by the characterization of phospholipase A$_2$ receptor 1 and thrombospondin type-1 domain-containing 7A (THSD7A) as podocyte antigens in membranous nephropathy, constitutes the most probable established mechanism for the formation of subepithelial deposits of immune complexes.\textsuperscript{3,4} It is unclear whether the initial recognition of antigens that leads to the formation of high-affinity antibodies occurs within the kidney or in other tissues, including malignant tumors. Antibodies that are produced in response to non-renal targets may recognize the same or related molecules expressed on podocytes through a mechanism known as molecular mimicry.

Here we describe a 40-year-old woman who presented with THSD7A-associated membranous nephropathy (Fig. 1A and 1B, and Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The condition was concomitant with the presence of mixed adenoneuroendocrine carcinoma of the gallbladder (Fig. S3A in the Supplementary Appendix). This study was approved by the local ethics committee of the chamber of physicians of Hamburg. The patient provided written informed consent.

The primary gallbladder tumor and corresponding lymph-node metastases were positive for THSD7A on immunohistochemical analysis (Fig. 1C and 1D). Fluorescence in situ hybridization assay revealed polysomy of chromosome 7, with six copies of THSD7A and the CEP7 chromosome 7 centromere (Fig. S3B in the Supplementary Appendix). The messenger RNA for THSD7A was detectable in the gallbladder carcinoma but not in the normal tissue of the gallbladder. Follicular dendritic cells of lymph nodes with metastatic infiltration were also positive for THSD7A (Fig. 1E, and Fig. S4 and S5 in the Supplementary Appendix). Follicular dendritic cells are unique stromal cells that present stored antigen to maturing B cells for the formation of high-affinity antibodies.\textsuperscript{5}

After chemotherapy, THSD7A antibodies in plasma were no longer detectable, and urinary protein excretion decreased from 5.0 to 0.7 g of protein per gram of creatinine (protein-to-creatinine ratio) (Fig. 1A). Serum samples from 1009 additional patients with membranous nephropathy were screened, and 25 patients were found to be positive for THSD7A antibodies. Of these 25 patients, 7 (including the index patient) had a malignant tumor. These findings support a causal relationship between the new expression of THSD7A in a gallbladder carcinoma and the development of membranous nephropathy and may thus describe a potential mechanism for the association between cancer and membranous nephropathy.

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Visual Acuity after Retinal Gene Therapy for Choroideremia

**TO THE EDITOR:** Two recent clinical reports of retinal gene therapy with adeno-associated virus (AAV) vectors in patients with Leber’s congenital amaurosis showed initial gains in visual function that subsequently declined.\textsuperscript{1,2} We previously reported early improvement in visual acuity in two of six patients who received retinal gene therapy in one eye (the study eye) to treat choroideremia,\textsuperscript{3} a disease that is characterized by atrophy of the choriocapillaris and retinal pigment epithelium and involves vision loss that leads to blindness.

Choroideremia is caused by loss-of-function
mutations in the gene CHM. We delivered non-mutated CHM in an AAV vector (AAV.REP1) by subfoveal injection into the vicinity of the retinal pigment epithelium and photoreceptor cells, the dysfunction of which is presumed to be a contributing factor in vision loss. Here we report that the early improvement that we observed in two of the six patients was sustained at 3.5 years after treatment, despite progressive degeneration in the other eyes (the control eyes). The control eyes did not receive the intervention, and visual acuity in the control eyes was better than the visual acuity in the study eyes at baseline.

The best corrected visual acuity was reported as the number of letters correctly read by the patient on an Early Treatment of Diabetic Retinopathy Study chart at 4 m. Two patients (Patients 1 and 4) had advanced disease, and the visual acuity in the study eyes at baseline in these patients was several lines below normal (each line contains 5 letters) on the ETDRS chart (Table 1). By 3.5 years, visual acuity in the treated study eye had increased by 21 letters (>4 lines) from baseline on the ETDRS chart in Patient 1 and by 18 letters (>3 lines) in Patient 4. In contrast, over the same period, visual acuity in the control eyes decreased by 18 letters in Patient 1 and by 6 letters in Patient 4.

A cataract developed in the study eye in Patient 4 at 2 years. This cataract was subsequently removed, but the removal was not the primary reason for the gain in visual acuity recorded at 3.5 years. The visual acuity at 3.5 years was similar to the level recorded 12 months after surgery, before the cataract was clinically significant.

The other four patients had good visual acuity at baseline and therefore a limited scope for improvement. Patient 3, the youngest patient, had the largest area of surviving retina and the best pretreatment visual acuity — 20/16 (89 ETDRS letters). This visual acuity returned to the baseline level 12 months after the administration of gene therapy and was sustained until the last follow-up. No loss of visual acuity was observed in the untreated control eye during this time, probably because the disease was still in the early stages. However, the treated eye of Patient 3 did show improvement on an electrophysiological study. This test measures a global macular response and may therefore be more relevant in younger patients with larger areas of surviving retina (Fig. S3 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

The levels of visual acuity in the study eyes in Patients 2, 5, and 6 all returned to baseline levels by 6 months after treatment, but by the 3.5-year follow-up, the visual acuity of the study and control eyes in Patient 6 had declined by 29 and 18 letters, respectively. Patient 6 received a lower total vector dose than the other patients in the trial; we speculate that the loss of visual acuity in this patient was caused by progressive degener-

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<th>Patient No.</th>
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<th>Visual Acuity, 2 Yr</th>
<th>Visual Acuity, 3.5 Yr</th>
<th>Change in Letter Score, Baseline to 3.5 Yr</th>
<th>Change in Letter Score, Study Eye vs. Control Eye, 3.5 Yr</th>
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* The best corrected visual acuity was reported as the number of letters correctly read by the patient on an Early Treatment of Diabetic Retinopathy Study chart at 4 m. Patients 2, 4, 5, and 6 underwent cataract surgery after the 2-year follow-up visit. Cataracts developed in all patients, and they reported subjective vision change. Ocular hypertension in both eyes also developed in Patient 3. Additional details are provided in Table S1 in the Supplementary Appendix.

† The injection volume of AAV.REP1 was 0.1 ml in Patients 1 through 5 and 0.06 ml in Patient 6. The abbreviation vg denotes vector genomes.
eration of cells in the fovea rather than a toxic effect of the vector. In contrast, at the 3.5-year follow-up, the visual acuity in the injected eyes in Patients 2 and 5 remained close to that at baseline, whereas the visual acuity of the control eye was lower by 10 and 11 letters, respectively.

Best corrected visual acuity is a reliable marker of visual function. In contrast to Leber’s congenital amaurosis, in which visual acuity is generally profoundly affected early in life, choroideremia and most types of retinitis pigmentosa are characterized by progressive loss of the visual field, with visual acuity remaining close to normal levels until the very late stages of disease. Therefore, in some patients, the effect of preserving visual acuity with the use of retinal gene therapy may take several years to become apparent.

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