Novel biomarkers of chronic neuropathic pain

THE BRITISH PAIN SOCIETY

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BACKGROUND

Chronic Neuropathic Pain (CNP) is one of the most underestimated health care problems in the world today, causing major consequences to the quality of life of the individual sufferer. CNP is a highly complex condition that results in long-term changes to nervous system functioning and is often found co-morbid with other diseases, including multiple sclerosis (MS). This makes CNP a very difficult condition to diagnose and treat. Furthermore, the CNP associated with MS only occurs in about 50% of MS patients, which would suggest there are differences in their sensitivity to pain. We are looking to identify blood biomarkers that could help us better understand and accurately diagnose CNP, in all its forms, and in turn allow clinicians to better diagnose and treat this highly debilitating condition.

CNP ARRAY STUDY

PAX RNA blood tubes were commercially obtained (ProteoGenex) for CNP and control group samples (total n=20). Transcriptomic analysis was performed using a GeneChip® Human Transcriptome Array 2.0 (Affymetrix) and 869 genes were found to be significantly differentially expressed between CNP and control samples. The adjacent table shows the top twenty candidate genes identified and were selected on the basis of relevance to CNP and associated co-morbid diseases, gene function and statistical significance. This encompasses genes relating to inflammation, neuronal injury, cell proliferation and development, apoptosis, pain sensitivity, stress and immune response.

GENE	Ratio*	*p* value	Reference
DFFA	0.84	0.0003	NM_213566
TRUB2	0.81	0.0005	NM_015679
ZCRB1	0.82	0.0005	NM_033114
SYT12	1.24	0.0020	NM_177963
KRT2	1.18	0.0022	NM_000423
MDM1	1.16	0.0025	NM_017440
ALCAM	0.81	0.0026	NM_001627
KIF2C	1.19	0.0030	NM_006845
SIGLEC8	0.80	0.0033	NM_014442
CBLN2	1.19	0.0034	NM_182511
RGSL1	1.21	0.0035	NM_001137669
TXNDC6	1.18	0.0037	NM_178130
DPEP1	1.17	0.0042	NM_004413
STK32A	1.20	0.0043	NM_001112724
STEAP1B	0.80	0.0046	NM_207342
JAZF1	0.66	0.0099	NM_175061
TIMP1	1.42	0.0109	NM_003254
ELF3	1.44	0.0143	NM_001114309
CD40	1.20	0.0171	NM_001250
NTRK3	1.25	0.0171	NM_001007156

*Mean expression ratios between CNP versus control samples (normalised by global mean).

FUTURE WORK

We are currently developing a multicentre study in the UK and Ireland to further investigate our findings in the context of developing biomarkers and identifying treatment targets for CNP. This work will hopefully provide clinicians with the tools to better diagnose and treat CNP.

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VALIDATION STUDY

To validate the array data we obtained RNA from a commercial MS set (SeraLab), where 50% of the MS patients presented with CNP (total n=30). We are in the process of validating our array data set via qRT-PCR analysis, but figure 1 shows a comparison of JAZF1 gene expression from (A) the array data and (B) the qRT-PCR analysis in all sample sets. In both graphs it is apparent that JAZF1 has decreased expression in both CNP groups, those with or without MS. JAZF1, known as juxtaposed with another zinc finger protein 1, is a transcriptional repressor that has been shown to reduce pro-inflammatory cytokines release via inhibition of stress kinases. It is conceivable that reduced levels of JAZF1 could be an important factor in the development of CNP, as well as potentially having an influence on individual variation in the sensitivity to pain. Variation in pain sensitivity is also apparent in peripheral diabetic neuropathy (PDN), where like MS, ~50% of PDN patients suffer with CNP.

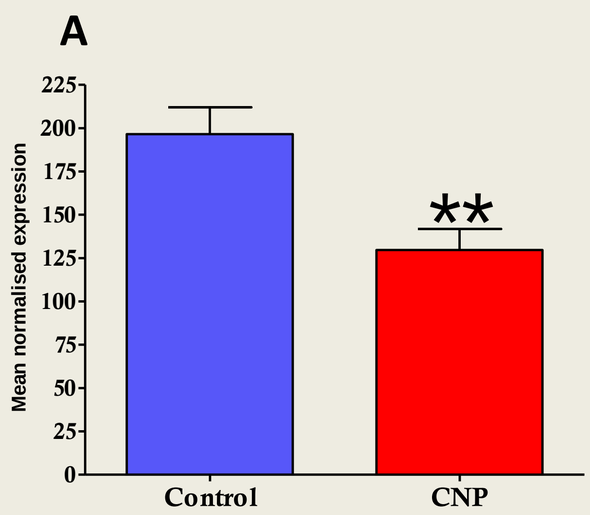

Figure 1. (A) Mean normalised (global mean) expression values for JAZF1 from the CNP array study with control versus CNP; ** $p = 0.0091$. **(B)** Mean normalised (reference gene) expression from the MS with or without CNP validation study; ** $p = 0.0043$. For the validation study a geNorm analysis determined the best three reference genes for normalisation as CYC1, SDHA & TOP1 with a mean reference stability of 0.522 and CV of 0.223.