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.

- A Global NF Picture: To keep you abreast of all NF research advances, *The Network Edge* includes publications from around the world. **Country 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 21 of *The Network Edge*:

- **NF1 Clinical Trials:** Selumetinib, which is already approved to treat symptomatic plexiform neurofibromas in children with NF1, may also help prevent symptoms from ever developing in children with asymptomatic plexiform tumors in high-risk locations of the body.
- **NF1 MPNSTs:** Research on a blood test to diagnose MPNSTs early expands, and a new, first-in-class REF1 inhibitor shows promising results in the lab to potentially treat MPNSTs.
- **NF1 Optic Pathway Gliomas**: Treating mice with the antiseizure medication lamotrigine helped prevent optic pathway gliomas from forming and growing.
- **NF1 Clinical Management:** Many internal neurofibromas may shrink over time without any treatment in adults with NF1.
- **NF1 Biology:** First genetically engineered mouse model of cutaneous neurofibromas established.
- **NF2 Clinical Trials**: A phase 2 clinical trial of icotinib shows modest success in shrinking/ stabilizing vestibular schwannomas and improving hearing over one year of treatment.
- **NF2 Biology**: Researchers test multiple strategies for gene therapy in NF2, including a technique to correct the mutated NF2 gene in tumors so that cells can produce a functional NF2 protein.
- **Schwannomatosis**: Two clinical trials to treat schwannomatosis-related pain are underway
- **Quality of Life and Other NF Updates:** People with NF1, NF2, and schwannomatosis do not appear to be at increased risk of getting COVID-19 or being hospitalized with COVID-19.

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1. NF1 Clinical Trials

<u>The Bottom Line</u>: Selumetinib, which is already approved to treat symptomatic plexiform neurofibromas in children with NF1, may also help prevent symptoms from ever developing in children with asymptomatic but high-risk plexiform tumors. In addition, a new formulation of selumetinib that is easier for very young children to swallow is being developed to expand access to this medication. Cobimetinib, a MEK-inhibitor, does not seem effective for the treatment of plexiform neurofibromas.

Selumetinib was approved by the FDA in 2020 specifically to treat children with NF1 who had inoperable plexiform neurofibromas causing symptoms (such as pain, disfigurement, motor problems, or difficulty breathing). However, it is unknown whether treatment with selumetinib should be given to children with plexiform neurofibromas earlier, before they ever develop symptoms. **Gross et al.** FREE, NIH (United States) now report results of a phase 2 clinical trial of selumetinib in children with NF1 whose plexiform neurofibromas weren't yet causing any symptoms, but who were at risk of developing symptoms later on due to the location of the tumor in their body.

Similar to prior clinical trials of selumetinib, 72% (18/25) of children in the trial had their plexiform neurofibroma shrink by at least 20% in size. Over the duration of the study, no one had their tumor grow more than 20% in size. Younger children were more likely to have their tumor shrink; the size of the tumor and whether it was growing before the trial were not related to whether tumors shrank or not. At the time this data was analyzed, when children had been in the study for about 2.5 to 5 years, 12 children (48%) still had tumors that were at least 20% smaller than at the start of the trial.

After about one year of treatment, none of the children developed new symptoms related to their plexiform neurofibroma. Despite the fact that they had tumors at high risk for developing complications, the children's functioning (including motor skills, vision, breathing, and bowel/bladder function) did not get any worse over the year. Furthermore, the children reported in questionnaires that they had stable or improved pain, physical functioning, and quality of life.

Overall, this data suggests the selumetinib may prevent the development of plexiform neurofibroma-related symptoms. However, the authors caution that a larger study is needed to determine the optimal time to start treatment in children with plexiform neurofibromas to help make sure the benefits of treatment outweigh the risks. While selumetinib is generally well tolerated, all participants in the trial did experience at least one side effect (such as rash or nausea), and treatment often needs to be continued for many years to maintain its effect.

In additional news related to selumetinib, **Cohen-Rabbie et al.** FREE, NIH (United States) report on a Phase 1 clinical trial of selumetinib granules. Currently, selumetinib is only approved as a capsule that needs to be swallowed, which can be difficult or impossible for very young children to do. A new formulation of the drug, consisting of small granules that are easier to ingest, was tested in a clinical trial to understand how it is absorbed by the body. This is important to make sure the granules deliver the medications just as well as the capsule, and to understand if any dosing adjustments need to be made based on the formulation of the drug someone receives. The results of this study showed that the granules are absorbed similarly to capsules, so development and manufacturing of this formulation will continue. This formulation will hopefully be available soon, so that even more young children with NF1 can benefit from this medication.

While selumetinib is the first (and at this time, only) MEK inhibitor medication approved by the FDA for people with NF1, multiple other MEK inhibitors are also under study for the treatment of plexiform neurofibromas and other NF1-related tumors. Now, **Trippett et al.** FREE (United States, Israel, United Kingdom, France, Spain, Germany, Canada) conducted a Phase 1/2 clinical trial of cobimetinib for children and young adults (up to age 30) with a variety of tumors involved in the MEK pathway. Cobimetinib is a MEK-inhibitor that is FDA-approved to treat melanoma and other rare cancers. Of the 56 patients enrolled in the trial, 15 had NF1: twelve with plexiform neurofibromas and three with optic pathway gliomas. Because this trial enrolled people with a variety of tumors, the researchers did not use the same criteria to measure tumor shrinkage as other NF1 clinical trials; still, only 5% of patients on the trial (all with low grade gliomas) had their tumors shrink significantly. In addition, most patients experienced some side effects, with 11% of patients stopping treatment due to side effects largely related to eye problems. Due to the low number of patients who responded to treatment, the clinical trial ended without further enrollment of new participants. While this MEK inhibitor unfortunately did not show any evidence of activity for NF1, additional clinical trials of other MEK inhibitor medications are underway with more promising results. For example, in Volume 19 of the Network Edge we reported results from a clinical trial of mirdametinib for symptomatic or rapidly growing plexiform neurofibromas in adolescents and adults with NF1.

2. NF1 Learning Disabilities, Cognition, and School Performance

The Bottom Line: Alectinib, an ALK-inhibitor currently approved to treat some forms of lung cancer, improved cognitive performance of mice with NF1. On average, children with NF1 have lower grades in school that their peers, emphasizing the need for learning support.

Krenik et al. NIH, CDMRP (United States) studied the effect of ALK-inhibitor medication on cognitive performance in mouse models of NF1. Previous research showed short-term (10 day) treatment with alectinib, an ALK-inhibitor that is FDA-approved to treat lung cancer, may improve cognitive function in mice with NF1 mutations. However, children with NF1 would likely need treatment for extended periods of time to treat learning disabilities, so longer-term assessments of drug efficacy and safety in mice were needed before deciding whether to move forward with research in humans. In this article, the researchers found that long-term treatment (24 weeks) with alectinib improved object recognition and spatial learning in mice with NF1. In addition, there were no noticeable increases in anxious or depressive behaviors in the mice (a potential side effect of ALK-inhibitors), making this therapy potentially suitable for testing in kids with NF1.

Doser et al. (Denmark) looked at the academic performance of children with NF1 in Denmark. They examined students' course grades during their last year of mandatory general schooling, which in Denmark happens when children are 15 or 16 years old. They compared the grades of 285 students with NF1 to the grades of 12,000 other children without NF1 enrolled at the same public schools. The parents of children with NF1 had slightly lower education and income that parents of children without NF1, but even after accounting for this difference, children with NF1 had lower grades on average compared to their peers. While not all children with NF1 will struggle with school, this study highlights the importance of offering additional school supports to help mitigate these gaps. For more information about school performance and accommodations for children with NF1, see https://nfnetwork.org/data/uploads/nf1-educational-materials/learning-problems-in-nf1.pdf

3. NF1 Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

The Bottom Line: Researchers launch a large-scale study to confirm whether a blood test can reliably diagnose MPNSTs in people with NF1, hopefully enabling a path to earlier treatment and better survival for affected individuals. Researchers also identify a new, first-in-class medication called APX3330 that successfully killed MPNST cells in the lab and slowed down MPNST growth in mice.

About 8-10% of people with NF1 will develop malignant peripheral nerve sheath tumors (MPNSTs) in their lifetime, but it can be difficult to tell based on imaging alone whether a tumor is a benign plexiform neurofibroma or a cancerous MPNST. Multiple NF research groups are working to develop blood tests that can detect whether people with NF1 have developed an MPNST by isolating and analyzing small fragments of tumor DNA that circulate in the bloodstream. In the last issue of the Network Edge, we reported that **Szymanski et al**. FREE, NIH (United States) developed a one-time blood test that was 86% accurate in distinguishing people with plexiform neurofibromas from people with MPNST in a small pilot study. The senior researchers of this study - Dr. Angela Hirbe and Dr. John Shern - have now received $2 million dollars of funding to expand this research project in a larger, 3-year study that will see whether the blood test can diagnose MPNSTs earlier, hopefully allowing people to get the MPNSTs surgically removed when they are smaller and easier to cure. Furthermore, **Mattox and Douville** et al. FREE, NIH, CDMRP (United States) have also confirmed the promise of this approach even when using different methods to analyze the tumor DNA in blood samples. By combining different methods of looking at tumor DNA in blood samples, researchers will hopefully be able to design a more accurate blood test to diagnose and monitor MPNSTs in people with NF1 moving forward.

Existing treatment options for MPNSTs that are not able to be surgically removed are unfortunately limited, with 50-65% of people with this cancer dying within 5 years of diagnosis. **Gampala** et al. FREE, NIH, CDMRP (United States, United Kingdom) tested whether a new, first-in-class medication may successfully treat MPNSTs in these individuals. The researchers found that a new REF-1 inhibitor called APX3330 effectively killed MPNST cells in the laboratory and slowed down MPNST growth in mice by regulating two pathways important to MPNST growth (STAT3 and HIF1-α). APX3330 has not yet been approved by the FDA for any indication, but has completed Phase 1 clinical trials to determine a safe dose in a variety of advanced cancers. This data excitingly support the testing of APX3330 or similar medications In clinical trials for treatment of MPNSTs.

4. NF1 Optic Pathway Gliomas

The Bottom Line: Research in mice suggests treatment with lamotrigine, an FDA-approved anti-seizure medication may be able to treat optic pathway gliomas by reducing the overactivity of optic nerves caused by NF1 mutations.

People with NF1 who have a specific mutation in their NF1 gene (c.5425C > T; p.Arg1809Cys) uniquely never develop optic gliomas or plexiform neurofibromas. **Anastasaki et al**. FREE, NIH, CDMRP (United States) genetically engineered mice to have this same mutation and compared them to mice with other NF1 mutations to understand what causes tumors to form in some people with NF1 but not others. They found that certain nerve cells in mice with NF1 fire too often, leading to the release of proteins that diffuse to nearby cells and cause optic gliomas and plexiform neurofibromas to grow. However, mice with the c.5425C > T mutation do not show the same hyperexcitability in their nerve cells.

The reason the nerve cells fire too often is likely due to overactivity of ion channels that the NF1 protein normally regulates. This suggests that using FDA-approved drugs that target these nerve cell ion channels, like the anti-seizure drug lamotrigine, could potentially be repurposed to treat or even prevent optic pathway gliomas. In fact, the researchers showed that injections of lamotrigine could reduce the formation of optic gliomas in mouse models of NF1. This preclinical data excitingly supports further testing in human clinical trials to determine whether treatment with lamotrigine can help prevent or slow the growth of optic pathway gliomas.

5. NF1 Clinical Management: Neurofibromas

The Bottom Line: Descriptive research on neurofibromas shows that about half of large plexiform neurofibromas cause symptoms and that many plexiform and other internal neurofibromas will spontaneously shrink over long time periods in adults with NF1 without any treatment.

Ejerskov et al. (Denmark) looked at the medical records of all NF1 patients seen at the two NF clinics in Denmark over the past 20 years to understand the prevalence of plexiform neurofibromas and their related symptoms. 12% of pediatric patients and 21% of adult patients had at least one large plexiform neurofibroma (defined as at least 3 cm in size). About half of people with large plexiform neurofibromas had symptoms related to their tumors; the other half were asymptomatic. The most common symptoms in children with large plexiform neurofibromas were pain (29%) and neurological deficits (23%); the most common symptoms in adults with large plexiform neurofibromas were pain (32%) and cosmetic issues (23%).

Ly et al. CDMRP (United States) studied the growth patterns of internal neurofibromas in 47 adults with NF1 over a decade using whole body MRIs. Across 304 neurofibromas, only 17% of tumors grew by at least 20% in volume, and 63% actually spontaneously shrunk by at least 20% in volume without any surgery or medical treatment. In fact, 30 tumors in 10 adults were either completely gone or were so small as to be undetectable on the follow-up scans about ten years later. Unfortunately, none of the factors researchers looked at - including tumor size or location - could predict which tumors would grow and which would shrink. As best as the researchers could determine, hormone exposure (through pregnancy or use of hormonal birth control) was not associated with tumor growth in women. Overall, this data shows that adults with NF1 can have very different neurofibroma growth patterns than children with NF1 (in whom tumors are known to grow more consistently and rapidly.) Importantly, 91% of the adults who had no internal neurofibromas at baseline still had no tumors after a decade, suggesting that adults who do not have any internal neurofibromas on whole-body MRI likely do not need continued imaging surveillance.

Disclosure: The author of this newsletter is a co-author of the article by Ly et al.

6. NF1 Bony Abnormalities

The Bottom Line: Researchers test new techniques for measuring bone strength in people with NF1 to enable future clinical research identifying which individuals with NF1 are most at risk for tibial bowing.

Ahmed et al. NIH, CDMRP (United States) developed new techniques for measuring bone strength. People with NF1 are susceptible to having the bones in their shin bend (tibial bowing) and potentially

break due to poor bone mineralization. Research in mice suggests that treatment with alkaline phosphatase could prevent this problem, but researchers have had a difficult time testing this compound in human clinical trials due to an inability to predict which children are at risk for tibial bowing. The researchers identified two measures of bone strength that differentiated mice who did and did not develop bone problems; these measures can now be tested as potential indicators of the onset of bone weakness in people with NF1. This will hopefully help predict which people are at higher risk for tibial bowing and would make good candidates for future clinical trials.

7. Heart and Blood Vessel Abnormalities in NF1

The Bottom Line: Researchers find new targets to potentially treat renal artery stenosis - a narrowing of the arteries near the kidney - in people with NF1.

People with NF1 are at increased risk for narrowing of arteries near their brain (Moyamoya disease), heart (aortic coarctation), and kidneys (renal artery stenosis) due to excess tissue produced by NF1 gene mutations. This same excess tissue, called a neointima, also forms after injury to blood vessels.

Tritz et al. FREE, NIH, CDMRP (United States) studied the process of excess tissue formation after injury in mouse models of NF1. They found that certain blood cells (neutrophils and macrophages) play an important role in remodeling arteries through activation of the MEK pathway. This pathway is known to be overactive in people with NF1, and a drug inhibiting this pathway (selumetinib) was recently approved by the FDA based in part on NFRP-funded research. Importantly, the researchers found a critical time window where treatment with MEK inhibitors like selumetinib could help prevent excess tissue formation and arterial narrowing after injury in a mouse model of NF1.

Coleman et al. FREE, NIH, CDMRP (United States) treated a series of children with NF1 and high blood pressure due to narrowing of the arteries near their kidneys. By analyzing samples from these patients' arteries after surgery, the researchers confirmed that the normal vascular remodeling process is overactive in people with NF1 due to overactivation of the MAPK pathway and increased levels of the pro-inflammatory protein MCP-1. This data helps validate these pathways as additional potential treatment targets for renal artery stenosis in people with NF1.

8. NF1 and Autism

The Bottom Line: Children with NF1 and suspected autism have similar difficulties in social communication as autistic kids without NF1, but are more likely to have a need for sameness/routine and are less likely to have repetitive movements (like hand flapping).

Chisholm et al. FREE, CDMRP (Australia, United States) performed extensive testing to characterize the autistic symptoms associated with NF1. They found that kids with NF1 and suspected autism have the same social communication difficulties as kids with autism who don't have NF1, but different problems with restricted behaviors (namely, an insistence on sameness and routine rather than repetitive movements). This data could help clinicians diagnose autism in kids with NF1 earlier and better address their unique behavioral challenges.

They found that kids with NF1 and suspected autism have the same social communication difficulties as kids with autism who don't have NF1. However, they often have different problems with restricted and repetitive behaviors (another category of behaviors related to autism). Kids with NF1 with difficulties in this area often had a high need for sameness, struggled with minor changes to routines, and/or had circumscribed interests, while kids without NF1 more frequently have repetitive movements (like hand flapping or other forms of stimming). This data could help clinicians diagnosis autism in kids with NF1 earlier and better address their unique behavioral challenges.

9. What's New in NF1 Biology?

The Bottom Line: Innovative research techniques help identify new treatment targets for plexiform neurofibromas and establish the first genetically engineered mouse model of cutaneous neurofibromas.

Kersner et al. FREE, NIH, CDMRP (United States) used innovative molecular techniques to identify the diverse cell types that make up plexiform neurofibromas. For the first time, they found specific types of immune and structural support cells within the tumors that likely play a role in suppressing the immune system and promoting tumor growth. Targeting these cells opens up new avenues for treatment, including by targeting the NF-κB protein and the CD74 cell membrane receptor.

Mo et al. FREE, NIH, CDMRP (United States) established the first ever genetically-engineered mouse model of cutaneous neurofibromas that mimics human cutaneous neurofibromas. They did this by reprogramming human stem cells into the kind of cell that neurofibromas originate from (Schwannian lineage cells), and implanting these cells into the sciatic nerve of mice, where they grew into nodular cutaneous neurofibromas. This mouse model will be an invaluable tool to test the efficacy of new treatment options for cutaneous neurofibromas in mice before moving to human clinical trials

10. NF2 Clinical Trials

The Bottom Line: A phase 2 clinical trial of EGFR inhibitor medication icotinib shows modest success in shrinking/stabilizing vestibular schwannomas and improving hearing over one year of treatment.

Zhao et al. (China) conducted a phase 2 clinical trial of the EGFR-inhibitor medication icotinib to treat progressive vestibular schwannomas in 10 people with NF2 ages 16 and up. A change of at least 20% in tumor volume is commonly used as a marker of tumor growth or tumor shrinkage in NF clinical trials so that researchers can be confident the change is real, and not just due to small differences in MRI techniques. In this trial, one person in the trial had both of their vestibular schwannomas shrink at least 20% in volume over one year of treatment. Two people had their vestibular schwannomas grow more than 20%, and the remaining seven people had stable tumors (tumors that grew or shrank less than 20%). In addition, four people had their hearing improve significantly in one ear over one year of treatment (out of seven people that had hearing that could potentially get better with medication). The most common side effects of treatment were a rash (which happened in 90% of people, sometimes requiring topical steroids to treat) and diarrhea (which happened in 50% of people, and required temporary medication to treat in one person).

11. What's New in NF2 Biology?

The Bottom Line: Researchers test multiple strategies for pursuing gene therapy in NF2, including a technique to correct the mutated NF2 gene in tumors so that cells can produce a functional NF2 protein.

Multiple research groups are actively working on gene therapy for NF2, with promising pre-clinical results. Gene therapy (or gene-directed therapy) is an array of treatment approaches that work by directly modifying or manipulating the expression of genes – the segments of DNA that carry the instructions for making proteins in the body. Gene therapy works by modifying, inactivating, or replacing a mutated gene such that it no longer causes a disease. In this way, gene therapy can be used to correct expression of the NF2 gene directly, in a way that current medications can't do.

Prabhakar et al. NIH, FREE (United States) developed a type of gene therapy that repurposes a virus to deliver a functional copy of the NF2 gene into cells. These cells can then make the NF2 protein, called merlin, which is normally missing in NF2-related tumors. The researchers used this type of gene therapy on sample human cells in the laboratory, and found it could restore function of the NF2 gene and lead the cells to produce the NF2 protein, called merlin. Furthermore, using a mouse model of NF2 that has a tumor in the sciatic nerve, they showed that a single injection of gene therapy directly into the tumor could lead the tumor to shrink and almost disappear in most cases (seven out of nine tested mice). This treatment approach is very promising for translation to humans with NF2, because it shows a single injection effectively treated NF2 tumors in mice for many months, using a technology (called AAV-mediated gene therapy) that is already being tested in clinical trials for other diseases.

There are also some types of gene therapy that may only work for some individuals with NF2, based on where exactly their mutation is in the NF2 gene or what type of mutation it is. The NF2 gene is composed of 17 segments of DNA called exons. During the biological process of translation, the DNA in these exons are read in order from 1 to 17 to create an RNA sequence and then proteins needed by the body. Some people with NF2 have a mutation in one of their NF2 gene exons that causes the translation process to stop early, resulting in an NF2 protein that is missing some parts and doesn't function well. **Catasus et al**. FREE (Spain) are working on a type of gene therapy that targets this type of mutation. This type of gene therapy introduce a single strand of synthetic DNA into the body which then binds to the matching sequence in the NF2 gene to alter the translation process. Instead of the translation process stopping at the mutated exon, that exon gets skipped and the translation process can continue reading the rest of the exons in the NF2 gene. The researchers found that this method of gene therapy seems most promising for people with mutations in exon 11. Instead of only translating exons 1-10 and then stopping – resulting in a nonfunctional NF2 protein - the cell would translate exons 1-10, skip exon 11, and translate exons 12-17. This process would make a protein that isn't exactly the same as the normal NF2 protein, but hopefully is close enough that it could still carry out essential functions in the cell. Further study is needed to see if this version of the NF2 protein is truly functional, but this study provides exciting proof of concept that this type of gene therapy, called antisense gene therapy, could one day help treat NF2 patients prior to the development of any tumors.

12. Schwannomatosis Update

The Bottom Line: Two clinical trials to treat schwannomatosis-related pain are underway; research shows combination therapy targeting two biological pathways could be an effective treatment strategy for schwannomatosis caused by LZTR1 mutations; delays and errors in diagnosing schwannomatosis in the U.S. are unfortunately common.

Da et al. NIH, CDMRP (United States) describe the design of a Phase 2 clinical trial testing whether tanezumab, an inhibitor of nerve growth factor, can treat pain in people with schwannomatosis. In this trial, up to 46 people with schwannomatosis who have moderate to severe pain will be randomized to receive either tanezumab or a placebo (sugar pill) for 8 weeks, and then everyone receives tanezumab for another 8 weeks. Treatment in the first 8 weeks is "double-bind", meaning that neither the participants nor the study doctors know which people are getting tanezumab and which are getting placebo. This kind of design is required by the FDA because sometimes people trying a new treatment can have their pain improve temporarily even when the drug is inactive or ineffective (a placebo response), and the FDA wants to make sure any improvements in pain are truly due to the medication working as it is intended. The primary outcome of the trial will be whether the intensity or severity of people's pain goes down, and researchers will also look for any improvements in how much pain interferes with people's daily activities, their physical functioning, anxiety, and depression.

While this trial is no longer enrolling new participants, a new trial for schwannomatosis-related pain recently received funding from the CDMRP and will hopefully be opening soon at Massachusetts General Hospital. This new trial, the Screening Trial for Pain Relief in Schwannomatosis (STARFISH), is a platform trial for schwannomatosis-related pain, meaning that it uses a similar schedule of study visits and similar participant eligibility criteria to test multiple new treatments over time. This kind of platform trial can make running clinical trials more efficient and allow researchers to more easily compare results across treatments. The first two drugs that will be tested in the trial are erenumab-aaoe (a CGRP antibody that is FDA-approved to treat migraine headache) and siltuximab (an IL-6 antibody that is FDA-approved to treat Castleman's disease).

Ko et al. NIH (United States, France, Italy) studied the function of *LZTR1*, which is one of the genes which can cause schwannomatosis. They found that *LZTR1* mutations cause too much of the EGFR and AXL proteins to accumulate in cells, leading to impaired signaling between cells. This extra protein was specific to schwannomas from people with *LZTR1* mutations, and was not found in schwannomas from people with *SMARCB1* mutations (another gene that can cause schwannomatosis). In mice with *LZTR1* mutations, treatment to reduce either EGFR or AXL protein levels alone was ineffective, but combining the treatments led to reduced tumor growth and the mice living longer. The two medications that were most effective when combined were osimertinib (an EGFR inhibitor that is FDA approved to treat certain types of lung cancer) and bemcentinib (an AXL inhibitor which is under study for use in lung cancer). This data suggests that combination therapy that simultaneously targets EGFR and AXL could be an effective treatment strategy for *LZTR1*-related schwannomatosis.

Merker et al. NIH (United States) looked at the degree to which people with schwannomatosis who were ultimately seen at major U.S. NF clinics faced delays in getting their diagnosis. They did this by reviewing the medical records of 97 people with confirmed or probable schwannomatosis seen at two major NF clinics. It took patients with schwannomatosis an average of 16.7 years from their first

symptom of schwannomatosis and 9.8 years from their first visit with a doctor about these symptoms to get diagnosed. People who were younger at the time of their first symptom and those who first presented with pain or neurological symptoms (rather than a mass that you could feel or that showed up on imaging) took a longer time to get diagnosed. In addition, a third of people had one of their schwannomatosis symptoms or tumors misdiagnosed during this time. 18% of people were incorrectly diagnosed with NF1 or NF2, and 8% of people had one of their schwannomas initially diagnosed as a neurofibroma or other NF1-related tumor, showing how it can be difficult for non-expert clinicians to distinguish between these disorders. In addition, 16% of people had their schwannomatosis pain attributed to another cause initially (such as sciatica, degenerative disc disease, arthritis, or carpal tunnel syndrome). The authors suggest ways to improve diagnosis of schwannomatosis in the future, including efforts to educate clinicians about schwannomatosis and increase the availability of genetic testing.

Disclosure: the author of this newsletter is also a co-author of the articles by Merker et al. and Da et al.

13. Quality of Life and Other Updates in NF1, NF2, and Schwannomatosis

The Bottom Line: People with NF1, NF2, and schwannomatosis do not appear to be at increased risk of contracting or being hospitalized for COVID; children with NF1 may have more difficulties with anxiety, depression, and adaptive skills than their peers; itch and muscle weakness appear common in NF1.

Banerjee et al. FREE, NIH, CDMRP (United States, Canada) used a large database of electronic medical records from hospitals across the U.S. to understand the impact of the COVID-19 pandemic on people with NF. They found that having NF1, NF2, or schwannomatosis did not appear to increase the risk of contracting the COVID-19 virus. They also found that people with NF1 who did test positive for COVID-19 were no more likely than other people to have severe complications (e.g., needing to be on a ventilator). The researchers unfortunately could not study the risk of severe outcomes in people with NF2 or schwannomatosis because there weren't enough people with NF2/schwannomatosis who had severe outcomes in the dataset to analyze statistically.

Hou et al. FREE, NIH, CDMRP (United States) studied the social and emotional functioning of children (ages 6 to 18) with NF1 and plexiform neurofibromas over a six year period. On average, children with NF1 had performed similarly to a reference group of their peers in most areas, including in externalizing problems (e.g., aggression, behavioral conduct problems), school connectedness (e.g., attitude towards school and teachers); and personal adjustment (self-esteem, self-reliance, relationships with peers). However, children with NF1 did have more difficulties with internalizing problems (e.g., anxiety and depression) and adaptive skills (e.g., social skills, adaptability, and communication of one's feelings and needs) than the reference group of their peers.

Fleming et al. FREE (Australia) found that itch and muscle weakness are both common health concerns of individuals with NF1 that deserve more research into potential treatments. In an online survey of 68 adults with NF1 and 32 parents of children with NF1 in Australia, 50-70% of survey respondents had itchiness, and 60-70% of survey had muscle weakness and tiredness. The survey also asked whether people with NF1 were getting regular check-ups for their NF1. While most children were getting regular care, less than half of adults got regular check-ups and many did not know where to access NF1 care if they wanted it, emphasizing the need to educate people with NF1 and their doctors about the healthcare services they need.

The Network Edge Archive

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NF2 Clinical Management		X	X		X	X	X		X	X	x	x
What's New in NF2 Biology?		X	X		X		X	X		X		x
Schwannomatosis Update			X	x	X	X		X	X	X	x	
Legius Syndrome Update			X									
The Evolving Link Between NF and Cancer				X								
Altered Brain Function in NF1	X	X										
NF1 and the Eye: Optic Pathway Gliomas and Other Features	X	X	X	X		X	X	X				x
NF Genetics Update		X	X									x
Pheochromocytoma in NF1		X										
Social Challenges in Neurofibromatosis	X	X	X		X		X	X				
NF1 and Autism			X					X				
REiNS Collaboration Update					X							x
Quality of Life in NF1, NF2, and Schwannomatosis				x	X	X	X		X	X	x	x

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