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# Gene alterations associated with closure of the cerebral aqueduct in hydrocephalic H-Tx rats

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## Background

To elucidate the pathogenesis of congenital hydrocephalus we utilized gene array technology as well as quantitative real-time PCR, to identify specific genetic components which act to influence the closure of the cerebral aqueduct in the H-Tx rat.

## Materials and methods

Midbrain regions which contain the cerebral aqueduct were micro-dissected from hydrocephalic and control animals at 5 days of age (n = 5). After RNA extraction and purification, total RNA was subjected to PCR techniques to generate cDNA that was subsequently labeled and hybridized (one brain per array) to the Rat 230 A oligonucleotide array from Affymetrix. Hybridization intensity for each array was measured using a confocal scanner, and results were normalized and reported as fold change differences. Raw expression data were subjected to a Student's t-test as well as the Bayesian t-test, which is a method that helps control for variations resulting from small sample size. Only those transcripts passing both the fold change of 1.5 fold and t-test cut-offs ($p < 0.05$) were examined further.

## Results

Forty-seven transcripts passed significance using our filtering criteria. Of these, 17 transcripts were up-regulated and 30 were down-regulated. These were grouped to a variety of different functional categories including transcription and translation, but also to other categories not typically associated with genetics such as vitamin transport, bone and tooth development. Some of the significantly altered genes correlated with literature found on earlier studies of hydrocephalus and were selected for further examination using quantitative real-time PCR. These were Cholecystokinin (Cck), a lectin (Lgals3), Tissue Factor Pathway Inhibitor 2 (Tfpi-2), Tumor Necrosis Super Family Member 4 (Tnfsf4), Pax-6 and Xanthine Dehydrogenase (Xdh). qrt-PCR results revealed significant changes in two genes Lgals 3 and Xdh while others failed to achieve statistical significance most likely due to sensitivity limits of the test.

## Conclusion

These results suggest that gene alterations occurring in the midbrain region may act to cause aqueductal stenosis in this rat model. It is notable that out of nearly 7,000 predicted genes of the rat, only 47 transcripts were significantly altered in this gene array study. Of these, 8 already had known associations to hydrocephalus. Narrowing the entire genome down to 47 significant transcripts that may act to cause aqueductal stenosis greatly narrows the focus for future studies, and identification of these genes provides a first step in attempting to reduce the occurrence of this disorder in humans.