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Review Article

The Role of Genetic Mutations in RHBDF2 Gene on the Howell-Evans Syndrome

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Abstract

Howell-Evans syndrome, also known as Tylosis with Esophageal Cancer (TOC), is an inherited condition that increases the risk of developing esophageal cancer. Symptoms of TOC include thickening of the skin of the palms and soles of the feet (palmoplantar keratoderma) and white lesions inside the mouth. People with TOC are at very high risk for developing esophageal cancer. Plantar keratoderma usually occurs in childhood, and esophageal cancer usually occurs in adulthood. TOC is caused by a variant in the RHBDF2 gene and is inherited in an autosomal dominant pattern. Diagnosis is based on symptoms, clinical examination, and family history. Howell-Evans syndrome is caused by mutations in the RHBDF2 gene, which is located on the long arm of chromosome 17 at 17q25.1. DNA changes, known as pathogenic variants, are responsible for causing genes to function incorrectly, sometimes without functioning at all. This mutation has been observed in several patients from Finnish, German, English, and American families

Overview of Howell-Evans Syndrome Howell-Evans syndrome, also known as Tylosis with Esophageal Cancer (TOC), is an inherited condition that increases the risk of developing esophageal cancer. Symptoms of TOC include thickening of the skin of the palms and soles of the feet (palmoplantar keratoderma) and white lesions inside the mouth. People with TOC are at very high risk for developing esophageal cancer. Plantar keratoderma usually occurs in childhood, and esophageal cancer usually occurs in adulthood. TOC is caused by a variant in the RHBDF2 gene and is inherited in an autosomal dominant pattern. Diagnosis diagnosis may be confirmed by genetic testing results. Treatment focuses on managing the risk of esophageal cancer through screening and avoiding smoking and alcohol. (1)

Clinical Signs and Symptoms of Howell-Evans Syndrome

These features may vary from person to person. Some people may have more symptoms than others, and the age at which symptoms appear may vary. This list does not include all of the symptoms described in this condition. Symptoms of tylosis with esophageal cancer may include:Thickened, yellowish skin on the palms of the hands and soles of the feet (palmoplantar keratoderma)

White patches on the tongue, cheeks, or mouth (oral leukoplakia) Esophageal cancer (1)

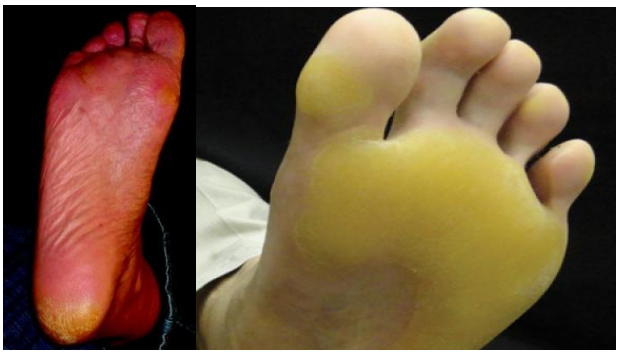


Figure 1: Images of the soles of feet affected by Howell-Evans syndrome. (1)

Skin findings usually begin in childhood. Esophageal cancer usually develops in mid adulthood. Symptoms of esophageal cancer may include difficulty swallowing, loss of appetite, and weight loss. Symptoms that people with this disease Abnormal morphology of the colonv may have include the following. It should be noted that for most diseases, symptoms vary from person to person. People with a disease may not have all of the symptoms listed.1,2

Abnormal morphology of the colon

Gastrointestinal bleeding

Nausea and vomiting

Palmoplantar keratoderma

Etiology of Howell-Evans Syndrome

Howell-Evans syndrome is caused by mutations in the RHBDF2 gene, which is located on the long arm of chromosome 17 at 17q25.1. DNA changes, known as pathogenic variants, are responsible for causing genes to function incorrectly, sometimes without functioning at all. This mutation has been observed in several patients from Finnish, German, English, and American families. The RHBDF2 protein is thought to play an important role in the epithelial response to injury in the esophagus and skin. The RHBDF2 gene is involved in regulating the secretion of several ligands from the epidermal growth factor receptor. (1,2)

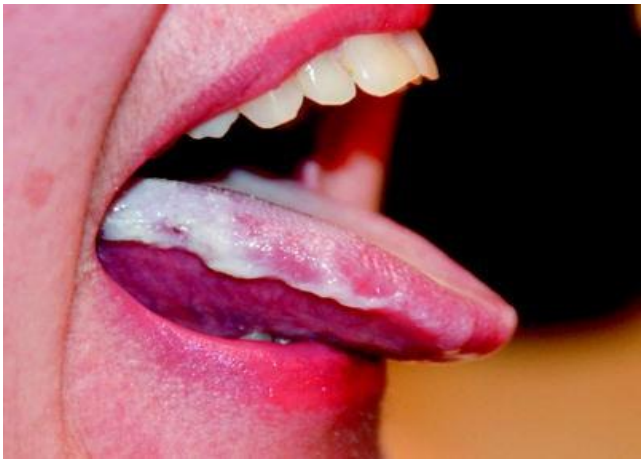
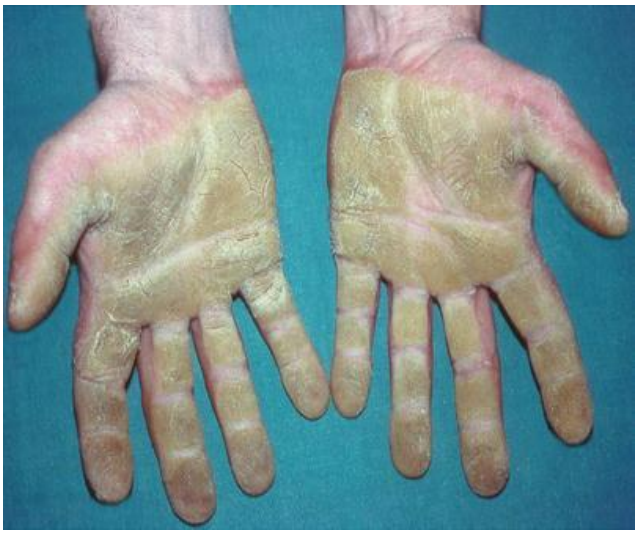


Figure 2: Image of the skin of the tongue with Howell-Evans syndrome

Howell-Evans syndrome, also known as tylosis with esophageal cancer, is inherited in an autosomal dominant pattern. Everyone inherits two copies of each gene. Autosomal means that the gene is found on one of the numbered chromosomes in both sexes. Dominant means that only one altered copy of a gene is necessary to have the condition. The variant can be inherited from either parent. Sometimes an autosomal dominant condition occurs because of a new genetic variant (de novo) and there is no family history of the condition. Each child of a person with an autosomal dominant condition has a 50% or 1 in 2 chance of inheriting the variant and the condition. Typically, children who inherit a dominant variant will have the condition, but they may be more or less severely affected than their parents. Sometimes a person may have one gene variant for an autosomal dominant disease and not show any signs or symptoms of the disease. (1,3)



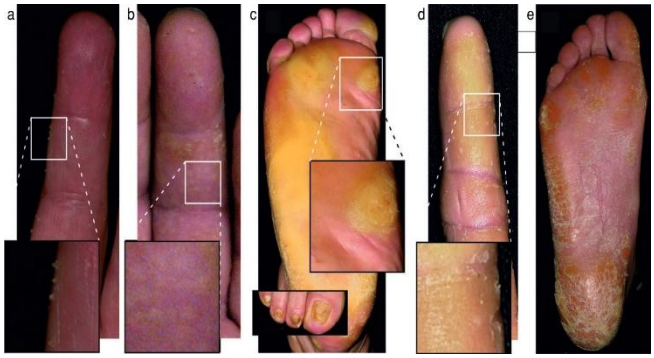


Figure 3: Images of skin disorder of the palms and soles in Howell-Evans syndrome. (1)

Howell-Evans Syndrome Frequency

Howell-Evans syndrome has been reported in only a few families worldwide. The exact number of people affected by this disease is unknown. The prevalence of esophageal cancer in patients increases with age, with about 40% of patients affected by the age of forty, and

almost all patients will develop esophageal cancer by the age of seventy. (1,3)

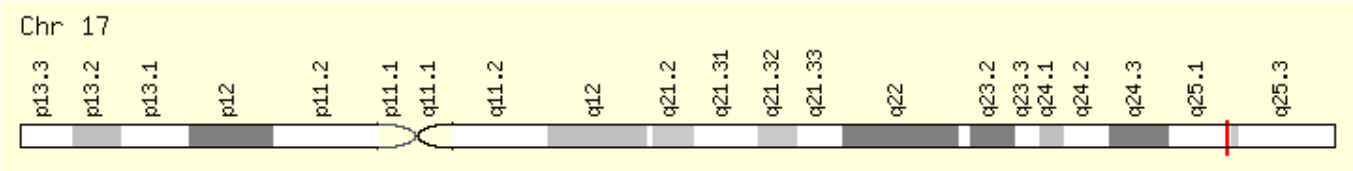


Figure 4: Schematic of the physical map of chromosome number 17, where the RHBDF2 gene is located on the long arm of this chromosome as 17q25.1.[1]

(biopsy) to help diagnose cancer. Imaging studies may also be helpful. (1,4)

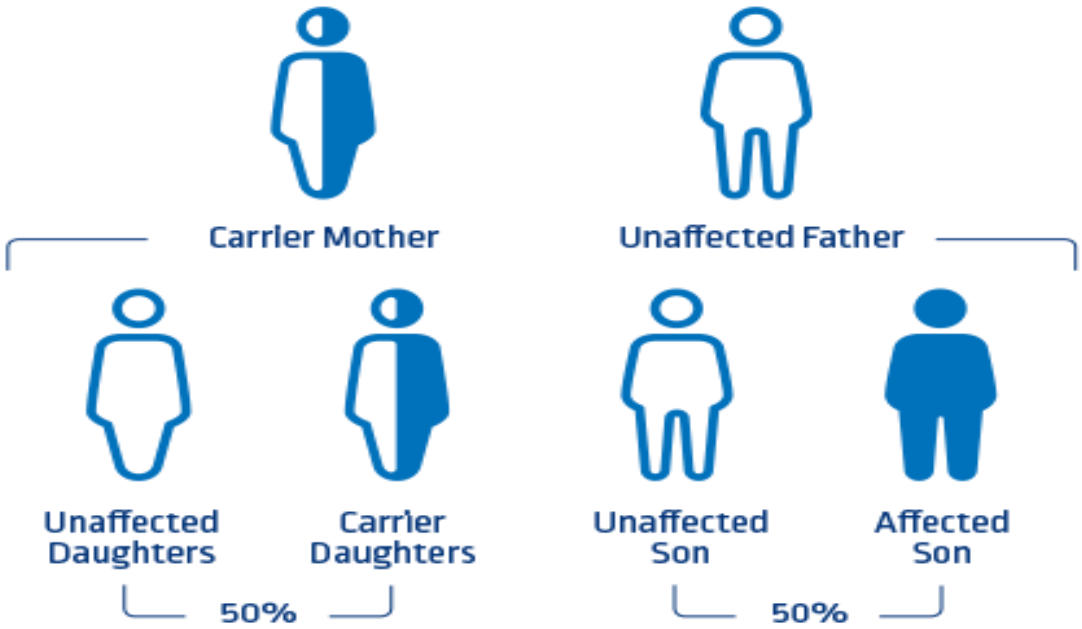


Figure 5: Schematic of the autosomal dominant inheritance pattern that Howell-Evans syndrome follows. (1)

Howell-Evans Syndrome Treatment Pathways

Treatment for Howell-Evans syndrome focuses on early detection of esophageal cancer as well as dietary and lifestyle modifications. These changes include quitting smoking and limiting alcohol consumption. Skin findings are treated with lotions and medications, if necessary Skin findings are treated with lotions and medications, if necessary Specialists involved in the care and weight loss. Symptoms that people with this disease

DiscussioSkin findings usually begin in childhood. Esophageal cancer usually develops in mid-adulthood. Symptoms of esophageal cancer may include difficulty swallowing, loss of appetite, and weight loss. Symptoms that people with this disease may have include the following. It should be noted that for most diseases, symptoms vary from person to person. The RHBDF2 protein is thought to play an important role in the epithelial response to injury in the esophagus and skin. The

RHBDF2 gene is involved in regulating the secretion of several ligands from the epidermal growth factor receptor. Autosomal means that the gene is found on one of the numbered chromosomes in both sexes. Dominant means that only one altered copy of a gene is necessary to have the condition. The variant can be inherited from either parent. Sometimes an autosomal dominant condition occurs because of a new genetic variant (de novo) and there is no family history of the condition. Treatment for Howell-Evans syndrome focuses on early detection of esophageal cancer as well as dietary and lifestyle modifications. These changes include quitting smoking and limiting alcohol consumption. (1,6)

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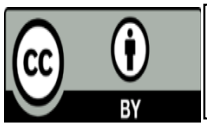

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