TheNetworkEdge

The NF Network presents A quarterly research review
by Science Writer Kim Hunter-Schaedle

The Network Edge Volume 11: Spring, 2016

***The Network Edge* brings you regular updates on the latest neurofibromatosis (NF) research and clinical advances from recent scientific publications. *The Network Edge* is organized into "bite sized" sections by specific subtopic, so you can focus on the information that interests you most.**

The Network Edge features…

- **The Bottom Line**: Each section starts with a **summary sentence** highlighting the "take home" points.

- **Federally-Funded Research**: All research identified as being either fully or partly funded by the Congressionally Directed Medical Research Neurofibromatosis Research Program (CDMRP NFRP) or the National Institutes of Health (NIH) is **tagged** CDMRP or NIH after the author name.

- **A Global NF Picture**: To keep you abreast of all NF research advances, *The Network Edge* includes publications from the United States and around the world. **Country of origin** of the research study is indicated after the author name.

- ***The Network Edge* Archive:** At the end of this volume of *The Network Edge*, there is a table showing topics covered by past volumes. This should help if you wish to search for further information in *The Network Edge* archive.

- **FREE Publications**: Many scientific publications are now available at no charge. These are tagged in the text as FREE. To download full articles visit www.pubmed.gov and "search" for the publication title, then follow the links to download.

Highlights from Volume 11 of *The Network Edge*:

- **Congressional Update**: $15 million in funding is secured for the Congressionally Directed Medical Research Program-Neurofibromatosis Research Program (CDMRP-NFRP) in 2016!
- **NF1 Learning Disabilities:** Large brain size in NF1 may relate to learning and social disabilities; the challenge of translating findings in mice to clinical applications in humans is examined.
- **NF1 Tumors:** Old imaging technologies to monitor MPNSTs are used in new ways; hormones and neurofibroma growth are examined; what makes plexiform tumors bleed during surgery?
- **NF2:** Successful use of cochlear implants and auditory brainstem implants in people with NF2 is reported; researchers focus on children with NF2.
- **Schwannomatosis:** New cell lines will help open up research into this rarest form of NF.
- **Breast Cancer in NF1:** Two different outcomes highlight the importance of this area.
- **New Roles for the NF1 Gene**: The NF1 gene emerges as a regulator of brain progenitor cells and also plays a role in chromosome organization and very early cardiovascular development.

The Network Edge: Volume 11 – Contents

1. **CDMRP NFRP Update**
    a. $15 Million for NF Research in 2016!

2. **NF Clinical Trials**
    a. Finding the Best Measures of Response for NF1 Learning and Behavior Disabilities Treatment Trials

3. **NF1 Clinical Management**
    a. Pinpointing the Role of Hormones in NF1 Tumor Growth
    b. Discovering What Makes Plexiform Tumors Bleed During Surgery
    c. Uncovering the Relationship between Diagnosis of NF1 and Risk of Diabetes

4. **NF2 Clinical Management**
    a. Utility of Cochlear Implants and Auditory Brainstem Implants in NF2
    b. Focus on NF2 in Childhood

5. **Breast Cancer Risk in NF1**
    a. Two Cases of Breast Cancer in NF1, Two Different Outcomes

6. **Social Challenges and Quality of Life in Neurofibromatosis**
    a. The Specificities of Learning Disabilities in NF1
    b. Brain Size and Structure Predictive of Learning and Social Disabilities in NF1
    c. Understanding Epilepsy in NF1
    d. Of Mice and Men: The Challenge of Translating Research from Animal to Human

7. **NF1 Malignant Peripheral Nerve Sheath Tumors**
    a. Expanded Uses for FDG-PET/CT Scanning in MPNST Management

8. **What's New in NF Biology?**
    a. New Roles for the NF1 Gene in Normal Brain Development
    b. Shedding Light on Optic Pathway Glioma Growth
    c. A Role for Merlin Interacting Molecule MED28 in Very Early Embryonic Development

9. **Schwannomatosis Update**
    a. New Schwannomatosis Cell Line an Opportunity for Expanding Research

10. **Heart and Blood Vessel Abnormalities in NF1**
    a. High Blood Pressure in Children with NF1
    b. A New Role for the NF1 Gene in the Earliest Events of Cardiovascular Development

11. **NF Genetics Update**
    a. NF1 Gene Mutations: A Brief Overview
    b. Understanding Exons and the Exome in NF1
    c. Impact of Whole Gene Deletion in NF1 vs. NF2
    d. Exploring Alternatives to NF1 Genetic Testing

12. **Legius Syndrome Update**
    a. New Understanding of the Biology of Legius Syndrome

1. CDMRP NFRP Update

a. $15 Million for NF Research in 2016!

The Congressionally Directed Medical Research Program for neurofibromatosis (CDMRP NFRP), overseen by the Department of Defense, is our critical partner in support of NF research. Since 1992, the NFRP has funded a remarkable $258 million of NF research, including some of the most forward-thinking and innovative work being undertaken today. Funding from this source has contributed to major advances toward understanding NF and bringing candidate treatments through the research pipeline and into a national NF Clinical Trials Network that is also funded by CDMRP NFRP.

We are therefore delighted that for fiscal year 2016, Congress has recommended an allocation of $15 million for NFRP! This terrific success is due in large part to the personal visits, letters, and phone calls to Capitol Hill by many individuals with NF and their families and friends as well as to the coordinated efforts of NF advocacy organizations across the country. We have been given an opportunity to explain to House Appropriations Committee staff how NFRP-funded research can benefit not only those with NF but also people facing other diseases, as well as warfighters (service members convalescing at military treatment facilities) who can benefit from NF research advances in areas such as brain tumors, bone repair, muscle weakness, pain management, psychosocial disabilities, quality of life, and vascular disease and wound healing. We are excited to see specifically what new NFRP-funded research will be supported by the 2016 CDMRP NFRP!

2. NF Clinical Trials

The Bottom Line: A review of NF1 learning disabilities clinical trial measures sheds light on differences in results and informs future study design.

a. Finding the Best Measures of Response for NF1 Learning and Behavior Disabilities Treatment Trials

One significant challenge for any clinical trial is how to monitor whether an individual is responding to the treatment being assessed. This is somewhat easier if a physical attribute can be measured, such as a tumor's volume; a response can be verified if the tumor stops growing or shrinks. But how can a researcher best monitor the effect of new candidate treatments for NF1-related learning and behavioral disabilities? There is a great need for such treatments, since these manifestations are estimated to affect as many as eighty percent of individuals with NF1.

Over the past few years, a total of six individual clinical trials that are testing interventions for NF1-related learning disabilities have been reported. These studies have yielded quite different findings, which has been confounding. However the trials have also used a variety of methods to assess the response to treatment. Does this explain the different results reported?

Van der Vaart *et al.* *(Belgium, The Netherlands)* take on this question. They reviewed one of these published trials, a Simvastatin trial conducted in Europe that assessed the effects of 12 months of the drug Simvastatin on learning disabilities and behavior in children with NF1. (Biologically, Simvastatin acts similarly to the drug Lovastatin, which has been assessed in children with NF1 in the United States.) However, unlike Lovastatin, which has shown promise as a treatment, in the initial trial Simvastatin appeared to impact neither learning ability nor behavior. The investigators pondered the possibility that the outcome measurement tests used in the Simvastatin study were in fact not the right ones, and that this problem led to results suggesting the drug had no effect.

To examine this possibility further, Van der Vaart *et al.* guided a group of children aged 8-16 with NF1 through various learning and behavior assessment tests that have been used in the different clinical trials reported. This detailed paper highlights the importance of using the right outcome measures in clinical trials. It also identifies a set of tests that could potentially be used in future clinical trials of treatment for NF1 learning and behavioral disabilities, which should be of interest to many researchers and clinicians working in this area.

3. NF1 Clinical Management

The Bottom Line: The extent of an inflicted individual's NF1 neurofibromas may be hormonally driven, with differences seen between men, women without children, and women with children; plexiform tumors can bleed extensively during surgery, potentially due to weaknesses in blood vessel walls within the area of the tumor; people with NF1 may have a decreased risk of diabetes.

a. Pinpointing the Role of Hormones in NF1 Tumor Growth

Clinical research has suggested that specific reproductive hormones (estradiol, progesterone etc.) might increase the severity of an inflicted individual's NF1-related tumors.

To explore this area further, **Sbidian *et al.*** *(France)* performed a comparison of subcutaneous neurofibromas in men and women with NF1, using a bank of data collected from 2002-2005 for a large-scale NF1 study. Tumor profiles from over one thousand individuals of average age thirty-six were studied.

The results suggest that men and women who have had children both have a greater chance of larger numbers of subcutaneous neurofibromas than do women who have not had children. Women with two or more children were at an increased risk of subcutaneous neurofibromas compared to women with one child. These differences were most prominent under age thirty.

Of over one hundred women with NF1 who were pregnant during the study, two-thirds reported new neurofibromas appearing during pregnancy, and over half reported an enlargement of existing neurofibromas during pregnancy.

The investigators note that data on hormonal levels was not routinely collected from these study participants and that this task should be completed during any future research. These are, however, intriguing findings that could lay the basis for future studies.

b. Discovering What Makes Plexiform Tumors Bleed During Surgery

Plexiform neurofibromas can become large and quite challenging to manage clinically. Surgical removal is a commonly used treatment for these NF1 tumors, but the tumors can bleed extensively during surgery, presenting a health risk. It is not well understood why this bleeding occurs.

Friedrich *et al.* *(Germany)* take on this question in a microscopic analysis of sixty-three clinical samples of neurofibromas. The structure of the blood vessels "feeding" these tumors, as well as the supply of fine nerves that go to the blood vessels, was examined. The results showed that the nerves feeding the blood vessels did not look different from similar nerves in a healthy skin sample from study participants. The investigators suggest, therefore, that differences or "weaknesses" in the walls of blood vessels feeding the tumors may be responsible for the excessive bleeding that can occur during surgical removal of plexiforms. This important topic requires further exploration.

c. Uncovering the Relationship between Diagnosis of NF1 and Risk of Diabetes

Past investigations have suggested that people with NF1 run a much lower risk than the general public of diabetes-related death. While this could potentially be a statistical anomaly due to other causes of mortality being more prominent in the NF1 population (tumors, etc.), it is still intriguing.

Martins *et al.* FREE *(Brazil, United Kingdom)* decided to investigate this further. They measured fasting blood glucose levels in individuals with NF1, as this is a measure most commonly used to identify persons in the general population with, or at risk of, diabetes. Data from fifty-seven individuals aged thirty-five to seventy-four with NF1 was compared to data from individuals drawn from a database of fifteen thousand Brazilians from the general population. For each person with NF1, three comparison individuals were drawn from the general population database based on parameters of sex, age, and body mass index. Anyone with a confirmed diabetes diagnosis was excluded from the study. High fasting blood glucose was defined as 100 mg/dL, the standard used by the American Diabetes Association.

The study showed that the NF1 group had median fasting blood glucose of 86 mg/dL, while in the "control" (database) group the measure was 102 mg/dL. Eighty-four percent of the NF1 group had normal fasting blood glucose, compared to only sixty-four percent in the "control" group. Though the reason for these findings is not immediately clear, the investigators suggest this might be due to different level of function of the hypothalamus or pituitary gland between the two populations; that people with NF1 may have a higher level of insulin sensitivity; or that tumors in individuals with NF1 may be producing insulin-like growth factor 2, which will in turn increase glucose metabolism. Though this study is not ideal in that the comparison "normal" population data is drawn from a historical database, these are interesting results.

4. NF2 Clinical Management

The Bottom Line: Reports detail successful use of cochlear implants and auditory brainstem implants in individuals with NF2; our understanding of NF2 diagnosed in young children is expanding, and the outlook for these children is growing more promising.

a. Utility of Cochlear Implants and Auditory Brainstem Implants in NF2

For individuals with NF2 and progressive hearing loss due to vestibular tumors, hearing function can be aided by placing a cochlear implant in the brain.

Pimentel *et al.* FREE *(Brazil)* present a case report of a fifty-year-old man with NF2 and with hearing loss to different degrees in each ear. The man did not want to have tumor surgery and was therefore treated with radiation therapy. Unfortunately, hearing loss continued, and a cochlear implant was placed in the right ear, which had retained the greatest hearing ability. One year later, the patient showed good results in terms of being able to hear, speak and communicate.

Cochlear implants will only be effective with individuals in whom a functioning auditory nerve remains. This is often not the case following vestibular schwannoma surgery. If the cochlear implant is not an option, the auditory brainstem implant (ABI) may be the next choice. The ABI does not restore hearing but can restore ability to hear some environmental sounds, as well as augment communication function, notably aiding lip reading ability.

Though it is a front burner topic in the NF2 community, the ABI is actually still a fairly new technology - it is estimated that only twelve hundred ABIs have been implanted worldwide – and the long-term impact of this technology on the lives of people with NF2 is still being examined.

Lundin *et al.* *(Sweden)* look at this issue and report very favorably on user experience and quality of life impact of the ABI. The researchers polled a group that included eleven adults living with NF2. These persons had received an ABI in Uppsala, Sweden sometime between 1993 and 2013. Eight of the eleven participants with NF2 reported that they "always" use the ABI. Participants gave largely positive ratings on the improved ability to read lips and to hear environmental sounds with the ABI. Ten of the eleven participants said if they had the choice again, they would still have the ABI placed, and they would recommend the ABI to others.

The group of eleven participants was polled using the NFTI-QoL, an NF2 quality of life survey (previously developed by Hornigold and colleagues in the United Kingdom and reported on in past volumes of *The Network Edge*). The poll demonstrated overall positivity toward the ABI, which participants felt improved their quality of life, made them feel safer and less like they were living in a "bubble."

b. Focus on NF2 in Childhood

Ruggieri *et al.* *(Italy, United Kingdom)* give special consideration to cases of NF2 diagnosed in childhood and the treatment options available. In young adults and those diagnosed even later life, NF2 typically first presents as hearing loss, tinnitus or balance problems. However, when NF2 is diagnosed before puberty, there are two broad categories:

In the first category - congenital NF2 - a child may present with bilateral vestibular schwannomas in the first days or months of life; these may be stable until early adulthood and then progress. In the second category - pre-puberty NF2 - children may present with tumors in parts of the

nervous system before any the vestibular schwannoma appears, and may also have skin tumors and eye features including a type of cataract, all indicators of NF2.

Diagnosis of NF2 in children can nevertheless be challenging. Proper diagnosis may be aided by fully cataloging a child's history with medical issues including seizures and hearing problems, as well as capturing a full family history of relatives who have experiences problems with hearing, balance, etc. Magnetic resonance imaging (MRI) can be employed to detect tumors, and both eye exams and hearing exams should be utilized. If a child is believed to have a diagnosis of NF2, follow-up exams should be administered at 3-6 month intervals, namely to monitor tumor growth.

Although those diagnosed with NF2 as children have in the past been reported as having high risk of early mortality, this situation appears to be improving. In terms of treatment of these tumors in children - as for adults - surgery for tumor removal is the most prominent option, with use of radiation therapy cautioned due to the benign nature of the tumors. Drug therapies are emerging for adults with NF2 and may be utilized in children as well once deemed safe. Some positive results have been reported when bevacizumab, the most promising drug for NF2 tumor treatment, is used as a treatment for children with NF2. These reports have come from a few different studies; the drug has been used cautiously and monitored for side effects. Children with congenital NF2 (born with vestibular tumors or developing these in early life) have seemed to reap the most benefit from bevacizumab.

5. Breast Cancer Risk in NF1

The Bottom Line: Two different outcomes of breast cancer in NF1 highlight the importance of vigilance in breast exams and screening for women with NF1.

a. Two Cases of Breast Cancer in NF1, Two Different Outcomes

Over the past few years, a body of evidence has emerged to suggest that women with NF1 have an increased risk of breast cancer compared to women in the general population. However, as in the general population, outcomes can be very different.

Seo and Park FREE *(Korea)* highlight this in a report of two cases of breast cancer in women with NF1. In the first case, a young woman of age twenty-five presented with invasive ductal carcinoma of the breast, which spread to the lymph nodes. This was treated by surgery, followed by chemotherapy and radiation. At the time of this publication, there had been no recurrence of the breast cancer. The second case involved a woman of forty-two, also with invasive ductal carcinoma of the breast with more extensive spreading to the lymph nodes and liver. Despite surgical treatment, this latter case of breast cancer proved to be fatal.

This report shows - through these two cases - that breast cancer in NF1 can follow different courses, just as it does in the general population. The authors highlight the importance of vigilance in breast cancer screening in NF1. Through a review of the literature, this FREE paper also offers a brief synopsis of what we know today about breast cancer risk in NF1 and is well worth a look for those interested in this topic.

6. Social Challenges and Quality of Life in Neurofibromatosis

The Bottom Line: Children with NF1 face executive function challenges that are quite different from those seen in children with low IQ or autism spectrum disorder; compared to the general population, individuals with NF1 have larger brains, including enlargement of select brain regions, which relates to the development of learning and social disabilities; results from mouse studies have provided clues to understanding and treating NF1 learning disabilities, but challenges still need to be addressed to fully transfer findings to humans.

People with NF can face a broad array of social challenges that affect their quality of life. This aspect of NF1 began with a focus on learning disabilities but has expanded significantly to encompass a range of issues. Some recent advances are presented below.

a. The Specificities of Learning Disabilities in NF1

It is estimated that as many as eighty percent of children with NF1 are at risk of a learning disability, which often affects executive function i.e. the ability to use one's working memory to hold information in the mind while performing a task, the ability to have goal-oriented thoughts and actions, the ability to plan ahead, etc. This can be assessed using specific tests. What is not fully understood is the level of impact of either IQ or autism spectrum disorders (ASD) on these issues (i.e. whether either lower IQ or ASD make executive function worse in these cases).

Plasschaert *et al.* *(Belgium)* explore this in a study of forty-two children with NF1, fifty-two children with autism spectrum disorder, and fifty-two children with typical development. All children in the study were given the same battery of tests to assess different areas of executive functioning. They were also assessed in "real life" using a monitoring scale called BRIEF, wherein higher scores meant the children were having greater problems with executive functioning in real life.

The children with NF1 performed at a lower level in the test than the children with typical development. A consideration of IQ suggested the reduced performance ability in the NF1 group is not simply or necessarily due to lower intelligence. The children with NF1 had higher BRIEF scores (increased executive function difficulties in real life scenarios) than the children with typical development, but lower BRIEF scores (fewer executive function difficulties in real life scenarios) than the children with ASD. Indeed, though just over a third of the NF1 children also had diagnosed ASD, it turned out that the ASD itself was not the major contributor to executive functioning difficulties in the NF1 group. The NF1 group and ASD group were actually shown to have different types of executive functioning difficulties. Children with NF1 in particular experience difficulties with spatial attention span and forward planning.

The authors note that results from this highly complex study will benefit from further exploration. But the study does highlight the specificity of learning difficulties in NF1 and the need for specific interventions to be developed.

b. Brain Size and Structure Predictive of Learning and Social Disabilities in NF1

It is an established fact that individuals with NF1 have overall larger brains than the general population.

Huijbregts *et al.* FREE *(Germany, The Netherlands)* now report evidence for a link between this enlarged brain size and the impact that a diagnosis of NF1 will have on a person's quality of life. The investigators used magnetic resonance imaging (MRI) to examine the volume of different brain regions in young persons with and without NF1 (averaging in age around the early teens). The young people also underwent a series of tests and assessments to measure social skills, behavior, and executive function (ability to plan and organize).

Overall, the MRI revealed that brain regions were larger in the group with NF1 than those from the general population. Specifically, in the NF1 brains, there is an increase in the size of the white matter of the brain (the brain tissue that contains nerve fibers), with reduced size of gray matter (the brain tissue that contains the living bodies of nerve cells). From the tests and assessments emerged the idea that the young people with NF1 experienced diminished social behavior and attention span, with autistic features and with reduced executive function, features not seen in the young people from the general population. Perhaps most intriguing, the size differences in specific brain region differences seemed to correlate with the presence of particular disabilities. There was no correlation of this type in the young people from the general population.

This preliminary but fascinating finding suggests there may be underlying differences in brain structure in people with NF1 that potentially contribute directly to certain behavioral brain functions.

c. Understanding Epilepsy in NF1

Epilepsy is a fairly rare occurrence in NF1, affecting only about five percent of that population. However, epilepsy is a lot more common in people with another rare disease, tuberous sclerosis complex (TSC). Around eighty percent of individuals afflicted with both NF1 and tuberous sclerosis have epilepsy. NF1 and TSC are both neurocutaneous disorders, and both cause tumors to grow in the nervous system, as well as other manifestations. While each of these are rare diseases on their own, it is even less common for an individual to be affected by *both* of them – risk estimate is about one per between twelve and twenty-seven million people.

Mishal *et al.* *(United States)* report on a case of a fifteen-year-old girl with NF1 inherited from her mother and NF1 from her father, and with serious and untreatable epilepsy from the age of five onward. No drugs were successful in treating the epilepsy until the patient was administered felbamate, a drug that acts to inhibit the N-methyl-D-aspartate receptors (NMDARs) in the brain, which have important roles in learning and memory. NMDARs dysfunction has also been linked to various conditions including Alzheimer's disease, Parkinson's disease, and psychiatric disorders, as well as epilepsy; the drug felbamate is fairly well understood and broadly used. The investigators present felbamate as a potentially useful drug for treatment of epilepsy in TSC and of course NF1. Though complicated by the dual diagnosis of TSC, research helps to shed light on the rare complication of epilepsy in NF1.

d. *Of Mice and Men: The Challenge of Translating Research from Animal to Human*

Understanding the biological basis of NF1-related learning disabilities and developing candidate treatments for these disabilities remains a challenging area. As mentioned earlier, researchers have struggled with figuring out how to most effectively measure response to treatments in clinical trials.

Payne FREE *(Australia)* presents a brief but fascinating commentary on the progress and challenges of recent years of study and progress in the field of NF1 learning disabilities. The pioneering findings from mouse models of NF1 learning disabilities that opened the door to our understanding of the biological cause of NF1-related learning disabilities were first reported over ten years ago, and mice have continued to yield intriguing results in this area. However, it has proved challenging to transfer these findings from mice over to human clinical trials.

This helpful FREE review serves as a commentary and introduction to a new report by **Zimerman *et al.*** FREE *(Argentina, Germany)*, who have returned to those original animal studies once more and endeavor to replicate them in humans. Mouse studies have pinpointed hyperactivity of the brain signal GABA as a key contributor to NF1-related learning disabilities. Though drugs to correct this signaling seemed to be effective in restoring learning capacity in the mice, they have not been fully effective in humans with NF1 learning disabilities.

Zimerman and colleagues go "back to basics" and try to understand *why* GABA signaling might be disrupted in the NF1 brain and what this phenomenon might be affecting human behavior. They used a model of motor task learning in a group of people with NF1 with no learning disabilities and compared them to a group of people without NF1. Over time, when learning a task, the brain will exhibit a "practice effect" with reduced ability to re-learn the same task. The NF1 group experienced a significant decline in ability compared to the non-NF1 group. A technique called transcranial magnetic stimulation was used to monitor GABA signaling during learning sessions, and there was some indication of impaired GABA signaling in the group with NF1.

These findings clarify our understanding of how NF1 learning disabilities are regulated in the brain, but they keep our focus on the ongoing challenges of transferring what we learn "from mouse to man."

7. NF1 Malignant Peripheral Nerve Sheath Tumors

The Bottom Line: FDG-PET/CT measures the energy taken into tumor cells and is useful for monitoring expansion of fast-growing MPNST tumor cells. New reports show additional uses for this technique in monitoring the whole body for MPNST location and size, and in tracking surgical biopsy of a tumor sample for pathology analysis ahead of full surgery.

a. *Expanded Uses for FDG-PET/CT Scanning in MPNST Management*

NF1-related plexiform neurofibromas are benign but carry a risk of transforming into malignant peripheral nerve sheath tumors (MPNST). These malignant tumors occur in about 10% of individuals with NF1. The molecular events that cause the transformation from benign plexiform tumor to MPNST

are being extensively studied. Though complex, they are being progressively unraveled so that treatments to prevent and treat these tumors may be developed and utilized.

A great challenge of monitoring and treating both plexiform neurofibromas and MPNSTs is that these tumors can be large and spread out, so it is difficult to get a real handle on their size and rate of growth and difficult to determine whether they might be shrinking in response to treatment. Magnetic resonance imaging (MRI) is now widely used to develop measures of "whole body tumor burden" in individuals with NF1, but MRI is unable to discriminate between malignant and benign tumors. A technique that can discriminate between the two is F-18-fluorodeoxyglucose positron emission tomography/computed tomography (or FDG-PET/CT for short). This technique works by monitoring uptake of sugar (energy) into the tumor cells. MPNSTs grow more actively than the benign plexiform neurofibromas and can be visualized. Recent publications look at the utility of FDG-PET/CT in the clinical management of NF1.

FDG-PET/CT is used widely for studying specific tumor areas, but **Salamon *et al.*** FREE *(Germany)* explore its use in whole body tumor analysis, in the same way MRI is currently used. They studied whole body FDG-PET/CT images and data from thirty-six individuals with NF1, ranging in age from sixteen to sixty-eight. Half of these individuals had been clinically diagnosed with plexiform neurofibromas but no MPNSTs, and half diagnosed with MPNSTs (but no metastases at the time of the study).

Thirty-four of the participants had some level of detectable metabolic activity in the tumors. This means that sixteen of the eighteen who had benign plexiform tumors but no malignancy did have active and ongoing tumor growth. The researchers propose there could be a broader role in the future for FDG-PET/CT in whole body monitoring of plexiform tumors and MPNSTs. Based on their observation of active growth in tumors, they note that this may be helpful for early detection of changes/growth in benign tumors. They also note that there is not always a relationship between a tumor size and growth rate.

Brahmi *et al.* FREE *(France)* further test FDG-PET/CT by using this process during clinical biopsy of a sample of tumor for pathology diagnosis. The FDG-PET/CT imaging was used to identify highly active areas of tumor growth that would be appropriate to biopsy for the most accurate diagnosis.

This study used data from twenty-six individuals aged sixteen to sixty-four with NF1 who had suspected MPNSTs as previously detected by PET/CT. The biopsy study accurately confirmed that seventeen of the tumors were MPNSTs and nine were benign tumors. The malignant tumors were surgically removed when possible, or treated with chemotherapy or radiotherapy in cases where tumors were unresectable. One false negative was identified through the biopsied tissue as benign but with presence of atypical cells; this tumor was confirmed by later surgery and pathology analysis as an MPNST. As can be the case in NF1, the tumor was of a complex makeup with more benign regions abutting malignant regions. Despite this one false negative, the report suggests that there may be a useful role for FDG-PET/CT in the process of NF1 tumor biopsy.

8. What's New in NF Biology?

The Bottom Line: Neurofibromin plays a role in chromosome organization during cell division; the *Nf1* gene is a key player in limiting the abilities of progenitor cells in generating new adult brain cell types; a new molecular regulator of optic pathway glioma growth is identified; a role is discovered for merlin interacting molecule Med28 in blastocyst implantation.

a. New Roles for the NF1 Gene in Normal Brain Development

In exploring some of the roles for the *NF1* gene in the normal cell, **Koliou *et al.*** *(Greece)* show that the *NF1* protein, neurofibromin, collects inside the cell just before the time of mitosis (i.e. when a cell divides and forms two cells). The reason for this is that neurofibromin protein has an important role in the way that chromosomes organize within the cell during the time of cell division. The researchers drill down to understand the complex molecular underpinnings. This is a very intriguing finding, considering that lack of neurofibromin leads to excessive cell division.

During the brain's earliest stages of development, brain matter consists of a cell type called progenitor cells. These have the capability to make the three different cell types the mature brain will need to function: neurons (nerve cells), astrocytes (the cells that support and scaffold the neurons), and oligodendrocytes (the cells that insulate nerve fibers). In some parts of the brain, a tiny number of these progenitor cells stick around in adulthood. They are greatly studied to understand whether they can be used to rebuild or recreate brain tissue after injury or stroke, for example.

A part of the adult brain called the hippocampus contains these progenitor cells, and it has been shown that within the brain these cells can generate neurons and astrocytes, but not oligodendrocytes. However, if these progenitor cells are removed to a dish and treated with particular growth factors they can be induced to generate oligodendrocytes showing they have retained the ability to do this. But what is preventing it from happening in the brain?

To understand this better, **Sun *et al.*** NIH *(United States)* studied mice that were genetically engineered to prevent *Nf1* gene function in its hippocampal progenitor cells. In the absence of *Nf1* gene activity the progenitor cells were able to make all three cell types including oligodendrocytes within the brain. These findings suggest that in the progression to adulthood, the progenitor cells become more and more restricted in their abilities to make the three cell types and that the *Nf1* gene is a key player in this restriction. These findings, published in the high profile journal *Nature Neuroscience,* demonstrate a very important action for NF1 in brain development.

b. Shedding Light on Optic Pathway Glioma Growth

The search for cellular signals that promote the growth of NF1-related tumors is important research, as it should help to identify molecular signals that - if targeted - might reduce or prevent the growth of tumors.

Solga *et al.* NIH, FREE *(United States)* have identified a factor called chemokine ligand 5 - Ccl5 - that promotes growth of NF1-related optic pathway glioma tumors, and may represent a target for treating these tumors and preventing their growth.

The researchers found that Ccl5 is present in tumors in theNF1-related optic pathway gliomas of mice that have been genetically engineered to develop these tumors. Ccl5 was also found to be present in a sampling of biopsies of human Ccl5. When the mouse tumors were treated with the drug minocycline, which reduces the rate of cell growth in the tumor, the levels of Ccl5 dropped.

The researchers were able to make a synthetic version of Ccl5. They then used the substance to treat astrocytes (the cell types that formNF1-related optic pathway gliomas) from the optic nerves of the mice genetically engineered to develop these tumors with NF1. Ccl5 caused the astrocytes to multiply, as they would if they were forming tumors. Most intriguingly, the researchers then made antibodies to Ccl5 and injected this into mice with NF1 optic pathway gliomas. The tumors reduced in

size, and the structure of the retina (the seeing part of the eye) was in a significantly healthier condition. Overall, these are promising findings.

c. A Role for Merlin Interacting Molecule Med28 in Very Early Embryonic Development

Li et al. CDMRP, NIH, FREE *(United States)* explore the biology of Mediator 28, or Med28, a molecular subunit known to interact with the *NF2* protein merlin inside cells, but whose function is not well understood. The investigators create a genetically engineered mouse model in which Med28 is not made. They found that lack of Med28 prevents fertilized early stage embryos (called blastocysts) to die around the time they should be implanting in the uterine wall. Further research suggests that the absence of Med28 affects the ability of cell multiplication and function in various ways.

9. Schwannomatosis Update

The Bottom Line: New schwannomatosis cell lines present an opportunity for expanding research and knowledge around this rare form of NF.

a. New Schwannomatosis Cell Line an Opportunity for Expanding Research

Schwannomatosis is the rarest form of NF, affecting an estimated 1:40,000 individuals. Significant progress has been made in the past few years in terms of unraveling the genetic basis of schwannomatosis, but much remains unknown. The rarity of this condition has contributed to the challenge of studying its clinical progression and testing candidate drug treatments.

Now **Ostrow *et al.*** *(United States)* report exciting progress: they have created immortalized cell lines from the tumors of two individuals with schwannomatosis. Immortalized cell lines must be carefully developed so that they result in cells that continue to replicate but do not lose the molecular features of the original tumors (if they did it would significantly reduce their value for study). The investigators monitored the expression of over 500 genes in the tumor and then in the cells as they were propagated. The results showed the expression patterns were holding, but this is an important step to continue on a regular basis to ensure the integrity of the cells.

Of the two immortalized schwannomatosis cell lines created, one of the individuals involved had reported pain, while the other did not; it turned out the painful tumor had less active SMARCB1 gene, which may be linked with the pain. In any regard, these investigators have generated a new resource that should be extremely valuable in advancing schwannomatosis research.

10. Heart and Blood Vessel Abnormalities in NF1

The Bottom Line: Children with NF1 are at increased risk of hypertension, and there are potential links between this and kidney function; the critical role for the *Nf1* gene in the very earliest events of cardiovascular development is explored.

a. High Blood Pressure in Children with NF1

Hypertension – or high blood pressure – is an increasing health issue for children at large and has also been previously reported as potentially even further increased in children with Nf1.

Dubov *et al.* *(Israel)* examined blood pressure in one hundred and fourteen children from a population aged two to seventeen years who were being regularly followed in a specialist NF1 clinic. A series of three blood pressure measures were taken from all of these children over time. Four children were found to meet the clinical definition of having hypertension (defined as three consecutive recordings of high blood pressure in the hypertensive range). This result was estimated to be about ten times the level of hypertension in the general pediatric population based on previously published results. The children with hypertension were more likely to have urinary tract and kidney-related abnormalities than the others, which suggested there may be a link - perhaps a causal link – to NF1-related hypertension. However, there was no link between children being overweight/obese and occurrence of hypertension in the NF1 population, even though such a link does exist in the general population. These findings support the idea that children with NF1 are at risk of hypertension and should be screened for this as well as for related kidney health issues.

b. A New Role for the NF1 Gene in the Earliest Events of Cardiovascular Development

Genetically engineered mouse models have been used in depth to study the role of the *Nf1* gene in heart and vascular system development. When there is absolutely no *Nf1* gene function in a mouse embryo, the embryo cannot survive to time of birth.

Now **Yzaguirre *et al.*** FREE *(United States)* report that a study of the very earliest events in these embryos lacking *Nf1* gene function can help us understand the genetic and molecular basis of why they might not survive. The researchers show that the embryos are unable to develop the early vestiges of a normal heart structure and start creating healthy blood islands, both which would normally go on to build a normal vascular system. Perhaps most interestingly, though, is the fact that if *Nf1* gene function is partially restored in these mice (rather than by deleting *Nf1* gene function a missense mutation is introduced to the gene so that there will be some gene function – specifically the GAP Related Domain (GRD)), normal vascular development can be at least partially restored. This study sheds light on the regulation of the very earliest events of cardiovascular development and the role of the *Nf1* gene.

11. NF Genetics Update

The Bottom Line: Scientists present a brief review of NF1 genetics and various mechanisms of gene mutations; exons, exomes, and whole gene deletions are examined; researchers attempt an alternative approach to NF1 gene testing.

a. NF1 Gene Mutations: A Brief Overview

Everyone has two copies of the *NF1* gene, but most people with NF1 will be born with a mutation in one copy. This mutation results in an individual's cells making less neurofibromin (NF1 protein) than normal. Neurofibromin's job is to prevent cells from multiplying too much. During all of our lives, gene mutations can develop at random for a range of reasons. In people with NF1, if the

second copy of the *NF1* gene becomes mutated in a cell, it is referred to as a "second hit." Once both copies of the *NF1* gene are mutated in a cell, the cell can no longer make enough working neurofibromin, and affected cells multiply too much. The result is that features of NF1 start to develop, and depending on the cell type, this means nerve tumors form, bone abnormalities develop, etc.

Ninety-five percent of people who present in the clinic with NF1 will have that first mutation in the NF1 gene in all cells throughout their body. Understanding the molecular basis of these mutations is a major focus of NF research. This might help us better understand how specific gene mutations contribute to different features of NF1, and in turn help inform the development of new treatments. Also, understanding of what gene mutations cause which features of NF1 could potentially help to predict the way a case of NF1 might progress.

Shofty *et al.* *(Israel)* present a nice review of this topic.

Key areas of NF1 genetics research include understanding whether specific gene mutations will later signify the appearance of particular features of NF1 (this is called finding genotype-phenotype links); and drilling down, understanding how these mutations come to be, and whether we can use this information to negate the impact of the mutation through some form of treatment.

Below are some recent reports that examine different aspects of NF1 genetics.

b. Understanding Exons and the Exome in NF1

Exons are very important stretches of our genes that code for proteins (such as neurofibromin). When mutations present in exons, they can interfere with the way a protein is made and the way it functions; for example, mutations in neurofibromin exons will lead to clinical NF1.

Hernández-Imaz *et al.* FREE *(Italy, Spain)* took an in-depth look at a genetic process called splicing that can contribute to mutations in an exon region of the *NF1* gene. Specifically, they looked at a region of the NF1 gene called exon 9 that is particularly prone to splicing events; twenty-five percent of exon-based mutations in people with NF1 are exon 9 splice mutations.

The investigators look at five different splicing mutations reported in people with NF1. In brief, regulatory events around exon 9 splice mutations include three specific areas of exon 9. This detailed FREE paper is worth a look for those who are curious about this complex topic.

As noted above, exons are the stretches of our genes that code for proteins. Collectively a person's exons are called the exome, and this can be studied as one large unit.

In an intriguing case study, **McPherson *et al.*** FREE *(Australia, Singapore)* report results from exome gene sequencing of tissue taken from breast cancer, MPNST, and neurofibroma in an adult woman with NF1. The investigators found the germline mutation (i.e. the mutation present at birth in inherited cases of NF1). They also found "second hit" mutations – those that had led to the initiation steps of tumor formation and growth. Second hit mutations were found that were the same in all three tumor types.

Most intriguing was the fact that while the different tumors shared these common mutations, they also each had a distinct genomic profile with mutations in different genes seen only in that tumor type, not in the others. This supports the idea of a background "NF1 syndrome" with common genetic links but also the requirement of tumor- and stage-specific mutations that will lead to the growth of different NF1-related tumors.

c. Impact of Whole Gene Deletion in NF1 vs. NF2

Whole gene deletions and partial gene deletions (microdeletions) are types of mutation that remove function of large stretches of genes all at once.

Smith *et al.* *(United Kingdom)* explored the extent to which these types of mutations are present in different tumor-causing syndromes. They looked at genetic materials from close to six thousand individuals who each had one of seven clinical tumor syndromes, including NF1 and NF2.

Of all syndromes assessed, NF1 had the greatest occurrence of whole gene deletions (just over eight percent of cases) while NF2 had just over three percent of cases with a whole gene deletion. In NF1, whole gene deletions give a more severe clinical impact. In contrast, whole gene deletions in NF2 will in most cases have milder clinical impact. It is suggested that this difference exists because there are other tumor suppressor genes around the location of the NF1 gene which are also lost in the whole gene deletion; the same is not true for NF2. This complex area could contribute to information that may be derived from genetic testing approaches.

d. Exploring Alternatives to NF1 Genetic Testing

Eighty percent of NF1gene mutations result in a shortened version of the NF1 protein, neurofibromin, being made. The shortened, or truncated, neurofibromin can't properly regulate cell growth, and this leads to the growth of tumors and other clinical features of NF1.

Esposito *et al.* *(Italy)* propose that if we can develop a way to detect truncated neurofibromin, this method could potentially be used as an alternative to NF1 genetic testing, which is much more expensive and complex.

The investigators piloted this idea in a study of three hundred and thirty-six individuals who each had at least two clinical signs of NF1 but no genetic diagnosis. Eighty-one percent of the group was found to be positive for truncated neurofibromin protein. Ten individuals with truncated protein were randomly selected and their genetic mutations characterized; from this data it was confirmed they indeed had *NF1* gene mutations of the type that would lead to protein truncation.

The investigators acknowledge that this method has its limitations, needs further development, and does not yield as detailed information as that garnered through genetic testing. However, it is an intriguing approach, and they suggest that it may have future possibility as a less expensive preliminary alternative to NF1 genetic testing.

12. Legius Syndrome Update

The Bottom Line: Scientists are shedding new light on the genetics and biology of Legius Syndrome and its link to NF1.

a. New Understanding of the Biology of Legius Syndrome

Legius Syndrome is a rare disease that can present clinically like a mild form of NF1. Features of Legius Syndrome include café-au-lait spots, armpit freckling, learning disabilities, and macrocephaly (large head circumference). Legius Syndrome is not a form of NF1 but rather is linked to mutations in a specific gene, called *SPRED1;* however, these mutations do lead to disruptions in the cellular RAS-ERK molecular signaling pathway, similar to those that are caused by *NF1* gene mutations.

It is widely known that NF1 protein neurofibromin does interact with the SPRED1 protein, but the details of this interaction have not been clear.

Hirata *et al.* *(Belgium, Japan, Spain, United States)* have studied this interaction, and their findings show that a region of SPRED1 protein called the EVH1 domain interacts with regions of the neurofibromin protein called N-terminal and C-terminal extended regions of the GRD. These interacting regions are vital for normal function of both proteins, and disruptions of these regions are associated with the presence of NF1 and Legius Syndrome. It is supposed that Legius Syndrome is quite mild compared to NF1 because there are three different SPRED proteins; and when SPRED1 function is compromised as it is in Legius Syndrome, SPRED2/3 fulfill the same function. This interesting work sheds light on Legius Syndrome and further highlights its link to NF1.

References

Brahmi M, Thiesse P, Ranchere D, Mognetti T, Pinson S, Renard C, Decouvelaere AV, Blay JY, Combemale P (2015) Diagnostic Accuracy of PET/CT-Guided Percutaneous Biopsies for Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis Type 1 Patients. PLoS One. Oct 7;10(10):e0138386. doi: 10.1371/journal.pone.0138386. eCollection 2015.

Dubov T, Toledano-Alhadef H, Chernin G, Constantini S, Cleper R, Ben-Shachar S. (2015) High prevalence of elevated blood pressure among children with neurofibromatosis type 1. Pediatr Nephrol. Aug 28. [Epub ahead of print]

Esposito T, Piluso G, Saracino D, Uccello R, Schettino C, Dato C, Capaldo G, Giugliano T, Varriale B, Paolisso G, Di Iorio G, Melone MA (2015) A novel diagnostic method to detect truncated neurofibromin in Neurofibromatosis 1. J Neurochem. Oct 19. doi: 10.1111/jnc.13396. [Epub ahead of print]

Friedrich RE, Behrendt CA, Glatzel M, Hagel C (2015) Vascular Innervation in Benign Neurofibromas of Patients with Neurofibromatosis Type 1. Anticancer Res. 35(12):6509-16.

Hernández-Imaz E, Martín Y, de Conti L, Melean G, Valero A, Baralle M, Hernández-Chico C (2015) Functional Analysis of Mutations in Exon 9 of NF1 Reveals the Presence of Several Elements Regulating Splicing. PLoS One. Oct 28;10(10):e0141735. doi: 10.1371/journal.pone.0141735. eCollection 2015.

Hirata Y, Brems H, Suzuki M, Kanamori M, Okada M, Morita R, Llano-Rivas I, Ose T, Messiaen L, Legius E, Yoshimura A (2015) Interaction between a domain of a negative regulator of the RAS-ERK pathway, SPRED1, and the GTPase-Activating Protein-Related Domain of neurofibromin is implicated in Legius Syndrome and Neurofibromatosis Type 1. J Biol Chem. Dec 3. pii: jbc.M115.703710. [Epub ahead of print]

Huijbregts SC, Loitfelder M, Rombouts SA, Swaab H, Verbist BM, Arkink EB, Van Buchem MA, Veer IM (2015) Cerebral volumetric abnormalities in Neurofibromatosis type 1: associations with parent ratings of social and attention problems, executive dysfunction, and autistic mannerisms. J Neurodev Disord. 7:32. doi: 10.1186/s11689-015-9128-3. Epub 2015 Oct 15.

Koliou X, Fedonidis C, Kalpachidou T, Mangoura D (2015) Mechanism of nuclear import of neurofibromin for localization on the spindle and function in chromosome congression. J Neurochem. Oct 22. doi: 10.1111/jnc.13401. [Epub ahead of print]

Li L, Walsh RM, Wagh V, James MF, Beauchamp RL, Chang YS, Gusella JF, Hochedlinger K, Ramesh V (2015) Mediator Subunit Med28 Is Essential for Mouse Peri-Implantation Development and Pluripotency. PLoS One. Oct 7;10(10):e0140192. doi: 10.1371/journal.pone.0140192. eCollection 2015.

Lundin K, Stillesjö F, Nyberg G, Rask-Andersen H (2015) Self-reported benefit, sound perception, and quality-of-life in patients with auditory brainstem implants (ABIs). Acta Otolaryngol. Oct 1:1-6. [Epub ahead of print.

Martins AS, Jansen AK, Rodrigues LO, de Matos CM, Souza ML, de Souza JF, Sander Diniz MF, Barreto SM, Diniz LM, Rezende NA, Riccardi VM (2015) Lower fasting blood glucose in neurofibromatosis type 1.Endocr Connect. Dec 2. pii: EC-15-0102. [Epub ahead of print]

McPherson JR, Ong CK, Ng CC, Rajasegaran V, Heng HL, Yu WS, Tan BK, Madhukumar P, Teo MC, Ngeow J, Thike AA, Rozen SG, Tan PH, Lee AS, Teh BT, Yap YS (2015) Whole-exome sequencing of breast cancer, malignant peripheral nerve sheath tumor and neurofibroma from a patient with neurofibromatosis type 1. Cancer Med. Oct 3. doi: 10.1002/cam4.551. [Epub ahead of print]

Mishal NM, Arkilo D, Tang J, Crawford JR, Wang SG (2015) A Potential Role for Felbamate in TSC- and NF1-Related Epilepsy: A Case Report and Review of the Literature. Case Rep Neurol Med. 2015:960746. doi: 10.1155/2015/960746. Epub 2015 Oct 22.

Ostrow KL, Donaldson K, Blakeley J, Belzberg A, Hoke A (2015) Immortalized Human Schwann Cell Lines Derived From Tumors of Schwannomatosis Patients. PLoS One. Dec 14;10(12):e0144620. doi: 10.1371/journal.pone.0144620. eCollection 2015.

Payne JM (2015) Bridging the Gap Between Mouse Behavior and Human Cognition in Neurofibromatosis Type 1. EBioMedicine. 2(10):1290-1. doi: 10.1016/j.ebiom.2015.09.013. eCollection 2015.

Pimentel PS, Ramos DS, Muniz L, de Carvalho Leal M, Caldas Neto SD (2015) Cochlear implant in a patient with neurofibromatosis type 2 undergoing radiotherapy. Braz J Otorhinolaryngol. Sep 7. pii: S1808-8694(15)00127-5. doi: 10.1016/j.bjorl.2015.04.004. [Epub ahead of print]

Plasschaert E, Van Eylen L, Descheemaeker MJ, Noens I, Legius E, Steyaert J (2016) Executive functioning deficits in children with neurofibromatosis type 1: The influence of intellectual and social functioning. Am J Med Genet B Neuropsychiatr Genet. Jan 15. doi: 10.1002/ajmg.b.32414. [Epub ahead of print]

Ruggieri M, Praticò AD, Evans DG (2015) Diagnosis, Management, and New Therapeutic Options in Childhood Neurofibromatosis Type 2 and Related Forms. Semin Pediatr Neurol Dec;22(4):240-58. doi: 10.1016/j.spen.2015.10.008. Epub 2015 Oct 28.

Salamon J, Papp L, Tóth Z, Laqmani A, Apostolova I, Adam G, Mautner VF, Derlin T. (2015) Nerve Sheath Tumors in Neurofibromatosis Type 1: Assessment of Whole-Body Metabolic Tumor Burden Using F-18-FDG PET/CT. PLoS One. Dec 1;10(12):e0143305. doi: 10.1371/journal.pone.0143305. eCollection 2015.

Sbidian E, Duong TA, Valeyrie-Allanore L, Wolkenstein P (2015) Neurofibromatosis type 1 : Neurofibromas and Gender. Br J Dermatol. Jun 26. doi: 10.1111/bjd.13966. [Epub ahead of print]

Seo YN, Park YM (2015) Association between Neurofibromatosis Type 1 and Breast Cancer: A Report of Two Cases with a Review of the Literature. Case Rep Med. 2015:456205. doi: 10.1155/2015/456205. Epub 2015 Oct 29.

Shofty B, Constantini S, Ben-Shachar S (2015) Advances in Molecular Diagnosis of Neurofibromatosis Type 1. Semin Pediatr Neurol. Dec;22(4):234-9. doi: 10.1016/j.spen.2015.10.007. Epub 2015 Oct 28.

Smith MJ, Urquhart JE, Harkness EF, Miles EK, Bowers NL, Byers HJ, Bulman M, Gokhale C, Wallace AJ, Newman WG, Evans DG (2015) The Contribution of Whole Gene Deletions and Large Rearrangements to the Mutation Spectrum in Inherited Tumor Predisposing Syndromes. Hum Mutat. Nov 30. doi: 10.1002/humu.22938. [Epub ahead of print]

Solga AC, Pong WW, Kim KY, Cimino PJ, Toonen JA, Walker J, Wylie T, Magrini V, Griffith M, Griffith OL, Ly A, Ellisman MH, Mardis ER, Gutmann DH (2015) RNA Sequencing of Tumor-Associated Microglia Reveals Ccl5 as a Stromal Chemokine Critical for Neurofibromatosis-1 Glioma Growth. Neoplasia. Oct;17(10):776-88. doi: 10.1016/j.neo.2015.10.002.

Sun GJ, Zhou Y, Ito S, Bonaguidi MA, Stein-O'Brien G, Kawasaki NK, Modak N, Zhu Y, Ming GL, Song H (2015) Latent tri-lineage potential of adult hippocampal neural stem cells revealed by Nf1 inactivation. Nat Neurosci. Nov 2. doi: 10.1038/nn.4159. [Epub ahead of print]

van der Vaart T, Rietman AB, Plasschaert E, Legius E, Elgersma Y, Moll HA and the NF1-SIMCODA Study Group (2015) Behavioral and cognitive outcomes for clinical trials in children with neurofibromatosis type 1. Neurology. 2015 Oct 30. pii: 10.1212/WNL.0000000000002118. [Epub ahead of print]

Yzaguirre AD, Padmanabhan A, de Groh ED, Engleka KA, Li J, Speck NA, Epstein JA (2015) Loss of neurofibromin Ras-GAP activity enhances the formation of cardiac blood islands in murine embryos. Elife. Oct 13;4. doi: 10.7554/eLife.07780. [Epub ahead of print]

Zimerman M, Wessel MJ, Timmermann JE, Granström S, Gerloff C, Mautner VF, Hummel FC (2015) Impairment of Procedural Learning and Motor Intracortical Inhibition in Neurofibromatosis Type 1 Patients. EBioMedicine. Sep 1;2(10):1430-7. doi: 10.1016/j.ebiom.2015.08.036. eCollection 2015.

The Network Edge Archive

This table indicates which topics have been covered in past volumes of *The Network Edge*. Past volumes may be accessed online at:
http://www.nfnetwork.org/understanding-nf/the-network-edge-science-column

CONTENTS	Volume 1 - Fall 2012	Volume 2 - Winter 2013	Volume 3 - Spring 2013	Volume 4 - Summer 2013	Volume 5 - Fall/ Winter 2013	Volume 6 - Fall 2014	Volume 7 - Winter 2014	Volume 8 - Spring 2015	Volume 9 - Summer 2015	Volume 10 - Fall 2015	Volume 11 - Winter 2016
CDMRP NFRP Updates	X	X						X			X
NF1 Clinical Trials	X		X			X	X	X			X
NF1 Clinical Management	X	X	X	X	X	X	X	X		X	X
NF1 Learning Disabilities	X	X	X	X	X	X	X		X	X	X
NF1 Bony Abnormalities	X	X	X	X	X	X	X	X	X		
NF1 Malignant Peripheral Nerve Sheath Tumors		X		X	X	X	X	X			X
Heart and Blood Vessel Abnormalities in NF1		X	X	X	X	X					X
Breast Cancer Risk in NF1	X			X					X		X
Other Clinical Features of NF1	X		X	X	X	X	X		X		
What's New in NF1 Biology?	X	X	X	X	X	X	X	X	X	X	X
NF2 Clinical Trials	X		X			X	X		X	X	
NF2 Clinical Management	X	X	X	X	X	X	X	X		X	X
What's New in NF2 Biology?	X	X	X	X	X	X	X	X		X	X
Schwannomatosis Update	X		X	X	X	X		X			X
Legius Syndrome Update	X		X			X					X
The Evolving Link Between NF and Cancer		X				X					
Altered Brain Function in NF1				X					X	X	
NF1 and the Eye: Optic Pathway Gliomas and Other Features				X	X	X		X	X	X	X
NF Genetics Update				X	X		X	X		X	X
Pheochromocytoma in NF1			X							X	
Social Challenges in Neurofibromatosis					X	X	X	X	X	X	X
NF1 and Autism					X			X			X

213 S. Wheaton Avenue, Wheaton, IL 60187
Phone 630-510-1115 **www.nfnetwork.org** **admin@nfnetwork.org**