl3-5), which consisted of the DIX and PDZ domains and a C-terminal segment corresponding to the DEP domains of Dvl3 (positions 389–717 of Dvl3-3), using a monoclonal antibody against a hemagglutinin epitope that is present in all Dvl constructs. The hemagglutinin epitope is also present in the control pGAD vector (pGAD). Panel B shows the results of a yeast two-hybrid assay. We produced diploid cells by mating yeast cells expressing Dvl segments (rows) and yeast cells expressing the *VANGL2* cytoplasmic domain. We plated the yeast cells on mediums of increasing stringency of selection to detect an interaction (growth). The –Leu/–Trp medium lacks leucine and tryptophan and supports the growth of diploid cells, regardless of whether there is protein interaction. The growth of diploid cells is supported by the –His/–Leu/–Trp medium (which lacks histidine, leucine, and tryptophan) and the –Ade/–His/–Leu/–Trp medium (which lacks adenine, histidine, leucine, and tryptophan) only if proteins interact. We verified the interaction between the various Dvl and *VANGL* chimeras by measuring  $\alpha$ -galactosidase (Panel C) and  $\beta$ -galactosidase (Panel D) activity. The I bars indicate standard deviations.

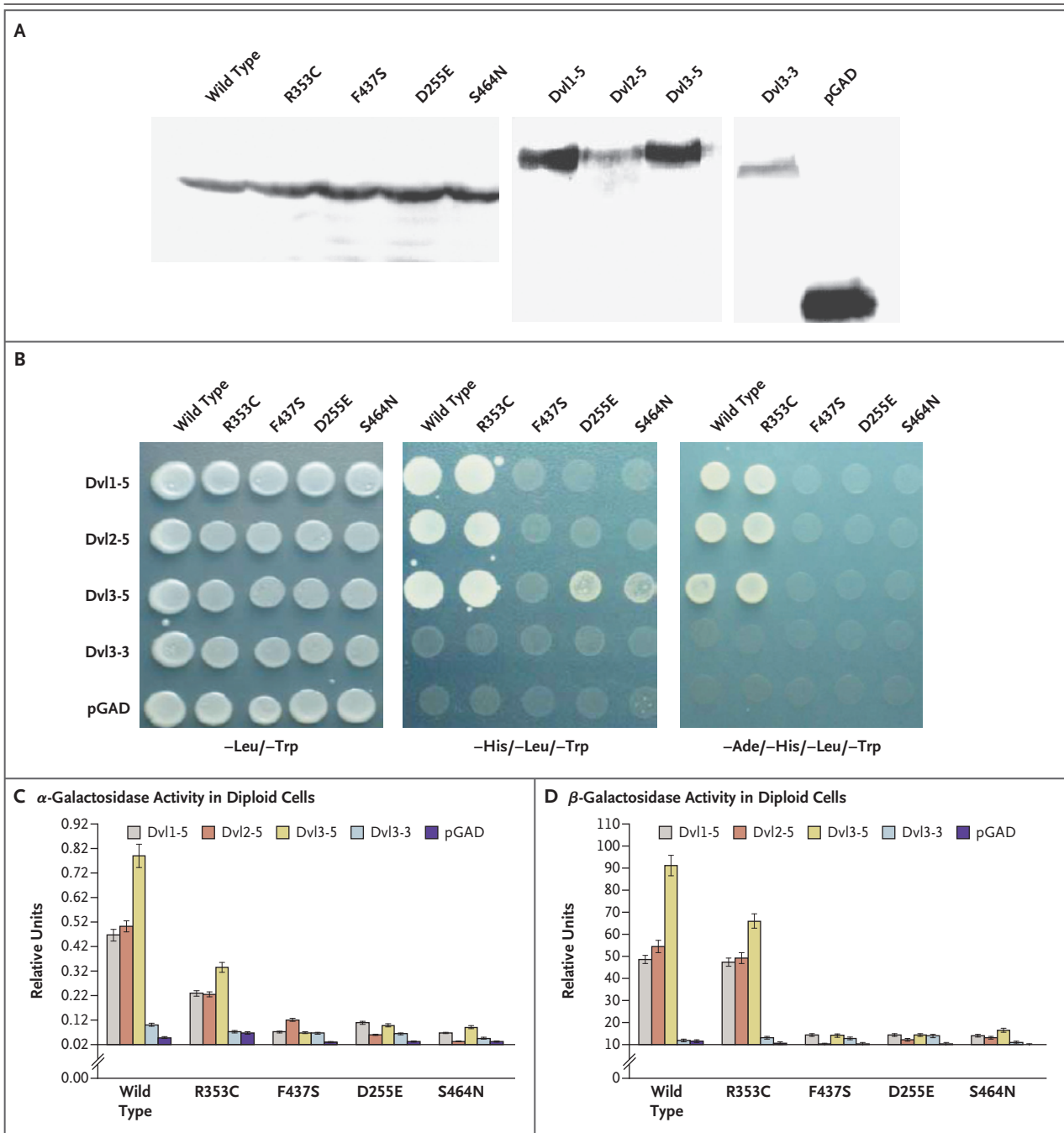
Because we identified *VANGL2* mutations in miscarried fetuses with severe cranial neural-tube defects, we surmise that their lethal effect during in utero development precludes their presence in living persons with less severe defects. Our results provide support for studies that emphasize the role of planar-cell-polarity genes in neural-tube closure, although craniorachischisis, not anencephaly, is the invariable phenotype in mice that are homozygously deficient in *Vangl2*.<sup>5</sup>

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### CORRECTIONS

Uric Acid and Cardiovascular Risk (October 23, 2008;359:1811-21). In the first paragraph of the Uric Acid, the Metabolic Syndrome, and Diabetes section (page 1816), the parenthetical information given near the end of the final sentence should have read, "(600  $\mu\text{mol}$  per liter)," rather than "(60  $\mu\text{mol}$  per liter)." We regret the error. The article has been corrected at NEJM.org.

Increasing the Value of the State Medical License (April 22, 2010;362:1459-61). In the paragraph beginning "But opportunities abound" (page 1460), the second sentence should have read, "For instance, the Joint Commission, which currently surveys and accredits nearly 90% of the country's approximate-

ly 4600 hospitals, has issued new professional credentialing requirements," rather than ". . . more than 90% of the country's approximately 13,500 hospitals. . . ." The article has been corrected at NEJM.org.

Early CPAP versus Surfactant in Extremely Preterm Infants (May 27, 2010;362:1970-9). In the Methods section, in the first paragraph of the Surfactant Group subsection (page 1972), both instances of "mean arterial pressure" in the second sentence should have read "mean airway pressure." We regret the error. The article has been corrected at NEJM.org.

### NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the *Journal*'s Web site (NEJM.org/meetings). The listings can be viewed in their entirety or searched by location, month, or key word.

#### MAYO CLINIC SCOTTSDALE

A course entitled "Cardiology Update 2010: The Heart of the Matter," will be offered in Sedona, AZ, Aug. 6-8.

Contact Staci King, Mayo Clinic Scottsdale, 13400 E. Shea Blvd., Scottsdale, AZ 85259; or call (480) 301-4580.

#### DALLAS-LEIPZIG INTERNATIONAL VALVE 2010

The conference will be held in Dallas, Dec. 9-11.

Contact Dallas-Leipzig International Valve, 7777 Forest Lane, Suite C-742, Dallas, TX 75230; or e-mail info@dallasleipzigvalve.org; or see <http://www.dallasleipzigvalve.org>.

#### INTERNATIONAL SCIENTIFIC CONFERENCE ON GASTRO-INTESTINAL MICROBIAL ECOLOGY

The conference will be held in Kosice, Slovakia, Nov. 9-11.

Contact the Organizing Secretariat, PAMIDA International Ltd., Komenského 2656, 024 01 Kysucké Nové Mesto, Slovak Republic; or call (421) 918 707371; or fax (421) 41 4000123; or e-mail info@GutMicroEcology.net; or see <http://www.gutmicroecology.net>.

#### MEDICAL MUSICAL GROUP

The VA-National Medical Musical Group is seeking members for its symphony orchestra and chorale. The group will perform a concert entitled "Healing for the Nations," to be held in Washington, DC, on Nov. 10 and in Paris on Nov. 15.

Contact VA-NMMMG, 1700 17th Street, NW, Suite 508, Washington, DC 20009; or call (202) 797-0700; or fax (202) 797-0771; or e-mail info@medicalmusical.org; or see <http://medicalmusical.com/home.htm>.

#### 24TH EUROPEAN CONFERENCE ON PHILOSOPHY OF MEDICINE AND HEALTH CARE

The conference, entitled "Human Nature, Medicine, and Health Care," will be held in Zagreb, Croatia, Aug. 18-21.

Contact Prof. Bert Gordijn, European Society for Philosophy of Medicine and Health Care, Institute of Ethics, Henry Grattan Building, Dublin City University, Glasnevin, Dublin 9, Ireland; or e-mail bert.gordijn@dcu.ie.

#### 1ST WORLD CONGRESS ON CONTROVERSIES IN GASTROENTEROLOGY & LIVER DISEASES (C-GOLD)

The congress will be held in Prague, Czech Republic, Sept. 23-26.

Contact Comtecmed, 53 Rothschild Blvd., P.O. Box 68, Tel Aviv 61000, Israel; or call (972) 3 566 6166; or e-mail cgold@comtecmed.com; or see <http://www.comtecmed.com/cgold>.