

LETTER TO THE EDITOR

Tylosis associated with squamous cell carcinoma of the oesophagus (TOC): Report of an African family with a novel *RHBDF2* variant

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Familial tylosis (focal non-epidermolytic palmar and plantar hyperkeratosis) with squamous cell carcinoma of the oesophagus (TOC) is a rare autosomal dominant disorder (OMIM 148500) that was first described in a family from Liverpool.¹ Other families have since been described from America, Germany, Brazil, Spain and Finland.² Three gain-of-function missense variants in the *RHBDF2*-gene, which encodes the inactive rhomboid protease, iRhom2, have been reported to segregate with TOC in four families of European descent.^{1,2,3} We here describe the first African family with tylosis and two cases of oesophageal cancer (Figure 1A), who carry a novel *RHBDF2* heterozygous germ-line variant.

The proband (II-4), a 46 year old African man, presented with carcinoma of the oesophagus and striking hyperkeratosis of both palmar and plantar surfaces (Figure 1B / C), which he said was present in other family members. He was managed with oesophageal dilatation and palliative radiotherapy. The family history revealed seven members with tylosis, including the proband's mother (Figure 1A). Endoscopic examinations on all members of the family with tylosis were normal except for that of the elder brother (Family member II-2). He was diagnosed with an early squamous cell carcinoma of the oesophagus but declined treatment. He died four years later of metastatic squamous cell carcinoma of the oesophagus (SCCO; Figure 1D / E). However, this family does not present with the classic oral leukokeratosis or painful fissuring of the palmoplantar skin, that is usually associated with TOC.

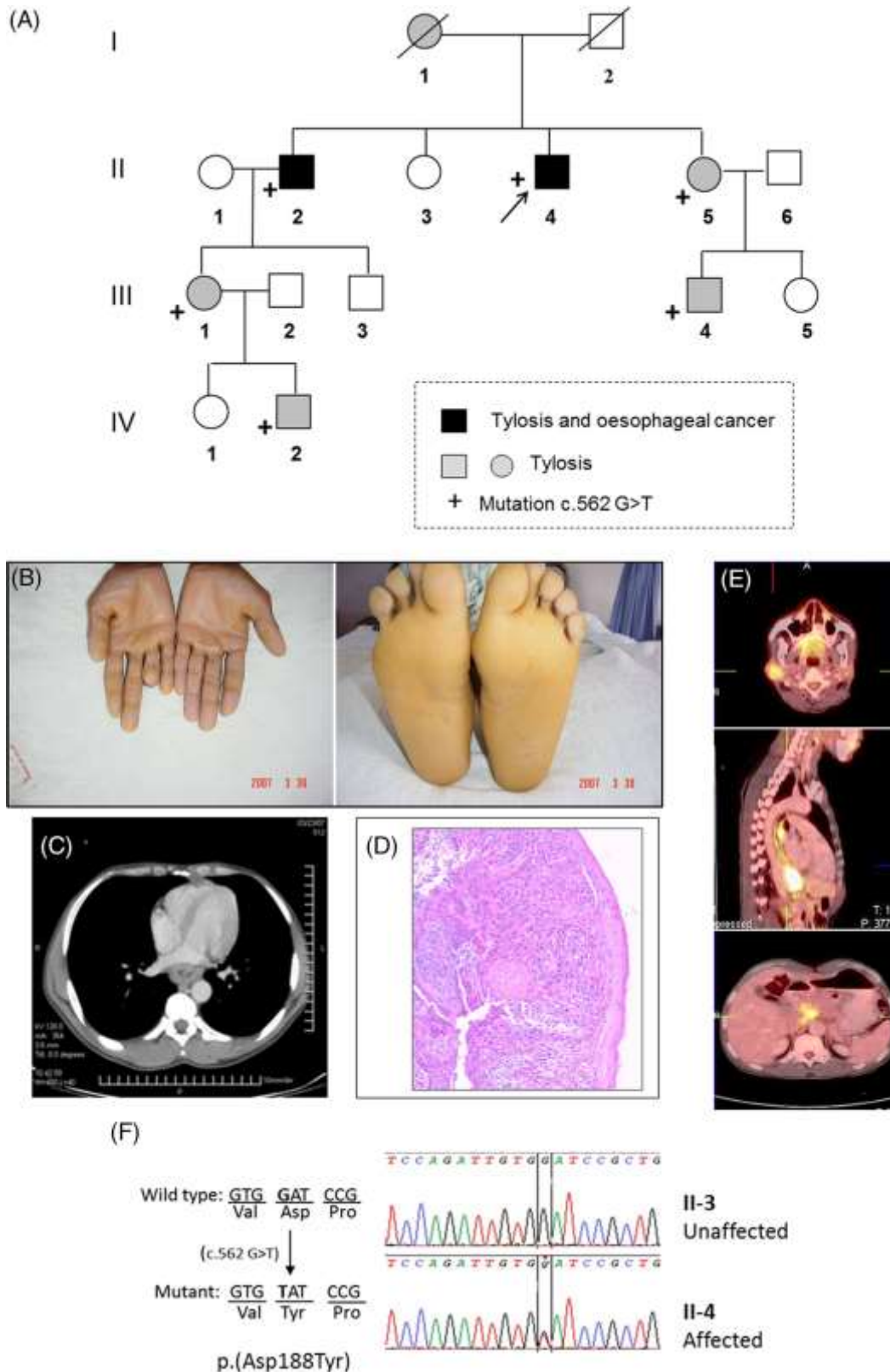


Figure 1. A, Abbreviated pedigree. B, Flat keratoderma of palmar and plantar surfaces (II-4). C, Computed tomography (CT)-scan showing oesophageal wall mass abutting pericardium and descending aorta of proband. D, Oesophageal biopsy of II-2 with H&E staining ($\times 10$) features a moderately differentiated keratinizing squamous carcinoma. E, Positron-emission tomography/computed tomography (PET-CT) scan of II-2, showing metabolically active lesion of the oesophagus and metastases to mediastinal lymph nodes and right parotid. F, Electropherogram of heterozygous *RHBDF2* c.562 G>T variant in the African family.

The Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria approved the research study involving this family. After written informed consent was obtained, blood samples were taken for *RHBDF2*-gene analysis. Genomic DNA was extracted and the *RHBDF2*-gene (GENBANK accession NC_000017.10) was amplified and subjected to Sanger sequencing using Life Technologies BigDyeV3.1 cycle sequencing. A novel heterozygous missense variant in exon 6 (c.562 G>T, p.Asp188Tyr) of *RHBDF2* (NM_024599.5) was detected in all affected members of the family and was absent in unaffected members (Figure 1A / F). We also screened 95 healthy unrelated African blood donors for this variant and found that none carried it. The variant is not present in dbSNP nor in the 1000 Genomes database. This variant affects the same codon as that in the Finnish family, where aspartic acid is substituted for an asparagine (p.Asp188Asn).² The missense variant detected in the UK and US families (p.Ile186Thr) affects codon 186, whereas the German family's variant (p.Pro189Leu) affects codon 189.¹ These amino acids are located in the cytosolic N-terminal domain of *RHBDF2* and are all highly conserved.¹

Two studies have shed more light on the effect of these pathogenic gain-of-function missense variants. One study noted an increase in the activity of the metalloprotease, ADAM17, in TOC epidermal keratinocytes, which significantly upregulated the shedding of EGF-family growth factors as well as pro-inflammatory cytokines.⁴ The second study found that the wild type *iRhom2* protein is short-lived, and that gain-of-function variants increased the stability of the variant protein. This in turn led to metalloprotease-independent secretion of EGFR family ligands, including amphiregulin. This growth factor is upregulated in cancers and is known to provide strong autocrine stimulation of keratinocyte growth.⁵ The variants induced accelerated wound-healing in vivo, and accelerated tumourigenesis. All of this is suggestive of an

upregulated wound-healing state in TOC patients' epithelia that are exposed to stress (wounding). It seems plausible that known risk factors for SCCO (such as alcohol and tobacco consumption) are also applicable to carcinogenesis in this and other families with TOC. The association of tobacco use with the occurrence of SCCO in the families is supported by the American family, where seven of the eight patients with SCCO had either smoked or chewed tobacco.³ Carcinogenesis is a complex interplay of genetic and environmental factors. Generation of cutaneous SCC may require different environmental milieus in tylotic individuals. Bronchogenic and laryngeal SCC have been described in tylotic individuals who smoked. In conclusion, our results further confirm *RHBDF2* involvement in TOC.

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