OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Louis J. Ptáček, MD

eRA COMMONS USER NAME (credential, e.g., agency login): PTACEK

POSITION TITLE: Distinguished Professor of Neurology

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE  (if applicable) | Completion Date  MM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of Wisconsin, Madison | B.S. | 1982 | Mathematics |
| University of Wisconsin, Madison | M.D. | 1986 | Medicine |
| University of Utah, Salt Lake City | Post-Doc | 1993 | Human Genetics |

A. Personal Statement

My work has focused on study of families with genetic phenotypes aiming to map and clone genes and genetic variants. In some cases, we have identified and characterized the human phenotypes (e.g. familial advanced sleep phase syndrome, Andersen-Tawil Syndrome). We have localized and cloned genes for many episodic phenotypes, neurodegenerative disorders, and more recently, human circadian variants and migraine headache. In some cases, we use assorted techniques to study the encoded proteins (both wild-type and mutant) to examine functional consequences of mutations and attempt to link these with understanding of disease pathogenesis. More recently, we’ve also become very invested in generating animal models of human mutations, primarily in mice but also using *Drosophila*. Such work translates from patients to biological understanding and ultimately, helps not only in diagnosis of human diseases, but also to therapies for the patients.

B. Positions and Honors

**Positions and Employment**

1986-1987 Intern in Medicine, University of Washington

1987-1990 Resident and Chief Resident in Neurology, University of Utah, Salt Lake City

1990-1994 Postdoctoral Fellow, Department of Human Genetics, University of Utah, Salt Lake City

1992-1996 Assistant Professor, Department of Neurology, University of Utah, Salt Lake City

1996-2002 Associate Professor, Departments of Neurology & Human Genetics, University of Utah, SLC

1997-2003 Associate Investigator, Howard Hughes Medical Institute

2002-2003 Professor, Departments of Neurology & Human Genetics, University of Utah, Salt Lake City

2003-pres Investigator, Howard Hughes Medical Institute

2003-pres Coleman Distinguished Professor, Dept. of Neurology, University of California at San Francisco

Other Experience and Professional Memberships

1998-2002 NIH Study Section Member, National Center for Research Resources

2004-2009 Trustee, Grass Foundation for Neuroscience Research

2005-pres Associate Editor, *Journal of Neuroscience*

2008-2010 Pfizer Neuroscience Therapeutic Area Scientific Advisory Panel

2004-2008 Board of Scientific Counselors, NIH/NINDS (2006-2008—Chair)

2008-2012 NINDS Council, NIH

Honors

1992 American Neurological Association Presidents Award

1996 Golden Anniversary Prize for Distinguished Clinical Investigation, U of Utah School of Medicine

1997 Derek Denny-Brown Neurological Scholar Award: American Neurological Association

2000 American Society for Clinical Investigation

2007 Elected to the Institute of Medicineat the National Academies

2008 Elected to the American Academy of Arts and Sciences

2009 Elected to the American Association of Physicians

2012 UCSF Faculty Lecture Award (highest award UCSF bestows on a faculty member)

2012 Elected Member of the National Academy of Sciences

2015 Stanley J. Korsmeyer Award from the American Society of Clinical Investigation

C. Contribution to Science

1. *Establishment of the field of Channelopathies and ongoing contributions in this field*: I have long been interested in the genetics of episodic disorders including migraine and epilepsy. However, my early work focused on the familial periodic paralysis because of the strong genetic (monogenic) nature of the phenotype, the availability of such families early in my career, and some striking similarities between this rare Mendelian (electrical) muscle disease and other episodic phenotypes. I set out to clone the genes causing familial forms of hyperkalemic periodic paralysis, paramyotonia congenita, potassium aggravated myotonia, and hypokalemic periodic paralysis. These were the first disorders characterized at the genetic and molecular level that were shown to result from ion channels and formed the basis of a new area that we now call the “Channelpathies”. My group was responsible for the cloning of all of these disease-genes and the new clinical classification scheme we proposed in 2004. We went on to study thyrotoxic hypokalemic periodic paralysis (TPP), a common and sporadic disease using knowledge of the pathogenetics of the familial periodic paralysis. This knowledge led us to clone and characterize a novel channel gene (*KCNJ18*) and to show it is mutated in a significant portion of patients with TPP.

1. **Ptáček LJ**, George AL, Griggs RC, Tawil R, Kallen RG, Barchi RL, Robertson M, Leppert MF. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cell. 1991; 67:1021-7.
2. **Ptáček LJ**, George AL, Barchi RL, Griggs RC, Riggs JE, Robertson M, Leppert MF. Mutations in an S4 segment of the adult skeletal muscle sodium channel cause paramyotonia congenita. Neuron. 1992; 8:891-7.
3. **Ptáček LJ**, Tawil R, Griggs RC, Engel AG, Layzer RB, Kwieciński H, McManis PG, Santiago L, Moore M, Fouad G, Bradley P, Leppert MF. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell. 1994; 77:863-8.
4. Ryan D, Dias da Silva M, Soong TW, Fontaine B, Donaldson M, Kung AWC, Jongjaroenprasert W, Liang MC, Khoo D, Cheah JS, Ho SC, Bernstein H, Maciel R, Brown R, **Ptáček LJ**. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. [Cell.](javascript:AL_get(this,%20'jour',%20'Cell.');) 2010 Jan 8; 140(1):88-98.

2. *Clinical, genetic, and molecular characterization of Andersen-Tawil Syndrome (ATS)*: This work falls into the category of Channelopathies described above but deserves separate recognition. My group contributed to the original recognition of this unique, familial, multisystem phenotype in 1994. We went on to clone the disease gene, identify many disease causing mutations (responsible for 2/3 of all ATS families), expansion of the developmental phenotype, and recognition of a unique neurocognitive phenotype. Current efforts are directed at identification of additional ATS gene(s).

1. Tawil R, **Ptáček LJ**, Pavlakis SG, DeVivo DC, Penn AS, Ozdemir C, Griggs RC. Andersen's syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol. 1994; 35:326-30.
2. Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, Clark J, Deymeer F, George AL, Fish FA, Hahn A, Nitu A, Ozdemir C, Serdaroglu P, Subramony SH, Wolfe G, Fu YH, **Ptáček LJ**. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen’s syndrome. Cell. 2001, 105:511-9.
3. Yoon G, Oberoi S, Tristani-Firouzi M, Etheridge SP, Quitania L, Kramer JH, Miller BL, Fu YH, **Ptáček LJ**. Andersen-Tawil syndrome: Prospective cohort analysis and expansion of the phenotype. Am J Med Genet A. 2006 Feb 15; 140(4):312-21.
4. Yoon G, Quitania L, Kramer JH, Fu YH, Miller BL, **Ptáček LJ**. Andersen-Tawil syndrome: definition of a neurocognitive phenotype. Neurology. 2006 Jun 13; 66(11):1703-10.

3. *Clinical, genetic, and molecular characterization of the paroxysmal dyskinesias*: Paroxysmal kinesigenic dyskinesia (PKD) and Paroxysmal non-kinesigenic dyskinesia (PNKD) have been recognized for a long time, both in sporadic and familial forms. However, we have amassed a large population of patients (and many more families than anyone else) that has allowed us to refine the diagnostic criteria for both PKD and PNKD. We’ve gone on to clone both the PNKD and the PKD genes and generated mouse models of both. We’ve shown that the PNKD gene encodes a protein that is a novel synaptic protein regulating exocytosis. Mice carrying the human mutations have abnormal dopamine signaling that is mediated via the indirect pathway of the basal ganglia.

1. Lee HY, Xu Y, Huang Y, Ahn AH, Aubuger GW, Pandolfo M, Kwieciński H, Grimes DA, Lang AE, Nielsen JE, Averyanov Y, Servidei S, Friedman A, Van Bogaert P, Abramowicz MJ, Bruno MK, Sorensen BF, Tang L, Fu YH, **Ptáček LJ**. The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. Hum Mol Genet. 2004; 13(24);3161-70.
2. Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen BF, Considine E, Tucker S, Lynch DR, Mathews KD, Swoboda KJ, Harris J, Soong BW, Ashizawa T, Jankovic J, Renner D, Fu YH, **Ptáček LJ**. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology. 2004; 63:2280-7.
3. Lee HY, Huang Y, Bruneau N, Roll P, Roberson E, Hermann M, QuinnE, MaasJ, EdwardsR, Ashizawa T, Baykan B**,** Bhatia K**,** Bressman S, Bruno MK, Brunt ER, Caraballo R, Echenne B, Fejerman N, Frucht S, Gurnett CA, Hirsch E, Houlden H, Jankovic J, Lee W-L, Lynch DR, Mohammed S, Müller U, Nespeca MP, Renner D, Rochette J, RudolfG, Saiki S, Soong B-W, Swoboda KJ, TuckerS, WoodN, HannaM , Bowcock AM, Szepetowski P, Fu Y-H, **Ptáček LJ**. Mutations in the novel protein PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Reports. 2012 Jan 26; 1(1):2-12.
4. Shen Y, Ge W-P, Li Y, Kaeser P, Tsien R, Südhof T, Jan L, Fu Y-H, **Ptáček LJ**. A protein mutated in paroxysmal dyskinesia suppresses synaptic vesicle exocytosis through the active zone protein RIM. [Proc Natl Acad Sci USA.](http://www.ncbi.nlm.nih.gov/pubmed/25730884) 2015 Feb 17. pii: 201501364. [Epub ahead of print]

4. *Established the field of human circadian rhythm/sleep genetics*: Most recently, I have become interested in Mendelian behavioral phenotypes of human sleep schedule and sleep duration. Together with collaborator, Dr. Ying-Hui Fu, we have cloned a growing list of genes causing early morning awakening (Familial Advanced Sleep Phase, FASP).

1. Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, Jones B, Czajkowski L, **Ptáček LJ**. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. Nat Med. 1999; 5:1062-5.
2. Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, **Ptáček LJ**, Fu YH. An h*Per2* phosphorylation site mutation in familial advanced sleep-phase syndrome. Science. 2001; 291:1040-3.
3. Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Saigoh K, **Ptáček LJ**, Fu YH. Functional consequences of a *CKIδ* mutation causing familial advanced sleep phase syndrome. Nature. 2005; 434:640-4.
4. Hirano A, Shi G, Jones CR, Lipzen A, Pennacchio LA, Xu Y, Hallows WC, McMahon T, Yamazaki M, **Ptáček LJ**, Fu Y-H. A novel Human Cryptochrome 2 variant yields Familial Advanced Sleep Phase. eLife. 2016 Aug 16;5. pii: e16695. doi: 10.7554/eLife.16695.

5. *Probing biology of human circadian clock in vitro and in vivo*: Identification of novel human circadian rhythm genes/mutations has led us to probe deeply into the biological consequences of such mutations in vitro and in vivo. Identification and characterization of these mutations have led to novel insight into the molecular machinery of mammalian circadian clock regulation. Insights we have gained from this approach could not have resulted from using traditional knockout mouse model approaches as the mutant human alleles have focused our attention on regions of the protein not previously known to harbor important regulatory domains. The dominant point mutations that we found in normal human population proved to be very revealing and provide opportunities to probe deeply into pathways of our sleep schedule regulation. This work will ultimately have an impact on many human diseases where chronic desynchrony of the clock or chronic sleep deprivation lead to increased risks of cancer, psychiatric disease, autoimmune disorders, and metabolic syndrome, to name a few.

1. Xu Y, Toh KL, Jones CR, Shin JY, Fu YH, **Ptáček LJ**. Modeling of a human circadian mutation yields insights into clock regulation by PER2. Cell. 2007 Jan 12; 128(1):59-70.
2. Brennan KC, Bates EA, Shapiro RE, Zyuzin J, Hallows WC, Huang Y, Lee H-Y, Jones CR, Fu Y-H, Charles AC, **Ptáček LJ**. Casein kinase Iδ mutations in familial migraine and advanced sleep phase. Science Translational Medicine. 2013 May 1;5(183):183ra56.
3. Zhang L, Hirano A, Hsu P-K, Jones CR, Sakai N, Okuro M, McMahon T, Yamazaki M, Xu Y, Saigoh N, Saigoh K, Lin S-T, Kaasik K, Nishino S, **Ptáček LJ**, Fu Y-H. A PERIOD3 Variant Causes a Circadian Phenotype and is Associated with a Seasonal Mood Trait. Proc Natl Acad Sci U S A. 2016 Feb 22. pii: 201600039.
4. Hirano A, Fu Y-H, **Ptáček LJ**. FAD regulates CRYPTOCHROME protein stability and circadian clock in mice. Cell Reports. 2017 (in press).

Team science: During the last ~18 years, I’ve worked in an extremely productive collaboration with the laboratory of Ying-Hui Fu. Thus, many of the nearly 100 manuscripts published during that time are co-authored by Dr. Fu and myself, often as co-corresponding authors. I’ve also benefited from working with an outstanding international network of remarkable clinicians. This has been important for many papers describing or characterizing large groups of patients with rare disorders that have been collected throughout the United States and indeed, from around the globe. In some cases, this has led to publications with many authors in order to acknowledge their critical contributions to such undertakings.

**Full list of publications:** <http://www.ncbi.nlm.nih.gov/sites/myncbi/louis.ptacek.1/bibliography/40443305/public/?sort=date&direction=ascending>

**D. Research Support**

**Ongoing Research Support**

Molecular characterization of polygenic brain disorders

Role: Principal Investigator Agency: Howard Hughes Medical Institute

Period: 09/01/13 – 08/31/18 Total direct costs: $360,000/year

The goal of this project is to apply knowledge of molecular pathogenesis from Mendelian episodic disorders to better understanding of complex genetic disorders like headache and epilepsy. In my last review (May 2013), my HHMI appointment was not renewed. My HHMI budget is in the midst of tapering funding as I move toward separation from HHMI.

Genetic and Molecular Characterization of Andersen-Tawil Syndrome

Role: Principal Investigator Agency: NIH/NINDS

NS091276

Period: 09/01/15 – 08/31/20 Total direct costs: $218,750/year

Clinical, genetic, and physiologic characterization of subjects with Andersen-Tawil Syndrome.

Investigating genetics of human natural short sleepers

Role: Co-Investigator (PI: Fu) Agency: NIH/NINDS

NS072360

Period: 09/01/11 – 08/31/16 Total direct costs: $218,750/year

Clinical, genetic, and physiologic characterization of subjects with Familial Natural Short Sleep.

**Pending Research Support**

Probing genetics and b iology of human circadian function

Role: Principal Investigator Agency: NIH/NINDS (7th percentile)

NS099333

Period: 09/01/16 – 08/31/21 Total direct costs: $440,671/year