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IS *PARKIN* PARKINSONISM A CANCER PREDISPOSITION SYNDROME?

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Mutations in the *PARKIN* gene (chromosome 6q25-27) were first described in 1998 in families with "juvenile" autosomal recessive parkinsonism. More than 180 causative variants in the *PARKIN* gene have been identified; point mutations and copy number variants (i.e., exon deletions or duplications) occur at nearly equal frequencies.[1] *PARKIN* is one of the largest genes in the human genome (1.3 Mb) and contains a chromosomal fragile site (CFS) FRA6E (6q26) between exons 2 and 8. This is of interest regarding the etiology of cancer because CFSs are prone to spontaneous breaks leading to chromosome alterations. Therefore, it is not surprising that *PARKIN* mutations have also been found in various cancer cell lines and primary tumors.[2,3] Mutations in *PARKIN* show decreased PARKIN E3 ligase function with resultant accumulation of cyclin E, creating the potential for mitotic instability in dividing cells.

Because the same *PARKIN* gene mutations that lead to early-onset parkinsonism are also found in numerous cancer types, particularly glioblastoma multiforme (GBM),[3] it is surprising that *PARKIN* mutations rarely result in both parkinsonism and GBM. This report describes such a patient with compound heterozygous mutations in *PARKIN*, early-onset parkinsonism, and GBM.

Methods. The patient was the oldest sibling of 5 brothers from family Ph and was a carrier of 2 causative mutations in the *PARKIN* gene: NM_004562.2 (*PARKIN*) [c.337_376del40]; [118 kb, exon 6 duplication]. Two of his younger brothers were also compound heterozygous, and his parents and paternal grandmother were carriers of 1 mutated allele.[4]

At 44 years of age, the patient began experiencing parkinsonian symptoms, which started with a rest tremor in the right leg and leg dystonia. He had a good response to dopamine agonists. At age 46, CT and MRI head scans revealed 2 masses in the left temporal lobe. He underwent subtotal resection of the temporal lobe masses followed by radiation and chemotherapy. Tumor histology was GBM. Six months after surgery, there was recurrence of the tumor, and the patient died 14 months after surgery. At autopsy, there was a 1.5-inch-diameter tumor located within the left temporal lobe. Histologically, the tumor was a typical infiltrating glioblastoma with pleomorphic dedifferentiated astrocytes and areas of necrosis with "pseudopalisading" cells. It infiltrated and obscured the nucleus basalis of Meynert. Additional pathology of note included severe nerve cell loss and gliosis in the substantia nigra but no Lewy bodies or Alzheimer pathology. The locus coeruleus had no definite nerve cell loss, but slight nerve cell loss and gliosis was seen in the dorsal motor nucleus of the vagus nerve.

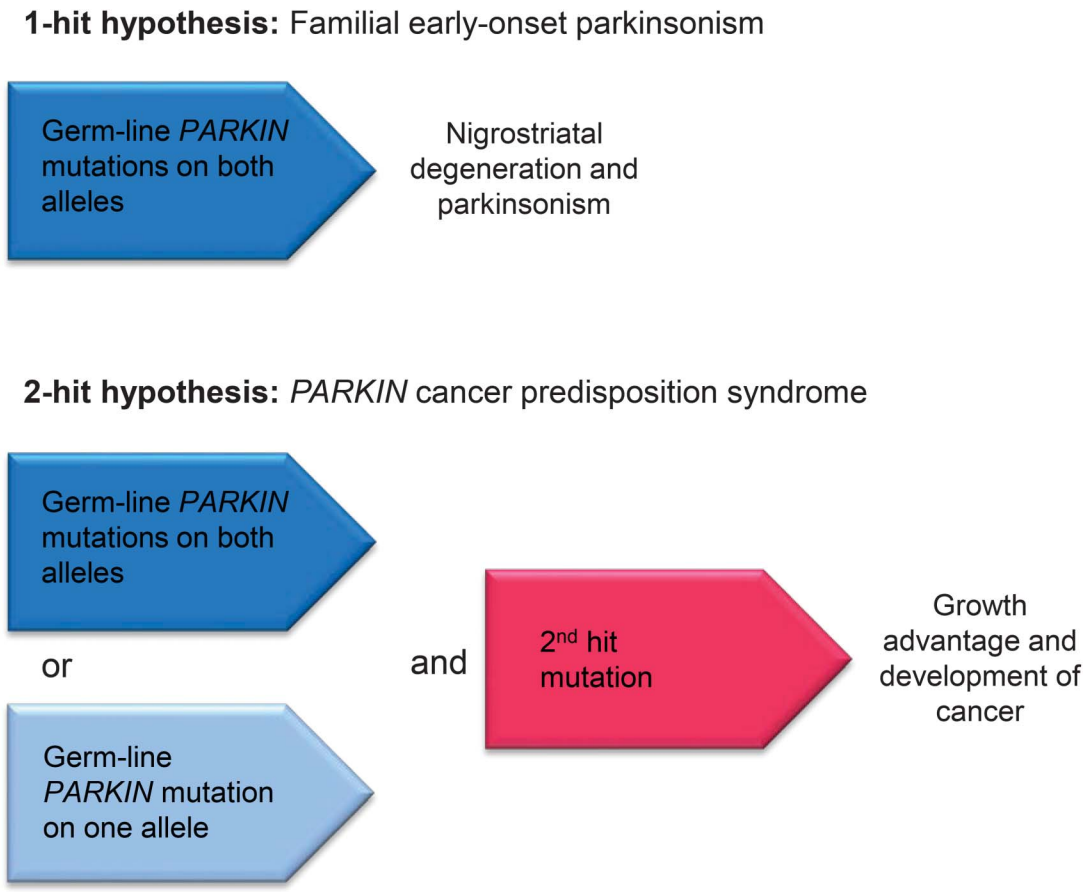
Discussion. Germ-line mutations in the *PARKIN* gene and GBM in the same patient is extremely rare. GBM has an incidence of 2–3 per 100,000 adults per year and is a primary intracranial tumor of astrocytic origin. The prognosis of GBM is typically very poor, with a median survival of 11–15 months.[5]

Given the rarity of *PARKIN* mutations and GBM, their concomitant occurrence in a single individual may well be more than a coincidence. In general, the etiopathogenesis of most cancer is based on the 2-hit or multiple-hit hypothesis. In the case of patients with parkinsonism with *PARKIN* mutations, they already carry the first hit in every cell (figure). A second hit due to environmental influences (e.g., radiation, toxicants) can then lead to cancer such as ovarian cancer, hepatocellular carcinoma, breast cancer, colon cancer, and GBM.[2,3] This concept is well described for cancer predisposition syndromes, i.e., breast cancer (*BRCA1* and *BRCA2* genes) and familial adenomatous polyposis (*APC* gene), in which an inherited genetic variant that is present in every cell of the human body combined with an acquired sporadic mutation induces tumor formation.

Future clinical genetic studies are needed to determine whether there is indeed an increased risk for development of malignancies in *PARKIN* carriers. Although there are epidemiologic studies that suggest a lower risk for cancer in patients with neurodegenerative diseases,[6] an increased cancer risk has been reported for *LRRK2* parkinsonism,[7] and several cohort studies are being conducted to further understand the causal relationship between cell death in Parkinson disease and uncontrolled cell growth in cancer. This could be a result of impairment in cell cycle regulation, resulting in both neurodegeneration and malignant proliferation.

If additional clinical and experimental evidence proves cause–effect relations for an association between *PARKIN* mutations and cancer, it could open up a new area of

Figure Hypothesis of nigrostriatal degeneration and development of cancer due to germ-line *PARKIN* mutations



Loss of PARKIN protein in familial Parkinson disease leads to accumulation of one of its substrates, cyclin E, which has been shown to cause neurodegeneration. We propose that our presented case of glioblastoma multiforme and familial parkinsonism could have developed by acquired somatic mutations in addition to the first hit of *PARKIN* mutations.

cancer research. Furthermore, if larger clinical studies in *PARKIN* mutation carriers confirm an increased cancer risk, families with *PARKIN* parkinsonism will be a critical group to target for cancer screening.

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