In Memoriam

Gabriele Schilling (September 5, 1968—July 4, 2014)

David R. Borchelt^a and Christopher A. Ross^b

^aDepartment of Neuroscience, Center for Translational Research in Neurodegenerative Disease, SantaFe Health-Care Alzheimer's Disease Research Center, University of Florida, Gainesville, FL, USA

^bBaltimore Huntington's Disease Center, Division of Neurobiology, Department of Psychiatry, and Departments of Neurology, Neuroscience and Pharmacology, and Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA



It is with a great sadness that we note the passing of Dr. Gabriele Schilling, who lost her battle with HD at the age of 46. Gabriele (or Gaby) was known to many investigators in the HD field as an energetic young investigator who was dedicated to finding new treatments. She first came to the United States as a visiting student in Christopher Ross's lab at Johns Hopkins, then returned to Dr. Ross's lab to complete a PhD (which she received from the University of Witten-Herdecke in 2000), during which time she developed one of the first mouse models of HD (N171-82Q), in

collaboration with David Borchelt and investigators at the National Cancer Institute. She stayed on at Hopkins to do a postdoc in Borchelt's lab, continuing cell and mouse studies of HD. She then returned to Germany in 2005 to set up her own lab at the University of Jena, Fritz-Lipmann-Institut), continuing to focus on HD.

Like many HD expansion carriers, she kept her personal risk for developing HD a secret. Only when she could no longer hide the emerging symptoms did she reveal her gene status. Her rationale for hiding her risk was the fear of discomfort that might arise when she engaged in research related discussions, which for better or worse often remove the human element and focus on the disease as an entity to be studied and understood rather than a human condition. It is hard to fathom the courage it took to look so hard at her possibilities with the constant daily reminders of what her future could hold.

Among her many publications [1–22], she will be best remembered for her ground-breaking contributions to the development of mouse models for HD (the fragment transgenic "N171-82Q") and the closely related polyglutamine disease DRPLA (9,10,15,19). A search of PubMed with the target of "N171-82Q" indicates that 64 papers have been published to date using this model, and it remains widely used for experimental therapeutics. Her passion and drive in generating the HD mice were born from her hope that they might enable the discovery of new treatments.

Dr. Borchelt remembers a conversation in which he highlighted the value of the HD mouse model to understand "what makes them sick", and she responded that "the only thing that matters is figuring out how to cure them."

Sadly, the breakthrough that she—and many other HD expansion carriers—desired did not come in time. As the disease began to take hold, she spoke of her continued dream that her effort would one day make a difference. She devoted her effort in the last productive years of her career to understanding how the endoproteolytic cleavage of huntingtin may contribute to the generation of toxic protein fragments.

She leaves us with a legacy of discovery, courage, and endurance that will hopefully motivate future generations of young scientists to work towards those breakthrough discoveries that we all desire.

ACKNOWLEDGMENT

Gabriele is survived by her sister Stefanie Schilling who provided the photograph and guidance on the content of the memorial.

REFERENCES

- [1] Li SH, Schilling G, Young WS 3rd, Li XJ, Margolis RL, Stine OC, Wagster MV, Abbott MH, Franz ML, Ranen NG. Huntington's disease gene (IT15) is widely expressed in human and rat tissues. Neuron. 1993;11:985-93.
- [2] Li XJ, Li SH, Sharp AH, Nucifora FC Jr, Schilling G, Lanahan A, Worley P, Snyder SH, Ross CA. A huntingtin-associated protein enriched in brain with implications for pathology. Nature. 1995;378:398-402.
- [3] Loev SJ, Margolis RL, Young WS, Li SH, Schilling G, Ashworth RG, Ross CA. Cloning and expression of the rat atrophin-I (DRPLA disease gene) homologue. Neurobiol Dis. 1995;2:129-38.
- [4] Schilling G, Sharp AH, Loev SJ, Wagster MV, Li SH, Stine OC, Ross CA. Expression of the huntington's disease (IT15) protein product in HD patients. Hum Mol Genet. 1995;4:1365-71.
- [5] Sharp AH, Loev SJ, Schilling G, Li SH, Li XJ, Bao J, Wagster MV, Kotzuk JA, Steiner JP, Lo A. Widespread expression of huntington's disease gene (IT15) protein product. Neuron. 1995;14:1065-74.
- [6] Khan AA, Soloski MJ, Sharp AH, Schilling G, Sabatini DM, Li SH, Ross CA, Snyder SH. Lymphocyte apoptosis: Mediation by increased type 3 inositol 1,4,5-trisphosphate receptor. Science. 1996;273:503-7.
- [7] Bao J, Sharp AH, Wagster MV, Becher M, Schilling G, Ross CA, Dawson VL, Dawson TM. Expansion of polyglutamine repeat in huntingtin leads to abnormal protein interactions involving calmodulin. Proc Natl Acad Sci U S A. 1996;93:5037-42.
- [8] Cooper JK, Schilling G, Peters MF, Herring WJ, Sharp AH, Kaminsky Z, Masone J, Khan FA, Delanoy M, Borchelt DR,

- et al. Truncated N-terminal fragments of huntingtin with expanded glutamine repeats form nuclear and cytoplasmic aggregates in cell culture. Hum Mol Genet. 1998;7:783-90.
- [9] Schilling G, Becher MW, Sharp AH, Jinnah HA, Duan K, Kotzuk JA, Slunt HH, Ratovitski T, Cooper JK, Jenkins NA, et al. Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Hum Mol Genet. 1999;8:397-407.
- [10] Schilling G, Wood JD, Duan K, Slunt HH, Gonzales V, Yamada M, Cooper JK, Margolis RL, Jenkins NA, Copeland NG, et al. Nuclear accumulation of truncated atrophin-1 fragments in a transgenic mouse model of DRPLA. Neuron. 1999;24:275-86.
- [11] Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G, et al. Decreased expression of striatal signaling genes in a mouse model of huntington's disease. Hum Mol Genet. 2000;9:1259-71.
- [12] Wood JD, Nucifora FC Jr, Duan K, Zhang C, Wang J, Kim Y, Schilling G, Sacchi N, Liu JM, Ross CA. Atrophin-1, the dentato-rubral and pallido-luysian atrophy gene product, interacts with ETO/MTG8 in the nuclear matrix and represses transcription. J Cell Biol. 2000;150: 939-48.
- [13] Schilling G, Coonfield ML, Ross CA, Borchelt DR. Coenzyme Q10 and remacemide hydrochloride ameliorate motor deficits in a huntington's disease transgenic mouse model. Neurosci Lett. 2001;315:149-53.
- [14] Andreassen OA, Dedeoglu A, Ferrante RJ, Jenkins BG, Ferrante KL, Thomas M, Friedlich A, Browne SE, Schilling G, Borchelt DR, et al. Creatine increase survival and delays motor symptoms in a transgenic animal model of huntington's disease. Neurobiol Dis. 2001;8:479-91.
- [15] Schilling G, Jinnah HA, Gonzales V, Coonfield ML, Kim Y, Wood JD, Price DL, Li XJ, Jenkins N, Copeland N, et al. Distinct behavioral and neuropathological abnormalities in transgenic mouse models of HD and DRPLA. Neurobiol Dis. 2001;8:405-18.
- [16] Wheeler VC, Gutekunst CA, Vrbanac V, Lebel LA, Schilling G, Hersch S, Friedlander RM, Gusella JF, Vonsattel JP, Borchelt DR, et al. Early phenotypes that presage lateonset neurodegenerative disease allow testing of modifiers in hdh CAG knock-in mice. Hum Mol Genet. 2002;11: 633-40.
- [17] Luthi-Carter R, Strand AD, Hanson SA, Kooperberg C, Schilling G, La Spada AR, Merry DE, Young AB, Ross CA, Borchelt DR, et al. Polyglutamine and transcription: Gene expression changes shared by DRPLA and huntington's disease mouse models reveal context-independent effects. Hum Mol Genet. 2002;11:1927-37.
- [18] Schilling G, Savonenko AV, Coonfield M, Morton JL, Vorovich E, Gale A, Nelson C, et al. Environmental, pharmacological, and genetic manipulation of the HD phenotype in transgenic mice. Exp Neurol. 2004;187:137-9.
- [19] Schilling G, Savonenko AV, Klevytska A, Morton JL, Tucker SM, Poirier M, Gale A, Chan N, Gonzales V, Slunt HH, et al. Nuclear-targeting of mutant huntingtin fragments produces huntington's disease-like phenotypes in transgenic mice. Hum Mol Genet. 2004;13:1599-610.
- [20] Tanaka Y, Igarashi S, Nakamura M, Gafni J, Torcassi C, Schilling G, Crippen D, Wood JD, Sawa A, Jenkins NA, et al. Progressive phenotype and nuclear accumulation of an aminoterminal cleavage fragment in a transgenic mouse model with inducible expression of full-length mutant huntingtin. Neurobiol Dis. 2006;21:381-91.

- [21] Schilling G, Klevytska A, Tebbenkamp AT, Juenemann K, Cooper J, Gonzales V, Slunt H, Poirer M, Ross CA, Borchelt DR. Characterization of huntingtin pathologic fragments in human Huntington disease, transgenic mice, and cell models. J Neuropathol Exp Neurol. 2007;66:313-20.
- [22] Juenemann K, Weisse C, Reichmann D, Kaether C, Calkhoven CF, Schilling G. Modulation of mutant huntingtin N-terminal cleavage and its effect on aggregation and cell death. Neurotox Res 2011;20(2):120-33. Epub 2010 Nov 30.