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Large Islets, Beta-Cell Proliferation, and a Glucokinase Mutation

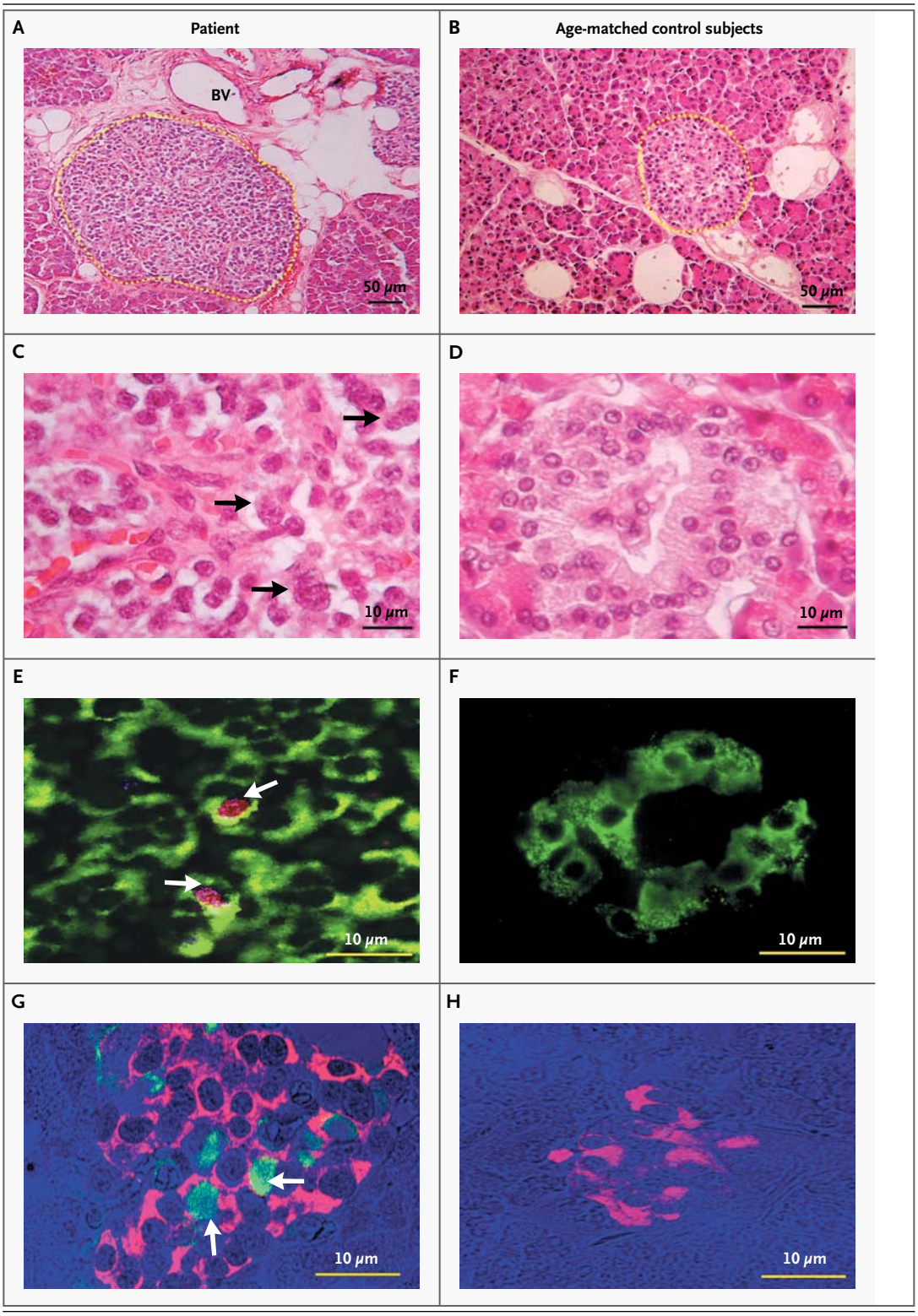
TO THE EDITOR: Rare, naturally occurring gene mutations provide important insights into normal human physiology. We report on a young girl with severe neonatal hypoglycemia due to a novel glucokinase mutation (V91L). Her father had a similar clinical course, but neither his DNA nor his pancreatic tissue was available for study.

V91L showed a markedly increased affinity for glucose that was more than 8.5 times as high, an enzyme efficiency that was 7 times as high, and a relative-activity index that was 30 times as high as that of the wild-type enzyme. The estimated threshold for glucose-stimulated insulin secretion was markedly lower than that of the wild-type enzyme (0.96 vs. 5.00 mmol per liter). Diazoxide and octreotide therapy did not control the patient's hypoglycemia, and a subtotal pancreatectomy was performed when she was 3 years of age.

Quantitative histologic examination revealed abnormally large islets (Fig. 1A) with some beta cells containing a large nucleus (Fig. 1C). The mean islet area was 7705 μm^2 in the head of the pancreas and 7048 μm^2 in the tail of the pancreas. Both areas were significantly larger than those in specimens obtained from five age-matched control subjects who did not have pancreatic disease (range, 1160 to 1997 μm^2; $P<0.001$) and in three specimens obtained from two age-matched subjects with diffuse hypoglycemia due to *ABCC8* gene mutations (ATP-sensitive potassium-channel [K_{ATP}]–related hypoglycemia) (range, 769 to 859 μm^2; $P<0.001$). All these subjects were in subgroups of a population from a previously published study.[1] Approximately 10% of the patient's islets were larger than 13,000 μm^2; this was generally larger than any islet in the pancreases of control subjects or subjects with K_{ATP}-related hypoglycemia. The relative beta-cell area (the percentage of the histologic section that stained positive for insulin) was 2.9% in the head of the pancreas and 6.7% in the tail of the pancreas in the patient, as compared with 1.8% in the pancreases of the control subjects and 1.1% in the pancreases of the subjects with K_{ATP}-related hypoglycemia. In the patient's pancreas, nine proliferating (Ki67-positive) beta cells were detected in 100 islets (Fig. 1E) and apoptotic (terminal deoxynucleotidyl transferase dUTP biotin nick end labeling [TUNEL]-positive) beta cells were observed clustering within some islets (Fig. 1G). Neither Ki67-positive nor TUNEL-positive cells were seen in

Figure 1 (facing page). Histologic Features of the Pancreas in the Patient and in Age-Matched Control Subjects with Normal Pancreases.

Panel A (hematoxylin and eosin) shows a large islet (dotted line) near blood vessels (BV) in a biopsy specimen obtained from the patient, and Panel B (hematoxylin and eosin) shows a normal-size islet (dotted line) in a specimen obtained from a control subject; both Panel A and Panel B are specimens shown at low magnification. Panel C shows abnormally large beta-cell nuclei (arrows) in the patient's specimen at higher magnification than in Panel A, and Panel D shows beta-cell nuclei in a control subject's specimen at the same magnification. Panel E (Cy5) shows Ki67-positive beta cells (reddish-purple nuclei, arrows) in a large islet in a specimen obtained from the patient; Panel F shows beta cells in a specimen obtained from a control subject. In Panels E and F, Cy2-labeled insulin shows green cytoplasmic staining. Panel G shows terminal deoxynucleotidyl transferase dUTP biotin nick end labeling–positive cells (green nuclei, arrows) in the patient's specimen; these cells were not detected in any of the specimens obtained from control subjects (a specimen from one control subject is shown in Panel H). In Panels G and H, Cy5-labeled insulin shows red cytoplasmic staining.



any of the pancreases of the control subjects (Fig. 1F and 1H), suggesting that increased intracellular glucose flux stimulates both proliferation and apoptosis pathways.

Normal histologic findings in four previous cases of glucokinase-related hypoglycemia have been reported, but none of these patients underwent detailed quantitative morphometric analysis.[2-4] In a previously reported case that included quantitative histologic analysis, a similar increase in the mean islet profile was confirmed (it was 2.5 times larger than that of control subjects and 8.0 to 10.0 times larger than that of patients with a K_{ATP}-channel deficiency).[5] In both that patient and our patient, the routine pathology report did not indicate any abnormality in islet size; this emphasizes the importance of quantitative morphometric analysis to determine islet size.

Thus, histologic findings in infants with hyperinsulinemic hypoglycemia may differ according to the genetic cause of the condition. Furthermore, intracellular glucose flux appears to regulate proliferation and apoptosis in human beta cells; this is consistent with previous findings in murine models. Small-molecule activators of glucokinase are currently being developed for the clinical management of diabetes. Although observations in this young child with a congenital glucokinase mutation may not be directly applicable to adults with diabetes, the effect of these glucokinase activators on human beta-cell mass may be of interest.

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CORRECTIONS

Sudden Death in Myotonic Dystrophy (October 9, 2008;359:1626-9). In Panel B of Figure 1 (page 1627), under the Controls heading, the value for N should have been 14 rather than 7. We regret the error. The article has been corrected at NEJM.org.

Case 13-2009: A 54-Year-Old Woman with Respiratory Failure and a Cavitary Lesion in the Lung (April 23, 2009;360:1770-9). In the fourth sentence of the Summary subsection under Differential Diagnosis (pages 1776-7), the phrase "receive pneumococcal and influenza vaccines annually" should have read "receive pneumococcal vaccines every 5 years and influenza vaccines annually." The article has been corrected at NEJM.org.