TheNetworkEdge

The NF Network presents a periodic 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 specific subtopic, so you can focus on the information that interests you most.**

The Network Edge features…

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

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

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Highlights from Volume 16 of *The Network Edge*:

- **NF1 Clinical Trials –** A pilot study of everolimus for cutaneous neurofibromas led to significant shrinkage of a minority of tumors for a small number of patients tested.
- **Breast Cancer Risk in NF1 –** New genetic information better informs breast cancer risk for patients with NF1, and reveals unique and targetable information about breast tumors.
- **NF1 and the Eye: Optic Pathway Gliomas and Other Features –** There are distinct differences in the genetic makeup of gliomas in patients with NF1 vs sporadic gliomas.
- **What's new in NF1 biology –** Researchers found both a vaccination and a medication that reduce pain in rodents with pain from NF1 and other sources.
- **Malignant Peripheral Nerve Sheath Tumors (MPNST) –** MPNST usually arise from plexiform neurofibromas, with an intermediary pathological stage as atypical neurofibroma. Here, researchers define the genetic changes that occur between atypical and malignant tumors.
- **NF1 and Autism –** Simvastatin treatment has a direct impact on MRI findings associated with autism spectrum disorder, and early indication of behavioral benefit as well

- **Social Challenges in Neurofibromatosis –** Social isolation and distress are reduced by participation in a social network specifically for caregivers of children with NF1.
- **Clinical Trials for NF2 –** A vaccination targeting VEGF (the same target as Avastin) shows early promising outcomes in controlling tumor size and hearing.
- **NF2 Diagnosis and Clinical Management –** Lapatinib treatment led to significant shrinkage of meningiomas in a large minority of tumors, and stabilization in another large proportion.
- **What's new in NF2 biology –** Crizotinib shows the ability to slow schwannoma cell growth in culture, and allows for a lower dose of radiation to have the same anti-tumor effect but with less side effect potential.
- **Schwannomatosis Update –** New research shows a correlation between genetic alteration and pain severity in schwannomatosis. Also, an updated study population frequency of schwannomatosis is presented.

The Network Edge: Volume 16 – Contents

1. NF1 Clinical Trials

Everolimus to Treat Cutaneous Neurofibromas in NF1

The Bottom Line: In an early stage clinical trial, everolimus led to reduction in cutaneous neurofibroma (skin tumor) size in a small number of tumors among a small number of patients.

NF1 mutations lead to overactivity of certain cell growth pathways, including through the mTOR complex. Everolimus is an FDA-approved agent that is used in other tumor syndromes (including in children) that inhibits mTOR activity.

Slopis et al. FREE (United States) report on the first use of everolimus for the treatment of cutaneous neurofibromas in NF1. Prior to this study, there was a small amount of evidence that everolimus may stabilize plexiform neurofibromas, and based on that, the authors sought to test whether everolimus may have beneficial effects in cutaneous neurofibromas.

The study was designed as a single arm study, wherein all patient received everolimus. They treated 22 adult patients (59% female, 77% white). In order to study the drug's effects, the investigators identified four target neurofibromas at baseline and photographed them with both 2-dimensional and 3-dimensional photography, and then biopsied lesion #1. After 3 months of therapy, lesions 2–4 were photographed and lesion #2 was biopsied. At the end of the 6-month trial, lesions 3 and 4 were photographed and lesion #3 was biopsied. The primary outcome for the study was reduction in the volume of target cutaneous neurofibromas. Investigators also looked at reduction in tumor height.

In the end, 17 patients completed the 6-month trial, and 16 of those had photographs of sufficient quality to judge their response to therapy. The authors found that 4 of 31 measured tumors (13%) had statistically significant reduction in volume, and these shrinking tumors were present in 3 out of 16 patients evaluated (19%). However, when they looked at tumors that had *any* amount of shrinkage, 21 of 31 tumors (68%) met this criteria, with shrinking tumors seen in 13 of 16 patients (81%). (Note that this sort of analysis is generally considered to overestimate drug effect due to normal variation in tumors and measurements that don't suggest true drug effect). They also found that 19 of 31 tumors (61%) had a reduction in tumor height, seen in 13 of 16 patients (81%). Also of note, three patients also had large plexiform neurofibromas with a skin component and all three had shrinkage of those plexiform tumors. No patient had major side effects on this study, though all patients had at least one side effect. The most common side effects reported were mouth sores, upper respiratory infections, gastrointestinal upset, and rash.

This study provides important, early evidence of an oral chemotherapy that may have the ability to shrink a minority of cutaneous neurofibromas. While this study was not intended to definitively answer the question of everolimus's effects for cutaneous neurofibromas, it is suggestive of a positive signal and may warrant additional study of everolimus or similar medications.

2. Breast Cancer Risk in NF1

The Bottom Line: Women with NF1 are at an increased risk of breast cancer, but specific information about individual *NF1* gene mutations may better estimate that risk. Further, NF1-associated breast cancer may have increased expression of the HER2 protein, for which there are targeted therapies.

a. Using genotype to predict breast cancer risk

The risk of breast cancer is increased 4-5 times for patients with NF1 compared to the general population, and currently annual breast cancer screening recommendations begin at 30 years old for female patients with NF1.

While there are several types of mutations in the *NF1* gene that cause the NF1 disease, including missense mutations (changes in a single letter of the gene), nonsense (cut the gene product short), and insertions or deletions of pieces of gene, to date it is not possible to use a patient's specific *NF1* mutation to predict disease severity or features for the vast majority of cases.

Frayling et al FREE (United Kingdom) report on the correlation between gene mutation type (genotype) and patient presentation (phenotype) from their database of 78 unrelated patients with NF1 and breast cancer, whose average age of breast cancer diagnosis was 47 years. First, they noted that no patients with NF1 and breast cancer had a whole or partial gene deletion. They also noted that patients with missense mutations were diagnosed with breast cancer at a significantly earlier age than other mutation types. As has been the case with most prior studies of this type, there was no correlation between the exact location of the patient's mutation within the *NF1* gene and their risk of breast cancer.

These findings represent an important step forward in utilizing genetic information to inform disease risk and prognosis. While not sufficient to alter screening strategies yet, these data may help physicians counsel patients on breast cancer risk for certain individuals. Overall, this study adds to the growing fund of knowledge helping clinicians to improve and personalize NF1 care.

b. HER2 expression in NF1-associated breast cancer

HER2 is a protein that is produced from the *ERBB2* gene, and is over-expressed on the surface of some breast cancers. The most common cause of protein over-expression is increased number of copies of a gene in a given cell. HER2 over-expression may be specifically targeted with certain types of antineoplastic therapy, thus making this a critical treatment marker among breast cancer patients.

Wang et al. CDMRP FREE (United States) report on pathology findings in patients with NF1-associated breast cancer seen within multiple institutions. Among 13 NF1-breast cancer samples, 70% had over-expression of the protein HER2, whereas the rate of HER2 over-expression in the non-NF1 breast cancer population is between 15-20% (Cronin, et al.). Surprisingly, only 44% of tumors had amplification of the gene that produces HER2 (*ERBB2*), suggesting an alternate cause of HER2 over-expression. They also used a large, federally funded cancer database to evaluate this correlation in a bigger group and found that, among tumors with *ERBB2* gene amplification, the presence of an *NF1* mutation led to marked over-expression of HER2 relative to tumors without *NF1* mutations. Taken together, they conclude from this data that an *NF1* mutation increases the likelihood of HER2 over-

expression through both *ERBB2* amplification as well as additional pathways of protein expression. This is important because HER2 overexpression plays a large role in breast cancer outcome, and there are effective HER2-targeting therapies for breast cancer. This study provides meaningful insights into the relative prevalence of HER2 overexpressing breast cancers among NF1 patients, as well as important data for future mechanistic studies of breast cancer development in this population.

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

The Bottom Line: NF1-associated gliomas (brain tumors) have important genetic differences from sporadic (non-NF1) gliomas, and these may lead to individualized treatment options.

Genetic landscape of gliomas in NF1

NF1 is associated with an increased risk of gliomas (brain tumors), seen in 15-20% of patients. Gliomas vary greatly, with different genetic abnormalities and responsiveness to therapy. Aside from the pre-existing NF1 mutation present in an NF1 patient with glioma, no research has been published to date on genetic differences between NF1-associated gliomas and sporadic gliomas.

D'Angelo et al [NIH] (United States and others) published a landmark paper on the genetics of NF1-associated gliomas. Most notably, they found that age and tumor grade associated with the number of mutations gained by a tumor (often thought to correlate with tumor behavior), and found particularly high rates of mutations in the TP53, CDKN2A and ATRX genes. In high grade gliomas, they also found frequent changes in the activity of the PI3K cellular growth pathway, while lower grade gliomas commonly had increased activity of the MAPK cellular growth pathway. They also found a large proportion of low grade NF1-associated gliomas with elevated immune activity.

Overall, this study provides a first look at the genetic and molecular drivers of NF1-associated brain tumors. It specifically highlights key differences between NF1-associated and sporadic gliomas, as well as high- and low-grade gliomas for patients with NF1. Worth noting, though, is the potentially biased sample of tissues tested here; often NF1-associated brain tumors are either surgically inaccessible (especially optic pathway gliomas) or do not grow and therefore do not undergo surgery. As such, those tumors tested in this study were likely either in less common (e.g. surgically accessible) locations or were aggressive enough to warrant surgery. With these findings in mind, though, targeted therapies may be possible in future clinical care or trials.

4. What's new in NF1 biology

The Bottom Line: Pain is a common symptom among individuals with NF1, and recent work has identified a protein that correlates with pain sensation and directly interacts with the protein product of the NF1 gene. Now, researchers have discovered two therapies targeting this protein that improves pain in rodent models with NF1-associated pain.

Molecular driver of pain in NF1

Pain is a common symptom experienced by patients with NF1, and does not always correlate with individual tumors or overall tumor burden. Recent research suggests that the collapsin response mediator protein 2 (CRMP-2), which helps regulate pain receptors, directly interacts with neurofibromin (the protein product of the NF1 gene). In fact, neurofibromin inhibits activity of the CRMP-2 gene, leaving this pain modulator inactive, and thereby increasing pain.

Moutal et al CDMRP, NIH FREE (United States) sought to recreate the inhibitory effect of the neurofibromin protein on CRMP2 even when neurofibromin is not present. Specifically they identified the precise region of interaction between neurofibromin and CRMP-2 and created a synthetic peptide (piece of a protein) to mimic that interaction. They used this treatment on neurons in a dish in the laboratory and found decreased activity of pain receptors. They then used this treatment in rodents with various types of pain (inflammation, post-surgical, and nerve pain) and found significant pain relief in all models.

In a separate paper, **Moutal et al** CDMRP, NIH FREE (United States) describe their creation of a rat model of NF1-associated pain using the novel gene editing tool CRISPR-Cas9 to mutate the NF1 gene. Rats who underwent the procedure to mutate the NF1 gene had overactive pain receptors and evidence of pain. The authors then made a small change to the structure of the medication lacosamide, an already FDA approved medication used for seizures, and made it directly inhibit CRMP-2 activation (replacing the usual activity of neurofibromin). When they treated their genetically engineered rats with NF1-associated pain with this medication, they saw reduced activity of pain receptors and behavioral evidence of pain improvement.

Taken together, these studies significantly advance our understanding of the mechanism of increased pain in patients with NF1, and highlight two potential disease-specific treatments for consideration of future human studies.

5. Malignant Peripheral Nerve Sheath Tumors (MPNST)

The Bottom Line: The transition from benign to malignant nerve sheath tumor has recurrent genetic mutation events, highlighting opportunities for therapeutic development.

Genetic roadmap from atypical to malignant peripheral nerve sheath tumor

NF1 is associated with an 8-16% lifetime risk of developing a malignant peripheral nerve sheath tumor (MPNST). These are highly aggressive tumors, often arising from pre-existing benign plexiform neurofibromas or atypical neurofibromas (aNFs). Identifying genetic changes that accompany the transition from benign to malignant tumors may allow for better diagnostics and/or treatment options.

Pemov et al NIH (United States) published a study performing multiple types of genomic analysis on aNFs and MPNST. They identified an overall low mutational burden within the aNFs, but notably there were recurrent losses of the genes *CDKN2A/B* and *SMARCA2.* Within the MPNST, they found additional recurrent mutations and deletions of the genes *EED* and *SUZ12*. Together, this data suggests

that mutations in *CDKN2A/B* and *SMARCA2* are key genetic events in the transition from benign neurofibromas to aNFs, while *EED* and *SUZ12* inactivating mutations are key events in the transition to MPNST. There were also larger chromosomal rearrangements seen in the MPNST.

This is the first study to evaluate the genetics involved in transition from benign to atypical to malignant peripheral nerve sheath tumors in NF1. The authors identified critical genetic events that occur between those stages of cancer development, which raise the possibility of developing therapies to stop the development of MPNST, or to better treat them when they occur.

6. NF1 and Autism

The Bottom Line: Autism spectrum disorder is common with NF1. A study of simvastatin therapy showed improvements MRI readings that correlate with autism spectrum disorder. The study was not designed to study social outcomes, but further study is warranted based on these findings.

Simvastatin therapy for NF1-associated autism spectrum disorder

The rate of autism spectrum disorder is increased among individuals with NF1, with an estimated prevalence of ~30%. (Garg, et al). In animal models, statin medications improve both cognitive and social abnormalities associated with NF1. However, clinical trials using statin medications for NF1-associated cognitive symptoms have not proven to be beneficial.

Stivaros et al FREE (United Kingdom) published the result of a clinical trial to test a statin medication for the treatment of NF1-associated autism spectrum disorders in children. The trial was designed as a randomized, placebo-controlled, triple-blinded study of simvastatin vs placebo. Included participants were between the ages of 4.5 years and 10.5 years who had a diagnosis of both NF1 and autism spectrum disorders (excluding individuals with severe learning disabilities).

Outcome measures for this study included MRI with spectroscopy and functional measures on *awake* children at baseline and at 12 weeks, a behavioral analysis (including both doctor and patient input) at baseline, at 4 weeks, and at 12 weeks, and a blood test for changes in the cellular activity caused by the statin medication.

A total of 30 participants were included and randomized, while only 26 completed all treatment and assessments at the end of the 12 week study. The average age of participants was 8.1 years, there were similar rates of ADHD within the groups (which was untreated in all cases), and similar severity of behavior abnormalities in both groups. Overall, simvastatin was well tolerated among participants. Simvastatin treatment led to significant MRI changes, including changes in blood flow and biochemical activity, in a manner consistent with an improvement in NF1-related neuropathology. On behavioral analysis, 25% of the participants taking simvastatin had significant improvements compared to 0% in the placebo group. Finally, blood tests did show biochemical changes consistent with the hypothesized activity of simvastatin.

This study was not designed to answer the question of whether or not simvastatin is an acceptable treatment for NF1-associated autism spectrum disorder. Instead, the authors determined that these tests of blood and MRI were appropriate and acceptable means of studying statin activity in the brain, and that areas of the brain that are important for social and behavioral health had a

significant change as a result of simvastatin treatment. Overall, they did identify a suggestion of positive effect of the medication for the behavioral aspects of the disease, and suggest that further study is warranted.

7. Social Challenges in Neurofibromatosis

The Bottom Line: Caregivers of children with NF1 report frequent social isolation, stress, doubt, and fear. An online, social networking platform created specifically for caregivers of children with NF1 demonstrated the ability to improve social and emotional stress.

Social Networking for NF1 Caregivers

Parents of children with chronic conditions often feel isolated when facing disease-related challenges in addition to routine childhood and adolescent challenges. More specifically, parents of children with NF1 report considerable stress, doubt, and fears in caring for their child/children. Studies have previously highlighted the importance of having a social network with which to share information and management strategies with parents with similar experiences and challenges.

Akre et al (Switzerland and United States) reported the outcome of a pilot study using an online portal for parents or caregivers of children with NF1. To begin, the participants created a series of videos outlining their experience in having a child with NF1, answering questions such as "How do you get along with your child with NF1?", "Talk about your worries about having an adolescent with NF1", and "Do I treat my child differently because s/he has NF1?". Participants uploaded their videos to a secure portal, and later had the opportunity for interaction with the other parents on the same portal, all of which was monitored by a research coordinator and physician. In the end, only 10 caregivers were included in final analyses but reported an overall positive experience. Participants had decreased feelings of isolation, felt relief in discussing NF1 without having to explain the disease, acquired new knowledge about NF1 from caregiver peers, and appreciated putting their own lives into perspective with respect to others in similar circumstances.

This study not only reinforces the emotional and social challenges of caring for children with NF1, but also presents a feasible, decentralized strategy to improve upon those challenges. Recognizing the invaluable role that they play in the wellbeing of a child with NF1, an improvement in caregivers' lives is very likely to result in an improvement in the lives of children with NF1.

8. Clinical Trials for NF2

The Bottom Line: Researchers showed early success in the development of a vaccine against VEGF, the same target as Avastin. This has the potential to be a great next step in schwannoma therapy with conceivably fewer side effects.

Vaccine therapy for schwannomas

Vestibular schwannomas are the hallmark tumor of neurofibromatosis 2 (NF2), and are known to express high levels of the vascular endothelial growth factor (VEGF) protein. Bevacizumab (Avastin), is an antibody that targets VEGF and has been shown to improve hearing for nearly half of patients with vestibular schwannomas, as well as to shrink nearly half of vestibular schwannomas (though tumor size and hearing do not correlate). Avastin treatment leads to lasting improvements, but may not be a great long-term solution for some patients due to the risk of side effects of the medicine. Avastin may have some benefit for schwannomas in other locations as well.

Tamura et al (Japan) report on their research to develop a vaccination against VEGF for the purpose of treating schwannomas. In their study, they treated seven adult patients with progressive intracranial schwannomas with a series of 8 vaccinations against the VEGF receptors.

One long-deafened patient was removed from the hearing analysis of the study, and among the other six patients, 3 (50%) had improvement in hearing with this vaccination therapy. Only one ear out of all 12 tested had worsening of hearing after all vaccinations. Using the standard cutoff of 20% reduction in tumor volume that is considered to be statistically significant shrinkage (e.g. not different due to chance or to variation in imaging), 4 out of 23 (17%) measured tumors (all intracranial schwannomas) had significant shrinkage, while 10 out of 23 tumors (43%) had at least 1% shrinkage. Among the measured vestibular schwannomas, 2 out of 14 (14%) had significant shrinkage (both were in the same patient), while 1 out of 14 had significant growth. Notably, one person with responding tumors had previously shown a lack of benefit from Avastin, suggesting that the two VEGF-targeting therapies don't overlap completely.

In all patients, immune reactivity against the VEGF receptor was identified by blood testing, though there were varying degrees of activity. Pathological testing also showed evidence of immune change within the tumors. The side effect profile for the vaccine was overall very mild.

This study is an important, first attempt at using immunotherapy in the treatment of schwannomas. The small size of the study, though, warrants caution in interpreting its results. With further development, though, VEGF receptor vaccinations could prove to be a promising treatment to avoid long-term toxicity from Avastin.

9. NF2 Diagnosis and Clinical Management

The Bottom Line: Lapatinib is an oral chemotherapy that has shown stabilizing properties in vestibular schwannomas. New retrospective research suggests it may have similar effects on meningiomas, though more research is warranted.

Lapatinib for adults with NF2 meningiomas

Meningiomas occur in 80% of patients with NF2 across their lifetime, and are associated with increased expression of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) proteins. Similarly, schwannomas have over-expression of EGFR and HER2. Laboratory testing suggests that lapatinib, a medication that inhibits EGFR and HER2 signaling, has antitumor effects for NF2 schwannomas. Until now, no data existed on the effect of lapatinib on NF2 meningiomas.

Osorio et al [NIH] (United States) reviewed the charts of eight patients with NF2 (with a total of 17 meningiomas) who were treated on a clinical trial with lapatinib for vestibular schwannomas. They limited their study to patients who had measurable meningiomas, and to those who had at least 5 months of lapatinib therapy. They found that 47% of evaluated meningiomas had significant shrinkage (>20%) during therapy, another 41% were stable during treatment, and only 12% of tumors had significant (>20%) growth during therapy. Comparing tumor growth rates on lapatinib treatment vs off lapatinib treatment within the same patients also suggested an anti-growth effect of the drug for meningiomas. Side effects for lapatinib were overall mild and tolerable to patients.

Taken together, this study suggests that lapatinib may have a positive effect on NF2-associated meningiomas by prohibiting growth, and even shrinking tumors in some cases. It is important to take into consideration not only that this was a small study, but also that it was an unplanned analysis of the study evaluating lapatinib for vestibular schwannomas. Thus, the findings are helpful in generating new scientific thoughts and clinical trial ideas, but are not confirmatory of effect.

10. What's new in NF2 biology

The Bottom Line: Crizotinib, an FDA-approved antineoplastic medication, may inhibit schwannoma growth and render lower doses of radiation to be more beneficial.

Crizotinib with or without radiation for schwannomas

Although radiation works well to stop vestibular schwannoma growth, the dose required to do so generally leads to deafness in the treated ear and may increase the risk of cancer as a long-term consequence of radiation. Finding ways to achieve similar tumor control with lower doses of radiation might reduce these unwanted side effects.

Zhao et al [CDMRP, NIH FREE] (United States) looked at implanted mouse schwannomas that were resistant to radiation and determined that cMET (a growth protein commonly activated in cancers) is turned on by radiation. Then, they tested an FDA-approved cMET inhibitor (crizotinib) and found that it sensitizes schwannoma cells to the cell-killing effects of radiation. Next, they used a genetic alteration technique (shRNA) to block expression of cMET and saw reduced schwannoma growth and improved radiation sensitivity. Next, in mice they saw that using crizotinib plus a 50% dose of radiation was more effective at killing tumor cells than a 100% dose of radiation without crizotinib. Finally, the authors evaluated human tumor samples (both from NF2 and sporadic vestibular schwannomas) and found increased expression of cMET compared to normal nerve. They grew those human tumor cells in dishes and found that crizotinib inhibited cell growth.

In summary, the cancer pathway cMET is overactive in schwannomas and appears to contribute to tumor resistance to radiation therapy. The authors identified a potential therapeutic (crizotinib) that could be considered alone or in combination with low-dose radiation for further human study in the treatment of schwannomas.

11. Schwannomatosis Update

The Bottom Line: New studies provide a better understanding of the population prevalence of schwannomatosis, as well as a correlation between genetics and schwannomatosis symptoms.

Population study of schwannomatosis

Schwannomatosis is the most recently defined entity of the neurofibromatoses, and there remains significant clinical overlap between schwannomatosis and NF2. As such, the true prevalence of schwannomatosis is not well understood.

Evans et al (United Kingdom) published the results of their epidemiology study from the Manchester region of England (population = 4.8 million) and from across the UK. The authors have a robust database of patients with neurofibromatosis within the UK which served as the primary data source for this study. They identified all patients meeting the current clinical diagnostic criteria for NF2 and schwannomatosis and performed genetic testing on blood samples where possible. They also used regional birth and death records to calculate the rate of diagnosis for these diseases relative to population trends.

The authors identified 1192 patients with a diagnosis of NF2 (932 of whom were living) and 399 patients with a diagnosis of schwannomatosis. Based on the birth rate in the region over a 31-year period, the highest estimated incidence of NF2 was 1 in 27,965 births and the highest estimated incidence of schwannomatosis was 1 in 57,464 births. Prevalence (total living with disease) was 1 in 50,500 living people for NF2 and 1 in 126,315 for people living with schwannomatosis. Interestingly, 9% of true schwannomatosis cases were misdiagnosed as mosaic NF2 due to the overlap of clinical presentations (ultimately determined by genetic testing).

This study not only provides an important glimpse of the epidemiology of schwannomatosis relative to NF2 within a large region of the UK, but also highlights the nearly 10% rate of diagnostic confusion between schwannomatosis and mosaic NF2 which is best determined by genetic testing. This will be important to compare to other population studies, and adds more emphasis to the importance of genetic testing for schwannoma predisposition syndromes.

Pain in Schwannomatosis

At least 80% of patients with schwannomatosis suffer from chronic pain. While there is a recognized relationship between pain and overall tumor burden, it is clear that a more generalized pain syndrome exists in many patients regardless of specific tumors. To date, two genes have been identified to cause schwannomatosis (SMARCB1 and LZTR1), but these do not represent all cases of schwannomatosis. Although a few differences have been identified already, determining disease symptoms that differ between gene mutation groups may help understand the disease better and may also allow for targeted treatment development.

Jordan et al CDMRP, NIH FREE (United States) report the results of their study of 37 patients with schwannomatosis who underwent whole body MRI. The authors performed genetic testing and correlated mutations with both whole body MRI findings and with patient-reported outcomes,

including pain severity and quality of life surveys. The authors identified that LZTR1 mutations were associated with a significantly higher risk of spinal schwannomas, as well as a significantly higher level of pain. However, there was no correlation between presence of spinal tumors and pain level, suggesting that both are related to the LZTR1 mutation but not related to each other. The authors also found that pain-related quality of life was much worse for patients with LZTR1 mutations than other groups. Pain also significantly correlated with total body tumor volume, but tumor volume was not associated with mutational status.

Although small, this study provides important insight into schwannomatosis genetics. Not only is there evidence of a predisposition to spinal tumors with LZTR1 mutations, but more importantly there is a correlation between disease genetics and pain. This offers an opportunity for focused study of pain mechanisms for this disease population.

***Disclosure –** The author of this newsletter is also the lead author of the publication above regarding pain in schwannomatosis.

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NF1 Clinical Management	X	X	X	X	X	X	X	X		X	X				X	
NF1 Learning Disabilities	X	X	X	X	X	X	X		X	X	X	X	X			
NF1 Bony Abnormalities	X	X	X	X	X	X	X	X	X							
NF1 Malignant Peripheral Nerve Sheath Tumors		X		X	X	X	X	X			X	X	X	X	X	X
Heart and Blood Vessel Abnormalities in NF1		X	X	X	X	X					X					
Breast Cancer Risk in NF1	X			X					X		X	X		X		X
Other Clinical Features of NF1	X		X	X	X	X	X		X							
What's New in NF1 Biology?	X	X	X	X	X	X	X	X	X	X	X		X			X
NF2 Clinical Trials	X		X			X	X		X	X		x				X
NF2 Clinical Management	X	X	X	X	X	X	X	X		X	X		X	X	X	
What's New in NF2 Biology?	X	X	X	X	X	X	X	X		X	X		X		X	X
Schwannomatosis Update	X		X	X	X	X		X			X	x	X	X		X
Legius Syndrome Update	X		X			X					X					
The Evolving Link Between NF and Cancer		X				X						X				
Altered Brain Function in NF1				X					X	X						
NF1 and the Eye: Optic Pathway Gliomas and Other Features				X	X	X		X	X	X	X	X		X	X	X
NF Genetics Update				X	X		X	X		X	X					
Pheochromocytoma in NF1			X							X						
Social Challenges in Neurofibromatosis					X	X	X	X	X	X	X		X		X	X
NF1 and Autism					X			X			X					X
REiNS Collaboration Update					X								X			
Quality of Life in NF1, NF2, and Schwannomatosis												x	X	X	X	

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