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Review

EMP3 (epithelial membrane protein 3)

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Abstract

Epithelial membrane protein 3 (EMP3) has recently been proposed as a candidate tumor suppressor gene (TSG) for some kinds of solid tumors. EMP3 down-regulation has been explained by its epigenetic silencing through aberrant hypermethylation of the promoter region.

EMP3 repression in cancer seems to be an organ-specific phenomenon, common in neuroblastoma and gliomas, relatively common in breast cancer, and rare in esophageal squamous cell carcinoma (ESCC). Among cancer-derived cell lines, it prevails in neuroblastoma, breast cancer and ESCC whereas it is rare in glioma, non-small cell lung carcnoma (NSCLC), gastric and colon cancer-derived cell lines.

EMP3 expression level is associated with clinical prognosis in neuoblastoma, ESCC, NSCLC and upper urinary tract urothelial carcinoma. In contrast, EMP3 expression may be a novel marker of tumor aggressiveness in breast cancer whereas in gliomas, EMP3 represssion by aberrant hypermethylation has a prognostic signifcance. In both tumor types, however, alternative mechanisms to the EMP3 epigenetic silencing may exist to explain EMP3 down-regulation.

Moreover, EMP3 may be involved in the prostate cancer suscpetibility.

Keywords

Epithelial membrane protein 3 (EMP3), tumor suppressor gene, solid tumors, promoter hypermethylation, prognosis.

Identity

Other names: YMP

HGNC (Hugo): EMP3

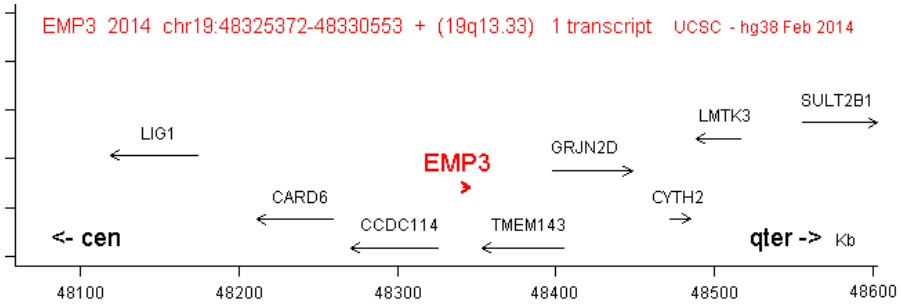
Location: 19q13.33

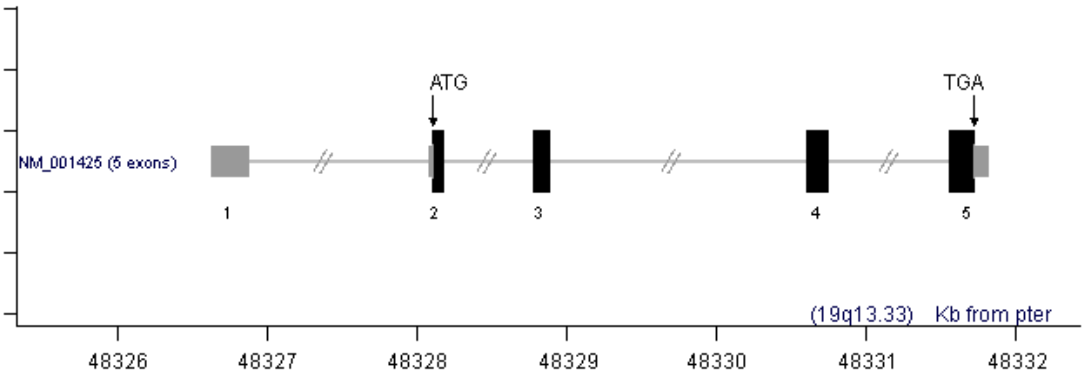
Local order

EMP3 is located centromeric to TMEM143 (transmembrane protein 143) and telomeric to CCDC114 (coiled-coil domain-containing protein 114).

Note

EMP3 is a hydrophobic membrane glycoprotein belonging to the PMP22 protein family. It displays a high degree of cross-species conservation in its nucleotide and protein sequence.





Graphical scheme of the human EMP3 gene. Grey boxes correspond to untranslated and black boxes to translated regions (all in scale). Arrows indicate the ATG and the stop codons, respectively.

DNA/RNA

Note

A human EMP3 cDNA was first identified by homology screening of databases (Ben-Porath and Benvenisty, 1996; Taylor and Suter, 1996). EMP3 belongs to the peripheral myelin protein 22-kDa (PMP22) gene family of small hydrophobic membrane glycoproteins (Taylor et al., 1995). It includes four closely related members (PMP22, EMP1, EMP2 and EMP3), as well as the additional and more distant member MP20. The amino acid sequence homology with PMP22, EMP1, EMP2 and MP20 is 41, 33, 38 and 23%, respectively, with the highest homology in the transmembrane domains (TMDs). The genomic structure, as well as the putative four TMD structure (included a PMP22 Claudin domain) are highly conserved among family members.

Functionally, the PMP22 gene family may control cell proliferation, cell differentiation and cell death. Remarkable, mutations in the PMP22 gene are responsible for various hereditary peripheral neuropathies in both humans and mice (Leal et al., 2001).

The human EMP3 gene maps on chromosome 19q13.33 (Lieher et al., 1999). The homologous gene in mouse maps on chromosome 7 (Ben-Porath et al., 1998).

Description

The genomic size of the human EMP3 gene is of 5.183 Kb, localized from 48325372 to 48330553.

The 5'-UTR region contains a CpG island (62 CpG dimers) localized around the transcription start site (from -13 to +241 bp) (GenBank reference sequence NM_001425) (Alaminos et al., 2005). Regulatory transcription factor binding sites in the promoter region are COUP-TF1, STAT1, Bach2, Rel4, HNF-4alpha1, E47, AREB6, RORalpha1, HEN1 and COUP-TF.

Transcription

The gene is composed of five exons, including a non-coding exon 1, and produces at least nine different alternative splicing isoforms.

Pseudogene

No known pseudogenes.

Protein

EMP3 is a 163-amino acid membrane glycoprotein.

Description

EMP3 belongs to the PMP22 protein family and shares with its members structural and functional homologies.

Expression

Promimently expressed in fetal lung, liver and kidney, but relatively weakly expressed in both fetal and adult brain. In adult, it is ubiquitariously expressed in various normal tissues including lung, liver, ovary, small intentistine, colon, thymus, kidney, pancreas, heart and placenta with the highest expression in peripheral blood leukocytes (Taylor and Suter, 1996).

Localisation

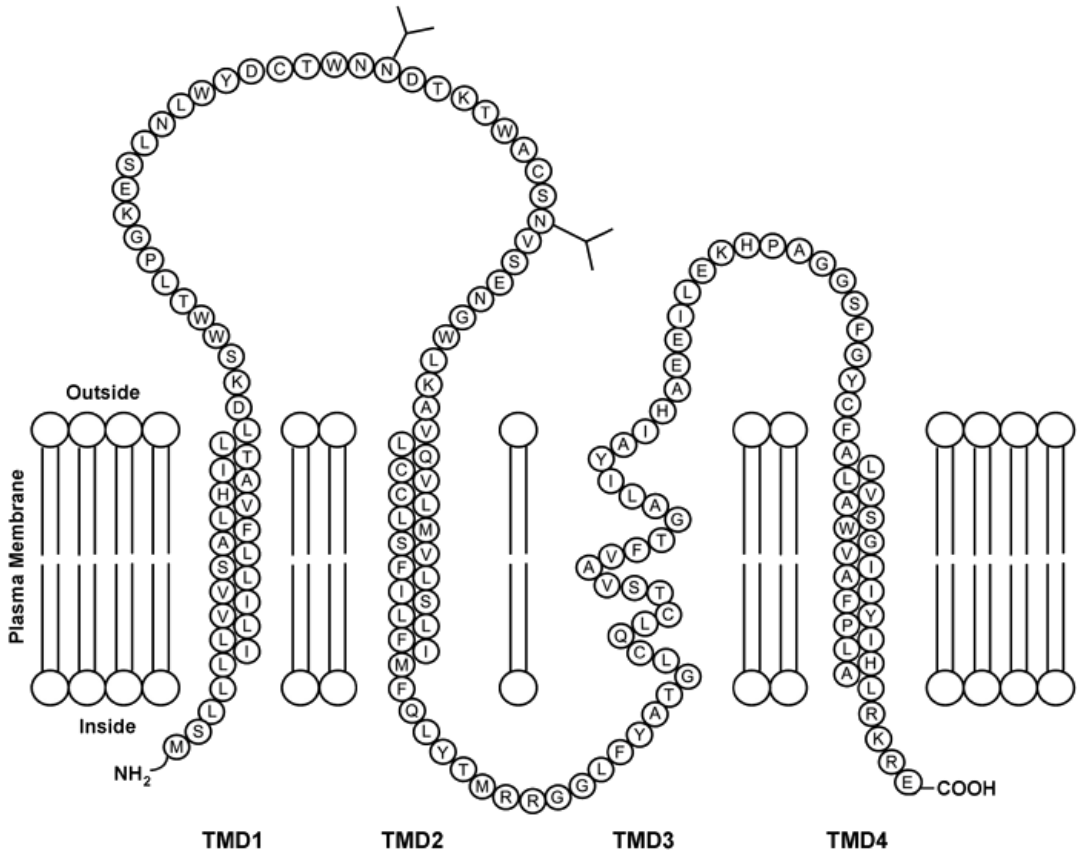
Localised in the cell-membrane and cytoplasm.

Function

The function of the EMP3 protein is largely unknown but it may be involved in the following physiological processes.

On the basis of its sequence similarity to EMP1, it may be involved in the regulation of cell proliferation (Bolin et al., 1997).

The higher expression levels in fetal brain, lung and kidney compared to the respective adult counterparts suggest a role in the developmental regulation, especially in neuronal development (Bolin et al., 1997).



Schematic view of the predicted structure of the multi-pass human EMP3 protein in a lipid bilayer. The Y-shape symbol indicates the putative N-linked carbohydrate sites in the first extracellular loop at Asn47 and Asn56 residues. The four hydrophobic TMDs (from 4 to 24, 66 to 86, 100 to 120 and 139 to 159 amino acid residues) and the PMP22 Claudin domain (from 20 to 156 residues) are shown with respect to the intracellular and extracellular sides of the membrane (Jetten and Suter, 2000). The molecular weight is of 18.429 kDa.

It may control the regulation of cell growth, differentiation and death, since its overexpression results in cell blebbing in embryonic kidney cell cultures and in the activation of the apoptosis pathway (Wilson et al., 2002).
In peripheral nervous system, it may regulate Schwann cell proliferation after injury and cell-cell interactions in active myelination (Bolin et al., 1997).
It may have possible roles in hematopoietic system (Bolin et al., 1997).

Homology

Comparative sequence analysis revealed the remarkable conservation of the EMP3 primary sequence. The EMP3 gene is present in the common ancestor of chordates and it is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, zebrafish and frog.
The PMP22 gene family probably evolved as result of a chromosome duplication event and divergence (Ben-Porath et al., 1998). Paralogs are PMP22, EMP1 and EMP2. Seventy-four organisms have orthologues with the human EMP3 gene.

Mutations

Note

Neither causative nor functional mutations reported. Eighteen human genomic variants from 12 studies described, three of which (nsv531627, nsv531628 and nsv531629, all copy number gains) with pathogenic clinical significance since associated to global developmental delay and seizure (Miller et al., 2010; Kaminsky et al., 2011).
In mouse, a single nucleotide polymorphism (SNP) is responsible for the reciprocal H4 minor histocompatibility alloantigens in the MHC-bound peptide derived from EMP3 and presented by the MHC class I molecule. The C>T nucleotide change results in the amino acid substitution from Thr (H4a, SGTVYIHL) to Ile (H4b, SGIVYIHL) in the minimal antigenic epitope SGIVYIHL (SYL8) derived from H4(b) (Yadav et al., 2003; Luedtke et al., 2003)

Germinal

No germinal mutations described.

Somatic

A total of eight putative somatic mutations reported in public databases. Six are missense substitutions identified in lung adenocarcinoma (p.Val7Leu), in colon adenocarcinoma (p.Val21Met, confirmed somatic), in squamous cell lung carcinoma (SCLC) (p.A22T, confirmed somatic), in endometrioid carcinoma (p.Cys34Arg), in esophageal carcinoma (p.Ala65Val) and in large intestine adenocarcinoma (p.Met70Val). A p.Asn47Asn synonimous substitution detected in colon adenocarcinoma and a p.Gly133fs*>31 frameshift deletion in endometrioid carcinoma. When not specificied, variants are of unknown origin.

Implicated in

Neuroblastoma / phaeochromocytoma

By methylation-specific PCR (MS-PCR) and direct bisulphate DNA sequencing, EMP3 hypermethylation is common in both tumor tissue (24-68.4%) and neuroblastoma cell lines (33.3%). It occurs with concomitant downregulation of EMP3 protein expression in all clinical samples and in only 33.3% of neuroblastoma cell lines (Alaminos et al., 2005; Margetts et al., 2008). EMP3 hypermethylation is associated with poor survival at two-year follow-up and with an high mortality rate (Alaminos et al., 2005).

In contrast, it is a rare event in sporadic (7.1%) and adult VHL-associated (6.1%) phaeochromocytomas (Margetts et al., 2008).

Brain tumors / gliomas

By MS-PCR, EMP3 hypermethylation is an early epigenetic event in gliomagenesis. It is common in pure (63%) and mixed (70%) oligodendroglial tumors in comparison to astrocytic ones (18%). It prevails in grade II (71.4%) upon grade III (44.7%) gliomas, and in secondary (89%) upon primary GBMs (17%) (Alaminos et al., 2005; Li et al., 2007; Kunitz et al., 2007; Mellai et al., 2013). Not found in GBM cell lines (Ernst et al., 2009).

Aberrant hypermethylation correlates with reduced mRNA expression and lack of EMP3 protein expression. It is strongly associated with IDH1/IDH2 somatic mutations in astrocytic and oligodendroglial tumors and inversely correlated with EGFR gene amplification. In oligodendrogliomas, it is also associated with loss of the 19q13.3 locus and with total 1p/19q co-deletion (Tews et al., 2006; Mellai et al., 2013), with prognostic significance on patient overall survival (Kunitz et al., 2007; Mellai et al., 2013).

The EMP3 gene belongs to the glioma CpG island methylator phenotype (G-CIMP) (Noushmehr et al., 2010), that identifies a distinct molecular glioma subclass, prevalent in low-grade tumors and associated with IDH1/2 mutations and with improved patient survival (Laffaire et al., 2011).

No tumor-specific mutations identified on 132 glioma patients, except for the SNPs rs4893 (p.Ile125Val, exon 5) and rs11671746 (3'-UTR) in four patients (Kunitz et al., 2007).

Esophageal squamous cell carcinoma (ESCC)

By MS-PCR, EMP3 hpermethylation is rare in tumor tissue (6%) but frequent in ESCC cell lines (75%), with an inverse correlation with mRNA expression levels (Fumoto et al., 2009a). Low EMP3 expression is associated with poor prognosis after recurrence, suggesting that EMP3 inactivation may confer an advantage for tumor growth only at late stage of disease.

Breast cancer

By RT-PCR, EMP3 mRNA expression is significantly higher in primary tumors than in normal breast tissue.

It correlates with the histologic grade III, lymph node metastatis and Her-2 expression in human mammary luminal epithelial cells (Mackey et al., 2003 ; Zhou et al., 2009). It may be a novel marker of tumor aggressiveness (Zhou et al., 2009).

By MS-PCR, EMP3 hypermethylation occurs occasionally in primary tumor tissue (36.5%) without association with mRNA expression levels. In breast cancer cell lines, EMP3 mRNA is frequently repressed in both invasive (70%) and non-invasive phenotype (75%).

Promoter hypermethylation may explain mRNA repression in almost all the non-invasive phenotype and in only a part of the invasive phenotype (Evtimova et al., 2003).

Non-small cell lung cancer (NSCLC)

By Western blotting, EMP3 expression in tumor tissue is signifcantly lower than in normal lung tissue, correlates with the p-TNM stage and negatively with the proliferation index Ki-67. EMP3 may be a TSG at late stage of disease and a potential marker of prognosis in lung patients (Xue et al., 2013).

In lung cell lines, EMP3 is repressed with partial CpG hypermethylation in 11.1% of cases (Fumoto et al, 2009a).

Upper urinary tract urothelial carcinoma

At mRNA and protein level, EMP3 overexpression promotes in vitro tumor cell proliferation and migration by activation of the ErbB2-PI3K-AKT pathway.

It suppresses cell adhesion. EMP3 and ErbB2 co-espression is the most important marker of

progression-free and metastasis-free patient survival (Wang et al., 2013).

Prostate cancer

By a case-control study in 275 multiplex sibships on candidate genes and genomic regions with linkage to tumor suscpetibility and/or aggressiveness, the rs4893 variant displays a highly significant association, confirmed in a age-matched subsample. The EMP3 association, together with HPN: gene (19q11-q13.2), suggests the involvement of multiple genes within this genomic region in the prostate cancer susceptibility. The rs4893 allelic variant is significantly more frequent in prostate cancer patients compared to controls (Burmester et al., 2004).

Other malignancies

By RT-PCR, EMP3 displays high mRNA expression in gastric and colon cancer-derived cell lines (Fumoto et al., 2009b).

Keratoconus (KC)

By RT-PCR, EMP3 is significantly upregulated (2.5-fold) in keratoconus patients compared to a reference control group (Nielsen et al., 2005). EMP3 may have a potential role in the epithelial changes of the disease in agreement with the finding of blebs on the surface of KC corneas (Pfister and Burstein, 1977).

Breakpoints

Unknown fusion proteins..

To be noted

No genetic variants in the regulatory or coding regions responsible for EMP3 repression in cancer-derived cell lines without EMP3 hypermethylation or for EMP3 overexpression in other cancer-derived cell lines. An exception is the finding of the rs4893 allelic variant in the Caucasian A549 NSCLC cell line (Fumoto et al., 2009a) within a panel of 45 representative cancer cell lines. A Japanese- or Asian-population specific haplotype of three SNPs (rs8102349, rs8355 and rs11665) in non-coding regions is reported without association with the EMP3 expression levels (Fumoto et al., 2009a).

References

Alaminos M, Dávalos V, Ropero S, Setién F, Paz MF, Herranz M, Fraga MF, Mora J, Cheung NK, Gerald WL, Esteller M. EMP3, a myelin-related gene located in the critical 19q13.3 region, is epigenetically silenced and exhibits features of a candidate tumor suppressor in glioma and neuroblastoma. Cancer Res. 2005 Apr 1;65(7):2565-71

Ben-Porath I, Kozak CA, Benvenisty N. Chromosomal mapping of Tmp (Emp1), Xmp (Emp2), and Ymp (Emp3), genes encoding membrane proteins related to Pmp22. Genomics. 1998 May 1;49(3):443-7

Bolin LM, McNeil T, Lucian LA, DeVaux B, Franz-Bacon K, Gorman DM, Zurawski S, Murray R, McClanahan TK. HNMP-1: a novel hematopoietic and neural membrane protein differentially regulated in neural development and injury. J Neurosci. 1997 Jul 15;17(14):5493-502

Burmester JK, Suarez BK, Lin JH, Jin CH, Miller RD, Zhang KQ, Salzman SA, Reding DJ, Catalona WJ. Analysis of candidate genes for prostate cancer. Hum Hered. 2004;57(4):172-8

Ernst A, Hofmann S, Ahmadi R, Becker N, Korshunov A, Engel F, Hartmann C, Felsberg J, Sabel M, Peterziel H, Durchdewald M, Hess J, Barbus S, Campos B, Starzinski-Powitz A, Unterberg A, Reifenberger G, Lichter P, Herold-Mende C, Radlwimmer B. Genomic and expression profiling of glioblastoma stem cell-like spheroid cultures identifies novel tumor-relevant genes associated with survival. Clin Cancer Res. 2009 Nov 1;15(21):6541-50

Evtimova V, Zeillinger R, Weidle UH. Identification of genes associated with the invasive status of human mammary carcinoma cell lines by transcriptional profiling. Tumour Biol. 2003 Aug-Sep;24(4):189-98

Fumoto S, Hiyama K, Tanimoto K, Noguchi T, Hihara J, Hiyama E, Noguchi T, Nishiyama M. EMP3 as a tumor suppressor gene for esophageal squamous cell carcinoma. Cancer Lett. 2009 Feb 8;274(1):25-32

Fumoto S, Tanimoto K, Hiyama E, Noguchi T, Nishiyama M, Hiyama K. EMP3 as a candidate tumor suppressor gene for solid tumors. Expert Opin Ther Targets. 2009 Jul;13(7):811-22

Jetten AM, Suter U. The peripheral myelin protein 22 and epithelial membrane protein family. Prog Nucleic Acid Res Mol Biol. 2000;64:97-129

Kaminsky EB, Kaul V, Paschall J, Church DM, Bunke B, Kunig D, Moreno-De-Luca D, Moreno-De-Luca A, Mulle JG, Warren ST, Richard G, Compton JG, Fuller AE, Gliem TJ, Huang S, Collinson MN, Beal SJ, Ackley T, Pickering DL, Golden DM, Aston E, Whitby H, Shetty S, Rossi MR, Rudd MK, South ST, Brothman AR, Sanger WG, Iyer RK, Crolla JA, Thorland EC, Aradhya S, Ledbetter DH, Martin CL. An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. Genet Med. 2011 Sep;13(9):777-84

Kunitz A, Wolter M, van den Boom J, Felsberg J, Tews B, Hahn M, Benner A, Sabel M, Lichter P, Reifenberger G, von Deimling A, Hartmann C. DNA hypermethylation and aberrant expression of the EMP3 gene at 19q13.3 in Human Gliomas. Brain Pathol. 2007 Oct;17(4):363-70

Laffaire J, Everhard S, Idbaih A, Crinière E, Marie Y, de Reyniès A, Schiappa R, Mokhtari K, Hoang-Xuan K, Sanson M, Delattre JY, Thillet J, Ducray F. Methylation profiling identifies 2 groups of gliomas according to their tumorigenesis. Neuro Oncol. 2011 Jan;13(1):84-98

Leal A, Morera B, Del Valle G, Heuss D, Kayser C, Berghoff M, Villegas R, Hernández E, Méndez M, Hennies HC, Neundörfer B, Barrantes R, Reis A, Rautenstrauss B. A second locus for an axonal form of autosomal recessive Charcot-Marie-Tooth disease maps to chromosome 19q13.3. Am J Hum Genet. 2001 Jan;68(1):269-74

Li KK, Pang JC, Chung NY, Ng YL, Chan NH, Zhou L, Poon WS, Ng HK. EMP3 overexpression is associated with oligodendroglial tumors retaining chromosome arms 1p and 19q. Int J Cancer. 2007 Feb 15;120(4):947-50

Liehr T, Kuhlenbäumer G, Wulf P, Taylor V, Suter U, Van Broeckhoven C, Lupski JR, Claussen U, Rautenstrauss B. Regional localization of the human epithelial membrane

protein genes 1, 2, and 3 (EMP1, EMP2, EMP3) to 12p12.3, 16p13.2, and 19q13.3. Genomics. 1999 May 15;58(1):106-8

Luedtke B, Pooler LM, Choi EY, Tranchita AM, Reinbold CJ, Brown AC, Shaffer DJ, Roopenian DC, Malarkannan S. A single nucleotide polymorphism in the Emp3 gene defines the H4 minor histocompatibility antigen. Immunogenetics. 2003 Aug;55(5):284-95

Mackay A, Jones C, Dexter T, Silva RL, Bulmer K, Jones A, Simpson P, Harris RA, Jat PS, Neville AM, Reis LF, Lakhani SR, O'Hare MJ. cDNA microarray analysis of genes associated with ERBB2 (HER2/neu) overexpression in human mammary luminal epithelial cells. Oncogene. 2003 May 1;22(17):2680-8

Margetts CD, Morris M, Astuti D, Gentle DC, Cascon A, McRonald FE, Catchpoole D, Robledo M, Neumann HP, Latif F, Maher ER. Evaluation of a functional epigenetic approach to identify promoter region methylation in phaeochromocytoma and neuroblastoma. Endocr Relat Cancer. 2008 Sep;15(3):777-86

Mellai M, Piazzi A, Caldera V, Annovazzi L, Monzeglio O, Senetta R, Cassoni P, Schiffer D. Promoter hypermethylation of the EMP3 gene in a series of 229 human gliomas. Biomed Res Int. 2013;2013:756302

Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14;86(5):749-64

Nielsen K, Heegaard S, Vorum H, Birkenkamp-Demtröder K, Ehlers N, Orntoft TF. Altered expression of CLC, DSG3, EMP3, S100A2, and SLPI in corneal epithelium from keratoconus patients. Cornea. 2005 Aug;24(6):661-8

Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, Pan F, Pelloski CE, Sulman EP, Bhat KP, Verhaak RG, Hoadley KA, Hayes DN, Perou CM, Schmidt HK, Ding L, Wilson RK, Van Den Berg D, Shen H, Bengtsson H, Neuvial P, Cope LM, Buckley J, Herman JG, Baylin SB, Laird PW, Aldape K. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010 May 18;17(5):510-22

Pfister RR, Burstein NL. The normal and abnormal human corneal epithelial surface: a scanning electron microscope study. Invest Ophthalmol Vis Sci. 1977 Jul;16(7):614-22

Taylor V, Suter U. Epithelial membrane protein-2 and epithelial membrane protein-3: two novel members of the peripheral myelin protein 22 gene family. Gene. 1996 Oct 10;175(1-2):115-20

Taylor V, Welcher AA, Program AE, Suter U. Epithelial membrane protein-1, peripheral myelin protein 22, and lens membrane protein 20 define a novel gene family. J Biol Chem. 1995 Dec 1;270(48):28824-33

Tews B, Felsberg J, Hartmann C, Kunitz A, Hahn M, Toedt G, Neben K, Hummerich L, von Deimling A, Reifenberger G, Lichter P. Identification of novel oligodendroglioma-associated candidate tumor suppressor genes in 1p36 and 19q13 using microarray-based expression profiling. Int J Cancer. 2006 Aug 15;119(4):792-800

Wang YW, Li WM, Wu WJ, Chai CY, Liu HS, Lai MD, Chow NH. Potential significance of EMP3 in patients with upper urinary tract urothelial carcinoma: crosstalk with ErbB2-PI3K-Akt pathway. J Urol. 2014 Jul;192(1):242-51

Wilson HL, Wilson SA, Surprenant A, North RA. Epithelial membrane proteins induce membrane blebbing and interact with the P2X7 receptor C terminus. J Biol Chem. 2002 Sep 13;277(37):34017-23

Xue Q, Zhou Y, Wan C, Lv L, Chen B, Cao X, Ju G, Huang Y, Ni R, Mao G. Epithelial membrane protein 3 is frequently shown as promoter methylation and functions as a tumor suppressor gene in non-small cell lung cancer. Exp Mol Pathol. 2013 Dec;95(3):313-8

Yadav R, Yoshimura Y, Boesteanu A, Christianson GJ, Ajayi WU, Shashidharamurthy R, Stanic AK, Roopenian DC, Joyce S. The H4b minor histocompatibility antigen is caused by a combination of genetically determined and posttranslational modifications. J Immunol. 2003 May 15;170(10):5133-42

Zhou W, Jiang Z, Li X, Xu F, Liu Y, Wen P, Kong L, Hou M, Yu J. EMP3 overexpression in primary breast carcinomas is not associated with epigenetic aberrations. J Korean Med Sci. 2009 Feb;24(1):97-103

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