

The Network Edge: Volume 3 - May 2013

The Network Edge brings you quarterly updates on the latest neurofibromatosis (NF) research and clinical advances from recent scientific publications. *The Network Edge* is organized into 'bite sized' sections by NF topic area, so you can focus in on the information that is of most interest for you.

NEW FEATURES in Volume 3 of *The Network Edge* ...

- **The Bottom Line**: Each section starts with a **summary sentence** highlighting the 'take home' points from that section.
- **Highlighting 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.

Highlights from Volume 3 of *The Network Edge*:

- Evaluating progress in the CDMRP NF Clinical Trial Consortium
- Bevacizumab is not effective in shrinking NF2 meningiomas
- Women with NF1: challenges faced in pregnancy
- Young adults with NF1 often overlook the importance of their clinical care
- New quality of life surveys for those with NF1 and NF2 could help detect health concerns
- High blood pressure and vascular health issues may affect children with NF1
- Breakthrough findings uncover the basis of nerve damage and pain in NF2
- International consensus update on schwannomatosis diagnosis and clinical care
- NF2 diagnosis in infancy may predict poorest outlook
- Update on genetic testing for Legius Syndrome

The Network Edge: Volume 3 - Contents

1. NF1 Clinical Trials
 2. NF2 Clinical Trials
 3. NF1 Clinical Management
 4. NF2 Clinical Management
 5. NF1 Learning Disabilities
 6. NF1 Bony Abnormalities
 7. Heart and Blood Vessel Abnormalities in NF1
 8. Other Clinical Features of NF1
 9. Schwannomatosis Update
 10. What's New in NF2 Biology?
 11. What's New in NF1 Biology?
 12. Legius Syndrome Update
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1. NF1 Clinical Trials

The Bottom Line: The CDMRP-funded Clinical Trials Consortium continues through 2017, reports challenges addressed and progress made to date; assessing radiofrequency therapy for dermal neurofibromas; natural dietary supplement complex may help relieve NF1 related migraines.

The largest research program ever funded by the Congressionally-Directed Medical Research Neurofibromatosis Program (CDMRP NFRP) is the Neurofibromatosis Clinical Trials Consortium (NFCTC). Opened in 2007, NFCTC has made it possible to do multi-center NF clinical trials on a national scale. NFCTC allows multiple clinics to recruit participants, which shortens the time needed to complete trials, and gives people in more regions the opportunity to participate in a clinical trial. NFCTC funding has now been extended by CDMRP NFRP through 2017, with more clinical sites potentially participating in future trials. It is not an exaggeration to say that NFCTC has opened a new era of hope for those with NF.

In **Gutmann et al.** ^{CDMRP} (*United States*) the physicians leading the NFCTC provide a summary of their activity to date, and their future plans. The clinical trials opened by NFCTC to date include Rapamycin for the treatment of NF1 plexiform tumors; Lovastatin for the treatment of NF1 learning disabilities; and RAD001 for the treatment of NF1 low grade gliomas. NFCTC is a groundbreaking initiative, but it has not been without its challenges. These have included the sheer logistics of managing the administration of paperwork for all sites, such as securing institutional approval in order for multiple clinics to participate in a shared trial. NFCTC also took time initially to carefully consider and select the best drug candidates for trials, and to create a 'pipeline' of drugs that would be the next to go into trials. One of the lessons learned by the NFCTC experience has been the importance of paying attention to the results emerging from preclinical trials (i.e. drug testing in mice) and to utilize preclinical results to inform decision making for future NFCTC clinical trial drugs.

The following two reports summarized are investigative studies rather than clinical trials, but they are included in this section as they report on treatment and therapy options that may be of interest.

Children with NF1 can have an increased risk of migraines, which can be temporarily disabling and impact significantly on quality of life. **Carotenuto et al.** (*Italy*) tested the use of natural dietary supplements - a complex of Ginkgolide B, Coenzyme Q10, Riboflavin and Magnesium - as a possible NF1 migraine preventative. The supplement complex was given twice daily for 6 months to school age children with NF1 who had a history of migraine without 'aura' (i.e. they did not having visual, language or motor disturbance preceding their migraines). The supplement appeared to reduce frequency, duration, intensity, and grade of disability of the migraines. Though this is a single, small study, it opens the way to further investigation of the use of these dietary supplements for management of NF1 related migraines.

NF1 frequently causes the growth of cutaneous neurofibromas (also known as dermal neurofibromas), tumors which are visible on the skin surface. These neurofibromas can be very numerous and large, so although they are benign (non-cancerous) tumors, they can have a significant impact on quality of life. Cutaneous neurofibromas may be removed by surgery, laser therapy, electrodesiccation and other approaches, though these treatments can be time consuming, expensive, and may leave scarring. There is also a significant chance that the tumors will grow back in time. **Kim et al.** (*Korea*) assessed the use of the technique of radiofrequency to remove cutaneous neurofibromas in 16 persons with NF1 aged 16 to 67 years. Most of the study participants had 1,000 or more dermal neurofibromas on the trunk of the body before the procedure. Radiofrequency was done under general anesthesia; an average treatment lasted 2 hours and targeted 80 neurofibromas during that time. In follow up, the participants reported that they were happy with the results, reporting only a little scarring. The authors suggest that because radiofrequency can target a large number of tumors at once, it should be considered as an option for cutaneous neurofibromas. While radiofrequency is currently used in the United States to treat other tumor types (e.g. <http://www.mayoclinic.org/radiofrequency-ablation/about.html>), this Korean study appears to be the first published report of its use in NF1 cutaneous neurofibromas.

2. NF2 Clinical Trials

The Bottom Line: Bevacizumab (Avastin) is not an effective drug therapy for NF2-related meningiomas.

The drug Bevacizumab (also known as Avastin) has shown positive results for the treatment vestibular schwannomas (VS tumors) in persons with NF2. The drug shrinks these tumors, and in some cases even restores hearing. However, there has been no definitive report on whether Bevacizumab also shrinks meningiomas, another type of brain tumor commonly seen in NF2. **Nunes *et al.*** ^{NIH} (*United States*) addressed this question in a small study of 15 people with NF2. This group all had VS tumors, and all had received Bevacizumab for the treatment of these tumors. These 15 persons also had, between them, a total of 48 individual meningiomas; these tumors were monitored for changes in volume following the Bevacizumab treatment. This study showed that although 30% or so of the meningiomas showed a response to Bevacizumab (as determined by at least 20% shrinkage of tumor) this was a temporary response on average lasting for less than 4 months. At the molecular level, it is known that Bevacizumab acts to 'correct' over-activity of the cell signal VEGF. In tumors, hyperactive VEGF signaling stimulates the growth of new blood vessels; these in turn 'feed' the tumor and help promote its growth. With that in mind, the group analyzed a number of NF2 meningioma tumor samples looking for evidence of overactive VEGF signaling and blood vessel growth irregularities. However, this was absent.

The study concluded that Bevacizumab is not an effective therapy for treatment and shrinkage of NF2 related meningiomas. Furthermore the results suggest that pursuing the avenue of drugs which target blood vessel growth might not be a rational strategy for treating meningioma.

3. NF1 Clinical Management

The Bottom Line: Women with NF1 face extra challenges in pregnancy and can benefit from 'clinical team' monitoring; new NF1 quality of life clinic survey is developed; young adults with NF1 may be likely to neglect their own NF1 clinical care; early life imaging of the eye socket in NF1 could help with early detection of potentially disfiguring plexiform neurofibromas.

a. *NF1 and Pregnancy*

Couples thinking of starting a family, and where one or both partners have NF1, will often seek genetic counseling to learn more about the potential effects of NF1 on the child to be conceived, and on the pregnant mother. More information is emerging about the challenges faced by women with NF1 during pregnancy; these vary between women, but might include onset of hypertension or enlargement of existing neurofibromas. There is also a possibility that new tumors will appear during pregnancy including pheochromocytoma (a tumor on the adrenal gland which can contribute to certain cardiovascular complications) or malignant peripheral nerve sheath tumors (MPNST). Two recent studies have delved into the issues faced by women with NF1 during pregnancy.

Cesaretti *et al.* (*Italy*) monitored the pregnancies of 43 women with NF1 who collectively gave birth to a total of 65 children over the course of the multiple-year study. These women were evaluated throughout pregnancy by a 'team' that included geneticists, gynecologists and other specialists depending on the individual clinical concerns and needs of the women. Almost half the women experienced an increase in the size of their neurofibromas during pregnancy, while two women developed neurofibromas for the first time during pregnancy. Other complications seen in the group

were the appearance of new café au lait spots (the pigmented skin markings that are characteristic of NF1) and the onset of hypertension and proteinuria.

All of the women on the study were offered prenatal diagnosis to determine whether the unborn child carried the *NF1* gene mutation. Interestingly, those who took advantage of this service were more likely to be women who themselves were the first person in their family to have NF1. In contrast, mothers-to-be who had a parent with NF1 were less likely to seek prenatal diagnosis. The authors suggested that this might be because mothers-to-be who had family members living with NF1 might have more of an idea of what to expect from such a diagnosis, and perhaps be less daunted by the prospect of having a child with NF1, than those with no affected family members.

Using a database of information called the United States Nationwide Inpatient Sample **Terry et al.** (*United States*) reviewed the cases of 1500 women with NF1 who were pregnant between the years 1988 and 2009. Pregnancy complications identified in this group of women with NF1 included pregnancy-related hypertension, pre-eclampsia, cerebro-vascular disease, preterm labor and cesarean delivery. However these women were not at increased risk for acute cardiac events, stillbirth, or death during childbirth compared to mothers-to-be without NF1.

Together, these two studies highlight the challenges faced by women with NF1 during pregnancy and the potential complications that may arise. The Italian study also lends support to the potential value of having, where possible, a multidisciplinary specialist team to monitor mothers-to-be who have NF1.

b. Quality of Life and Access to Care

When someone with NF1 gets positive results from taking a drug, such as shrinkage of their tumors or improvement of learning disabilities, this is likely to bring with it an improved quality of life for that person. The same is true if the individual is receiving good standard health care on an ongoing basis that is keeping their NF1 stable and manageable. However, quality of life can be a tricky parameter to measure: there are often no hard and fast numbers to track, only subjective factors such as a feeling of well being. **Nutakki et al.** ^{CDMRP, NIH} (*United States*) have taken on this area and developed an NF1 health-related quality of life measuring 'tool' (NF1 HRQOL). This 'tool' is actually a survey for individuals with NF1 that asks a variety of questions about their state of physical and mental well being. The results are converted into a 'measure' that can then be recorded for each person taking the survey. NF1 HRQOL was pilot-tested in 134 adults with NF1, and the feedback from this group was used to improve the survey, which is now ready to be more widely used. Looking ahead, NF1 HRQOL could be used by NF1 clinics for example at annual check-ups and might help to identify problems that are missed by the clinical exam. This measure can also monitor a person over many years to identify gradual changes.

The transition from childhood to young adulthood can be a challenging time for anyone, and perhaps more so for someone with NF1. At this time, the young person often becomes responsible for managing their own NF1 care. This might include switching from a pediatrician to an adult doctor, or it might include geographical relocation for college or work, which means finding a new NF doctor. To learn more about this, **Oates et al.** (*Australia*) interviewed and examined 17 young adults with NF1 aged 25 to 33. Most of the group had not been clinically examined in 8 years, and a few of them had not gone to a doctor even when they had an NF1-related symptom that they felt might need attention. When clinically examined, these young people were found to have NF1-related concerns including spinal cord compression, vascular defects, tumor related pain, potential malignancy and brain tumors. The study found that these young people were generally not well informed about NF1 or how they should be

taking care of it. Although the health care systems are different in Australia than in the US and elsewhere in the world, this study highlights the importance of making sure young adults with NF1 receive sufficient support and information during this period of transition in life.

c. Management of NF1 Tumors Affecting Eye and Vision

Optic pathway gliomas are a type of tumor that can occur in NF1, and they can have a significant impact on eye function and vision. Though often less well discussed, NF1 plexiform neurofibromas can also develop around the eye, where they can press directly on the eye itself, or on the bone socket around the eye, affecting development and function. Two recent studies have identified measures that can be used for measurement and early detection of plexiform neurofibromas around the eye.

If plexiform neurofibromas develop around the eye early in life they can cause abnormal growth of the skull eye socket, leading to what is called sphenoid wing dysplasia. **Friedrich et al.** (United States) examined radiographs of eye sockets in 73 persons with NF1 and indications of some abnormality of the eye socket area. Radiographs are often the first tool that doctors use to diagnose NF1 limb bone or spine abnormalities, but radiographs are not routinely used to look at the eye socket. The study found that 53 of the 73 NF1 cases examined had plexiform neurofibromas in the area of the eye, and that 30 of these people had an associated sphenoid wing dysplasia. From this study, the authors suggest that radiograph imaging of the eye in early life might provide a simple approach for early detection of these tumors around the eye. This would allow for early surgery or treatment and might allay the further progression of bony abnormalities around the eye which could be hard to correct later.

Avery, Dombi et al. ^{NIH} (United States) also analyzed plexiform neurofibromas around the eye in 21 children with NF1, in this case using the technique of volumetric magnetic resonance imaging (3D MRI). 13 of the children examined were found to have developed amblyopia ('lazy eye') due to having a plexiform neurofibroma of greater than 10ml in volume around the eye. In 3 children studied, both eyes were affected in this way. The authors recommended that volumetric MRIs can be useful to monitor tumor progression and determine when surgical intervention may be needed.

Finally in the arena of NF1 eye-related manifestations, **Büyükkapu-Bay et al.** (Turkey) reported a case of a 4-year-old boy with NF1 and with two tumor types - a meningioma and an OPG - within the same optic nerve. Though this is a single case and considered to be a very rare finding, it highlights the importance of a thorough clinical evaluation for tumor identification.

d. NF1 Genetic Testing Update

One of the greatest challenges for physicians caring for someone with NF1 is being able to detect the potential development of a malignant peripheral nerve sheath tumor (MPNST). These tumors are cancerous and difficult to treat, so earliest possible detection is critical. Three recent studies have identified possible new markers for MPNSTs. Note that MPNSTs can also occur in people who do not have NF1, and this is mentioned in the study below.

Weng et al. (Japan) looked at specific markers in the blood called microRNAs, comparing these between people with NF1 - either with or without MPNSTs - and people who had MPNSTs but did not have NF1. The study identified three microRNAs – called MiR-801, miR-214, and miR-24 – which are present only in the blood of people who have MPNSTs, regardless of whether these people also have NF1. Though this is a research report and therefore early stage work, these markers may in the future help to detect MPNSTs early, in people with NF1 as well as in the general population.

Microdeletions are a genetic mutation type seen in about 5% of individuals with NF1. Microdeletions affect the NF1 gene and also genes adjacent to it on the chromosome. A diagnosis of a microdeletion in NF1 can lead to more severe NF1 manifestations including dermal neurofibromas (dNFs), significant mental challenges and increased risk of MPNSTs. **Teribas et al.** (*Spain*) report the development a new quantitative gene test to identify NF1 microdeletions. This is a research study report, so further validation studies will be required before this genetic test is used in the clinic setting. However in the future this could potentially be a valuable clinical diagnostic tool.

Spinal nerve tumors occur in about 40% of cases of NF1 and fall into two clinical groups: ‘classical’ NF1, where the person has one or just a few spinal tumors; and ‘spinal neurofibromatosis’, where the person has multiple spinal tumors on both sides of the spinal cord, but otherwise only minimal features of NF1. **Carman et al.** (*Turkey*) report on a young individual who appears to be a crossover case between these two diagnoses, having features of classical NF1 as well as numerous spinal neurofibromas. This person also carried a novel *NF1* gene mutation – a single base deletion, called c.389delA in exon 4a of the *NF1* gene. Though just a single case, this may represent a new variant form of NF1.

4. NF2 Clinical Management

The Bottom Line: The age when NF2 is diagnosed may predict the likely long-term clinical outcome; the importance of monitoring for spinal tumors in NF2; occurrence of meningiomas in NF2 may predict a poor clinical outcome; a new NF2 ‘quality of life’ clinic survey is developed; clinical management approaches for hearing preservation.

a. *The Impact of Age of NF2 Diagnosis on Clinical Outcome*

NF2 has in the past largely been diagnosed in the teens or twenties. However there are an increasing number of diagnoses in young children, and NF2 can also be diagnosed in older people. Two recent studies take on two extremes of NF2 diagnosis age – persons under 1 year, and persons over 70 – to compare the progression of NF2 in these different groups.

NF2 diagnoses in children under 1 year of age have been reported anecdotally as case studies, but there has been no long term follow-up on this age group. **Ruggieri et al.** (*Italy*) tracked three children diagnosed with NF2 by 5 months of age, monitoring them in the clinic from 1997 to 2012. The children were all diagnosed with small bilateral vestibular schwannomas (VS tumors). The three children had no other symptoms until their early teens, but two of the children saw a rapid progress in their NF2, at ages 11 and 15. These children developed more rare features of NF2: skin plaques, retinal lesions, and lens opacity, as well as additional brain tumors. Though a tiny study, this is the first of its kind to follow such young children with NF2 through early life. The authors conclude that when NF2 is diagnosed in infants, it might have a more severe progression than when NF2 is diagnosed later in life. They also suggest that infant diagnosis of NF2 may actually represent a unique congenital form of NF2.

At the other end of the age scale, **Goutagny et al.** (*France*) monitored 7 people diagnosed with NF2 at age 70 or older. None of these individuals had an *NF2* gene mutation detectable in the blood, which suggests that they had segmental NF2 which is typically less severe. Overall tumor growth was slow in this group, and the NF2 more or less stabilized. Though a small study, it suggests that NF2 diagnosed in later life may be less severe and can be managed by ‘watch and wait’ strategies.

Matsuo et al. (Japan) used the Japanese NF2 Registry to examine the records of 312 persons diagnosed with NF2 at ages 2-76 years. The study focused in on one third of this group who expressed NF2 symptoms and received diagnosis before age 20. Over time, this group was found to be more likely than the rest of the group to develop spinal schwannomas, new brain tumors, skin lesions and to experience convulsions. Again this supports to the idea that earlier diagnosis of NF2 may bring a more severe outcome.

Earlier in this Volume of *The Network Edge* we reported the development of a new NF1 quality of life survey. We are happy to also report that **Hornigold et al. (United Kingdom)** have created an NF2 quality of life survey (NFTI-QOL). The survey was pilot tested in a number of persons with NF2, and is now ready for broad use. Like the NF1 survey, this will be useful in identifying issues that may be missed in clinic, and in tracking issues as they change over time for those living with NF2.

b. Tumor Monitoring and Surgery for NF2

A diagnosis of NF2 brings with it a risk of developing schwannoma tumors along the spine. **Aboukais, Baroncini et al. (France)** studied 80 individuals diagnosed with NF2 and tracked them during the period 1987 to 2011. The average age of NF2 diagnosis in the group was around 27 years, and the average follow up period per person was around 9 years. All participants received annual MRIs to monitor tumors in the skull and spine. 48 members of the group had spinal tumors. 20 of these tumors were symptomatic but were not surgically removed; another 21 were symptomatic and were surgically removed. On average, the persons that developed spinal tumors had NF2 diagnosed at a younger age than those without spinal tumors. Examining the genetics of these persons, those with spinal tumors also had a greater occurrence of types of genetic mutations in the *NF2* gene called nonsense and frame shift mutations. These mutations are typically associated with more aggressive cases of NF2. The study presents a case for routine spinal monitoring in NF2.

Meningiomas can occur in NF2 in the brain and spinal cord, but the way in which these tumors grow is not well understood. To address this, the same group that conducted the spinal tumor study above, **Aboukais, Zairi et al. (France)** also studied the same population of 80 individuals with NF2 to look at meningiomas. 46 people in the group had meningiomas, and 34 did not. As mentioned above, the group all received annual brain and spine MRIs to monitor tumor growth. The group that had meningiomas also had an increased risk of developing additional brain schwannomas, spinal tumors and skin tumors. The persons with meningiomas also underwent more surgical procedure over the period of studies. The authors conclude that the presence of meningiomas in NF2 may predict a poor outcome and the likelihood of further complications of NF2.

Two recent studies examine different aspects of hearing preservation in NF2.

Moffat et al. (United Kingdom) examined the long-term outcome of using the translabyrinthine surgery approach for management of VS tumors in 148 persons with NF2. The surgeries were conducted at two NF2 medical units in the United Kingdom. The surgery was deemed to be a satisfactory tool for the management of VS tumor size in NF2. Some facial nerves had been replaced by grafting after surgery, but the majority of persons undergoing surgery were found to have good facial nerve function at 2 years after surgery. Just under a third of these persons had to have a subsequent auditory brainstem implant, and just two persons had to have a subsequent cochlear implant, indicating the

surgery was - at least in the two-year time frame monitored - successful in maintain hearing preservation in the majority of cases.

As new drugs such as Bevacizumab (Avastin) - which has shown promise in shrinking VS tumors - become available in the clinic for NF2 management, it is important for clinicians to keep building their knowledge of VS tumor size and its relationship to hearing loss. With this in mind, **Peyre et al. (France)** examined 46 persons with NF2, all with two small VS tumors being managed conservatively. This group all had serviceable hearing; surgical intervention for VS tumor management was utilized only when absolutely needed. The group was followed in the clinic over 6 years, and by radiology imaging over 4 years. The study showed that in people diagnosed with NF2 at an earlier age, VS tumor growth over the study period was greater, and just over a third underwent surgery. The number of persons with at least one serviceable ear was 85% at the start of the study and 74% at the conclusion. This study suggests a conservative 'watch and wait' strategy for management of NF2 can be successful, bearing in mind that those diagnosed at a younger age may be more likely to need special consideration (as also discussed above).

Finally, in an unusual NF2 report, **Bendon and Giele (United Kingdom)** describe a case of macrodactyly – which means finger overgrowth - in NF2. Macrodactyly is quite rare in the general population, and in this case it seemed to be associated with a plexiform schwannoma in a finger nerve. The condition was resolved by surgery.

5. NF1 Learning Disabilities

The Bottom Line: Learning disabilities in NF1 are associated with altered brain structure and reduced neurotransmitter signaling; revisiting autism links to NF1.

Two recent studies look for physical and chemical changes in the brain that may help us better understand learning disabilities seen in NF1.

Violante, Ribeiro, Silva et al. (Portugal) examined the question of whether the structure of the brain is altered in NF1. They studied a group of 28 children – 14 with NF1 and 14 without NF1. The study showed that certain regions of the brain are indeed larger in children with NF1, and that other regions of the brain had fewer gyri (brain ridges) than the brains of children without NF1. These features contributed to an increased brain size in NF1. These unique features of brain structure might be due to specific *NF1* gene mutations. This is an area will certainly benefit from further study; understanding and early imaging of structural alterations in the brain might help predict whether NF1-related learning disabilities could occur later.

In mice that have been genetically engineered to have NF1-related learning disabilities, the brain signal called gamma-aminobutyric acid (GABA) is impaired in its function. GABA's function in the brain is to inhibit signal transmission between nerve cells, which means that this signaling is 'overactive' in the brain of the NF1 mouse. This GABA over-activity is believed to contribute to learning disabilities. From the same group that described the brain structural changes described above, **Violante, Ribeiro, Edden et al. (Portugal)** imaged GABA signaling in the brains of 20 children with NF1, and compared them to 26 persons without NF1. Consistent with the findings in mice, GABA was found to be lowered in the

brains of humans with NF1. This intriguing finding should provide a basis for further studies and testing of interventional treatments for NF1 learning disabilities.

In the Volume 2 of *The Network Edge* (February 2013), we reported on two clinical studies (*Garg et al.* and *Walsh et al.* – see Vol. 2 for summary of these reports) that suggested that children with NF1 display some symptoms of autism. These were the first publications to closely examine the common features of NF1 and autism in the clinic. **Payne (Australia)** wrote a helpful commentary about these two publications. This highlighted the importance of these studies, but also expressed caution that seeing some autistic features in NF1 does not always mean a full diagnosis of autism. The articles and this commentary have opened up an important area of NF1 research, given the behavioral and social challenges that many children with NF1 can face.

Finally, looking at the molecular basis of NF1 learning disabilities, **Arun et al. (Canada)** report that the *NF1* gene has a tubulin-binding domain within its structure. The authors propose that this domain might have a role in NF1's non-tumor-related manifestations, and could potentially help shed light on behavioral differences in NF1.

6. NF1 Bony Abnormalities

The Bottom Line: Children with NF1 don't have an increased risk of fracture overall, but are more likely to fracture a leg bone; skull abnormalities in NF1; international NF1 bone consortium builds collaboration.

NF1 can cause an increased risk of bony abnormalities, most commonly seen in dysplasia of the arms and legs, or in spine defects. The skull can also be affected, though this is quite rare, and the defects seen in the skull in NF1 are not well understood. **Arrington et al. (United States)** identified 21 cases of NF1-related skull abnormalities from medical records captured between 1994 and 2010. The average age of NF1 diagnosis in the group was just over 4 years of age, and the average age of diagnosis of skull defects was close to 9 years of age. In the majority of cases, the skull defects were associated with the presence of an adjacent plexiform neurofibroma or the presence of dural ectasia (ballooning of the membrane around the spinal cord) pressing on and impeding bone growth. In more than half the children diagnosed with skull defects, these continued to develop over time. The authors emphasize the importance of continued monitoring of skull defects once these are diagnosed.

George-Abraham et al. (United States) surveyed 256 children and adults with NF1, and 178 children and adults without NF1, to track the number of fractures they had sustained and where the fractures occurred in the body. The survey also captured information about each person's bone mineral density (BMD), calcium intake and overall level of physical activity e.g. regular participation in sports. The results showed that people with NF1 didn't have a greater overall risk of fracture than those without NF1, but were more likely to sustain a leg fracture. This was true even for those with NF1 who didn't have a diagnosis of long bone dysplasia (which would enhance risk of a leg fracture). Though it might have been expected that the NF1 group would have an overall increased risk of fracture, the survey also showed that the NF1 group were overall less physically active than those without NF1. The authors suggest that lack of participation in physical activities by those with NF1 lowers the risk of fracture and levels the results out. Neither BMD nor calcium intake seemed to influence fracture incidence. The authors suggest low BMD in NF1 may be more significant for adults than children.

To assess whether tibial (leg long bone) defects increase the risk of other manifestations of NF1 (e.g. tumors, learning disabilities), **Morcaldi et al. (Italy)** examined 49 persons with NF1 and tibial defects, and compared them to 98 persons with NF1 but no tibial defects. The only significant finding was that the tibial defects group had been diagnosed with NF1 at a younger age. Other NF1 manifestations had the same rate of occurrence in both groups.

Finally, **Stevenson et al. (United States)** provided an update on the NF1 International Bone Abnormalities Consortium, an initiative to build consensus and collaboration between biologists and clinicians focused on understanding and treating NF1-related bone dysplasia. This report, from the group's last meeting in 2011, reviews the status of the field and reports highlights and recommendations for the optimal management of tibial dysplasia. These included bone fixation to achieve stability; debridement of the "fibrous pseudarthrosis tissue" between the bone segments associated with the pseudarthrosis; creating a healthy vascular bed for bone repair; promoting osteogenesis; controlling overactive bone resorption (catabolism); prevention of recurrence of the "fibrous pseudarthrosis tissue"; and achievement of long-term bone health to prevent recurrence. The report particularly highlights the need for more clinical trials for NF1 tibial dysplasia. These trials must be done collaboratively, to secure sufficient participants in a timely manner, and should include assessment of new surgical approaches as well as candidate drug therapies.

7. Heart and Blood Vessel Abnormalities in NF1

The Bottom Line: Case studies highlight the importance of monitoring blood pressure and arterial function even in young persons with NF1; moyamoya diagnosis and future stroke risk in children with NF1.

a. Factors Contributing to High Blood Pressure and Stroke in NF1

Heart and blood vessel abnormalities can occur in NF1, but much still needs to be unraveled in this research area. One of the approaches being used to study vascular health in NF1 is to measure strength and elasticity of the endothelium (blood vessel lining). **Rodrigues et al. (Brazil)** measured endothelial function 29 persons with NF1, and 30 persons without either NF1 or any risk factor for vascular disease. Participants were aged between 18 and 35 years. Endothelial function was measured using a new technology called EndoPAT, which monitored arterial tone (vessel wall strength), and also the response of blood vessels when they experience periods of ischemia (blood supply is temporarily cut off). EndoPAT showed that both groups, those with and without NF1, had similar levels of endothelial function. Though no difference between groups was seen, the authors plan to use this data as a baseline for future studies of aging populations with or without NF1.

A number of recent NF1 clinical case studies NF1 have reported heart and blood vessel findings of interest. These are summarized below.

Strokes can occur in young persons with NF1, which is somewhat confounding, since strokes in older persons are usually caused by deterioration of blood vessels over time. **Yilmaz et al. (Turkey)** report on a 31 year old woman with NF1 who had a stroke. Genetic analysis revealed that this woman had a mutation in the *NF1* gene and also a mutation in the *MTHFR C677T* gene which codes for an enzyme called methylenetetrahydrofolate reductase. In the absence of this enzyme, high levels of

homocysteine built up in the blood and urine. Homocysteine can attack the endothelial lining of blood vessels and is a risk factor for stroke. The woman was given anti-clotting drug and aspirin, and with rehabilitation therapy made a level of recovery. This case report highlights the importance of searching for other genetic mutations besides *NF1* in individuals diagnosed with NF1.

Two reports on case studies highlight the importance of routine evaluation of blood pressure and if needed further investigation of the vascular system in young persons with NF1. **Kimura *et al.* (Japan)** report on a 4-year old girl with NF1 and high blood pressure. Further investigation identified narrowing of the aorta, the large blood vessel that exits the heart and supplies blood to the body. This was corrected with surgery. **Ueda *et al.* (Japan)** report on a 13-year-old boy with NF1 and high blood pressure. Detailed investigation finally linked this to arterial stiffness and vasculopathy.

Finally in factors affecting vascular status in NF1, **Njei and Sanchez (United States)** report on the case of a man with NF1 with recurrent thromboembolic disease who died. Autopsy revealed a periampullary duodenal tumor (i.e. tumor located in the area of the pancreas and duodenum of the gut) which may have contributed to his heart condition. This report shows that factors other than vascular health – in this case, an unfortunately located tumor – can contribute to vascular disease in NF1.

b. Moyamoya Update

Moyamoya is a vascular disease that causes the blood vessels serving the brain to progressively become constricted and malformed. Moyamoya can affect anyone in the general population. However children with NF1 can develop a specific form of moyamoya that is not well understood. **Koss *et al.* (United States)** took on the challenge of unraveling moyamoya in NF1 by studying the medical records, including radiographs and angiographs, of 32 children who had been diagnosed with NF1-related moyamoya and had received surgical treatment to restore blood flow to the brain. The children had frequently received a diagnosis of moyamoya in the absence of any symptoms. Instead, moyamoya was identified coincidentally when the head was imaged for other aspects of NF1 (brain tumors, etc). The majority of the children affected responded well to surgery. Unfortunately, however, this study also revealed that if a child with NF1 and undiagnosed moyamoya is given irradiation to the head for a brain tumor, this might increase the risk of a future stroke or other complications.

Witmer *et al.* (United States) present the first ever case report of moyamoya in NF1 leading to loss of vision in an eye. This was seen in a 12-month old girl whose moyamoya appeared to have progressed from the brain then into the blood flow to the optic nerve which supplies the right eye.

Both of these studies highlight the importance of monitoring children with NF1 for moyamoya.

8. Other Clinical Features of NF1

The Bottom Line: Pheochromocytoma and GIST link; oral tumors in NF1; children's head circumference/height ratio as an NF1 diagnostic approach; is muscle function normal in NF1?

Children with NF1 tend to have larger heads, and to be shorter, than children without NF1. **Karvonen *et al.* (Finland)** examined 80 children with NF1 under age 7 to get a better understanding of this feature of NF1 and to see if there is a particular age at which the head size difference becomes apparent. They measured the ratio of head circumference/height in children with and without NF1, and

found that the difference becomes apparent at about 4 months of age. This information may be helpful in contributing to conclusive early clinical diagnosis of NF1.

The role of abnormal Vitamin D metabolism has been discussed previously in *The Network Edge* as a factor affecting bone health in persons with NF1. **Hockett et al.** (*United States*) have expanded the discussion to consider the role of Vitamin D in muscle function in persons with NF1. The study compared children age 5 to 18 with NF1 to their unaffected siblings, and measured a range of Vitamin D metabolites as well as jumping ability in the children. No difference was found between the children with NF1 and their unaffected siblings in any of the measures taken. This suggests that Vitamin D metabolism does not affect muscle function in NF1.

Keeping in the theme of muscle function and activity, **Souza et al.** (*Brazil*) assessed exercise capability differences in a small group of persons with and without NF1, aged 18 to 58 years. The study found that maximal oxygen uptake ability was reduced in the NF1 group, which is a factor that could restrict the ability to exercise. During exercise, NF1 participants were found to have a lower maximal systolic blood pressure than participants without NF1. Men with NF1 had a lower BMI than the men without NF1, but it was not clear if this was due to reduced muscle mass. This pilot study has raised some interesting questions about differences in exercise ability in NF1, but further investigation is needed to be conclusive about these issues.

Vlenterie et al. (*The Netherlands*) saw two patients in their 50s with NF1 who presented with both of the tumor types, pheochromocytoma and gastrointestinal stromal tumors (GIST). Pheochromocytoma tumors grow on the adrenal glands. Though usually benign, these tumors produce excess hormones called catecholamines, which can promote cardiovascular complications, including during surgery. GIST is a tumor type which grows in the gut and can become malignant. Pheochromocytoma and GIST are each rare tumors in NF1, so seeing both of these tumor types in the same persons prompted the authors to look back at the published scientific literature to see if any similar cases of NF1 had been reported. They found papers on 12 persons with NF1 who had presented with both pheochromocytoma and GIST. 4 of these persons had a pulmonary embolism. From these findings, the authors concluded that when either GIST or pheochromocytoma is diagnosed in NF1, the person should also be examined for presence of the other tumor type. This is particularly important before GIST surgery is done, when pheochromocytoma might contribute to cardiovascular complications.

One aspect of NF1 rarely mentioned is oral tumors. **Asgary and Aminzadeh** (*Iran*) report on a case of neurofibroma in the gingiva (gum) of the mouth. They examined the literature and identified past reports of this. Oral health is often overlooked in the general population, and is not necessarily a special consideration for those with NF1. However, this finding highlights the possibility that oral neurofibromas may develop.

9. Schwannomatosis Update

The Bottom Line: International consortium identifies and addresses key issues in schwannomatosis.

Schwannomatosis has been a fast moving area of research since the identification of the schwannomatosis candidate gene *SMARCB1* in 2007. In a publication by the collective leaders in the

schwannomatosis research and clinical field, **Plotkin et al.** (*United States*) provide a consensus report on the state of research and an update of the clinical diagnosis criteria for this very rare form of NF which affects an estimated 1:40,000 persons.

The group report that the *SMARCB1* gene is involved in only around half of inherited cases of schwannomatosis and in 10% of spontaneous (first in family) cases. In order for schwannomatosis tumors to grow, it is proposed there must be a complex series of genetic mutation events involving the *SMARCB1* gene (for cases where that is involved), the *NF2* gene, and a loss of a portion of Chromosome 22.

The publication also presents revised diagnostic criteria for schwannomatosis and an update on the progress of research. Though there are as yet no therapies for schwannomatosis, good mouse models of schwannomatosis are now available and biology is making progress in understanding the underlying mechanisms of tumors and of the unmanageable pain that is a hallmark of schwannomatosis. The report is hopeful that initial therapies for schwannomatosis could be identified in the next few years.

10. What's New in NF2 Biology?

The Bottom Line: New molecular insights into nerve degeneration in NF2; SOX10 could be a new candidate drug target for NF2.

Individuals with NF2, as well as schwannomatosis, can develop peripheral neuropathy, or nerve degeneration, which affects nerve function and impacts on quality of life. One of the most confounding aspects of this pain is that nerve damage often occurs in a different location from that where tumors are growing on the nerve. This has made it hard to understand how and why nerve degeneration can occur in NF2, and even harder to develop treatment strategies for the resulting pain.

Now, an international collaborative study has reported a significant breakthrough in this area, focused on merlin, the protein that is encoded and made by the *NF2* gene. **Schultz et al.** (*United Kingdom/United States/Germany*) have discovered that one particular form of merlin, called merlin-iso2, actually has an important function in normal nerve to maintain its structure and integrity. This study further unraveled the mechanisms by how merlin-iso2 is maintaining nerve structure: by activating the GTPase RhoA signaling pathway, which in turn regulates the function of neurofilaments. As their name suggests, neurofilaments provide nerve cells with a 'backbone', giving them physical structure and also regulating nerve cell function. In mice where merlin-iso2 is removed through genetic engineering, the mice had movement disabilities and altered sensory nerve function. When the mouse nerves are examined under the microscope, they showed signs of nerve degeneration, including disordered neurofilaments.

To follow up on the potential clinical relevance of this finding, the group looked at nerve samples taken from humans with NF2. They found that here too, the neurofilament organization inside the human nerve cells was also disrupted. This is an extremely exciting report because it sheds light on an area of NF2 research - nerve degeneration and pain - that has been poorly understood. It also opens up new avenues for the future development of treatments for this aspect of NF2 and – given the involvement of the *NF2* gene described in the last section – possibly also for schwannomatosis.

Doddrell et al. (*United Kingdom*) used cell lines that are representative of normal Schwann cells and of NF2 schwannoma tumor cells to look for clues as to what causes schwannoma tumor growth. The cells were analyzed using a range of molecular assays and techniques for expression of growth signals that are known to regulate normal Schwann cell development. The study found that a number of cell signals are impaired in the schwannoma cells compared to the normal cells. Expression of one important signal, SOX10, was found to be reduced in the tumor cells, and when this signaling was restored in the cells through genetic engineering the cells were able to behave less like tumor cells and more like normal cells. This study suggests that SOX10 may be a worthwhile candidate drug target.

11. What's New in NF1 Biology?

The Bottom Line: New insight into MPNST biology shed light on how and why these tumors develop, and highlight new candidate drug targets for treatment; still seeking the basis of pain and itch in NF1.

a. *MPNST: Biology Update*

The last Volume of *The Network Edge* included a special focus on malignant peripheral nerve sheath tumors (MPNST), a cancer that can occur in NF1 when a plexiform neurofibroma undergoes malignant changes. A large amount of research is focused on understanding these changes and how this cancer can be treated.

Mo et al. ^{NIH} (*United States*) used a molecular technique called comparative transcriptome analysis to show that the cell receptor CXCR4 is present at high levels in NF1 mouse MPNSTs but not in the benign cells that these tumors arise from. CXCR4 binds the cell signal CXCL12 which promotes MPNST growth. When CXCR4 activity is blocked, MPNST cell growth decreases in the mice and it appears to be harder for benign cells to transform into MPNSTs. The group shows that these same pathways are active in human MPNSTs too. CXCR4 could represent a new target for MPNST drug intervention.

As MPNSTs grow, one of the cell signaling pathways they feed upon is the abnormal expression of the signal epidermal growth factor receptor (EGFR). This signaling pathway helps to propagate tumor cell growth but it is not clear how EGFR does this. **Byer et al.** ^{NIH} (*United States*) took on this question, and showed that when EGFR is inappropriately expressed in the cell it localizes to certain regions within the cell and forms structures that the group termed 'invadopodia'. The invadopodia seem to be important in the transformation of the cell as it takes on cancerous behavior. Studying these cells in the dish showed that the cell signal transforming growth factor-alpha (TGF-alpha) helps with the formation of invadopodia. It therefore seems that TGF-alpha and EGFR are working together to promote cancerous behavior of MPNST cells. Further investigation will unravel this picture further.

It is known that Schwann cells from people with NF1 over-express the beta-type receptor for the cell signal platelet growth factor (PDGF). When these NF1 Schwann cells are treated with the BB form of PDGF that binds to this receptor, the cells show an increase of calcium levels. **Farrer et al.** ^{CDMRP} (*United States*) used a human MPNST Schwann cell line to show that following PDGF-BB stimulation, these cells undergo a signaling change - sustained phosphorylation of the cell signal AKT -which appears to be dependent on increase of calcium levels in the cells. Further studies by the group have implicated calcium and this overall pathway in promoting cell survival and tumor-like behavior. These two papers

have identified an intriguing area of research that may help inform the understanding the mechanisms of NF1 MPNST growth and in figuring out how to treat these tumors.

Reuss et al. (Germany) examined the effects of a growth factor called tumor necrosis factor-related apoptosis inducing ligand (TRAIL) on MPNST cells in relation to NF1 gene activity. MPNST cells with functional neurofibromin (i.e. representing MPNSTs from someone without NF1) were not sensitive to TRAIL. However MPNST cells without functional NF1 (i.e. representative of MPNSTs from someone with NF1) were sensitive to TRAIL. The effect of TRAIL was further enhanced by the presence of curcumin, an extract of turmeric that has been suggested as a potential natural adjunct therapy for tumor treatment. Sensitivity to TRAIL was associated with modulation of the MYC/MAX/MAD signaling pathway network. Further analysis of this may shed light on future drug strategies for MPNST.

Exploring further new drug targets for the treatment of NF1 MPNSTs, **Kazmi et al.** ^{NIH} (United States) developed genetically engineered mouse models that express high levels of the growth factor neuregulin 1 in their Schwann cells. These mice were allowed to grow up and develop tumors then were autopsied. The majority of mice developed neurofibromas, and 70% developed MPNSTs. Study of these tumors showed that the MPNSTs were developing out of the benign neurofibromas. The MPNSTs were also found to have genetic and molecular changes that would be expected to be associated with human MPNSTs, as well as with some previously unseen genetic and molecular changes. This study opens the path to identify new molecular causes, as well as candidate drug targets, for MPNST.

b. Other Tumors: Biology Update

Pong et al. ^{NIH} (United States) demonstrate a new role for microglia, a type of cell present within the optic nerve, in promoting the growth of optic pathway glioma (OPG). Microglia will not give rise to tumors themselves, but they might promote other cells to form tumors by expressing the CXCCR1 chemokine receptor on their surface. Reducing expression of the *Cx3cr1* gene in mice actually delays the formation of optic nerve, which supports this idea of a role for microglia. Targeting microglia might present a potential future therapeutic strategy for NF1 OPG.

Hinman et al. ^{CDMRP} (United States) examined the regulation of NF1 pre-mRNA by a cellular element called HuC protein. HuC belongs to the Hu protein family which regulates certain aspects of gene expression. In the nervous system, where NF1 can tumors arise, Hu proteins have multiple roles in regulating the growth and behavior of nerve cells. HuC is a poorly understood Hu protein, but this study confirmed it to be a regulator of NF1 gene expression. This exploratory study will benefit from further investigation to see if HuC has a role in NF1 tumor development or indeed in any other aspect of NF1.

Hirayama et al. (Japan) inactivated the NF1 gene in a nerve cell line and assessed the resulting molecular changes, using a variety of molecular screening approaches. One of the effects seen from NF1 activation was an alteration in IC2-GR-COX-1 signaling, which may be worth further exploration.

In NF1 tumors, one of the signaling pathway alterations seen is an increase in growth factor VEGF1, which helps drive the growth of new blood vessels that will feed the tumor and aid its growth. **Kawachi et al.** (Japan) investigated this signaling in NF1 mouse Schwann cell lines, and showed that when the NF1 gene function is impaired, there is increased expression of additional signals HIF-1alpha, phosphorylated mTOR and interleukin-6, also implicating these signals in tumor formation.

In persons with NF1, the *RAS* gene is hyperactive and this is a critical underlying cause of NF1 clinical manifestations. In figuring out how to treat NF1, *RAS* function has been a major focus as a candidate drug candidate. However scientists have had a difficult time fully understanding *RAS* function.

Smith et al. (Canada) used nuclear magnetic resonance spectroscopy to study the *RAS* gene. They revealed a number of novel features – such as how specific mutant forms of *RAS* target the cell membrane - that may help unravel *RAS* biology further.

The gene *P53* encodes a protein whose normal job is to ‘tell’ cells to die when appropriate (such as when a cell is ‘sick’), but in some circumstances *P53* can also protect cells from death, such as when cells are under metabolic stress from which they can eventually recover. **Sanchez-Macedo et al. (Switzerland)** found that carnitine palmitoyltransferase 1C (*Cpt1c*), a brain-specific member of a family of mitochondria-associated enzymes that have a central role in fatty acid metabolism, is a target of the *p53* gene in mice that helps mediate cell survival and tumor growth activities. Depleting *Cpt1c* gene activity in an *Nf1* mouse model inhibited tumor formation. *Cpt1c* therefore may be a promising new candidate drug target for treating tumors.

c. Cause of Pain and Itch in NF1?

Pain and itch are symptoms that many people with NF1 develop and experience, but they are very poorly understood. **O’Brien et al. (United States)** showed that an *Nf1*^{+/-} mouse model (lacking one copy of the *Nf1* gene) has increased sensory sensitivity and an increased number of mast cells (these are cells that play an important role in causing inflammation and itch). However the *Nf1* mouse does not have increased pain compared to normal mice, nor does it have an enhanced itch response. This finding suggests that while an absent *Nf1* gene copy might lay the groundwork for a pain and itch response in NF1, other factors – such as additional gene mutations or altered cell signals – are needed to contribute to this phenomenon.

12. Legius Syndrome Update

The Bottom Line: Genetic testing for Legius Syndrome in suspect NF1 diagnoses does not incur significant added care costs and could be widely deployed.

Legius Syndrome, or NF1-Like Syndrome, is caused by mutations in the *SPRED1* gene, but in terms of clinical diagnosis it can look very much like NF1. Since Legius Syndrome overall has a less severe potential outcome than NF1, families and doctors are anxious to ensure it is accurately identified, since this will impact on planning for clinical follow up. **Muram et al. (United States)** analyzed the potential added cost of genetically testing for *SPRED1* gene mutations every child diagnosed clinically with NF1 but not exhibiting either tumors or bone dysplasia (two features seen in NF1, but not seen in Legius Syndrome). This cost of adding in *SPRED1* testing for this population was compared to standard clinical practice, which may include additional *NF1* mutation testing for the children later in childhood to get a definitive yes/no for NF1 diagnosis. The group found the increased cost of using the *SPRED1* test earlier than later to be very small, only \$4- to \$16- extra per person. Therefore, based on their clinical experience, the authors suggest that doctors should not be inhibited from using *SPRED1* testing in cases where an NF1 diagnosis is in question, since it will offer peace of mind to the family and also better inform the type of clinical follow up the child is likely to need.

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CONTENTS	Volume 1 - Fall 2012	Volume 2 - Winter 2013	Volume 3 - Spring 2013
CDMRP NFRP Updates	X	X	
NF1 Clinical Trials	X		X
NF1 Clinical Management	X	X	X
NF1 Learning Disabilities	X	X	X
NF1 Bony Abnormalities	X	X	X
NF1 Malignant Peripheral Nerve Sheath Tumors		X	
Heart and Blood Vessel Abnormalities in NF1		X	X
Increased Breast Cancer Risk in NF1	X		
Other Clinical Features of NF1	X		X
What's New in NF1 Biology?	X	X	X
NF2 Clinical Trials	X		X
NF2 Clinical Management	X	X	X
What's New in NF2 Biology?	X	X	X
Schwannomatosis Update	X		X
Legius Syndrome Update	X		X
The Evolving Link Between NF and Cancer		X	

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