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Gene Section

Mini Review

RSPO1 (R-spondin homolog (Xenopus laevis))

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Identity

Other names: FLJ40906; R-spondin1; RP11-566C13; RSPONDIN; hRspo1

HGNC (Hugo): RSPO1

Location: 1p34.3

DNA/RNA

Description

8 exons, 5 coding exons, 24 kb of genomic DNA.

Transcription

mRNA about 2.5 kb, 263 residues in full-length translated protein, which contains an N-terminal signal peptide, followed by two cysteine-rich furin-like domains, one thrombospondin type 1 domain (TSP1 domain) and a putative C-terminal nuclear localization signal domain.
Three alternatively spliced isoforms have been identified: one lacking the signal peptide encoded by exon 4, one lacking the thrombospondin domain encoded exon 7 and the third has an alternative 5' UTR.

Pseudogene

None known.

Protein

Description

Secreted ligand with an N-terminal signal peptide, two cysteine-rich furin-like domains, one thrombospondin type 1 domain (TSP1) and a putative C-terminal nuclear localization signal domain.

Expression

R-spondin1 expression is seen in a number of organs and appears to coincide with expression of genes that form part of the Wnt signaling pathway.
In the developing mouse Rspo1 transcripts are undetectable at E7, dramatically increased by E11 and significantly reduced again by E17. Rspo1 expression is predominantly found in mesenchymal cells in a number of developing organs, including the forebrain, dorsal neural tube (roof plate), whisker follicles, kidney, mammary gland, small intestine, the long bones and vertebrae (Nam et al., 2007).
Rspo1 expression is also detected in the mesenchyme underlying the developing dermis, while in adult skin, expression is restricted to the dermal papilla of the hair (Parma et al., 2006).
Similarly, in humans, RSPO1 expression is detected in the small intestine, kidney, prostate, adrenal gland and pancreas (Kim et al., 2005).
Expression of RSPO1 is detected in cultured primary human fibroblasts but not in cultured keratinocytes, indicating that R-spondin1 may be acting as a paracrine signaling molecule.

Localisation

Secreted.

Function

R-spondin1 is implicated in the Wnt signaling pathway where it seems to act as an enhancer of Wnt signaling. R-spondin1 appears to antagonize Dickkopf1 action, an inhibitor of the Wnt signaling pathway, by binding to the receptor Kremen1 and inhibiting the internalization of LRP6, a Wnt signaling co-receptor (Binnerts et al., 2007).

Homology

There are 3 paralogs of human RSPO1: RSPO2, RSPO3 and RSPO4. Orthologs have been identified in: mouse, chicken, dog, cow and chimpanzee.

Mutations

Germinal

To date, three homozygous RSPO1 mutations have been identified: a single base pair insertion, 896insG, a 2752 bp deletion that includes exon 4 (the first coding exon) and 286+1G>A, a splice site mutation.

896insG and the 2752 bp deletion were identified in two families exhibiting palmoplantar hyperkeratosis with a predisposition to squamous cell carcinoma of the skin and XX sex reversal. 896insG leads to a frameshift and stop codon after 10 amino acids resulting in the abolition of all normal isoforms of RSPO1. While the 2752 bp deletion allows production of a shorter form of RSPO1 mRNA, that may translate to a shorter protein lacking the signal peptide and first furin-like domain (Parma et al., 2006).

The splice site mutation 286+1G>A was identified in a 46,XX female with true hermaphroditism, palmoplantar keratoderma, congenital bilateral corneal opacities, onychodystrophy and hearing impairment. 286+1G>A leads to aberrant splicing of the mRNA and skipping of the second coding exon in all RSPO1 isoforms and a predicted shortened R-spondin1 protein that lacks the entire first furin-like domain and the first two residues of the second furin-like repeat (Tomaselli et al., 2007).

Implicated in

Palmoplantar hyperkeratosis with a predisposition to squamous cell carcinoma of the skin and XX sex reversal

Note

Two families.

Disease

Mutations in the RSPO1 gene have been implicated in an autosomal recessive syndrome identified in an Italian family spanning three generations (Micali et al., 2005). The syndrome is characterized by: sclerodactyly, non-epidermolytic palmar plantar keratoderma (PPK) associated with multiple cutaneous squamous cell carcinomas, dental anomlies and early tooth loss due to chronic periodontal disease (in three out of five brothers), hypogenitalism with hypospadias, gynecomastia (in one brother), altered plasma sex hormone levels in the two brothers with abnormal genitalia and hypertriglyceridemia. Four out of the five affected brothers had an abnormal XX karyotype that was associated with the genital abnormalities. None of the five sisters, or their offspring, were affected.

The squamous cell carcinoma lesions found in these patients first developed in the hyperkeratotic skin of the hands and feet (PPK) and then metastasized to other parts of the body, indicating that a single gene is responsible for both the PPK and predisposition to SCC (Radi et al., 2005). However, the sex reversal can be considered to be non-penetrant in affected XY individuals. In this extended Italian family there are eleven 46,XX individuals in two sibships, all of the affected individuals have a male phenotype (two 46,XY and four 46,XX), while none of the seven genetic females with a female phenotype show any sign of the PPK/SCC phenotype or sexual ambiguity. This indicates that a single gene defect underlies both the PPK/SCC and sex reversal, rather than two independent mutations. The family is informative for linkage analysis for the PPK trait and allows linkage exclusion for the sex reversal trait.

Linkage analysis performed on this family detected positive LOD scores for two markers at 1p34-p35. Furthermore, an additional affected individual, also from Southern Italy, who presented with XX sex reversal, PPK and SCC, also showed linkage to 1p34, but with a different haplotype (Parma et al., 2006). Sequencing identified two homozygous RSPO1 mutations in the two families. A single nucleotide insertion in codon 36 results in a frame-shift and stop codon after ten amino acid residues, predicted to lead to abolition of all RSPO1 isoforms. However, the second mutation, a 2752 bp deletion including exon 4, leads to a shorter mRNA that may translate to a putative, shorter protein lacking the signal peptide and first furin domain.

In situ hybridization analysis has identified expression of mRspo1 in the urogenital ridge at E10.5, with sex-specific differences appearing at E12.5 inline with an increase in the somatic cells of the XX gonad. Furthermore, qPCR detected no differences in mRspo1 levels between XX and XY gonads at E10.5 and E11.5, by E12.5, however, there is a clear increase of expression in XX gonads which is five-fold higher than XY gonads by E14.5. Therefore, there is a sex-specific regulation of R spondin1 at a crucial time in sex determination (Parma et al., 2006). What is more, in the XX sex reversal patients, functional testes are present, but the individuals are sterile, indicating that R-spondin1 is not required for testis differentiation and function (Parma et al., 2006).

RT-PCR has shown that RSPO1 is not expressed in cultured keratinocytes, but it is expressed in fibroblasts. Furthermore, plantar keratinocytes from an affected individual did not differentiate in organotypic culture. Together, this data suggests that R-spondin1 might act as a paracrine signal from fibroblasts to keratinocytes, regulating keratinocyte proliferation and differentiation (Parma et al., 2006).

Syndromic true hermaphroditism with palmoplantar keratoderma, congenital bilateral corneal opacities, onychodystrophy and hearing impairment

Note

One patient.

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