A Somatic p.G45E GJB2 Mutation Causing Porokeratotic Eccrine Ostial and Dermal Duct Nevus

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Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) is a mosaic disorder presenting clinically as a linear epidermal nevus with spiny hyperkeratosis, and the results of histologic examination show hyperkeratosis, acanthosis, and porokeratotic plugs emerging from eccrine ducts. Like other epidermal mosaic disorders, PEODDN typically appears in linear patterns following lines of Blaschko, which represent migration paths of neuroectodermal precursors during development. Our group and others have shown that lesions following these patterns typically result from somatic mutations affecting keratinocyte precursors, with the extent of cutaneous lesions determined by mutation timing. Notably, PEODDN lesions have been identified in Blaschkoid patterns in healthy individuals and in those with keratitis-ichthyosis-deafness syndrome (KID) due to autosomal dominant GJB2 mutation, which is characterized by keratitis, widespread keratodermia, and deafness. It has been hypothesized that PEODDN lesions in individuals with KID syndrome may result from loss of the wild-type GJB2 allele, although this hypothesis remains unproven.

We aimed to use whole-exome sequencing to determine whether GJB2 mutation alone is sufficient to cause PEODDN.

Report of a Case

We identified a primary school-aged female patient with bands of hyperkeratotic-affected skin on the upper and lower extremities and trunk (Figure 1A and B). These lesions were present at birth and did not appear to change in shape or relative size over time. Results of histopathologic examination showed characteristic hyperkeratosis, acanthosis, and coronoïd lamellae (Figure 1C and D), and we made the diagnosis of PEODDN. The patient's parent provided written informed consent. Our study was approved by the Yale University Human Investigations Committee and complies with the Declaration of Helsinki principles.

Suspecting that PEODDN could be caused by somatic genetic mosaicism, we used paired whole-exome sequencing of the patient's blood and affected tissue samples isolated from a PEODDN lesion of a primary school-aged female patient with bands of hyperkeratotic-affected skin on the upper and lower extremities and trunk, and identified a single, protein-damaging p.Gly45Glu GJB2 mutation present in tissue samples but not in blood samples.

Our results prove that somatic GJB2 mutation is sufficient to cause PEODDN. Dominantly inherited GJB2 mutations, including the p.Gly45Glu found in our case, have been shown to cause the severe multisystem disorder keratitis-ichthyosis-deafness syndrome. GJB2 encodes connexin 26, a gap junction protein, which permits intercellular ion and macromolecule flux. Individuals with somatic mosaicism are at risk for transmitting systemic disease to their offspring, and all individuals with PEODDN lesions should be counseled regarding the risk of having a child with keratitis-ichthyosis-deafness syndrome.
tations could be causing her skin lesions. Whole-exome data were aligned to the hg18 reference genome, and all variations from the reference were annotated. Recognizing that somatic mutation was likely, we used a Perl script to identify single nucleotide variations present in affected tissue samples but absent in blood samples. In so doing, we first filtered for variants not found in healthy controls (1000 genomes; the National Heart, Lung, and Blood Institute exome variant server and 2577 in-house controls) and then identified those that were predicted to be protein damaging and specific to tissue. Our data revealed 1 somatic single nucleotide variation reaching genome-wide significance: GJB2, c.G134A, p.Gly45Glu (Figure 2 and eAppendix and eFigure 1 in the Supplement). Using ExomeCNV, we assayed for loss of heterozygosity across the genome, finding none (eFigure 2 in the Supplement). This result suggested that somatic GJB2 mutation is sufficient to cause PEODDN.

Using whole-skin biopsy tissue samples for sequencing, we found that the tissue-specific p.Gly45Glu GJB2 mutation was present in only 17.5% of total reads. This finding suggested an admixture of wild-type and mutant DNA, and we used laser capture microdissection to obtain pure affected epidermal tissue DNA for polymerase chain reaction and sequencing of GJB2. This process confirmed that the p.Gly45Glu mutation is present solely within the epidermis, and we found that the p.Gly45Glu mutation was present in an eqimolar ratio to the wild-type allele (Figure 2).

Discussion

Porokeratotic eccrine ostial and dermal duct nevus lesions have been identified in patients with KID syndrome, raising the possibility that this disorder could result from type II segmental mosaicism, in which the patient is heterozygous for a disease-causing mutation and loss of the wild-type allele gives rise to affected skin. While such lesions in those with KID syndrome have not been examined, Easton et al provided the first evidence that type I segmental mosaicism resulting from a single GJB2 somatic mutation could cause PEODDN. Our study proves that PEODDN is caused by GJB2 mutation, finding that a p.Gly45Glu mutation is the only somatic mutation present in PEODDN tissue samples without evidence of loss of heterozygosity across the genome.

GJB2 encodes connexin 26, a gap junction protein. Connexins are tetraspan membrane proteins that are translated in the endoplasmic reticulum and undergo homotypic and heterotypic assembly to form hexameric connexons within the Golgi. These connexons are transported to the cell membrane, where they can either dock with connexons of adjacent cells to form a gap junction or can function as hemichannels when unassociated on the cell surface membrane.

The mutation we identified in PEODDN (GJB2, c.G134A, p.Gly45Glu) has been found in a severe case of KID syndrome, demonstrating complete atrichia, progressive severe...
Whole-exome data were run through a Perl script to look for single nucleotide variations that had greater than 2 nonreference (nonref) reads in tissue and fewer than 6 nonreference reads in blood. These single nucleotide variations were ranked by Fisher score, and the top 10 were manually analyzed to detect mismapping. The 5 single nucleotide variations with the best Fisher scores are listed. Genome-wide significance is $1.7 \times 10^{-6}$ after Bonferroni correction for multiple testing of approximately 30,000 genes. Targeted sequencing confirms a heterozygous $GJB2$, c.G134A, p.Gly45Glu tissue-specific mutation. Polymerase chain reaction amplicons from laser-microdissected porokeratotic eccrine ostial and dermal duct nevus tissue reveal G and A peaks of approximately equimolar amounts. No such mutation was found in polymerase chain reaction amplicons from blood, confirming that this case represents a heterozygous tissue-specific mutation. Ref indicates reference allele.

Conclusions

Like the mutation found in our patient, 1 of the 2 mutations found by Easton et al\textsuperscript{18}—$GJB2$ p.Asn14Tyr—has been found in individuals with KID syndrome.\textsuperscript{15} Since early somatic mutation can affect multiple embryonic lineages, individuals with PEODDN are at risk of conceiving children with KID syndrome and should be counseled regarding this risk. While greater body surface area involvement is generally correlated with higher risk, a report of twins with KID syndrome born to a mother with limited linear palmoplantar keratoderma argues that genetic counseling should be provided to all pregnant females and expectant fathers with PEODDN lesions.\textsuperscript{15}

References


NOTABLE NOTES

True Colors
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“True colors are beautiful like a rainbow”
From the song True Colors by Billy Steinberg and Tom Kelly

Dermatology may be medicine’s most colorful specialty. Just about every color has a dermatology-related eponym, including the patriotic colors of red, (erythoderma), white (leukoderma), and blue (blue nevus, blue man syndrome [argyria], and cyanosis [Latin for “blue disease”]).

Here are some interesting facts behind dermatology’s colorful eponyms.

Yellow
There are many beautiful yellow birds, one of which was believed, during ancient times, to cure jaundice (Old French for “yellowness”). The Roman naturalist, Pliny the Elder, relates this myth as follows: “There is a bird, known as the ‘icterus,’ from its peculiar color: if the patient looks at it, he will be cured of jaundice, they say, and the bird will die.” Icterus is Latin for jaundice, which is derived from the ancient Greek “ikteros.” The yellow nail syndrome was first described by Peter Derrick Samman (1914-1992), a leading expert on nail pathology. This condition features a triad of lymphedema, pulmonary disease, and yellow nails.

Salmon Color
The noted British physician, Sir Jonathan Hutchinson (1828-1913), described a salmon-colored neovascularized area (patch) of the cornea seen in syphilitic interstitial keratitis. He proposed the famed triad of keratitis, notched teeth, and deafness for the diagnosis of congenital syphilis.

Black
Black hairy tongue was important in medical history. In 1937, Conrad Elvehjem showed that niacin cured pellagra in dogs, which manifested as black tongue. Melanoma (Latin for “tumor containing black [dark] pigment”) was first described as a disease entity by Rene Laennec (1781-1826), the French physician who invented the stethoscope. He used the term “les melanoses.”

Pink
Fortunately, pink disease, also called acrodynia, is now rare. During the first half of the 20th century, many young children developed this potentially fatal condition caused by a hypersensitivity to mercury (calomel) present in teething powder. A striking clinical feature was the bright pink color of the hands and feet.

Green
Chlorosis (from the Greek “chloros” meaning “pale green”) referred to a green skin tint once seen in iron deficiency anemia. It was commonly called “green sickness.” Jean Varandal, a French professor of medicine, introduced the term in 1615.

Bronze
By contrast, iron overload, as occurs in hereditary hemochromatosis, has been called bronze diabetes. The brownish skin discoloration is due to hypermelanosis caused by iron excess.

Purple
If purple is your favorite color, you can enjoy 2 medical eponyms: (1) porphyria (from the Greek “porphyros” meaning “purple”) and (2) purpura, a Latin word meaning “purple dye.” In antiquity, purple dye was derived from secretions produced by sea snails in the family murexidae.

Yes, dermatology may be medicine’s most colorful specialty. We should be proud of its true colors, which are beautiful like a rainbow.

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Additional Information: This article was written in honor of Dr Walter H. C. Burgdorf, one of today’s great teachers of medicine, in recognition of his many contributions to the field of dermatology.
