How to Predict the Risk of Parkinson Disease in Relatives of Parkin Mutation Carriers

A Complex Puzzle of Age, Penetrance, and Number of Mutated Alleles

Doubt is not a pleasant condition, but certainty is absurd.
Voltaire (1694-1778)

Mutations in the recessively inherited Parkin gene (OMIM 600116) are the most common known cause of early-onset Parkinson disease (PD) and account for as many as 77% of the patients with a juvenile or very young age of onset (<30 years) and about 10% of a population-based sample with early-onset PD beginning at younger than 50 years. Although homozygous or compound-heterozygous Parkin mutations (ie, 2 mutated Parkin alleles) have only rarely been found in late-onset disease, the presence of a single heterozygous mutation has been suggested as a susceptibility factor for the development of later-onset PD based on family, case-control, and neuroimaging studies. A similar role has been discussed in the other recessive PD genes (ie, PINK1 [OMIM 605909], DJ-1 [OMIM 606324], and, recently, ATP13A2 [OMIM 606693]). Although 2 mutated alleles are a relatively rare finding even in the case of the Parkin gene, single heterozygous mutations are much less uncommon and are estimated to occur at a frequency of about 0.6% to 3.0% in the healthy population. If, indeed, single Parkin mutations represented a risk factor for PD, a higher prevalence of PD among carriers of heterozygous mutations would be expected than in individuals without such alterations. To our knowledge, only 4 studies systematically examine the role of different numbers of mutated Parkin alleles using a case-control design. Two of these studies6,7 reported equal numbers of mutations among patients and control subjects, whereas the other 2 investigations8,9 found an excess of mutations among patients.

Knowledge about the prevalence of Parkin mutations in patients vs controls may shed light on the potential pathogenesis of a subset of PD. In the clinical setting, however, the neurologist is faced with a related but slightly different and much more practical question (“doubt is not a pleasant condition”). A patient with an identified Parkin mutation wants to know about the risk of his or her relatives also developing PD. To this end, 2 pieces of information are required: (1) Who else in the family is a mutation carrier? (2) Who of the carriers will actually develop disease? The first question can be answered relatively easily by molecular genetic testing for a known mutation. Conversely, the second question regarding penetrance of a given Parkin mutation remains largely unresolved. Although 2 mutated Parkin alleles seem to be associated with full, albeit age-dependent, penetrance, the penetrance of heterozygous mutations (if considered a risk factor at all) is probably small.

In this issue of the Archives, Wang and colleagues9 use an innovative study design to assess the risk of PD in carriers of Parkin mutations by employing the kin-cohort method. The kin-cohort method estimates penetrance independent of the relatives’ mutational status, assuming a known mode of inheritance, and is, thus, able to take into account information on many family members without the need for expensive mutational analyses. Wang et al identified Parkin mutations in 10.1% of their probands (25 of 247 probands), most of whom were heterozygotes (18 [72%] of 25). In this carefully performed study, the cumulative incidence of PD to age 65 years was estimated to be 7.0% in relatives of carriers, compared with 1.7% in family members of noncarriers and 1.1% in relatives of controls. As the authors state, there are 2 important caveats that need to be considered when interpreting the results of their study: (1) because of the limited number of estimated Parkin mutation carriers among relatives, the confidence interval for this group of family members is wide (0.4%-71.9%) and (2) half of the relatives were younger than 50 years and may still manifest signs of PD later in life. Although the study design did not allow differentiating between carriers of 1 or 2 mutations, the study mainly addressed cumulative incidence of PD (ie, age-specific penetrance) in carriers of a single mutated Parkin allele. Since most of the initially identified mutation carriers were heterozygotes to begin with, as will be their relatives, most relatives of the 7 homozygous or compound-heterozygous mutation carriers will also be carriers of a single mutation. Thus, the investigation by Wang et al is predominantly studying risk of PD in heterozygous Parkin mutation carriers, raising the important question of the actual mode of inheritance in this carrier group. Because the kin-cohort method requires exact information on mode of inheritance,10 inheritance and penetrance patterns of 2 vs 1 mutated Parkin alleles are a crucial issue for the present and future studies. Assuming that a single mutated Parkin allele may confer risk to develop PD, this would be in keeping with a dominant pattern of inheritance with markedly reduced penetrance, rather than with classic recessive transmission. As suggested by Wang and colleagues, larger multicenter samples with personal clinical examination and molecular analysis of the relatives of carrier probands are warranted to refine estimates of penetrance.
Voltaire clearly reminds us that extreme positions are often untenable, and this takes us back to the clinical problem of counseling patients and family members. Given the variable penetrance of Parkin mutation(s) and, if manifest, different expressivity of the disease even in carriers of an identical mutation belonging to the same family, no predictions on course and severity of the disease should be made in an individual patient or family. However, large-scale innovative studies, such as the one by Wang and coworkers,9 will help to make further progress in bridging the gap between “doubt” and “certainty,” with important implications on our understanding of the role of Parkin mutations and PD pathogenesis in general and on counseling of our patients in particular.

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References


Announcement

Calendar of Events: A New Web Feature

On the new Calendar of Events site, available at http://pubs.ama-assn.org/cgi/calendarcontent and linked off the home page of the Archives of Neurology, individuals can now submit meetings to be listed. Just go to http://pubs.ama-assn.org/cgi/cal-submit/ (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.