IS PARKIN PARKINOSM A CANCER PREDISPOSITION SYNDROME?

OPEN

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),4 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 “psuedopalisading” 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.2-5 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
1-hit hypothesis: Familial early-onset parkinsonism

Germ-line PARKIN mutations on both alleles → Nigrostriatal degeneration and parkinsonism

2-hit hypothesis: PARKIN cancer predisposition syndrome

Germ-line PARKIN mutations on both alleles or
Germ-line PARKIN mutation on one allele → 2nd hit mutation
→ Growth advantage and development of cancer

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.

Dr. Langston receives research funds from GE Healthcare, Biogen, and Department of Defense (grant #W81XWH-11-1-0310). He serves on the Michael J. Fox Scientific Advisory committee. He is the coeditor of the Journal of Parkinson’s Disease. Dr. Langston spends 35% of his time in his clinical practice. Go to Neurology.org for full disclosure forms. The Article Processing Charge was paid by The Parkinson’s Institute.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Received August 13, 2015. Accepted in final form September 14, 2015.

Correspondence to Dr. Schüle: bschuele@thepi.org


Is PARKIN parkinsonism a cancer predisposition syndrome?
Birgitt Schüle, Christie Byrne, Linda Rees, et al.
Neurol Genet 2015;1;
DOI 10.1212/NXG.0000000000000031

This information is current as of October 15, 2015

Updated Information & Services
including high resolution figures, can be found at:
http://ng.neurology.org/content/1/4/e31.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://ng.neurology.org/content/1/4/e31.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Clinical Neurology
http://ng.neurology.org/cgi/collection/all_clinical_neurology
All Genetics
http://ng.neurology.org/cgi/collection/all_genetics
Parkinson's disease/Parkinsonism
http://ng.neurology.org/cgi/collection/parkinsons_disease_parkinsonism

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://ng.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://ng.neurology.org/misc/addir.xhtml#reprintsus

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2015 American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.