Early-onset parkinsonism associated with *PINK1* mutations: Frequency, genotypes, and phenotypes

To the Editor: We read with great interest the recent report by Bonifati et al. demonstrating that the transcript of an allele bearing the c.1366C>T (Gln456Stop) mutation in the *PINK1* gene associated with early-onset Parkinson disease (PD) is not detectable by PCR in two unrelated families.¹

The authors explained this finding by either lack of expression of the mutant allele or by instability due to the mutation or another change in linkage disequilibrium with the c.1366T alteration. They conclude that this variant is an example of a mutant allele that exerts its major pathogenic effect in PD at the mRNA rather than at the protein level.¹

We identified a large German PD family with four affected siblings who were all homozygous for the c.1366C>T mutation. We also studied 11 of their asymptomatic heterozygous children and 5 mutation-negative family members. To address the question of an effect of this mutation on the mRNA level, we collected fresh blood from all 20 family members and extracted RNA that was reverse transcribed.

We first carried out an RT-PCR spanning exons 4–7 including the mutation (Primers Ex4F: CCAAGAGAGGTCCCAAGC; Ex7R: CCTCACCAACTGTCTCACG). We observed no difference in product intensity even in the homozygous mutation carriers, suggesting that the mutated allele is expressed at a similar level and has a similar stability as the wild type allele (figure, A).

To separately investigate the mRNA level of the wild type and mutated allele, we designed mutation-specific primers and performed another RT-PCR (Ex7FWT: TCAATCCCTTCTACGGCC, Ex7FMUT: TCAATCCCTTCTACGGCT, Ex8R: CTCCTCAGTC-CAGCCTCAT). We demonstrated the specificity of the primers and the expression of both alleles in all heterozygous carriers (figure, B).

We showed that the pathogenic effect of the recurrent c.1366C>T mutation in our family is not related to lack of expression or instability. Our results rather support the hypothesis that the lack of mutated transcripts in the families described by Bonifati et al. may be caused by another change in linkage disequilibrium with the mutation.

Interestingly, the c.1366C>T mutation likely has arisen twice independently in our family or bases on an ancient founder since the haplotypes are partly different (figure, C). It remains unclear which haplotypes the reported unrelated Italian families carry.¹ Our heterozygous mutation carriers were asymptomatic, whereas Bonifati et al.'s patients had full-blown PD. It remains to be determined whether RNA expression levels of the mutated allele may be correlated with disease status.

Christine Klein, MD, Anne Grünewald, Katja Hedrich, Lübeck, Germany

Reply from the Authors: We thank Klein et al. for their interest in our article.¹ Their identification of a fourth family with autosomal recessive early-onset PD (AREP) associated with the *PINK1* c.1366C>T (Gln456Stop) mutation confirms our findings of a recurrent pathogenic mutation. We cannot exclude that the c.1366C>T mutation (in heterozygous or homozygous state) has different biological effects in different patients, because of a variation in cis or many other factors. However, we believe that the conclusions by Klein et al. concerning the biologic effect of this mutation are not supported by their findings.

First, they present data about amplification of wild type and mutant *PINK1* transcripts from cDNA material obtained from heterozygous and homozygous carriers of this mutation. However, none of the experiments shown by Klein et al. are quantitative, and therefore, their results do not allow any conclusion to be made about levels or stability of mRNA. These conclusions can only be drawn from quantitative PCR analysis.

Second, regarding the haplotype analysis, Klein et al. should explore whether their patients are compound heterozygous for c.1366C>T and a *PINK1* genomic deletion.

Since the time of the publication of our article,¹ we repeated the experiments shown there using new cDNA material prepared from blood, and novel sets of primers. The results (not

Figure. mRNA level and haplotypes in a large German family with the c.1366C>T mutation in *PINK1*. **A)** An RT-PCR product of *PINK1* is shown for three homozygous mutation carriers (MUT/MUT) and for four mutation-negative family members (WT/WT). The intensity of the product is comparable, suggesting similar mRNA levels. **B)** With mutation specific primers we selectively amplified either the wild type allele (top panel) or the mutated allele (bottom panel) of *PINK1* (643 bp product). As expected, the wild type primer did not lead to a PCR product in the homozygous mutation carriers, whereas the mutation-specific primer fails to amplify the wild type allele in the mutation-negative family members as shown for three examples each. In the heterozygous mutation carriers both alleles are expressed, which is demonstrated here for 3 of the 11 carriers. The co-amplification of beta-globin as a housekeeping gene (313 bp product) demonstrates RNA loading in all samples. **C)** The *PINK1* haplotype at six microsatellite markers surrounding the mutation is shown for the four affected homozygous siblings (black symbols). A crossing over event occurred in the male patient. In the other three siblings only the markers flanking the mutation were homozygous, indicating either an ancient founder or independently arisen mutations.

shown) replicate those of figure 2 of our article,¹ again suggesting a major pathogenic effect of the c.1366C>T mutation at the mRNA level, most likely an example of nonsense-mediated mRNA decay.² Similar to the results of Klein et al., our agarose-gel analysis (not shown) using non-quantitative allele-specific PCR yielded evidence of robust amplification of both wild type and c.1366C>T PINK1 transcripts, a finding compatible with the presence of even minimal residual amounts of mutant c.1366C>T transcript.

We then performed different quantitative real-time PCR assays for the total PINK1 transcript (protocols and results available on request); the results show consistently a ~50% decrease in levels of PINK1 mRNA in heterozygous carriers of c.1366C>T compared with non-carriers. Unfortunately, mRNA was not available from our homozygous mutation carrier.

In our view, the data presented by Klein et al. confirm that the PINK1 c.1366C>T mutation is associated with AREP. Further quantitative PCR assays are necessary to assess the bio-

logical effects of this mutation on the levels and stability of mRNA.

Vincenzo Bonifati, Christan F. Rohé, Guido J. Breedveld, Ben A. Oostra, *Rotterdam, The Netherlands*

Note: Supported by a grant from the Deutsche Forschungsgemeinschaft (C.K., K.H.), the Bundesministerium für Bildung und Forschung (01G0201, C.K.), and a Lichtenberg Grant from the Volkswagen Foundation (C.K.).

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The impact of standardized stroke orders on adherence to best practices

To the Editor: I read with great interest the article by the Californian Acute Stroke Pilot Registry (CASPR) Investigators.¹ The investigators should be commended for performing such a well-designed, large-scaled multicenter before-and-after study to test the effectiveness of standardized orders for admission and discharge of stroke patients. Physicians often struggle to find practical ways of improving quality of stroke care, and the implementation of standardized orders seems to be a logical step toward bringing evidence-based stroke treatments closer to the bedside. However, there are several methodologic issues about this study that deserve clarification.

First, one of the major confounding factors in this study is the retrospective nature of data collection through case notes examination. Year 2 data were presumably retrieved through examination of the standardized orders in the case notes, and the quality of documentation was presumably extremely high. However, since the standardized orders did not exist in Year 1, data retrieval was presumably achieved through examination of the conventional case notes. It is possible that the observed differences in outcome merely reflected poor documentation in the Year 1 case notes (since if an intervention was not documented, it was presumed not to have occurred), rather than a real change in practice.

Secondly, since the authors used an intention-to-treat method of data analysis, it would be helpful if the authors reported the data for compliance with the standardized orders (i.e., what proportion of patients was managed using the standardized orders, were there differences among the six hospitals, when were the standardized orders used, and how completely were they filled in). Moreover, it would be interesting to explore the correlation between compliance and outcome.

Standardized orders used in this study are similar to care pathways in terms of their intention and format, especially when documented “variances” (i.e., acceptable reasons for not undertaking an intervention or achieving a goal) were analyzed. In theory, care pathways involve standardized orders that are designed around a pre-defined timeline and should involve multiple disciplines. However, in practice, care pathways vary and many would resemble the standardized orders used in this study.

In the Cochrane review on the use of “in-hospital care pathways for stroke,”² we included 3 randomized and 12 nonrandomized studies (4,421 patients). The Cochrane review did not find any significant differences between care pathway and control groups in terms of death or discharge destination. However, care pathway management was associated with fewer urinary tract infections, fewer readmissions, and more patients receiving a computed tomography scan. Interestingly, the Cochrane review also found evidence that patients managed with a care pathway were more dependent at discharge, had lower patient satisfaction, and lower quality of life, although the reasons for these findings are unclear.

Although interventions involving standardized orders (such as care pathways) may improve certain processes of stroke care and quality of documentation, evidence for improved functional outcome is unclear.

Joseph Kwan, *Southampton, UK*

Reply from the Author: We thank Dr. Kwan for his comments and are glad he has drawn attention to his excellent meta-analysis on care pathways. He raises an important point about the possibility that standardized stroke orders could have made documentation of medication usage more complete. We did demonstrate that documentation of contraindications to therapy had improved. However, we also demonstrated that for most of the interventions we were tracking, actual usage also increased after institution of standardized orders. We do not believe that the order templates simply improved documentation of receipt of these interventions; we required that a specific physician order was present and these were carefully and completely documented at all our hospitals both before and after institution of the standardized orders.

Dr. Kwan also raises an interesting point about correlating extent of order usage with improvements. We recognized at the initiation of the intervention that implementing the orders would have collateral benefits at the hospitals by educating physicians about standards of care and would likely improve care even when they were not used. Therefore, we did not gather these data. Even so, utilization might have been a surrogate measure of enthusiasm for the intervention and it would certainly be interesting to produce the analysis suggested.

In the Quality Improvement in Stroke Prevention (QUISP) trial, we have randomized seven hospitals to receive an intervention based upon standardized discharge orders and seven to continue usual care. The primary outcome is utilization of optimal medications for secondary prevention 6 months after discharge. Actual use of the orders is tracked as part of the trial. The primary analysis will be intention to treat, but we will certainly evaluate the correlation between usage and outcomes.

When those results are available, we will be able to respond to Dr. Kwan's second point, and we will also have much more solid data about the impact of standardized orders, which are only one component of care pathways.

S. Claiborne Johnston, CASPR Investigators, *San Francisco, CA*

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Effect of genetic modifiers on cerebral lesions in Fabry disease

To the Editor: We read the article by Altarescu et al. with great interest.¹ They showed that factor V Leiden (FVL) and protein Z polymorphisms were significantly associated with cerebral lesions in Fabry disease. It is unclear whether it is only the heterozygous and not the homozygous carrier state that appears to be associated with the occurrence of vascular lesions. It is possible that the patient numbers were too small and the incidence of the homozygous carriers was too low to show a significant difference.

The authors do not provide any pathophysiologic consideration regarding the relationship between a procoagulant state and Fabry disease. We think that there might be a pathophysiologic link between FVL with increased activated protein C (APC) resistance and the accumulation of glycosphingolipids in Fabry disease. Sphingolipids are important components of cell membranes and tend to be clustered together with cholesterol in microdomains, called lipid rafts.² Lipid rafts have to cluster together to engage in specialized membrane function.³ The ordered lipid environment might directly affect raft function and in lipid storage diseases involving raft lipids, the accumulation of one raft lipid class would slowly lead to trapping of other raft lipids in late endosomes.²

Lipoproteins and membrane surfaces accelerate the proteolytic inactivation of factor Va by APC demonstrating the crucial role of glycosphingolipids in the blood coagulation system.⁴ Neutral glycosphingolipids (e.g., globotriaosylceramide [Gb3Cer]) can enhance anticoagulant activity of APC.⁴ It is possible that neutral glycosphingolipids may help form microdomains where they could enhance the binding of APC to a subset of microdomains, called "antithrombotic" microdomains because they could bind APC to interact with protein S and to enhance factor Va inactivation.⁵

We think that accumulation of Gb3Cer in patients with Fabry disease may influence the formation and function of the antithrombotic lipid rafts, and by doing so alter the glycosphingolipid-dependent inactivation of factor Va by activated protein C. In patients with Fabry disease and FVL this would lead to an increased poor anticoagulant response to APC and an increased procoagulant state (compared to patients with FVL and without Fabry disease) leading to cerebral white matter lesions and stroke.

This mechanism is speculative and is based on partial results yet we believe this hypothesis merits further experimental assessment.

Dimitri M. Hemelsoet, Anna Vantilborgh, Jan L. De Bleeker, *Gent, Belgium*

Reply from the Authors: We thank Hemelsoet et al. for their comments regarding our article.¹ The most likely explanation for the increased risk of stroke being found mainly in heterozygotes

for polymorphisms for factor V Leiden and protein Z is that there were very few if any homozygotes in our patient population.

We agree with the speculation of Hemelsoet et al. that globotriaosylceramide (Gb3) interferes with the function of rafts. We recently proposed that hypothesis.⁶ We would like to emphasize that it has not yet been demonstrated that Gb3 is indeed an offending metabolite. In addition, the mechanism for stroke in Fabry is likely to be complex and multifaceted. We, and others, previously described the following abnormalities in Fabry disease: a prothrombotic state, endothelium-dependent vascular hyperactivity, cerebral hyperperfusion associated with brain MRI lesions, abnormal regulation of cerebrovascular tone, and strong evidence for increased production of reactive oxygen species.⁶⁻¹⁰

These and other unclear mechanisms, all modulated by other genetic factors, lead to a marked increased risk of stroke in Fabry disease.

We hope that renewed interest in Fabry disease as a risk factor for stroke will lead to better understanding and treatment of this rare disorder and stroke in the general population.

Raphael Schiffmann, David F. Moore, Gheona Altarescu, *Bethesda, MD*

Disclosure: The authors report no conflicts of interest.

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Quantitative proton MRS of Pelizaeus-Merzbacher disease: Evidence of dys- and hypomyelination

To the Editor: Hanefeld et al.¹ report interesting findings from a quantitative proton MRS study of Pelizaeus-Merzbacher disease (PMD). The proton MRS observations made by the authors have implications for childhood dysmyelinating disorders and also adult demyelinating disorders including multiple sclerosis (MS). However, we request response and clarification on some aspects of their data.

We would like to inquire why the authors did not use point-resolved spectroscopy (PRESS) instead of stimulated echo acquisition mode (STEAM) if they planned to do single-voxel imaging instead of chemical shift imaging employing multiple voxels. In our and others' experience, even with short echo times of 30 or 20 ms, the signal to noise from PRESS is much better and reproducible than STEAM, particularly in single voxel imaging studies.

We appreciate the argument Hanefeld et al. present regarding the elevated tNAA levels in patients with PMD. However, the relative increased density of axons by itself should not account for the elevation in tNAA using absolute levels. It would be important

to examine "relatively" less affected parts of the white matter to demonstrate this "gradient" effect dependent on the relative density of axons. It would be interesting to see if the authors have gathered these data during their studies with patients with PMD. Other mechanisms including an exaggerated neuronal response in the presence of widespread myelin absence accounting for some of the elevation in tNAA should be explored.

Can the authors comment on the source of "free" myo-inositol (Ins) signal in PMD? Is it entirely as a result of rapid membrane turnover and astrocytic proliferation or are other mechanisms also involved? Although thought to be an astrocytic marker,² Ins, which we are studying in MS, it is not clear if one can differentiate the "free" Ins signal from astrocytes and oligodendrocytes, which may be important in inflammatory injury (which is not the case in PMD but in MS).

Omar A. Khan, *Detroit, MI*

Reply from the Authors: We thank Dr. Khan for his comments and inquiries. Assuming otherwise identical conditions the use of

three 90° rf pulses in STEAM as opposed to one 90° rf pulse followed by two 180° refocusing pulses in PRESS results in a better spatial definition of the VOI (individual slice profiles). This particularly holds true if the duration of the rf pulses is kept short to minimize echo times. As a consequence, STEAM results in less contamination from outer volume signals and allows for a safe positioning of the VOI close to tissue boundaries without the need of additional suppression techniques. Moreover, STEAM will always have a shorter echo time than PRESS, which involves two echo times. Thus, PRESS loses part of its SNR advantage by slightly stronger T2 attenuation. Finally, even for the same echo time as in STEAM, PRESS doubles the unwanted J modulation of strongly spin-coupled metabolite resonances (glutamate, glutamine, myo-inositol, glucose, taurine).

Cheng et al.³ found an excellent correlation between neuronal loss shown by traditional neurohistopathology and a decrease of the tNAA level measured by proton MRS. Therefore, a close correlation between increased density of axons and elevated tNAA levels can be concluded. We are not aware of any evidence for an “exaggerated neuronal response” in PMD.

The concentration of myo-inositol (Ins) as a secondary messenger involved in cellular signal processing is much too small for a reliable detection by localized proton MRS.⁴ The Ins signal detected by MRS reflects free Ins, an important non-nitrogenous organic osmolyte in mammalian brain tissue.⁵ There is no evidence for a “special” source of free Ins in PMD. Ins has been

detected in high concentrations in astrocytic cell cultures and identified as an astrocytic marker for in vivo MRS studies.² On the other hand, oligodendrocytes show very high concentrations of choline-containing compounds (Cho). An increase of Cho rather than Ins indicates rapid membrane turnover as seen in demyelinating conditions. Nevertheless, classical demyelinating disorders in childhood are often accompanied by elevated Ins as well.

P. Dechent, F.A. Hanefeld, K. Brockmann, P.J.W. Pouwels, B. Wilken, J. Frahm, *Goettingen, Germany*

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MRI-guided, open trial of abciximab for ischemic stroke within a 3- to 24-hour window

To the Editor: We read with interest the article by Mitsias et al.¹ providing MRI evidence for early benefit of abciximab on stroke progression. This report joins others exploring abciximab in the acute stroke setting,² including ours.³ The purpose of this letter is to compare these protocols, explain the rationale for differences, and report interim results.

A common finding of the AbESTT trial² and Mitsias et al.¹ is the uncertain long-term benefits. We hypothesized that efficacy would be improved with concomitant use of heparin based on reports of enhanced thrombolytic activity with this combination and that a lower abciximab dose would convey additional safety.³ We noted a long track record of safety for abciximab in anticoagulated patients in the cardiac literature,³ yet anticoagulation is an exclusion in both these stroke protocols.^{1,2}

Our open label protocol utilizes a 0.2 mg/kg bolus and a 12-hour infusion of 0.05 µg/kg/h in conjunction with short course intravenous heparin and permits a time window of 6 hours for anterior circulation and 24 hours for posterior.³ This lower abciximab bolus dose showed identical efficacy with a lower incidence of bleeding in the dose-escalation precursor to AbESTT.⁴

Results of our first 14 patients have been published³ and 22 patients have now achieved 90-day outcomes and are reported here. Many were treated in the context of a surgical or other invasive procedure. The median baseline NIHSS of the 22 subjects was 22, considerably more severe than that in Mitsias et al.¹ (median NIHSS: 10). Our safety results are comparable, including no symptomatic ICH, and a 12.5% incidence of asymptomatic hemorrhages (compared to 20% in Mitsias et al.). There were no serious bleeding events. Although comparison is difficult because cohorts are dissimilar, functional outcome appears promising, with mean ± SD change in 3-month NIHSS of 12.5 ± 7.86 vs 5.7 ± 4.4 in Mitsias et al. ($p < 0.01$; t -test).

Because of concern that this lower dose may not sufficiently inhibit platelet GP IIb/IIIa activity, inhibition was measured in our most recent two patients.⁵ Activity was reduced by 97 and 90% after the bolus and by 85% to 73% at 1 to 2 hours after the

12-hour infusion. The initial values are within a range considered effective in the cardiac literature.⁵

We agree with Mitsias et al. that abciximab is a promising treatment in acute stroke. Our experience indicates that, used somewhat differently, it may provide an alternative for patients more severely affected. A Phase 2 trial is planned.

(Note: Since submission of our letter, the AbESTT II trial has been stopped [http://www.strokecenter.org/trials/trialDetail.aspx?tid=568&search_string=abestt] for a “high rate of intracranial hemorrhage,” although it is said that unblinding is not expected until March. We plan on continuing our study, using the lower dose of abciximab described here and monitoring platelet GP IIb/IIIa inhibition.)

Pitchaiah Mandava, Jane A. Anderson, Thomas A. Kent, *Houston, TX*

Disclosure: The authors report no conflicts of interest.

Editor's Note: The authors of the article had the opportunity to respond to this Correspondence but did not.

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Women in neurology

To the Editor: I read with interest the Presidential Address of Dr. Sandra Olson, which focused on the role of women in neurology.¹ In her address, she honored great female neurologists/neuroscientists, specifically highlighting pioneers like Augusta Dejerine-Klumpke and Cecile Vogt. I would like to champion the cause of three other

women, not mentioned by Dr. Olson, but whom I feel deserve equal recognition for their contributions to our specialty.

The first is Rita Levi-Montalcini, who introduced the concept of neurotrophism and discovered nerve growth factor. Levi-Montalcini, an Italian Jew, found her plans to become a neurologist blocked by Mussolini's “Manifesto per la difesa della razza,” a document that prevented “non-Aryans” from pursuing careers in

medicine. Undaunted, Levi-Montalcini carried on researching the growth of nerve fibers in chick embryos from a primitive laboratory in her own bedroom. This work later served as the background to her subsequent isolation of nerve growth factors. In 1986, she became only the fourth woman to be awarded the Nobel Prize in Physiology or Medicine.

The second is the Scottish physician Mary Broadfoot Walker. Despite never receiving the honors she deserved (e.g., some of her seminal work in the 1930s could not be published as original articles because she could not be a consultant), Walker was the first to successfully treat myasthenia gravis, after correctly surmising that if the paralyzing effects of the South American poison arrow (curare) were reversed by physostigmine, a similar effect might treat myasthenic patients. Initially dismissed, not least because "a lady doctor from a small English hospital" was promulgating it, the "miracle of St Alfege's" was eventually recognized as one of the pivotal therapeutic observations in clinical neurology.

Finally, the late Anita Harding from Queen Square should be mentioned. Although dying in her prime, aged 42 years, Harding can be credited as one of the first neurologists to span the twin disciplines of genetics and clinical neurology. Finding disorders such as hereditary spastic paraparesis, the familial neuropathies, and ataxia in diagnostic chaos, she painstakingly set validated diagnostic criteria for these disorders that would eventually enable both her and others to discover the causative genes. Harding

was the first to associate mutations of the mitochondrial genome with human disease. In her short career, she published over 250 papers and should be recognized as an essential catalyst for the explosion of genetic information that influences modern-day neurology.

Daniel G. Healy, MRCPI, *London, UK*

Reply from the Author: I thank Dr. Healy for his letter, which refers to three outstanding women neurologists including Drs. Levi-Montalcini, Walker, and Harding, whom I did not mention in my Presidential Address. I am especially aware of Dr. Walker, as my chief and mentor Dr. Benjamin Boshes mentioned her several times during my residency at Northwestern. I believe he was well acquainted with her personally, as well as with her work, and I have the sense he greatly admired her. There are many outstanding female neurologists but it was necessary to keep the list manageable so I concentrated on American neurologists (especially AAN members).

Sandra F. Olson, *Chicago, IL*

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1. Olson SF. Women in neurology. *Neurology* 2005;65:344–348.

Correction

Prediction of poor outcome within the first 3 days of postanoxic coma

In the Appendix of the article, "Prediction of poor outcome within the first 3 days of postanoxic coma" (*Neurology* 2006;66:62–68) by Zandbergen et al., two of the PROPAC Collaborators were unintentionally omitted. These authors were Drs. P. Verlooy and D.F. Zandstra of the Onze Lieve Vrouwe Gasthuis in Amsterdam, The Netherlands.

The authors apologize for this error.

Neurology[®]

Correction

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