TheNetworkEdge

The NF Network presents A quarterly research review
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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 NF topic area, so you can focus in on the information that is of most interest for you.**

The Network Edge Also Features…

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

- **Highlighting Federally Funded Research**: Research identified as 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.

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Highlights from Volume 8 of *The Network Edge*:

- A new NF1 patient registry highlights the value of patient-reported data
- rhBMP-2, a candidate drug for promoting bone healing shows promise in NF1 mouse models
- In NF1, understanding autism spectrum disorder and finding evidence for depression risk
- *SUZ12,* a new genetic regulator of MPNSTs and candidate drug target; testing new MPNST drugs
- Methylphenidate shows promise for treatment of AD(H)D in NF1
- Children with NF1 have compromised motor skills, not necessarily due to attention deficits
- Implicating the NF1 gene in alcohol dependence
- A closer look at Sirolimus treatment of plexiform tumors – do people respond differently to this?
- What makes meningiomas become malignant?; new candidate treatments for these NF2 tumors
- Hope comes from a promising single-case trial of Bevacizumab to treat schwannomatosis

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1. NF1 Clinical Management

The Bottom Line: An NF1 patient registry shows value of patient-reported data, explores paternal age in NF1 cases; rates of NF1 may exceed currently used statistics; a 'window' into monitoring dermal nerofibromas.

a. Reporting on the Utility of a New NF1 Patient Registry

Studying populations of people with NF1 can be very informative about the way in which NF1 develops. A useful approach to doing this is to develop a NF1 Patient Registry where people report their own information. Two recent reports describe findings from a NF1 Patient Registry Initiative (NPRI) established at Washington University.

One of the potentially valuable aspects of a patient registry is that people can provide information about their own state of health in an ongoing manner. But it is important to know that this information provided is accurate. To examine this question in the NPRI, **Sharkey *et al.*** *(United States)* looked at almost fifteen hundred people who had enrolled in the registry. They compared self-reported information with the participants' medical records, and found that yes - the results provided in the registry are indeed valid. This supports the idea that a registry is indeed a valuable tool for NF1 research.

Liu *et al.* *(United States)* used the NPRI to look at the age of parents who had a child with NF1 to see if there was any significance to this. They found that when a parent had NF1 (i.e. the child has inherited case of NF1), fathers tended to be a few years younger than fathers whose child had a first-in-family (sporadic) case of NF1. The group tentatively speculated that a contributor to sporadic NF1 may be aging sperm and accumulating genetic mutations. But they do acknowledge that this needs further investigation. Learn more about the NF1 Patient Registry Initiative (NPRI) (http://nf1registry.wustl.edu)

b. Revisiting NF1 'By the Numbers'

It can be easier to study the medical information of large populations in European countries where socialized healthcare tracks individuals throughout life through more centralized administrative systems. **Uusitalo *et al.*** FREE *(Finland, Sweden)* utilize this to look at the incidence (rate of occurrence) of NF1 as well as its effect on lifespan, in a Scandinavian population of around fifteen hundred people with NF1. From their studies they conclude that NF1 occurs in 1:2,000 persons – a higher rate than the current United States standard of 1:2,500. The group noted this may be due to enhanced rates of diagnosis in their system; or due to differences in the genetics of this population compared to the United States. They also report that NF1 can reduce the life expectancy in women to a greater extent than in men: compared to the unaffected population, life span in women with NF1 is shortened by around twenty six years, and in men, by around sixteen years.

c. A New Approach For Monitoring NF1 Dermal Neurofibromas

Dermal neurofibromas are visible skin tumors affecting affect almost everyone with NF1. Some people will have just a few; others, hundreds or thousands. It can be overwhelming for clinicians to accurately count these tumors. As new NF1 drugs are developed it is possible that dermal neurofibromas might benefit. But how can dermal neurofibromas easily be counted and monitored to see if they are reducing in number or size? To address this, **Cunha *et al.*** FREE *(Brazil)* examined dermal neurofibromas on ninety two persons with NF1. They created a paper frame with a central square of $100cm^2$. This was placed on the back, abdomen or thigh, digitally photographed and then the image transferred to the computer. The number of dermal neurofibromas was counted by two independent examiners and the results averaged. For comparison, forty nine people also had their tumors counted manually. The data was statistically analyzed. Overall it was confirmed that the paper frame method was valid and reliable. This simple tool could potentially be used both for monitoring these tumors clinical care and clinical trials.

d. NF1 Bony Abnormalities

The Bottom Line: Drug rhBMP-2 shows promise in mice as a treatment for bone repair in NF1.

A New Candidate Drug for Bone Healing Shows Promise in NF1 Mouse Models

A variety of bone abnormalities can develop in NF1, one of the most devastating being tibial dysplasia were long bones in the leg develop abnormally, are weakened, can break easily, and are unable to repair. In children, if a bone chronically fails to heal, this can require limb amputation. There is a great need for effective treatments to help these bones grow and repair normally. The good news is that significant progress is being made in this area.

Exploring candidate drug treatment for tibial dysplasia, **El-Hoss et al.** *(Australia)* examined the effects of two drugs, MEK inhibitor PD0325901 and bone morphogenic protein rhBMP-2. These drugs were given either individually or together to mice that had been genetically engineered to develop NF1-related tibial dysplasia. MEK inhibitor alone didn't have much effect (which actually contradicted previously published reports by other groups) but rhBMP-2 alone supported healing in over two-thirds of mice. Both drugs together enhanced healing rate a little more, but also caused a large fibrotic callous at the site of bone healing.

Addressing the difference between the MEK inhibitor results here and reported by others, the authors claim that the genetic mouse model used here is more representative than the model used previously where MEK inhibitor had been shown to be effective. Also the MEK inhibitor used here is clinical trial grade and targets MEK more specifically than the drug used in the previously reported study. Though it promoted callous growth, this study supports a role for rhBMP-2 as a treatment and sheds further light on our understanding of the role of MEK inhibitors in NF1 bone healing.

e. NF1 and Autism

The Bottom Line: Autism spectrum disorder in NF1 manifests more so as social and communication problems, less as repetitive behaviors; how the brain's amygdala may regulate this, and exploring candidate drugs to restore normal brain signaling.

Understanding the Specific Features of Autism Spectrum Disorder in NF1

As reported previously in *The Network Edge,* some of the features of NF1 have been likened to autism spectrum disorder (ASD). **Plasschaert *et al.*** *(Belgium, The Netherlands)* investigated this area by testing eighty two children with NF1 aged five to seventeen at a single Belgian hospital with standard tests for social problems. They found that children with NF1 have more social problems than a comparable group of children without NF1. This was more likely seen when children were older than eight, or were male. Social problems included inability to connect with or understand a social situation.

Thirty one children with NF1 were suspected of having ASD and were more fully evaluated for this. Twenty seven were confirmed as having ASD. In comparison to children with ASD who *don't* have NF1 the children *with* NF1 and ASD had more of a problem with social-communication and less of a problem with the repetitive behaviors usually associated with ASD.

Overall, this study sheds more light on the specifics of ASD when it is diagnosed in children with NF1. The authors also highlight the fact that even when children with NF1 do not have diagnosed ASD they can have social and communication problems that impact on quality of life.

Exploring the Amygdala: Brain Signaling and Autism in NF1

The amygdala is a region of the brain that regulates emotion and motivation, and is also associated with fear and reward situations. Recent findings in mice suggest that altered cell signaling in the amygdala might contribute to social learning and ASD related features in NF1, and are start to figure out a way to correct these signals and restore normal function. Mice genetically engineered to lack one copy of the *Nf1* gene throughout the body have previously been shown to have learning disabilities. **Molosh *et al.*** [NIH] *(United States)* show that these mice also have socially deficient behavior in the way they interact with other mice in specific situations. The *Nf1* deficient mice have altered signaling in the brain in pathways involving signals glutamate and GABA which leads to increased activity of a gene called *Pak1*. The social deficits of the mice were corrected when the mice were further genetically engineered to delete the function of *Pak1* in the amygdala, or when the mice received a drug to block Pak1 signaling. These findings expand our understanding of ASD in NF1 and identify candidate treatment approaches for further exploration.

f. NF1 Malignant Peripheral Nerve Sheath Tumors

The Bottom Line: A new drug combination, tamoxifen and trifluoroperazine, shows promise for treating human MPNST cells implanted in mice; identifying *SUZ12* as a critical genetic regulator of MPNST growth and a new drug target for tumor treatment; evidence that risk of MPNSTs, and the underlying tumor biology, may be different in men and women; another look at radiation therapy for MPNSTs.

Malignant peripheral nerve sheath tumors (MPNSTs) are cancerous tumors that will develop in about 10% of NF1 cases from benign plexiform tumors. MPNSTs have an extremely poor outcome, as there are no effective drugs to halt their growth. The transition from benign plexiform tumor to cancerous MPNST requires a series of genetic mutations – changes - to occur within the tumor

cells but these genetic changes are not fully understood. Recent studies look at these tumors from a variety of perspectives.

Exploring A New Drug Combination for MPNST Treatment

Brosius *et al.* NIH *(United States)* show that the drugs tamoxifen or trifluoroperazine will individually reduce the growth of human MPNST cells implanted into mice by about 50%. However when these two drugs are given to the mice in combination, their effect is 90% growth reduction.

Using an approach called kinomic analysis the group confirmed that tamoxifen and trifluoperazine are acting through different signaling pathways and therefore make a good drug combination therapy. Tamoxifen can act through estrogen receptors, which are present on MPNST cells, but it doesn't need estrogen to be present in order for tamoxifen to work. This was demonstrated when experimental mice have their ovaries/testes (sources of estrogen) removed before implanting the human MPNSTs; tamoxifen still reduces tumor growth as usual. Making the connection back to humans, the authors note that while hormones are believed to play a part in plexiform tumor growth (e.g. these tumors can show growth spurts in puberty) this new research suggests that MPNSTs can grow independent of estrogen which tells us something about the ways they might grow and be treated. Given that tamoxifen and trifluoperazine are drugs currently prescribed for other conditions the authors are hopeful that these drugs might continue investigation as potential clinical treatments for MPNSTs.

SUZ12: A New Genetic Cause of - and Potential Drug Target for - MPNSTs

Two new reports explore the possibility that MPNST growth is driven in part by a gene called *SUZ12*. **Zhang, Wang *et al.*** *(United States)* looked at tumors from fifty NF1 cases and found sixteen MPNST s with *SUZ12* mutations. However these were never seen in plexiform tumors. *SUZ12* mutations are not inherited but occur during the course of life, add on to the existing *NF1* gene mutations, and contribute to causing malignancy. *SUZ12* mutations have already been implicated in certain lung, colon, gastric, endometrial and blood cancers. This finding pinpoints a potential role in MPNSTs and adds knowledge to the complex process that leads to the development of these deadly tumors in NF1.

In a large international collaborative study, **De Raedt *et al.*** CDMRP *(Belgium, Denmark, France, Germany, United Kingdom, United States)* explore *SUZ12* biology further by developing genetically engineered mice with deficiencies in both *NF1* and *SUZ12* gene function. These mice are highly prone to a range of NF1-associated tumors and have decreased survival. When these mice were further developed to alter function of the cancer-associated gene *p53* the mice developed MPNSTs in just 3 months. In comparison when only the *NF1* and *p53* genes are mutated it takes 9 months for MPNSTs to develop. Also over half of the mice with three mutated genes develop malignant gliomas. This highlighted a role for *SUZ12* in magnifying the induction of malignant tumors.

The group endeavored to treat these malignancies in the mice with drugs. The most effective was a combination of MEK inhibitor PD-901 and a bromodomain inhibitor JQ1; each of these targets a specific cellular pathway and so the drugs act in concert. In response to these drugs, half the tumors shrank in size by three-quarters which is quite impressive. These are impressive findings, as recognized by their publication in top scientific journal *Nature.* They shed light on new mechanisms contributing to malignancy in NF1 tumors as well as potential approaches to treating these tumors.

Are MPNSTs Fundamentally Different in Men and Women?

Two recent papers explore the question of whether there are differences between MPNSTs in men and women with NF1. In a two-tiered approach, **Shurell *et al.*** NIH, FREE *(United States)* examine the question in male and female mice genetically engineered to develop MPNSTs; and also in male and female humans with NF1-related MPNSTs. The group examines over one hundred people from their

own institutional database from 1974-2011, and also look back at publications in this area that report findings on over nine hundred people. In both the mice and in the humans in the institution's clinical database, the males seem to develop NF1-related MPNSTs before the females do. In the mice, this is a couple of weeks earlier in the males; and in the humans, about five years earlier in the males. However when the group looked at what had been reported in the broader literature and took all of these results together they could not see a difference between the time of reported MPNST onset between males and females with NF1 even though individual publication was in support of the idea of males developing MPNSTs earlier. The group felt this question needs further exploration.

In a second paper, **Johansson *et al.*** FREE *(Taiwan, United States)* investigate a role for the tyrosine kinase receptor AXL in the growth of MPNSTs, since AXL has been implicated in other forms of cancer. Compared to normal human Schwann cells, significantly high levels of AXL was found in three of the four MPNST cell lines and two of three MPNST tumors examined. When human MPNST cells are grafted into mice and tumors form, these mice develop high levels of AXL in the blood which are proportionate to the sizes of the tumors. When the mouse tumors were treated with photodynamic therapy, and shrank, the mouse's blood levels of AXL also reduced. Testing the relevance of these findings to humans, the group looked at seventy eight people with NF1 and forty-six people from the general population. They found that people with NF1-related plexiform neurofibromas had high levels of AXL in the blood. Interestingly, in the males participating, the AXL level corresponded to the overall tumor burden. This correlation was not seen for the females participating.

In contrast to these plexiform findings, people without plexiform neurofibromas but with NF1-related dermal neurofibromas didn't have high levels of AXL in the blood and indeed had AXL levels close to those of the general population/non-NF1 group. Two patients with MPNSTs were evaluated and found to have the highest AXL levels of all patients in the study. Together, these findings suggest that AXL is an indicator of tumor severity in NF1, and possibly of tumor load in men (but not women), and that AXL may represent a new candidate drug target for NF1 tumor treatment.

Together these studies raise the interesting prospect of MPNSTs develop differently in men and women, and this is an area where hopefully further investigations will be done since in the long term it might help to determine best monitoring and treatment strategies for these cancerous tumors.

Radiation Therapy for MPNSTs, Revisited

Finally in MPNST, **Kahn *et al.*** FREE *(United States)* present a review on a controversial topic – the use of radiation therapy for the treatment and management of MPNSTs. They review the cases of 33 NF1 patients with MPNSTs and seen at the National Institutes of Health between 1990 and 2012. 20 of these persons were treated with radiation therapy. The group reviews the data and concludes that radiation therapy can be effective in controlling tumors, with key factors on its effectiveness including tumor location, tumor biological make up and extent to which the tumor has been surgically removed before the radiation treatment. This is an interesting, thorough FREE review from a knowledgeable team that considers both the possibilities and limitations of radiation therapy for MPNSTs.

g. NF1 and the Eye: Optic Pathway Gliomas and Other Features

The Bottom Line: A new report of eye blood vessel differences in individuals with NF1.

Abnormal Blood Vessels in the NF1 Eye: Another Look

There is an increasing body of knowledge about alterations that are seen in blood vessels in the brain and body of people with NF1. **Abdolrahimzadeh *et al.*** FREE *(Italy)* look specifically at the blood

vessels of the retina in the eye in seventeen people with NF1 and compare them to seventeen people of matched ages from the general population. Six of the people with NF1 had specific alterations in the retinal blood vessels, these having a 'spiral' or 'corkscrew' appearance. These were associated with changes in the choroid, another region of the eye reported to have alterations in some cases of NF1. All persons had 20/20 vision so this had not yet been impacted.

These findings agree with a single case report by the Japanese group of Makino *et al.* which was included in Volume 4 of *The Network Edge*, which was then believed then to be the first ever reported case. Though the appearance of these blood vessel abnormalities in the eye is not yet fully understood, it may emerge to be a predictor or indicator of future alterations in the eye and warrants further study.

2. NF1 Learning & Development: Social Challenges in NF1

The Bottom Line: Evidence for a high risk of depression in the NF1 population; when motor skills are affected in children with NF1, this is not necessarily due to attention deficits; understanding the brain signaling pathways involved in this; is the NF1 gene involved in the biology of alcohol dependence?; exploring brain wiring and impulse control in children with NF1.

There is a growing field of clinical research around understanding the ways that having NF1 can affect the way a person thinks, feels and behaves. In the past few months there has been a variety of very interesting reports that fit under this expanding umbrella topic. These are discussed below.

a. Depression in NF1

Through anecdotal reports and smaller research studies it has long been recognized that suffering from depression can be a significant part of having NF1. Reporting the results of the biggest study to date on this topic, **Cohen *et al.*** NIH *(United States)* assessed the prevalence of *clinically diagnosed* depression in NF1 and its impact on quality of life. The study included an internet survey that was completed by four hundred and ninety eight adults who self-report as having NF1. The average age of participants was thirty-nine, and approximately three-quarters were women. The survey asked a series of questions to help diagnose signs of clinical depression. The answers showed that over half of those who participated have a high likelihood of developing clinical depression. The people at risk tended to have a poorer quality of life (income, living situation, physical disabilities, etc.) This study concluded that people with NF1 are at increased risk of clinical psychiatric illness compared to the general public. Depression in NF1 has not been heavily studied, but this report highlights the risk and the need for possible support and counseling for depression as part of the NF1 clinical care continuum.

b. How Does the Brain Regulate Impulse Control in NF1?

Ribeiro *et al.* *(Portugal, United States)* studied impulse control in a group of sixteen children with NF1 and sixteen children from the general population. The children were assessed for their response to a 'go/no-go' task where numbers flashed on a computer screen for milliseconds. Participants were asked to press a buzzer only if they saw certain numbers. The way that the children responded indicated their level of impulse control. During the test brain activity was monitored by the techniques EEG and magnetic resonance spectroscopy. The fluctuating levels of brain signals GABA, glutamate and glutamine in the brain during tasks were monitored.

The study found that children with NF1 have impairments impulse control and alterations in GABA levels that might be responsible for this. When children with at NF1 had high levels of GABA, they were more impulsive, whereas children without NF1 high GABA were more cautious. Though the

outcome of these studies was not fully understood, this has certainly studies open up a new area of study for NF1-related social challenges.

c. Motor Skills Deficits in NF1

Recent Volumes of *The Network Edge* have reported on progress in both the clinical and biological understanding of why children with NF1 can develop motor skills. **Casnar *et al.*** *(United States)* look at this area in a study of children aged four to six: thirty-eight with NF1 and twenty-three without NF1. Motor function was assessed through a series of tasks at various levels of complexity. The children with NF1 were 'motor skill compromised' in all but the simplest tasks. There didn't seem to be a clear link between these deficits and parent-reported attention difficulties though. This suggests that NF1-related motor impairments may have a direct biological cause not necessarily due to attention deficits.

Kim *et al.* NIH, CDMRP, FREE *(United States)* looked into the underlying molecular biology of these NF1 motor deficits by creating genetically engineered mouse models where *Nf1* gene function was disrupted in a developing region of the brain called the cerebellum. This is of interest because the cerebellum is involved in controlling motor function. *Nf1* gene function was disrupted at different points in brain development. The group pinpointed a certain time in early embryonic development when *Nf1* gene disruption in the cerebellum causes motor deficits. When young mice with these gene deficits were treated with drugs to block cell signals MEK and ERK they show improved motor function.

Together these exciting studies suggest that there is a biological basis for NF1-related motor function deficits that are unrelated to attention deficit and that there may be ways for drug therapy to treat these. This opens up a new area of clinical study for NF1.

d. A Role for the NF1 Gene in Alcohol Dependence?

The amygdala is a region of the brain that regulates emotion, motivation, fear and reward. Now, **Repunte-Canonigo *et al.*** NIH *(United States)* reveal a surprise possible link between the NF1 gene and the alcohol dependence. The group used a laboratory approach to inducing alcohol dependence in mice and found that in normal mice, this leads to increased GABA signaling in the amygdala. However, mice that lack one copy of the *Nf1* gene throughout the body already have elevated GABA levels; and attempts to induce alcohol dependence in these mice were unsuccessful. The group then looked at humans with alcohol dependence and found many of them to have small genetic variants in the NF1 gene. This study concludes that the NF1 gene might play some role in the development of alcohol dependence.

The potential role of the amygdala in NF1 behavioral differences is also a focus in the section on autism and NF1, below.

3. What's New in NF Biology?

The Bottom Line: Nilotinib shows promise in treating human NF1 plexiform tumor cells; targeting PI3 kinase as a potential strategy for NF2 tumors; NF1 tumor marker may differentiate between men and women, highlighting a future path of personalized treatment strategies.

a. New Candidate Treatment Approaches for NF1 and NF2 Tumor Cells

Wei *et al.* FREE *(Germany, Korea, Switzerland)* compare the efficacy of two drugs that target tyrosine kinase – Nilotinib and Imatinib – for their ability to reduce growth of NF1 human plexiform neurofibroma cells following implantation into mice where they formed tumors. The tumor cells used were derived from a plexiform tumor donated by a young patient. Drugs were given daily for four

weeks, and tumor size was monitored by ultrasound. None of the tumors grew, as the timeframe of the study was too brief; and also plexiform tumor cells actually grow very slowly. Indeed as these tumors become established they undergo some shrinkage, even the untreated tumors undergo some shrinkage. Nevertheless both drugs increased greater shrinkage than any seen in untreated tumors; and Nilotinib was the more effective of the two drugs in shrinking tumors. In addition Imatinib treatment prevented weight gain in the mice, and increased death of spleen cells, both of which suggest that it was less well tolerated than Nilotinib. This drug is being explored by other research groups and continues to hold promise as a candidate NF1 tumor treatment.

Petrilli *et al.* NIH *(United States)* report on a chemical genomic, high-throughput screen to identify potential drug targets for the treatment of NF2 tumors. The group used a cell line representative of NF2 tumors to screen a vast chemical library of compounds to see what might slow cell growth. This complex experiment tested compounds from multiple chemical structural families. This type of technology is used by drug companies use to screen and optimize the structure of candidate compounds. This study identified PI3K as a candidate drug target for NF2 tumors.

b. Personalized Medicine in NF1 Tumor Assessment

Personalized medicine – the concept of tailoring the clinical care to each individual – can still seem like a futuristic idea but **Warrington et al.** CDMRP, NIH *(United States)* touch on this concept in a new report. They look for molecular markers that might indicate risk of developing a glioma – a form of brain tumor – in NF1. From a study of human DNA, the group finds that there are discrete differences in a specific gene called ADCY8 which is involved in regulating the cell signal cAMP. The differences seen may indicate a greater risk of these tumors developing in women with NF1 than in men with NF1. The group verified this idea by expanding the study in genetically engineered mice. These types of findings could in the future help to determine dictate drugs that are likely to work better in males or females.

4. NF1 Clinical Trials Update

The Bottom Line: Methylphenidate show promise for treatment of AD(H)D in NF1; Update on Sirolimus trials for NF1 Plexiform tumors.

a. Methylphenidate Trial for NF1-related AD(H)D

Diagnosis of attention deficit disorder/attention deficit and hyperactivity disorder (AD(H)D) in children with NF1 has been linked to academic underperformance. Volume 6 of *The Network Edge* included a publication that reviewed historical clinical data from studies on this topic, and reached the conclusion that the drug Methylphenidate could improve intelligence test scores and attention in children with NF1, and was working by way of regulating signals in the brain called neurotransmitters.

Building on this retrospective data analysis, **Lion-Francois *et al.*** *(France)* have reported on a new controlled clinical trial of thirty-nine children with NF1 aged seven to twelve, all with diagnoses of ADHD, ADD or hyperactivity. The children were stringently selected from a much larger NF1 registry.

The study period was nine weeks and the design was ‘placebo controlled crossover’, which means it was structured as follows. During the first four weeks, half of the children received drug, and half received placebo (sugar pill); in the fifth week no one received any drug or placebo; and in the last four weeks, those who had previously received drug now received placebo; and those who had previously received placebo now received drug. The idea behind this trial structure was that Methylphenidate, which has a very short half-life of only a couple of hours, would wash out of the children’s systems during the middle week.

While taking Methylphenidate, thirty-seven children showed significant improvement on a parent-reported scale of behavior. A few participants also returned a teacher-reported scale and this also reported improvement. At the close of the study, all participants opted to take Methylphenidate on an ongoing basis based on the positive effects they'd seen from the drug. However, it remains to be seen whether Methylphenidate will be effective as a long term treatment.

Methylphenidate does carry a risk of affecting a child's growth, but this may be avoided by taking 'drug holidays' – i.e. taking the child off the drug - during school vacation. But overall these findings suggest promise Methylphenidate as a treatment for AD(H)D in NF1.

b. Sirolimus Trials for NF1 Plexiform Tumors: An Update

Plexiform neurofibromas are the most common tumors of NF1. Though largely non-cancerous, they can present a significant health burden. Volume 7 of *The Network Edge* included a report from the CDMRP- funded NF Clinical Trials Consortium Phase II clinical trial of Sirolimus which had no significant effect as a treatment for non-growing but inoperable plexiform neurofibromas.

In a companion publication, **Weiss *et al.*** CDMRP *(United States)* report on a Phase II trial that looks at whether Sirolimus might be effective on plexiform tumors that *are* at risk of malignant progression (as defined by a series of measures including seeing an increase in volume of at least twenty percent in one year). Participants received Sirolimus for up to five years. Overall this drug delayed tumor progression by almost four months (when compared to historical observations where there had been no Sirolimus treatment). However, the drug did not actually shrink the tumors, and there were not consistent findings between patients in regards to changes in pain, quality of life or other measures.

From these findings it is suggested there may be a subset of people who are more responsive to Sirolimus than others. It will be important to identify these people and understand why they show a more robust drug response. At a minimum these results suggest Sirolimus could be used with other drugs in combined drug therapy for treatment of progressive plexiform tumors.

5. NF2 Clinical Management

The Bottom Line: A promising report of cochlear implant use in NF2.

a. Cochlear Implants for NF2

Lassaletta *et al.* *(Italy, Spain)* examine the reliability of cochlear implants (CI) from analysis of past medical records captured at three medical centers for eight persons with NF2 who had received a CI implantation between 2001 and 2012. In each case the CI was placed in the only or better hearing ear. CI was placed at the time of tumor surgery or soon after. Overall the study found CI implantation to be promising. The majority of participants had continued to use the CI when followed up. There was no difference in results between the NF2 group and a parallel group with sporadic vestibular schwannoma who underwent the same tumor surgery and CI implantation. In as much as they could with this small group, the authors concluded CI to be a promising option both for NF2 and sporadic schwannoma cases, as long as a functional cochlear nerve can be preserved after surgery.

6. What's New in NF2 Biology?

The Bottom Line: Pak inhibitors show promise in the treatment of meningiomas; study identifies genes that may contribute to meningioma malignant transformation.

Meningiomas are brain tumors which develop from the meninges (covering) of the brain in about half of people with NF2. They are also among the most common of all brain tumors in the general population. While largely non-cancerous they present a significant health burden and can comprise multiple tumors in different brain regions, making surgery difficult. In addition these tumors carry a risk of becoming malignant and if they do, there is a very poor prognosis. A primary cause of meningiomas is the mutation of the *NF2* gene which occurs in all of the NF2 population and 60% of the general population. The search for additional genetic contributors to meningioma is ongoing. To date research has largely focused on benign meningiomas as these are more common and more readily accessible for study. Two recent reports expand our understanding of these tumors.

a. Assessing Pak Inhibitors for Meningioma Treatment

Chow *et al.* NIH, CDMRP, FREE *(United States)* aim to understand what makes meningiomas grow and how this can be halted. The group wanted to explore the impact of targeting the activity of *Pak* genes which are known to be important in NF2 tumor growth. The group used an experimental tool called short hairpin RNA (shRNA) to target the *Pak* genes called *Pak1* and *Pak2*. In brief, shRNA alters the activity of these genes in both benign and malignant meningioma cells so that when the cells were exposed to a drug called doxycycline, the gene signals would be silenced. These cells were implanted into mice and tumors formed. When the mice were fed doxycycline, the tumor did indeed grow at a much slower rate than mice on a normal diet and there was evidence of tumor cells undergoing active death (apoptosis). Silencing the *Pak 1* gene had greater impact than silencing *Pak2*.

To explore this area further, the group then tested Pak inhibitor drugs - Frax597, 716 and 1036 – on the meningioma cells. These inhibitors reduced the multiplication and mobility of both benign and malignant meningioma cells either grown in the dish or when implanted into the mouse. Again when examined, it could be seen that tumor cells were undergoing apoptosis. Overall, benign meningioma cells were more responsive to the drugs than were malignant meningioma cells.

Together these findings provide promising support a role for Pak inhibitors as treatments for meningioma. Further investigation will look more closely into the mechanism of action of these drugs and at the possibility of combining these inhibitors with other drugs.

b. Finding the Genes that Make Meningiomas Malignant

Zhang, Jia *et al.* NIH, FREE *(China, United States)* aimed to identify the genes that are involved in the benign-to-cancerous transformation of meningiomas. Malignant meningiomas are very rare but the group identified nine cases - four men and five women – for study. (Note: it was not stated whether these persons had a clinical diagnosis of NF2). Through a series of complex genetic screens, five genes of interest were identified - *NF2*, *MN1, ARID1B, SEMA4D*, and *MUC2* – all bearing mutations in the malignant meningiomas. Further analysis narrowed the two key genes down to *NF2* and *MN1* and this was verified by looking for these mutations in a further four persons with malignant meningiomas and confirming the presence of these mutations. The group acknowledges that these are preliminary findings verified on a small population of patients, but they shed further light on the genetic underpinnings of these rare but difficult to treat tumors.

7. NF2 Clinical Trials Update

The Bottom Line: Considering the benefits and risks of Bevacizumab as an NF2 tumor treatment.

a. *Benefits and Side Effects of Bevacizumab for NF2 Tumors*

Alanin *et al.* *(Denmark)* looked back at twelve people with a total of eighteen NF2 vestibular schwannomas between them, who had been treated with Bevacizumab (Avastin) over twenty-two months. As reported from previous studies, Bevacizumab had some impact on tumor shrinkage. Six of the eighteen tumors maintained shrinkage for at least two months and three people reported measurably improved hearing. Overall drug toxicity was low. However one person died due to brain hemorrhage that may have been due to Bevacizumab. The authors recognized the potential benefits of Bevacizumab but also cautioned about the importance of considering the risks before embarking on treatment.

8. Schwannomatosis Update

The Bottom Line: The positive outcome of a single case trial of Bevacizumab offers cautious hope for schwannomatosis; an expanding picture of the role of gene *LTZR1* in schwannomatosis.

a. *Bevacizumab Shows Promise for Schwannomatosis in Single Patient Study*

Schwannomatosis is the rarest form of neurofibromatosis affecting an estimated 1:40,000 people. In schwannomatosis, nerve tumors may develop throughout the body, as well as chronic and unmanageable pain. There are no effective treatments for schwannomatosis, and surgical removal of tumors can actually exacerbate the pain. Now **Blakeley *et al.*** [NIH] *(United States)* report on the successful treatment of a twenty-three year old man, diagnosed with schwannomatosis at age 12, with the drug Bevacizumab, which has been widely tested as a treatment option for NF2 vestibular schwannomas. This drug acts by targeting the overgrowth of tumor blood vessels, both reducing tumor size (which itself may alleviate symptoms such as pain) and 'starving' the tumor, aiming to kill tumor cells. The young man had undergone multiple extensive surgeries with no real resolution of pain and he was at the stage of being released from the hospital to hospice care at home. Given his advanced condition, Bevacizumab was given off label and after ten months of treatment improvement in pain and in physical ability was seen. By fifty months of drug treatment pain was fully under control and the young man was able to return to independent living.

This is an incredibly exciting report offering hope to those living with this intractable condition. The authors do caution that Bevacizumab may not work for everyone with schwannomatosis but that effectiveness may be dictated by the genetic mutations of the individual. In addition Bevacizumab itself does carry significant side effects that need consideration, including impact on cardiovascular system and kidney function. Nevertheless this result is very promising.

b. *More Progress in Understanding Gene LTZR1's Role in Schwannomatosis*

Last year the *Network Edge* reported on the identification of a new candidate gene, called *LTZR1*, for some inherited forms of schwannomatosis. A tumor suppressor gene on Chromosome 22, *LTZR1* mutations were found in 80% of inherited cases of schwannomatosis that lacked mutations in the other schwannomatosis associated gene *SMARCB1.*

Smith *et al.* *(France, Germany, Norway, United Kingdom)* examine the role of LTZR1 in schwannomatosis and find mutations in this gene in six out of sixteen patients with schwannomatosis

and one affected relative, in eleven of forty nine patients with first in family cases of schwannomatosis, as well as in two of thirty-nine cases where a patient has a unilateral vestibular schwannoma. The findings confirmed a role for LTZR1 in schwannomatosis but also suggested LTZR1 causes an increased risk of vestibular schwannoma.

Paganini *et al.* NIH *(Italy, Netherlands, United States)* report a detailed genetic analysis of thirteen patients with diagnoses schwannomatosis but no identifiable *SMARCB1* mutation. Four of the group had *LTZR1* mutations. Further expanding this to sixty more schwannomatosis patients revealed eighteen further *LTZR1* mutations. Amalysis of tumor cells with an without functional *LTZR1* genes showed that when the gene mutations are present, normal LTZR1 protein can't be made and it is believed this leads to (or at least contributes to) tumor growth. Though the authors caution that this area needs much more exploration, this study further expands the emerging picture of schwannomatosis, not just its genetic cause, but also how it can be properly diagnosed in the clinic.

These are both important and remarkable studies by these groups, considering the rarity of schwannomatosis as well as the significant progress that has been made in the past few years in understanding schwannomatosis.

9. NF Genetics Update

The Bottom Line: Specific gene mutations as associated with the formation of NF1 café-au-lait marks; candidate 'second hit' genes are identified in dermal neurofibromas.

Note: Additional NF Genetics updates for specific tumor types are included in sections Schwannomatosis Update, NF2 Meningioma Update and NF1 Malignant Peripheral Nerve Sheath Tumors.

a. Looking for the 'Second Hit' Mutation in NF1 Dermal Neurofibromas

When someone inherits NF1 they have a mutated copy of the NF1 gene in every cell in their body. For NF1 tumors to develop there must be an event that also causes the healthy copy of the gene to mutate (this is called a 'second hit'). This only needs to happen in one cell, and from that single cell a tumor can develop. But what exactly causes this 'second hit' is not really well understood. **Emmerich *et al.*** *(Germany)* tackle this question looking at seven individual dermal neurofibromas taken from a single person with NF1. In five of the seven tumors the group was able to identify the second hit mutations; furthermore four of the five had never been seen before. This fascinating study shows the diversity of these 'second hits', and highlights the complex and different mechanisms by which seemingly similar dermal neurofibroma tumors can form.

b. Specific Genes Linked to Café-au-Lait Marks

Seeking to identify the genetic cause of specific features of NF1, **Pemov *et al.*** NIH, FREE *(United States)* look for specific gene mutations that might correlate with certain physical features of NF1 (this is known as genotype-phenotype correlation). Through a complex gene analysis on a large group of people with NF1, the group found that when mutations associated with genes called *MSH6, DPH2* and *ATP6V0B* were present people had a greater number of café-au-lait macules on the skin. This is an intriguing finding because it is one of the first reports to show a genotype-phenotype link in NF1.

10. Special Feature: CDMRP NFRP Update

This January brought the announcement that for 2015, the Congressionally Directed Medical Research Program for Neurofibromatosis Research (CDMRP NFRP) will receive an allocation of $15 Million! Since 1996, the program has committed $258 Million to NF research. CDMRP NFRP has been a critical funder of the most cutting edge NF research including supporting the first national NF Clinical Trials Consortium.

From the start, the NF Network has played an important role in securing CDMRP NFRP funds annually. And while the research community prepares to submit their 2015 project funding applications to CDMRP NFRP, a delegation from the NF Network is already looking ahead to 2016, visiting Congress to explain the importance of CDMRP NFRP and the lives on which it touches, with a goal of ensuring that this funding renewed once again next year.

The more we are learning from NF research, the more we are seeing that its findings can benefit not only those with NF but also those in the military and the broader public through NF's links to a myriad of common diseases. In the past couple of years alone CDMRP NFRP has supported NF research that can impact on primary and secondary cancers, bone disease and healing, pain, autism, muscle weakness and psychosocial issues.

For more updates on the NF Network's Congressional activities and how you can get involved in this, visit http://www.nfnetwork.org/.

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