

— ON THE — HORIZON

As researchers hone in on the causes of genetic diseases, physicians turn their focus to viable therapies

BY VICTORIA HOUGHTON, ASSISTANT MANAGING EDITOR

For many dermatologists, the chance of encountering a patient with a genetic skin disease is slim. Many of these genetic disorders are rare and affect a tiny fraction of the patient population. However, Amy Paller, MD, chair of the department of dermatology at Northwestern University Feinberg School of Medicine, argues that staying current on the recent discoveries in genetic skin disorders will serve physicians well even if they never see even one of these patients. “I think that so many of these patients teach us lessons about the way skin functions that may also be applicable to a more common disorder. I do think it’s important to have some — not in-depth but at least superficial — understanding, because they may be relevant to practice.”

Overall, when it comes to treatment for many genetic disorders, according to Keith A. Choate, MD, PhD, associate professor of dermatology, genetics, and pathology at Yale University School of Medicine, there has been a lot of progress made in discovering the genetic mutations associated with these diseases. However, determining an appropriate therapy takes time. “The fact of the matter is: simply identifying the genetic cause of a disorder doesn’t frequently lead to therapy. The first step is to comprehensively understand the genetic basis of these disorders, and once you’ve defined the players, you can then think about how these individual genes work in common pathways relevant to genetic skin disease.” For the practicing dermatologist looking for a status update on genetic skin conditions, discoveries within the following diseases are continuing to evolve:

- Epidermolysis bullosa
- Ichthyosis
- Basal cell nevus syndrome
- Tuberous sclerosis
- Neurofibromatosis
- Sturge-Weber syndrome >>



According to Dr. Paller, researchers first discovered the cause of one form of EB more than 20 years ago and the discovery of other major forms followed. EB is a disease that causes the skin to be so delicate that it blisters easily when injured and, in many forms, heals slowly. While it mostly impacts the skin, it also can involve the mouth, esophagus, and bladder. According to the National Epidermolysis Bullosa Registry, about 1 in 50,000 infants in the U.S. are born with EB. “Our genetic investigations have pretty much illuminated all of the underlying causes of the major forms of EB,” Dr. Paller said. “Understanding the basic biology of the proteins which may be altered or lacking in EB is the first step in helping these patients. You can think about EB as largely one of two situations,” Dr. Paller said. “Either you’re missing a critical element in the adherence of epidermis to dermis and often allowing cells to migrate across the wound (the recessive forms of EB), or you have both abnormal and normal forms of a protein produced and the incorporation of the abnormal form leads to dysfunction.”

Recessive dystrophic EB (DEB) is a form of the disease that is caused by a mutation in the COL7A1 gene that codes for collagen VII — the main component of the anchoring fibrils that span the basement membrane zone to upper dermis. When this gene is mutated, collagen VII either does not exist or does not function normally. According to Dr. Choate, strides have been made in replacing nonexistent collagen VII in DEB patients, particularly involving the use of hematopoietic stem cell transplantation. “We’ve actually discovered that if you do stem cell transplantation it can significantly improve the disease,” Dr. Choate said. Researchers at the University of Minnesota transplanted allogeneic marrow in seven children with recessive DEB. While two patients died during the study (one from cardiomyopathy and the other from a graft rejection and infection) the five remaining patients saw increased amounts of collagen VII in the skin, improved wound healing, and a decrease in blister formation (*N Engl J Med.* 2010 Aug 12;363(7):629-39). Additionally, according to Dr. Choate, researchers are currently testing methods to take induced pluripotent stem cells (iPSC) from EB patients, genetically correct them, and then return them to the EB patient. “Right now, the most significant evidence of efficacy has been achieved in a mouse model, but I believe that gene editing technology has the potential to enable patients’ own cells to be used to actually provide treatment for recessive dystrophic EB.”

Researchers are also testing the option of utilizing gene therapy on EB patients through autografts — correcting the genes in tissue cultures from EB patients and then transplanting the cells back to the patient. “I think that is a very exciting potential avenue, because in that case they’re looking at just doing correction and grafting back,” Dr. Choate said. In a recent study published in *Science Translational Medicine* researchers took skin biopsies from three adult DEB patients, created iPSCs from the skin cells and fibroblasts in the cultured tissue, and corrected the COL7A1 mutation in the iPSCs. In mice, the new skin cells successfully formed skin grafts with “a defined layer of collagen VII.” (*Science Translational Medicine.*

26 Nov 2014;(6);264,264ra163). These results have prompted researchers at Stanford University to test the safety and efficacy of this therapy in a phase 1 clinical trial. According to Leslie Castelo-Soccio, MD, PhD, assistant professor of pediatrics and dermatology at The Children’s Hospital of Philadelphia, the Genegraft project — a European research consortium devoted to developing treatments for DEB patients — is looking to test this skin-grafting gene therapy in humans. “By the end of the project in late 2016, the aim is to have grafted up to three people with DEB, in a small-scale, early-stage, clinical trial to demonstrate the effectiveness of the treatment, and to assess how well tolerated it is by the patients,” Dr. Castelo-Soccio explained.

“Another really interesting potential therapy is protein therapy for DEB,” Dr. Choate said. “It was shown that if you inject recombinant type VII collagen intravenously it actually localizes properly to the skin.” (*J Invest Dermatol* (2015) 135, 1705-1707). In terms of topical treatments, in July the U.S. Food and Drug Administration (FDA) agreed to allow Scioderm, Inc., which was recently acquired by Amicus Therapeutics, to submit an accelerated application for the approval of allantoin as a topical therapy for EB-related wounds. Allantoin is an ingredient that is thought to reduce inflammation and stimulate both the removal of damaged tissue and the growth of new tissue. Results from the drug’s phase 2 trial — presented at the Dystrophic Epidermolysis Bullosa Research Association International Congress in 2014 — showed that once-daily treatment over the entire body caused complete closure of 88 percent of chronic EB wounds within one month, and a 57 percent reduction in EB wounds throughout the body. Phase 3 trials for the therapy are currently underway.

EB simplex is a dominant form of the disease that occurs when the keratin 5 (KRT5) or keratin 14 (KRT14) genes are mutated, creating a defect in the keratin proteins and causing the skin to be fragile. However, according to Dr. Paller, this type of EB is not likely to be treated by just adding more normal keratin. “For the dominant types, the ideal treatment would be replacing the abnormal gene or selectively suppressing the abnormal gene expression or gene product,” Dr. Paller said. “There are a variety of different techniques that people are using to try to either suppress the gene using siRNA, or swap out part of the normal gene for the abnormal gene (such as with TALE nucleases); however, these techniques are not ready for patient trials,” Dr. Paller said. According to a recent study published in the *Journal of Investigative Dermatology*, researchers used siRNA to successfully target and inhibit the K5 gene mutation in cultured cells (2011 Oct;131(10):2079-86). “However, the challenge is getting the siRNA into wounded and particularly intact skin. Progress is being made with techniques ranging from using micro-needles to topically applied siRNA. We’ve created an ointment with siRNA in a spherical configuration, which promotes its penetration through the epidermal barrier to knock down targeted genes in skin. I think the genetic approaches are very exciting and, although it will take time, we’ll have better therapies for them within a decade.”



According to the Foundation for Ichthyosis and Related Skin Types (FIRST), 16,000 infants are born with ichthyosis every year. This disease is marked by dry, scaling skin that can blister and get infected. While this disease is genetic in nature, the parents can be carriers of this disorder even if they are not showing signs of it. In addition to physical symptoms, patients with this condition often present with signs of depression because of low self-esteem and isolation. As such, researchers have been trying to develop treatments based on what we know and are still learning about the genetic discrepancies associated with this condition. “Tremendous progress has been made in understanding the underlying genetic basis of so many forms of ichthyosis,” Dr. Paller said. “The availability of next-generation sequencing has accelerated these discoveries in the last few years.”

In terms of recent findings, according to Dr. Choate, ichthyosis with confetti — a rare disorder that has affected only a handful of patients — has been turning researchers’ heads because over time the disease appears to reverse its mutation, bringing the skin back to normal. “Ichthyosis with confetti represents a really unique class of disorders where a patient is born with skin disease all over their body but early in infancy individuals start to develop patches of normal skin which increase in number and size over time to the point where someone who’s in their 40s could have thousands of revertant normal spots,” Dr. Choate said. “Someone who is two or three might have just dozens. It’s a really attractive disorder in that it is self-correcting.” According to Dr. Paller, this mosaic syndrome is caused by a mutation in keratin 10 or keratin 1. “This is just like the gene that’s involved in a blistering form of ichthyosis, called epidermolytic ichthyosis, except that these are at a different place in a gene that seems to be predisposed to these reverse mutations that start to correct the gene.” Dr. Choate’s laboratory has been trying to figure out how the reversal occurs, and what the factors are that influence the reversal in the skin. “We’ve been doing this with primarily mouse models and cell culture systems, but in fact we have not yet developed any technologies that would be directly relevant to treating patients. We’re eager to see it happen.”

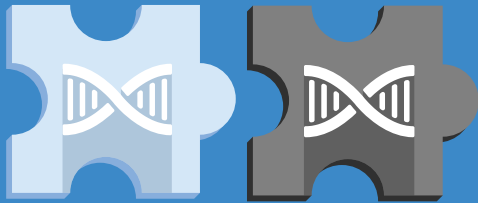
One of the most recent discoveries in the ichthyosis family of diseases involves erythrokeratoderma variabilis — a condition that results in plaques of scaling. Researchers determined that a mutation in the GJA1 (gap junction protein alpha 1) gene was the likely culprit of a subset of patients with this disorder.

“The patients tend to have leukonychia — whitening of nails — and progressive darkening of the thickened skin,” Dr. Choate said. Using exome sequencing, researchers determined that the mutation for this autosomal dominant disorder occurred in the GJA1 gene — which encodes connexin 43 (*J Invest Dermatol.* 2015 Jun;135(6):1540-7).

Dr. Paller and her colleagues have also recently looked at pathogenesis-based therapy for CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects). “CHILD syndrome results from deficiency of an enzyme involved in cholesterol biosynthesis, so that pathway blockade gives an affected individual both insufficient cholesterol in skin and bones, but also and more importantly, the accumulation of toxic metabolites,” Dr. Choate said. Dr. Paller has analyzed the affected skin in patients with CHILD syndrome and has tested therapies that can block the accumulation of toxic metabolites (*J Invest Dermatol* (2011) 131, 2242–2248). “We ended up treating these children and adults with a topical combination of cholesterol and lovastatin. The statin blocks the rate-limiting, early step in the cholesterol synthesis pathway and thus prevents the deleterious build-up of toxic metabolites,” Dr. Paller said. “The topical cholesterol replaces the end product, which is important in the epidermal barrier. The result is dramatic improvement in the skin appearance clinically, histologically, and ultrastructurally.” “This example beautifully proves the value of pathogenesis-based drug therapy for genetic disease,” Dr. Choate said. “That’s where I think a lot of future efforts in treating genetic disorders will be directed.”

Finally, when it comes to the most common form of ichthyosis, ichthyosis vulgaris, researchers are trying to figure out how to replace or increase the expression of filaggrin. Filaggrin, the key component of the stratum granulosum, is important in epidermal barrier function. Its deficiency leads to increased water loss through the epidermis (with dryness and scaling) and an increased tendency toward atopic dermatitis and allergic co-morbidities. Filaggrin also breaks down into humectants that serve to retain water in the skin, providing an additional rationale for the dry skin of ichthyosis vulgaris. The development of pathogenesis-based therapy remains in its infancy. “Ichthyosis vulgaris is a common genetic skin disease and finding a way to increase filaggrin in skin is likely to decrease the risk of developing atopic dermatitis and perhaps the severity in individuals affected with atopic dermatitis,” Dr. Paller said.

Multigenic puzzle pieces



While researchers are moving from a point of identifying the genes that trigger many monogenic diseases, determining the genetic culprits in multigenic conditions can seem like searching for a handful of needles in a hay stack. “With inflammatory diseases, it’s almost never a single gene,” said John E. Harris, MD, PhD, assistant professor in the dermatology division at the University of Massachusetts Medical School. “It’s a panel of a large number of genes.” According to Dr. Harris, so far 25 to 30 genes have been identified as risk factors for vitiligo, 15 to 20 genes in alopecia areata, and about 30 to 40 in psoriasis. Additionally, while Dr. Harris says that genes are a key component in the risk factor equation, other factors need to be examined to better understand these multigenic conditions. “Genes clearly play a role because these diseases are more common in family members. But two other factors in play are chance and environment.”

Using vitiligo as an example, Dr. Harris indicates that researchers already know some of the environmental factors that contribute to that risk factor equation. “One of them is a chemical called Benzoquin, or monobenzone. In 1939, a group of factory workers developed vitiligo because they were all wearing gloves that contained the chemical monobenzone. It was that chemical that was inducing vitiligo which, by definition, was a clear environmental factor inducing the disease.” Similarly, according to Dr. Harris, in 2013 a cosmetic company in Japan developed a skin-whitening, complexion-smoothing cream. “Over 18,000 people who used the cream developed vitiligo. There was a chemical in the cream that served as an environmental exposure to cause vitiligo.”

Indeed, when it comes to understanding multi-genic inflammatory diseases, genes are only one piece of the puzzle. According to Dr. Harris, if a patient has vitiligo, the likelihood that his or her identical twin will have the disease is only about 23 percent. So while genes represent 100 percent of the risk for monogenic conditions, in a multigenic disease like vitiligo, “we know that chance plus environment amounts to 77 percent of the risk, and genes amount to 23 percent of the risk.”



Basal cell nevus syndrome (BCCNS) — also known as Gorlin syndrome or Gorlin-Goltz syndrome — is characterized as a genetic defect that affects the skin and other systems such as the nervous, skeletal, and endocrine systems. Symptoms include the development of basal cell carcinoma (BCC) at a young age, as well as ovarian cancer, non-Hodgkin’s lymphoma, and other cancers. The disease can also cause tumors in the jaw, as well as blindness, deafness, mental retardation, and seizures.

Fortunately, researchers have identified the specific gene involved in the development of this disease. The *PTCH1* gene is responsible for regulating cell proliferation and signaling of the hedgehog (Hh) pathway which is responsible for the development of organs and tissues. When the *PTCH1* gene does not function properly and the Hh pathway is activated, uncontrolled cell proliferation results in the development of cancer and other abnormalities. Fortunately, “hedgehog signaling pathway inhibitors are available for selected individuals with Gorlin syndrome and advanced basal cell cancers,” Dr. Paller said. The Hh pathway inhibitor vismodegib was approved by the FDA for the treatment of advanced BCC in 2012, and is now being studied for operable nodular BCC, multiple myeloma, prostate cancer, and other cancers. Additionally, in July 2015 the FDA approved Hh pathway inhibitor sonidegib as treatment for recurrent or advanced BCC. In clinical trials, when taken once-daily, the drug reduced the size of tumors or caused the tumors to disappear in 58 percent of patients.

However, Hh inhibitors are not approved for patients under the age of 18. As such, physicians are left to treat these young BCCNS patients with surgery, when appropriate, or standard topical therapies for basal cells. “I think there should be trials in these medicines in younger patients,” Dr. Castelo-Soccio said. “The patients are accumulating all of these basal cells with time so if we could head them off so patients would have fewer of them, then there would probably be fewer complications. But it’s hard to give kids off-label medicines that have a lot of known side effects.”

Indeed, these potential treatments for BCCs can come at a price. “Hedgehog signaling is very important in stem cells and hair follicle development, so the patients who take these orally tend to lose hair and their sense of taste,” Dr. Paller said. According to a study published in the *Journal of Pharmacology and Therapeutics*, in clinical trials, 20 to 40 percent of patients on vismodegib experienced alopecia, loss of appetite, muscle spasms, nausea, diarrhea, fatigue, and weight loss (2013:Jan-Mar;4(1):4-7). Additionally, the FDA has warned that pregnant women should not take sonidegib, as it can cause fetal death or birth defects. However, “The whole concept of inhibition of these activated pathways is one of the most exciting areas of investigation,” Dr. Paller said. “Ultimately, I predict that topical formulations will be available to suppress BCCs in BCCNS and even more universally.”



Affecting one in every 6,000 infants, tuberous sclerosis is a genetic disorder that causes benign tumors to grow on the skin, brain, and other organs. It also affects the nervous system which can cause mental retardation, seizures, and skin abnormalities. According to the NIH National Institute of Neurological Disorders and Stroke (NINDS), the disease is estimated to affect up to 40,000 people in the U.S. and up to 2 million people worldwide.

In the '90s, researchers determined that the disease stems from mutations in tumor suppressor genes, TSC1 and/or TSC2 genes. "We know that all of the patients with tuberous sclerosis have mutations in one or two of those genes and, as a result, have activation of mTOR signaling," Dr. Paller said. TSC1 is located on chromosome 9 which produces the hamartin protein and TSC2 is found on chromosome 16, which creates the tuberlin protein. According to NINDS, these proteins regulate the mTOR kinase — which is responsible for cell growth — so when the TSC1 and 2 genes mutate, the mTOR becomes overactive and creates these abnormalities.

Fortunately, there are some promising prospects for the management of the skin tumors associated with tuberous sclerosis. "Oral rapamycin, an mTOR inhibitor, has been shown to limit tumor growth," Dr. Paller said, "and also shrunk the facial angiofibromas of affected patients." This led to the now common prescription of compounded topical rapamycin (up to 1 percent) for facial angiofibromas. In 2010, researchers first described a 16-year-old patient whose multiple facial angiofibromas decreased after 12 weeks of treatment with twice daily topical rapamycin. Blood tests showed no absorption in the patient's system (*Arch Dermatol.* 2010;146(7):715-718). The only potential side effect is irritation, which has not been a limiting issue for most patients. According to Dr. Castelo-Soccio, "It makes a huge difference for the preteen and adolescents who already may have some developmental delay or learning difficulties from their TS. Then they have angiofibromas on top of that," Dr. Castelo-Soccio said. "When they come in they're often shy, but after they've had treatment for a few months, they seem to be more extroverted, and they're happier and pleased with their appearance."

Beyond research: The patient experience

Growing up, Kristi Schmitt Burr did not know anyone who had the same condition as her. At the time, medical advice for basal cell carcinoma nevus syndrome (BCCNS) was sparse. Years later, Burr's children also developed the condition. "This is what prompted my family and friends to start the Basal Cell Carcinoma Nevus Syndrome Life Support Network 15 years ago," Burr said. The BCCNS Life Support Network provides support centers, physician referrals, and other resources to more than 1,200 families affected by BCCNS throughout the U.S. and in more than 20 countries. "Patients really want someone to help navigate their condition. Every patient advocacy organization can help patients understand the condition and how to truly manage it."

Fortunately for patients with BCCNS, the FDA has approved Hh pathway inhibitors, vismodegib and sonidegib, to treat basal cell cancers in adults. The treatment does not come without significant side effects such as hair loss, loss of the sense of taste, and weight loss. However, Burr and her team at the Support Network know that what may be adverse to one patient is simply an inconvenience for another. "I would say that the majority of people on this new class of drugs now feel that the side effects do not negate the positive effects that they're receiving by not having to face surgery every month," Burr said. "Frequently, those with the highest burden of disease get lost to follow-up due to their refusal to continue curettage, topical treatment, and Mohs, with no end in sight. Both patients and health care providers now have choices, which can work in combination, for better outcomes and patient satisfaction." Support Network spokesperson Samantha White agrees and adds, "The Network now connects and hears from people who say the approved medications have positively changed their quality of life and dramatically improved their interaction in the workplace and with families, who are so grateful for having a systemic approach to treating the cause of the condition. Then you hear from the people who express that it is just not worth the side effects," White said. "That's a reminder, that even though they all have the same condition, they're all still individual people. Surgery has the same reaction; some people just cannot face repeated surgery and recovery."

In addition to those individual patient experiences, Leslie Castelo-Soccio, MD, PhD, assistant professor of pediatrics and dermatology at The Children's Hospital of Philadelphia, argues that these support networks provide patients with care beyond clinical therapies. "Patients benefit from talking to other families who have gone through the exact same process." Dr. Castelo-Soccio sees a lot of ichthyosis patients and finds value in referring them to the Foundation for Ichthyosis and Related Skin Types (FIRST). "FIRST has family meetings every one or two years, and at these meetings, experts who know a lot about these come and can talk about strategies and therapies. Often families will know more than their providers about what works for thickened skin on the heels, or which shampoos are better for the scalp, or how do you clip nails that are really thick. I do think they benefit from talking to each other." Burr agrees and adds, "These organizations almost all act like compasses. You want to help them navigate the system, navigate their lives, and in some cases alter some of their activities so they can live fruitful lives, and be productive members of society — that provides a tremendous amount of value to the families as a whole."



Among many of these genetic diseases, neurofibromatosis is one that the average dermatologist could come across in their lifetime. “Neurofibromatosis type 1 (NF-1) occurs in approximately one in 3,000 individuals,” Dr. Paller said. “Most affected children have only multiple café-au-lait spots that can range from five to 15 millimeters in diameter; however, tumors are the feared concern.”

Fortunately, researchers have known what causes the condition for several years. “It results from a mutation in the gene that encodes neurofibromin,” Dr. Paller said. Neurofibromin is another protein that regulates signaling and limits cell growth. “Plexiform neurofibromas result from loss of heterozygosity in the gene (i.e., loss of the normal allele) and loss of neurofibromin protein

expression specifically in Schwann cells. Other cells, particularly the mast cell, play a major role in encouraging their development.” The presence of mast cells likely contributes to the pruritus noted in many neurofibromas.

Although surgical resection is often the treatment of choice, surgery can be challenging. “There has been some success in treating with imatinib, which inhibits mast cell activation,” Dr. Paller said. In a study, published in *The Lancet Oncology*, six of the 23 patients who were treated with oral imatinib mesylate twice daily for six months showed at least a 20 percent reduction in volume of one or more of the tumors (2012; 13(12):1218–1224). While these results come as welcome news for patients with NF-1, additional clinical trials are needed.



When it comes to Sturge-Weber syndrome, a congenital, non-familial disorder, dermatologists are mostly concerned with capillary vascular malformations associated with the disease. These facial birthmarks (also known as port wine stains) usually involve the eyelids and/or forehead. According to the Sturge-Weber Foundation, although the number of people with this disorder is unknown, estimates range from 1 in every 40,000 to 400,000 people.

For years it has been suspected that Sturge-Weber was caused by a somatic mosaic mutation. The recent introduction of next-generation gene sequencing technologies has placed researchers in the ideal position to search for the mutations that exist in Sturge-Weber and other somatic diseases. “Technology keeps changing,” Dr. Paller said. “The availability of next-gen sequencing is totally increasing the speed of discovery.”

In a 2013 study published in the *New England Journal of Medicine*, researchers used whole-genome sequencing to test for the presence of somatic mosaic mutations in three patients with Sturge-Weber syndrome, and found a variant in the GNAQ gene on chromosome 9 — which encodes the G-alpha protein that is responsible for regulating a signaling pathway in blood vessel cells. When the gene mutation occurs, the protein remains active. The researchers confirmed their findings by comparing the results to 97 samples

from 50 patients (*N Engl J Med* 2013; 368:1971-1979). In terms of next steps, researchers will investigate potential therapies that can inhibit the G-alpha receptor.

In the meantime, “some recent work suggests that oral or topical rapamycin may help to limit the recurrence of the port wine stains after laser therapy,” Dr. Paller said. In a recent phase 2 study published in the *Journal of the American Academy of Dermatology*, researchers conducted a randomized, placebo-controlled, double-blind clinical trial that tested the efficacy of topical rapamycin in combination with pulsed dye laser (PDL) treatment, and as a result found a statistically significant improvement in the patients’ port wine stains when treated with both therapies (2015; 72(1):151-8).

All told, Dr. Paller maintains that with port wine stains, as it is with many of these genetic conditions, the therapeutic options will expand as more is learned about each individual disorder and as technology continues to evolve. “We’re starting to be able to match new therapies that impact signaling with discoveries about the underlying basis of these mosaic disorders,” Dr. Paller said. “To me, that’s extremely exciting. Bringing things from bench to bedside takes time, but I think we’re really on a roll from both a discovery standpoint and the availability of new technology.” *dw*

Genetic breakdown: Discoveries and therapies



Genetic Disorder	Genetic Defect	Potential Therapies
Dystrophic EB	Mutation in COL7A1 gene that causes collagen VII to either deplete or not function	Can replace collagen VII intravenously, by injection, or topically
EB simplex	Mutation in Keratin 5 or Keratin 14 creates defects in keratin proteins	siRNA cream that targets and inhibits K5 gene mutation
Ichthyosis with confetti	Mutation in Keratin 10 or Keratin 1 gene, however, appears to reverse over time	Current research focusing on methods to encourage the disease to reverse
Erythrokeratoderma variabilis	Mutation in the gap junction protein alpha 1 (GJA1) gene	More research required
CHILD syndrome	Disorder within the cholesterol biosynthesis pathway, causes cholesterol depletion and accumulation of toxic metabolites	Topical combination of cholesterol in a simvastatin to block accumulation of toxic metabolites
Ichthyosis vulgaris	Mutation of filaggrin gene, causes loss of water retention/hydration in the skin	More research required
Basal cell nevus syndrome (Gorlin/Gorlin-Goltz syndrome)	Mutation in the PTCH1 gene which inhibits regulation hedgehog (Hh) pathway	Hh pathway inhibitors, vismodegib and sonidegib approved for treatment of advanced BCC in adults
Tuberous sclerosis	Mutations in TSC1 and/or TSC2 genes which inhibits regulation of mTOR signaling	Oral and compounded topical rapamycin to inhibit mTOR response
Neurofibromatosis (primarily NF-1)	Mutation in NF-1 gene that encodes neurofibromin, causes lack of regulation of signaling pathways that suppress cell production	Pathway inhibitors, including imatinib, which may reduce size of tumors in selected patients
Sturge-Weber Syndrome (Port Wine Stains)	Mutation in GNAQ gene on chromosome 9 causes lack of signaling/regulation of blood vessels	More research required for G-alpha receptor inhibitors; currently testing topical rapamycin in conjunction with pulsed dye laser therapy