Supplementary text

Description of NRG4 distribution in normal tissues

**Skin.** The epidermis showed moderate positivity with anti-128 (NRG4A1) and anti-135 (NRG4A2) and dermal fibroblasts showed weak positivity with these antibodies. The epidermal positivity was basal with anti-128, and diffuse with anti-135 with a greater intensity of staining in the upper half, in contrast dermal fibroblast positivity was limited to the upper third with anti-128 and was diffuse with anti-135 (Figure 2 A & B).

**Gastrointestinal system.** In salivary gland, ductal epithelium showed weak staining with anti-127, anti-134 and anti-135 and moderate positivity with anti-123 and anti-128 which suggests that it is NRG4A1 that shows moderate positivity in this tissue. With anti-135 acini also stained weakly. Stratified oesophageal squamous epithelium was negative with all antibodies. There was reactivity for all antibodies in the stomach. Weak staining was seen in the specialised cells in the lower two thirds of the mucosa with anti-127, anti-134 and anti-135. With anti-123 staining was moderate in the lower two thirds and weak in the upper third. With anti-128 there was strong staining in the upper third and weak staining in the lower two thirds (Supplementary Figure 1). In the small intestine the villous epithelium showed mainly weak staining with anti-127, anti-128, anti-134 and moderate staining with anti-123. In the colon, there was patchy weak staining in the surface epithelium with anti-123. In the liver a few hepatocytes showed weak staining with anti-134 only. Staining in the gallbladder epithelium was moderate with anti-123, and weak with anti-128 and anti-135. There was also weak positivity in smooth muscle in the gallbladder wall with anti-123, anti-128 and anti-134. In the pancreas moderate positivity was seen in acinar cells with all antibodies except anti-134. With anti-134 there was strong staining in an islet of Langherhan’s.

**Cardiovascular system.** Positivity in the heart was limited to weak staining in myocytes with anti-123. In the aorta weak staining was present in smooth muscle cells with anti-134. Cross striations in skeletal muscle were weakly positive with all antibodies.

**Lymphoreticular system.** There was mainly weak staining in macrophages in lymph nodes with anti-123, anti-128, anti-135 but with anti-134 the staining was moderate. Moderate staining was present in plasma cells with anti-128. Small lymphoid cells were highlighted by anti-123 and anti-128 in the tonsil. In the thymus, adipocytes showed weak positivity with anti-123, anti-128, anti-134 and moderate positivity with anti-127. In the spleen moderate positivity was present in lymphoid cells in the paracortex and in sinuses with anti-123.

**Respiratory Tract.** There was weak to strong positivity in alveolar macrophages with all antibodies. Weak staining was seen in bronchiolar epithelium with anti-123, with terminal bar acumination. Pneumocytes showed patchy weak staining with anti-127 and anti-128.

**Nervous system.** There was no staining in any cells in the cerebral cortex or in the cerebellum with any antibodies.

**Endocrine system.** Patchy weak positivity was present in follicular cells in the thyroid with anti-123 and anti-128. In the adrenal gland there was no staining with the antibodies.
**Urogenital system.** In the kidney, anti-123 highlighted proximal tubules weakly, and the antibodies to anti-127 and anti-128 stained the distal tubules weakly (Supplementary Figure 1). In the prostate there was weak positivity with anti-123, anti-128 and anti-134. The endometrium showed no staining. In the placenta trophoblastic cells stained weakly with anti-127, anti-128, anti-134 and moderately strongly with anti-123. Fibroblasts also stained weakly with anti-134. In the breast there was weak positivity in lobular epithelial cells with anti-123. Fibroblasts also stained weakly with anti-134. The umbilical cord showed no staining with the antibodies except for weak to moderate positivity in fibroblasts with anti-134.

**Distribution of the NRG4B3 isoform.** The anti-134 specific antibody stained endothelial cells in all organs except in brain and adipose tissue. Weak positivity in endothelial cells was present in skin, pancreas, prostate, endometrium, thyroid and adrenal gland. Moderate positivity was present in endothelial cells in thymus, tonsil, salivary gland, oesophagus, stomach, small intestine, colon, liver, gallbladder, skeletal muscle, heart, aorta, placenta and umbilical cord. Strong positivity was seen in endothelial cells in lymph node, lung, kidney, breast and spleen (Supplementary Figure 1). In adipose tissue the absence of staining may be due to sampling error as only a couple of small blood vessels were present in the sections examined. In the brain several small blood vessels were included in the sections. Small nerve fibres showed weak staining with anti-134 in skin, adipose tissue and in the adventitious of the aorta. The subcellular distribution of staining also varied. Most normal tissues displayed weak to moderate cytoplasmic staining. In salivary gland, glandular cells displayed nuclear staining and ducts cytoplasmic immunoreactivity. Spermatocytes in testis showed moderate nuclear staining.