

# FOCUS ON RESEARCH

## NOVEL SCREENING MARKERS FOR NEURAL TUBE DEFECTS?

### Researchers

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### Aim

The aim of this pilot study was to determine if altered activity of protein kinase A (PKA) and/or protein kinase C (PKC) were associated with the occurrence of neural tube defects.

### Project Outline/Methodology

Neural tube defects (including anencephaly, encephalocele and spina bifida) and congenital hydrocephalus are common, devastating and costly disorders of the central nervous system (CNS). We have preliminary data showing that mice with inappropriate levels of a cell membrane protein (a G-protein coupled receptor called "PAC1") may develop these CNS abnormalities. Actions of the PAC1 protein are mediated by molecules including PKA and PKC. It is unknown whether altered PKA and/or PKC activity is associated with human CNS disorders.

This project is to carry out a pilot study to determine the PKA/PKC activity in blood samples of healthy controls and of parents of neural tube defect patients. Human blood of volunteers was sampled at the Aberdeen Maternity Hospital. Proteins were extracted from the total blood cells. The PKA and PKC activity were analysed by immunoblotting and by radioactivity coupling assays.

### Key Results

We have optimised the methodologies with proteins extracted from mouse brain. The key results of this project include:

- (1) PKA and PKC activity are significantly increased in hydrocephaly mouse brains with higher levels of the PAC1 protein,
- (2) an altered PKA activity is associated with anatomic structures that are important for the flow of brain fluid in mice, and
- (3) a molecule that is modified by the PKC is likely altered in one of limited number of patients tested.

### Conclusions

We have found increased PKA and PKC activity in hydrocephaly mouse brain with too much of the PAC1

protein. Our pilot study on human blood samples suggests that a protein that is modified by the PKC is likely mutated in an affected parent.

### What does this study add to the field?

We are the first to show that a G-protein coupled receptor can be associated with hydrocephalus in mice. There has been no report on association of PKA or PKC on human neural tube defects or hydrocephalus. Therefore, our preliminary observation is entirely novel.

### Implications for Practice or Policy

Detailed characterisation of human patient blood samples at the DNA, RNA and protein levels shall facilitate our understanding of genetics of human CNS disorders, and lead to the development of novel screening tests and/or preventive treatments.

### Where to next?

We shall study the genetics of human CNS disorders to determine whether and how mutations and/or polymorphisms of these genes are associated with human CNS defects. We shall compare the total RNA/protein profiles in patients and healthy controls, which may lead to identification of novel screening markers.

### Further details from:

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### Reference:

Lang B, Song B, Davidson W, MacKenzie A, Smith N, McCaig CD, Harmar AJ, Shen S. 2006. Expression of the human PAC1 receptor leads to dose-dependent hydrocephalus-related abnormalities in mice. *J Clin Invest.* 116:1924-34.

