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NCBI Coffee Break

22 October 2001

Article reference: CB22.221001
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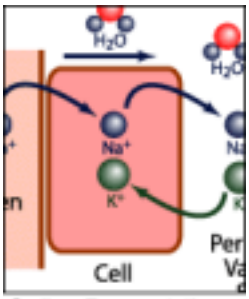

Sodium Transportation. The proximal tubules transport sodium to help maintain proper osmotic balance within the body.

Click on the figure for more information.

Finding Fanconi

The human genome lays down the blueprint for our physiology, and thus provides a framework by which to study genetic-based diseases. Researchers have recently focused on a region that may be responsible for a debilitating kidney disease autosomal dominant renal Fanconi syndrome (RFS). In RFS, the proximal tubules of the kidney are functionally impaired. This causes many essential compounds that would normally be returned to the bloodstream to instead be excreted into urine and removed from the body.

Genetic as well as environmental factors can lead to the development of RFS. An autosomal dominant form of RFS has been observed in several families; one of these was used as the basis for an attempt to find a genetic locus to the disease. The inheritable form of the syndrome is of particular interest for researchers because it can potentially provide insight into the workings of the proximal tubules.

Correlating a disease with a genetic mutation is not an easy task. In order to successfully map a disease gene on the human genome, it is necessary to have a series of genomic landmarks. This has been one of the major accomplishments of the Human Genome Project; over 10,000 polymorphic markers have been identified and contextually placed onto framework maps.

To find the region associated with RFS, DNA samples from the afflicted family were initially scanned using polymorphic markers that were distributed throughout the genome. Linkage analysis implicated marker D15S659, which is found on the long arm of chromosome 15. This initial hit gave researchers a rough area to further scrutinize by conducting a more detailed screen with 24 localized markers. From the secondary screen, two markers D15S182 and D15S537 were determined to exhibit the greatest correlation with RFS.

Genes in the 15q15.3 region are now being considered candidates for association with RFS. By definitively associating autosomal dominant RFS with a gene, new insights into the pathology of the disease can be gained. One possible candidate gene, HSPC129, codes for a hypothetical protein with unknown function.

Further clues as to the possible function of an uncharacterized protein can be discerned by comparing it to other, characterized proteins (e.g. using NCBI's Related Sequences feature). In the case of HSPC129, one of the proteins it shares similarity with is the yeast protein Psr2P. This protein is involved in the indirect regulation of transmembrane sodium transportation. Active transport of ions such as sodium takes place in the proximal tubules of the kidneys, and is a key component of healthy kidney function. Could HSPC129 also be involved in the regulation of ion transport in the kidneys similar to Psr2P regulation of sodium transportation in yeast cells? While the presence of HSPC129 in the proximal tubules of the kidneys remains to be determined, studies on Psr2P in yeast may give insight into human HSPC129 function, and possibly lead to a treatment for autosomal dominant RFS.

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Roadmap
1. Original Paper
2. The first marker's location in the genome
3. Secondary screen implicates two markers
4. HSPC129 gene in Locus Link
5. Sequence of the hypothetical protein
6. Related sequences
7. Psr2P, a yeast gene
8. Function of Psr2P

Further resources
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Comments? Questions?
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Figure Coffee Break

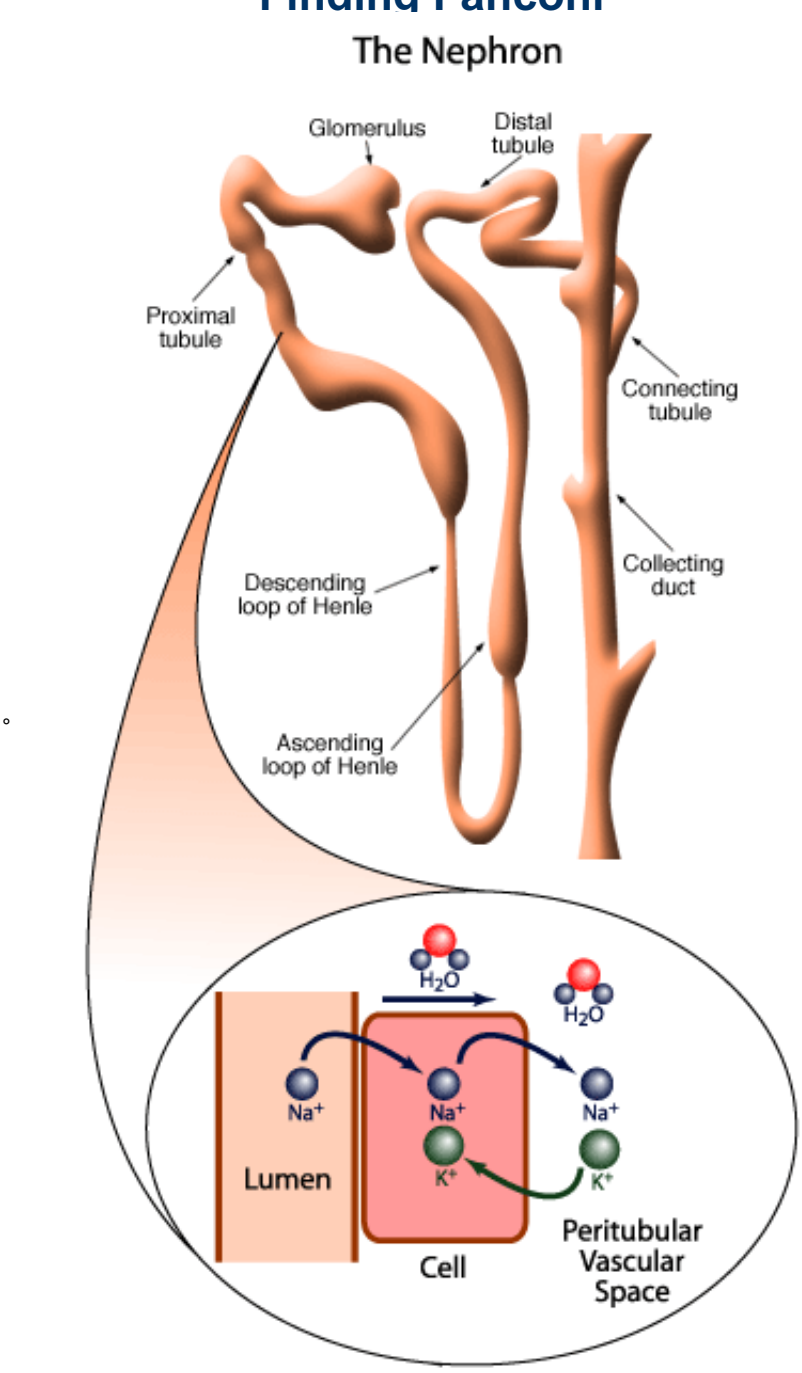

Figure 1. ˚Active sodium transportation in the proximal tubule. The kidneys are responsible for a number of important regulatory functions such as the maintenance of ion levels in the body, water retention/removal, waste excretion, blood pressure regulation, and maintenance of proper blood acidity. Nephrons are the functional unit of the kidney. Within the proximal tubule portion of

the nephron is found the highest concentration of sodium transporters. These transporters are responsible for the active reabsorption of sodium ions from filtrate present in the lumen of the nephron. Water is absorbed passively during this process due to the accumulation of sodium in the peritubular spaces. Any disruption to this system would result in the loss of large amounts of water, sodium, and other ions.

1: Am J Hum Genet 2001 Jan;68(1):264-8

Related Articles, OMIM, Books, LinkOut

Genetic and physical mapping of the locus for autosomal dominant renal Fanconi syndrome, on chromosome 15q15.3.

Lichter-Konecki U, Broman KW, Blau EB, Konecki DS.

Center for Medical Genetics, Marshfield Medical Research Foundation, Marshfield, WI, USA.

Autosomal dominant renal Fanconi syndrome is a genetic model for the study of proximal renal tubular transport pathology. We were able to map the locus for this disease to human chromosome 15q15.3 by genotyping a central Wisconsin pedigree with 10 affected individuals. After a whole-genome scan with highly polymorphic simple sequence repeat markers, a maximum LOD score of 3.01 was calculated for marker D15S659 on chromosome 15q15.3. Linkage and haplotype analysis for an additional 24 markers flanking D15S659 narrowed the interval to approximately 3 cM, with the two highest single-point LOD scores observed being 4.44 and 4.68 (for D15S182 and D15S537, respectively). Subsequently, a complete bacterial artificial chromosome contig was constructed, from the High Throughput Genomic Sequence Database, for the region bounded by D15S182 and D15S143. The identification of the gene and gene product altered in autosomal dominant renal Fanconi syndrome will allow the study of the physiology of proximal renal tubular transport.

PMID: 11090339 [PubMed - indexed for MEDLINE]

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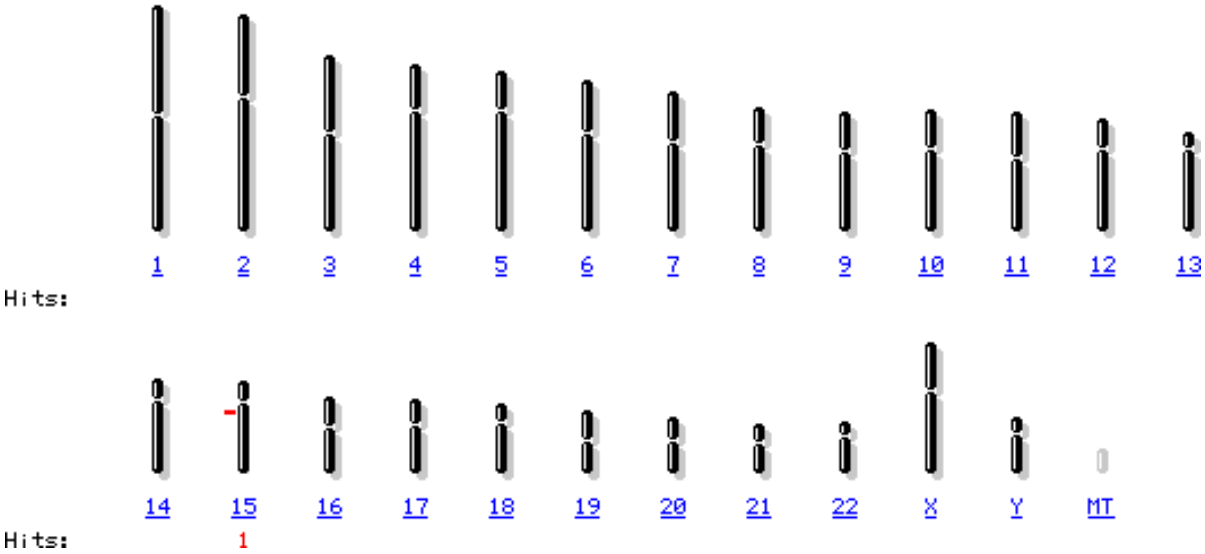
Homo sapiens genome view build 26

BLAST search the human genome



Search results for query "D15S659": 1 hit

Chr	Match	Map element	Type	Maps
15	D15S659	SHGC-17599	sts	TNG | NCBI_RH | WI_RH | STS | Stanford_G3 | Marshfield

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Human Maps Help
FTP
Chr. 15 Resource

Data As Table View

Region Shown:

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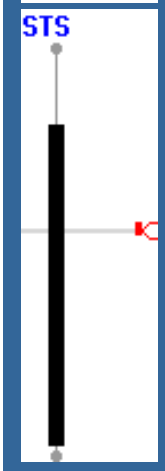


Homo sapiens Map View build 26

Chromosome: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 **[15]** 16 17 18 19 20 21 22 X Y

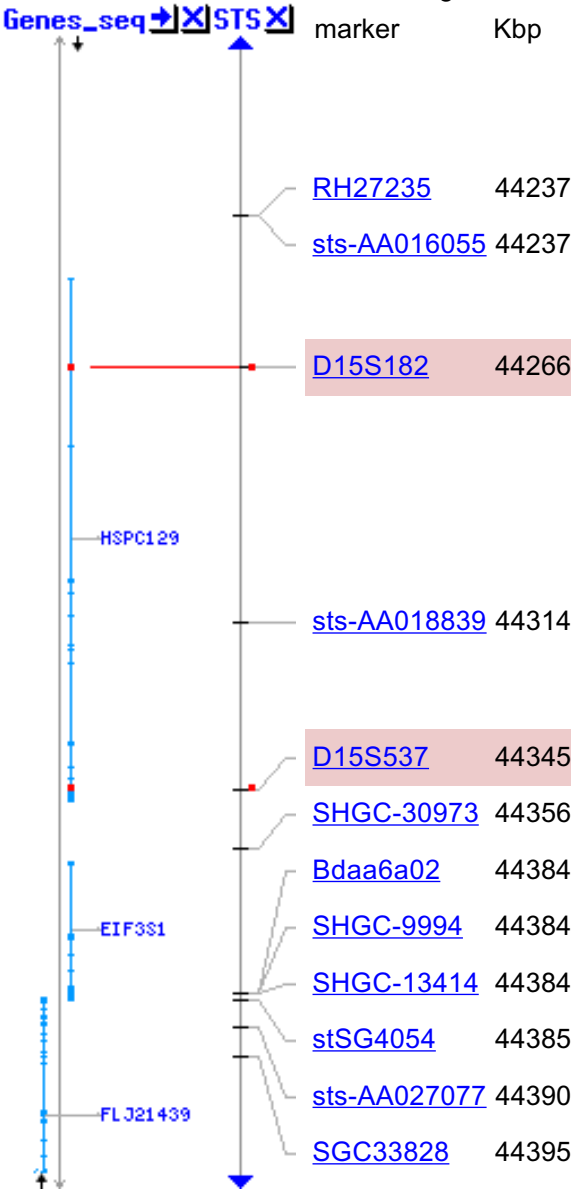
Query: d15s182 OR d15s537 [clear]

Master: STS Map **Display settings**

Total STSs On Chromosome: **3215** [42 not localized]

Region Displayed: **44,206K-44,418K bp** Download/View Sequence/Evidence

STSs Labeled: **12** Total STSs in Region: **12**



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Click to Display mRNA-Genomic Alignments (spanning 97990 bps)

PUB UNIGENE MAP VAR HOMOL e! UCSC

Homo sapiens Official Gene Symbol and Name

None Available

Interim Gene Symbol and Name:

HSPC129: hypothetical protein

LocusID: 51496

Overview

Submit GeneRIF ?

Locus Type:	gene with protein product, function unknown
Product:	hypothetical protein
Alternate Symbols:	HSPC058

Relationships ?

Mouse Homology Maps:

NCBI vs. EST-based RH Map	2 1538.74 cR	AV272515	**Hs Mm**
UCSC vs. EST-based RH Map	2 1538.74 cR	AV272515	**Hs Mm**

Map Information ?

Chromosome:	15			**mv**
Cytogenetic:	15q11.2		RefSeq	
Markers:	Chr. X	D15S798	D15S798	**mv**
	Chr. X	RH112436		**mv**

NCBI Reference Sequences (RefSeq) ?

Category: PREDICTED

mRNA:	NM_016396	
Protein:	NP_057480 hypothetical protein	**BL**
GenBank Source:	AF161478	

Category: NCBI Genome Annotation

	Genomic Contig:	NT_010194	**sv mv ev**
1.	**Evidence:**	supported by alignment with mRNA	
	Model mRNA:	XM_032383	
2.	**Evidence:**	supported by alignment with mRNA	
	Model mRNA:	XM_057527	

GenBank Sequences ?

Nucleotide	Type	Protein	
AF161478	m	AAF29093	BL
AF161543	m	AAF29030	BL

Additional Links ?

- **UniGene:** Hs.104336

To Top

Questions or Comments?
Write to the NCBI Service Desk

1: NP_057480. hypothetical prot...[gi:7705461] BLink, Related Sequences, Nucleotide, Taxonomy, LinkOut

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REFERENCE   1  (residues 1 to 466)
  AUTHORS   Ye,M., Zhang,Q.H., Zhou,J., Shen,Y., Wu,X.Y., Guan,Z.Q., Wang,L.,
            Fan,H.Y., Mao,Y.F., Dai,M., Huang,Q.H., Chen,S.J. and Chen,Z.
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1: NP_057480 BLink, Related Sequences, Nucleotide, Taxonomy
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9: NP_196747 BLink, Related Sequences, Genome, Nucleotide, PubMed, Taxonomy
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10: T48545 BLink, Related Sequences, Taxonomy
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Revised: July 16, 2001.

1: NP_013119. Plasma membrane S...[gi:6323047]

BLink, Related Sequences, Genome, Nucleotide, PubMed, Taxonomy, LinkOut

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  AUTHORS   Goffeau,A., Barrell,B.G., Bussey,H., Davis,R.W., Dujon,B.,
            Feldmann,H., Galibert,F., Hoheisel,J.D., Jacq,C., Johnston,M.,
            Louis,E.J., Mewes,H.W., Murakami,Y., Philippsen,P., Tettelin,H. and
            Oliver,S.G.
  TITLE     Life with 6000 genes
  JOURNAL   Science 274 (5287), 546 (1996)
  MEDLINE   97002444
REFERENCE   2  (residues 1 to 397)
  AUTHORS   Johnston,M., Hillier,L., Riles,L., Albermann,K., Andre,B.,
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            Heumann,K., Heuss-Neitzel,D., Hilbert,H., Hilger,F., Kleine,K.,
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            al.
  TITLE     The nucleotide sequence of Saccharomyces cerevisiae chromosome XII
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  AUTHORS   Saccharomyces Genome Database (yeast-curator@genome.stanford.ed.
  TITLE     Direct Submission
  JOURNAL   Submitted (17-NOV-1999) Department of Genetics, Stanford
            University, Saccharomyces Genome Database, Stanford, CA 94305-5120,
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1: J Biol Chem 2000 Jun 23;275(25):19352-60

Related Articles, Books, LinkOut

Psr1p/Psr2p, two plasma membrane phosphatases with an essential DXDX(T/V) motif required for sodium stress response in yeast.

Siniossoglou S, Hurt EC, Pelham HR.

Medical Research Council Laboratory of Molecular Biology, Hills Road, Car CB2 2QH, United Kingdom.

Regulation of intracellular ion concentration is an essential function of this study, we report the identification of two previously uncharacteriz PSR1 and PSR2, that perform an essential function under conditions of so stress in the yeast Saccharomyces cerevisiae. Psr1p and Psr2p are highly homologous and were identified through their homology with the endoplasr reticulum membrane protein Nem1p. Localization and biochemical fractionat studies show that Psr1p is associated with the plasma membrane via a sh amino-terminal sequence also present in Psr2p. Growth of the psr1psr2 mu severely inhibited under conditions of sodium but not potassium ion or s stress. This growth defect is due to the inability of the psr1psr2 mutan properly induce transcription of ENA1/PMR2, the major sodium extrusion pu yeast cells. We provide genetic evidence that this regulation is indepen phosphatase calcineurin, previously implicated in the sodium stress resp yeast. We show that Psr1p contains a DXDX(T/V) phosphatase motif essenti its function in vivo and that a Psr1p-PtA fusion purified from yeast ext exhibits phosphatase activity. Based on these data, we suggest that Psr Psr2p, members of an emerging class of eukaryotic phosphatases, are nove regulators of salt stress response in yeast.

PMID: 10777497 [PubMed - indexed for MEDLINE]

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