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REVIEW

Characteristics of PVT1 and Its Roles in Diseases[△]

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With the development of genome-wide sequencing technology, 195 types of functional, long non-coding RNAs (lncRNAs) have been identified so far, and their cellular roles are gradually being revealed. LncRNAs have now become a hotspot in the field of life sciences. These small molecules exist in almost all higher eukaryotes and play very important regulatory roles in these organisms. This review briefly summarizes the recent progress in research on plasmacytoma variant translocation 1 gene (PVT1), an lncRNA.

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LONG non-coding RNAs (lncRNAs) are a class of RNAs whose transcripts are longer than 200 nt. These molecules do not encode proteins but have a structure resembling that of mRNA and show polyA tails and promoter structure through splicing. Most lncRNAs show a distinct spatial and temporal specificity during histological differentiation and development. Dynamic expression and different splicing methods may appear during the differentiation process.¹

CHARACTERISTICS OF PVT1

Plasmacytoma variant translocation 1 gene (PVT1, non-protein encoding Pvt1 oncogene) is an RNA gene belonging to the lncRNA class. On chromosome 8q24, PVT1 is located at 128, 806, 779-129, 113, and 499 bp and contains 53 exons. The transcription initiation site of

PVT1 is at 670 bp (<http://www.genecards.org/cgi-bin/carddisp.pl?gene=PVT1&search=0cbe743864f7959078c5c8a353854410>). Table 1 shows the most relevant transcription factor binding sites in the gene promoter as predicted by SABiosciences' text mining application and the UCSC Genome Browser.

ROLES OF PVT1 IN DISEASES

The human PVT1 gene is located on chromosome 8 telomeric to the c-MYC gene, and it is frequently involved in the translocations occurring in variant Burkitt's lymphoma and murine plasmacytoma.² The murine pvt1 locus lies at an unknown distance at the 3' side of c-myc; DNA analysis from several tumors with c-myc amplification has shown that pvt-1 is co-amplified in at least one case, placing it approximately 100-500 kb at the 3' end of c-myc.³ Collectively, these findings point to the role of pvt1 in tumorigenesis. Unlike the widespread distribution of c-MYC RNA, PVT1 expression is restricted to relatively few normal tissues; however, the latter gene is strongly expressed in neuroblastoma cells that do not express c-MYC.³ In addition,

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Table 1. Transcription factors binding to PVT1

Gene	TF	TFBS position (NC)	Assay to TFBS	ChIP-qPCR assay Cat. number
PVT1	TBP	128795065	478	GPH1012814(-)12A
PVT1	AhR	128806754	389	GPH1012814(-)01A
PVT1	FOXF2	128797702	303	GPH1012814(-)10A
PVT1	p53	128808026	346	GPH1012814(+)02A
PVT1	AML1a	128807297	72	GPH1012814(+)01A
PVT1	Pax-2a	128806755	390	GPH1012814(-)01A
PVT1	E4BP4	128806749	384	GPH1012814(-)01A
PVT1	Arnt	128806754	389	GPH1012814(-)01A
PVT1	C/EBPalpha	128795124	419	GPH1012814(-)12A
PVT1	Pax-2b	128807146	223	GPH1012814(+)01A

PVT1: plasmacytoma variant translocation 1 gene; TF: transcription factor; TFBS: transcription factor binding site.

PVT1 is a downstream target of Myc proteins.⁴⁻⁶ PVT1-mediated inhibition of apoptosis may explain why amplification of chromosome 8q24 is associated with reduced survival in patients treated with agents that act through apoptotic mechanisms. When overexpressed because of genomic abnormalities, MYC and PVT1 contribute independently to ovarian and breast cancer pathogenesis.⁷ With the genome-wide screening approach, PVT1 was identified as a regulator of gemcitabine sensitivity in pancreatic cancer cells.⁸ Using chromatin conformation capture (3C) technique, studies have found that the region surrounding the risk allele rs378854 interacts with the MYC and PVT1 promoters. Moreover, a study found that expression of the PVT1 oncogene in normal prostate tissue increased with the presence of rs378854, while expression of MYC was not affected.⁹ A new functional prostate cancer risk variant at the 8q24 locus, rs378854 allele G, reduces binding of the YY1 protein and is associated with increased expression of PVT1 located 0.5 Mb downstream.⁹ Another study confirmed the role played by PVT1 in mediating susceptibility to end-stage renal disease attributable to diabetes.¹⁰ PVT1 knockdown was found significantly reduce mRNA and protein levels of the major extracellular matrix (ECM) proteins and two key regulators of ECM proteins. PVT1 expression was found to be significantly upregulated by glucose treatment in human mesangial cells, similar with the changes in fibronectin 1, collagen, type IV, alpha 1, transforming growth factor beta 1, and plasminogen activator inhibitor-1. These results indicate that PVT1 may mediate the development and progression of diabetic nephropathy through mechanisms involving ECM accumulation.¹¹ A genome-wide association study detected that a 640-kb region at chromosome 8q24.21 contained multiple markers with highly significant

evidence of association with cleft lip with or without cleft palate.¹² This 640-kb cleft-associated region was saturated with 146 single nucleotide polymorphism markers, among which the most significant one had a population attributable risk of 0.41. The findings suggested that a major susceptibility locus for nonsyndromic cleft lip with or without cleft palate was identified.¹² Hanson and colleagues¹³ reported an association between variants (rs2720709, A>G) in PVT1 and end-stage renal disease (ESRD) attributed to both type 1 and type 2 diabetes.

In conclusion, PVT1 is expressed at a high level in peripheral blood mononuclear cells and may serve as a diagnostic marker for type 2 diabetes. Some studies have indicated that PVT1 contributes to the development of tumors such as Burkitt's lymphoma, prostate cancer, and ovarian cancer. LncRNA molecules are involved in different gene regulatory pathways, but the intrinsic properties or extrinsic features (such as protein interactions, microRNA interactions, cellular and developmental context) of these molecules that are decisive for any given pathway are yet to be clearly identified. Thus, some important and fundamental regulatory mechanisms related to PVT1 remain to be elucidated.

REFERENCES

1. Chen G, Wang Z, Wang D, et al. LncRNADisease: a database for long-non-coding RNA-associated diseases. *Nucleic Acids Res* 2013; 41: D983-6.
2. Graham M, Adams JM. Chromosome 8 breakpoint far 3' of the c-myc oncogene in a Burkitt's lymphoma 2; 8 variant translocation is equivalent to the murine pvt-1 locus. *EMBO J* 1986; 5: 2845-51.
3. Enciso-Mora V, Broderick P, Ma Y, et al. A genome-wide

- association study of Hodgkin's lymphoma identifies new susceptibility loci at 2p16.1 (REL), 8q24.21 and 10p14 (GATA3). *Nat Genet* 2010; 42: 1126-30.
4. Shtivelman E, Bishop JM. The PVT gene frequently amplifies with MYC in tumor cells. *Mol Cell Biol* 1989; 9: 1148-54.
 5. Shtivelman E, Henglein B, Groitl P, et al. Identification of a human transcription unit affected by the variant chromosomal translocations 2;8 and 8;22 of Burkitt lymphoma. *Proc Natl Acad Sci* 1989; 86: 3257-60.
 6. Carramusa L, Contino F, Ferro A, et al. The PVT-1 oncogene is a Myc protein target that is overexpressed in transformed cells. *J Cell Physiol* 2007; 213: 511-8.
 7. Guan Y, Kuo WL, Stilwell JL, et al. Amplification of PVT1 contributes to the pathophysiology of ovarian and breast cancer. *Clin Cancer Res* 2007; 13: 5745-55.
 8. You L, Chang D, Du HZ, et al. Genome-wide screen identifies PVT1 as a regulator of Gemcitabine sensitivity in human pancreatic cancer cells. *Biochem Biophys Res Commun* 2011; 407: 1-6.
 9. Meyer KB, Maia AT, O'Reilly M, et al. A functional variant at a prostate cancer predisposition locus at 8q24 is associated with PVT1 expression. *PLoS Genet* 2011 Jul [cited 2014 Jul 1]; 7: e1002165. Available from: <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002165>.
 10. Millis MP, Bowen D, Kingsley C, et al. Variants in the plasmacytoma variant translocation gene (PVT1) are associated with end-stage renal disease attributed to type 1 diabetes. *Diabetes* 2007; 56: 3027-32.
 11. Alvarez ML, DiStefano JK. Functional characterization of the plasmacytoma variant translocation 1 gene (PVT1) in diabetic nephropathy. *PLoS One* 2011 Apr 22 [cited 2014 Jul 1]; 6:e18671. Available from: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0018671>.
 12. Birnbaum S, Ludwig KU, Reutter H, et al. Key susceptibility locus for nonsyndromic cleft lip with or without cleft palate on chromosome 8q24. *Nat Genet* 2009; 41:473-7.
 13. Hanson RL, Craig DW, Millis MP, et al. Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single nucleotide polymorphism association study. *Diabetes* 2007; 56: 975-83.