NF1 Patient Registry Initiative (NPRI)
Spring/Summer 2015 Newsletter

INSIDE THIS ISSUE:

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Progress and publications: A report from the NPRI

Since its launch in 2011, the NPRI team has strived to meet its mission of advancing understanding of the medical and social consequences of living with NF1. Since its inception, the research team has worked hard to recruit and engage registry participants and to disseminate findings from NPRI data analyses. A summary of our accomplishments to date is provided below.

PARTICIPATION

- Over 2,000 individuals with NF1 have enrolled in the NPRI
- These individuals represent all 50 US states and 52 countries from around the world

ENGAGEMENT

- This is the 11th edition of the NPRI newsletter
- Recent versions of the newsletter have highlighted amazing participant personal stories
- We have engaged more than a dozen students and trainees, 15+ clinics and over 50 advocacy groups in NPRI efforts.

PUBLICATIONS

We have published five studies to date (listed below) in scientific journals. This work is helping to establish methods for rare disease online registries and to identify risk factors for NF1 and pediatric brain tumors.

- Johnson KJ *et al*. Development of an International Internet-Based Neurofibromatosis Type 1 Patient Registry. *Contemp Clin Trials*. 2012 Dec 14
- Johnson KJ, *et al*. Evaluation of participant recruitment methods to a rare disease online registry. *Am J Med Genet A* 2014 Apr 3
- Liu Q *et al*. Parental age and Neurofibromatosis Type 1: a report from the NF1 Patient Registry Initiative. *Fam Cancer*. 2014 Dec 10
- Sharkey EK *et al*. Validity of participant-reported diagnoses in an online patient registry: A report from the NF1 Patient Registry Initiative. *Contemp Clin Trials*. 2014 Dec 19.
- Abadin SA *et al*. Racial/ethnic differences in pediatric brain tumor diagnoses in individuals with Neurofibromatosis Type 1. In Press *J Pediatrics*

FUTURE DIRECTIONS

The NPRI team will continue to develop new NF1 research efforts, strive to further identify risks for NF1 and related health outcomes, and to incorporate additional data sources to advance our NF1 mission.

We want to express our heartfelt gratitude to all the individuals with NF1 who have contributed to this important effort. We also want to acknowledge our extreme appreciation to Alex's Lemonade Stand Foundation and the American Cancer Society for supporting this work. Without their support, this work would not have been possible.

Living with NF:

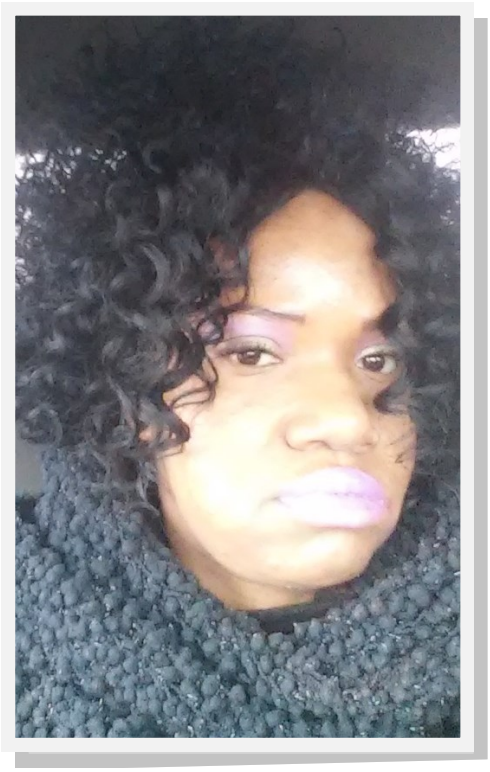
Personal stories of NPRI participants

The research that is made possible through the NPRI would not be possible without the help of our participants. We are grateful for their enthusiasm in being a part of the registry.

Joining the NPRI is one way of showing commitment to the progress of NF1 research and each individual's contribution is valued. To recognize the impact a single individual can have to help people understand what it's like to live with NF1, we want to highlight some of our participants' stories.

In this edition, we feature two women's experiences with NF1.

Melissa H.



Melissa grew up not knowing that she had a rare disease. In her late twenties, she mentioned to a doctor that her mother had a condition called NF. She was diagnosed simply by a physical exam noting her "spots and bumps." Her diagnosis was confirmed by a saliva swab and blood test.

Remembering back, she felt as though she took the news pretty well at the time, "nothing in my life would surprise me." She went home and researched NF1 and realized that her children had it too. Melissa states, "that was a shocker for me, 7 of my 8 children have various symptoms and were eventually diagnosed with NF1. How could this be when I had a 50/50 chance of passing this on to my children?"

Melissa has had three surgeries, radiation therapy and chemotherapy over the past 3 years. She has gone from being independent to being dependent. For her, "the pain all day long in the worst part."

Melissa prays and meditates and believes in "divine healing." This is how she gets through her day. "It is very upsetting to me that a lot of health care workers (including physicians) never heard of NF1, it's very frustrating to try to explain such a complex disease in any emergency room."

Melissa wishes she could educate more people about NF1 and tell them how this has affected her family. She's hoping to raise awareness and money for research by organizing a winter gala in 2016, and believes "there is a cure for everything, we have to keep striving."

"That was a shocker for me, 7 of my 8 children have various symptoms and were eventually diagnosed with NF1."

"There is a cure for everything, we have to keep striving."

Brittany M.

Brittany is 27 years old. When she was a child her mom found a tumor on her leg and after having it removed, Brittany was diagnosed with NF.

Her dad and grandma had cafe au lait spots too. Despite a family history Brittany states, “I was the first person in the family to show many of the NF1 symptoms.” Thankfully, she believes she has had a relatively easy path, despite having several painful tumors removed.

Currently, she has some that cause her pain but are in locations that make it too risky to remove them, so she tries to manage the pain with medication. There is one pushing slightly against her spinal column but over the years since it was discovered, it has remained stable and has not caused significant problems.

Brittany has been able to go on to obtain her Master's degree in counseling psychology and currently works at a children's hospital doing research primarily in the diabetes/endocrine clinic and a little in cystic fibrosis. At times it was difficult for her to get through, she even had surgery during grad school but recovered quickly.

“I was the first person in the family to show many of the NF1 symptoms.”

She was also diagnosed with multiple sclerosis when she was 21 (after over two years of suspecting it), along with suspected chronic inflammatory demyelinating polyneuropathy. Brittany stated, “my NF made it a little harder to diagnose some of these diseases as we didn't know which ones were causing which symptoms.” However, she thankfully reports that she has been fairly stable with all of her diseases after a more difficult time in her late teens/early 20s. It can make things a little harder sometimes when a new symptom or issue comes up and it's not entirely clear if it's her MS or NF, but after all these years she has become more familiar with both diseases and how they feel and has learned how to listen to her body so she can see the right doctor to address her issues. She has a great medical team and support network, which has made it a lot easier to deal with.

“My NF made it a little harder to diagnose some of these diseases as we didn’t know which ones were causing which symptoms.”

Share Your Story.

If you, a friend, or a family member are part of the NPRI and would like to be featured in our newsletter, please email us at: **nf1registry@brownschool.wustl.edu.**

Current NF Research

In order to improve the ways we care for both children and adults affected with NF, we need a better understanding of the condition. Ongoing clinical research studies at the Washington University NF Center and elsewhere will accelerate the pace at which new treatments are developed.

Featured in this edition of the newsletter are recently published journal articles from NF1 researchers as well as members of the NPRI team.

Subtle changes in the genes of children with NF1 may increase their risk of developing a brain tumor (glioma).

Researchers Identify New Genetic Risk Factor for NF1-Associated Glioma

A new study, spearheaded by Dr. Joshua Rubin and his colleagues, found that subtle changes in the genes of children with NF1 may increase their risk of developing a brain tumor (glioma). Using a combination of *Nf1* genetically-engineered mice and NF1 patient DNA samples, they found that slight changes, termed genetic polymorphisms, in the *ADCY8* gene, altered the likelihood of glioma formation in children with NF1.

In this report, the investigative team discovered that these genetic polymorphisms increased the risk of glioma in boys. The *ADCY8* gene controls cyclic AMP levels in the brain, which are important for cell survival. Importantly, using *Nf1* genetically-engineered mice developed in the laboratory of Dr. David Gutmann, they found that sex differences exist in cyclic AMP regulation. Previous studies from Dr. Rubin's laboratory had shown that cyclic AMP is one of the key molecules important for *Nf1* optic glioma growth in mice.

These exciting findings could help support personalized approaches to risk assessment, advance our understanding of the factors that favor glioma formation, and potentially identify new treatments for these common brain tumors in children with NF1.

Warrington NM *et al*. The cyclic AMP pathway is a sex-specific modifier of glioma risk in type 1 neurofibromatosis patients. *Cancer Res*. 75(1): 16-2, 2015.

Researchers Discover New Treatments for NF1 Optic Glioma

Children with NF1 develop optic gliomas that can impair vision. Currently, treatments for these brain tumors involve the use of chemotherapies originally designed to slow the growth of similar cancers in children without NF1. With the identification of the *NF1* gene, it is possible to develop treatments specifically targeted to the kinds of brain tumors arising in children with NF1.

Using *Nf1* genetically-engineered mice, Dr. Aparna Kaul, a post-doctoral fellow in the laboratory of Dr. David Gutmann, recently showed that two therapies that block the activity of RAS effector proteins are effective treatments for optic glioma. Previous studies performed nearly 20 years ago revealed that the *NF1* gene controls cell growth

by suppressing the activity of a protein called RAS. RAS, in turn, transmits its growth-promoting signal through two effector molecules, AKT and MEK.

Dr. Kaul demonstrated that drugs that block AKT or MEK activity are effective at reducing optic glioma growth. Importantly, they show that both AKT and MEK work to activate the same protein complex, called the mammalian target of rapamycin (mTOR) complex. This finding builds upon previous work in Dr. Gutmann's laboratory, which revealed that mTOR inhibition reduced optic glioma growth in mice. Based on this preclinical result, mTOR inhibitors are now being used to treat gliomas in children with NF1.

Moreover, MEK or AKT inhibition in *Nf1* genetically-engineered mice also improved the retinal dysfunction that underlies reduced vision. In light of these exciting findings, a clinical trial is now being launched to evaluate MEK inhibitors for NF1 optic glioma.

Kaul A, Toonen JA, Cimino PJ, Gianino SM, Gutmann DH. Akt- or MEK-mediated mTOR inhibition suppresses NF1 optic glioma growth. *Neuro Oncol*. doi:10.1093/neuonc/nou329, 2014. Epub ahead of print.

New Study Uncovers Potential Origin of Plexiform Neurofibromas in Mice

Understanding how plexiform neurofibromas form is an important step towards identifying new treatments for these common tumors in children and adults with neurofibromatosis type 1 (NF1). Plexiform neurofibromas are benign tumors that arise from cells surrounding the developing nerve. A recent study spearheaded by Dr. Lu Le at the University of Texas- Southwestern revealed that these tumors likely arise from a small population of immature cells that eventually give rise to Schwann cells. Loss of *Nf1* gene function in these Schwann cell precursors is sufficient for a plexiform neurofibroma to develop in a mouse.

Plexiform neurofibromas are benign tumors that arise from cells surrounding the developing nerve.

Leveraging this exciting finding, they developed methods to screen promising drugs for the treatment of plexiform neurofibromas. This report was published in the prestigious journal Cancer Cell.

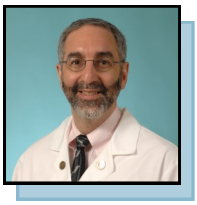
Accompanying this landmark paper was an invited editorial by Dr. David Gutmann, Director of the Washington University NF Center. The importance of Dr. Le's findings and their relevance to future treatments for NF1-associated plexiform neurofibromas was discussed.

Chen Z, Liu C, Patel AJ, Liao CP, Wang Y, Le LQ. Cells of Origin in the Embryonic Nerve Roots for NF1-Associated Plexiform Neurofibroma. *Cancer Cell*. 26(5):695-706, 2014.

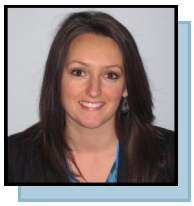
To read more about NF1 research and a listing of recently published articles by NF researchers, please visit: http://nfcenter.wustl.edu/medical-professionals/select-nf-center-medical-articles/. Interested in learning more about clinical studies? Please visit: http://nfcenter.wustl.edu/patients/nf-clinical-trials/

Meet the team

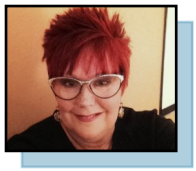
Dr. Kimberly Johnson is an Assistant Professor at Washington University. She has spearheaded work at the Washington University NF Center to develop the international registry of individuals with Neurofibromatosis Type I. She serves as the principal investigator of the initiative. What Kim enjoys most about working with the registry is building a virtual community to conduct research that she hopes will ultimately improve the quality of life for both children and adults living with NF1.



Dr. David H. Gutmann is the Donald O. Schnuck Family Professor of Neurology. Dr. Gutmann was awarded the 2012 Friedrich von Recklinghausen Award and the Distinguished Researcher Award from Washington University School of Medicine in 2013 for his significant contributions to NF research and clinical care.



Nancy Zoellner is the manager for the registry. Nancy holds a Masters Degree in Public Health and a Bachelors degree from Washington University. Nancy has worked with the registry and participants for over two years and enjoys advancing NF1 research with people from all over the world and working to constantly improve registry and team procedures to accommodate all participant needs.



Cathi Klinger is a registered nurse (RN) with over 20 years of experience as a research coordinator/ recruiter. She joined the NPRI in May of 2014 as a research assistant. Cathi most enjoys the challenge of helping new participants to feel comfortable and trusting of our team while contributing to such important research.

Salma Abadin works as a research assistant and facilitates follow up with new registry participants, works with medical records, and assists with data analysis. Salma is from Milwaukee, WI and has a Bachelor of Arts degree in Classics from Macalester College. She enjoys having the opportunity to gain experience with data collection and management as well as interacting directly with participants.

Pan Zhao works as a research assistant and focuses exclusively on data management and cleaning. Pan is from China and has a Bachelor degree in Finance and Accounting. What she enjoys most about working with the NPRI is having the opportunity to enhance her skills with data management and analysis.

Kazi Ahsan recently joined the team as a research assistant and is helping with registry operations as well as studies childhood brain tumors. Kazi is from Bangladesh where he completed his Bachelor of Medicine and Surgery from Chittagong Medical College. What he enjoys most about working with the team is getting to use his clinical background as well as learn new skills surrounding research in public health.

We want to hear what you think about the NPRI Newsletter! For comments, questions, or to submit ideas for future NPRI newsletters please email us at: nf1registry@brownschool.wustl.edu.

This and other newsletters can be viewed at https://nf1registry.wustl.edu/newsletter.aspx.