Genetics and Hydrocephalus

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1. Underscore multi-genetic aspects of hydrocephalus

2. Illustrate how genetic changes *cause* hydrocephalus
   ♦ Hydrocephalus *ex vacuo* – effects of cell birth and development
   ♦ Closure/narrowing of the cerebral aqueduct
Gene Defects in H-Tx rats with Aqueductal Stenosis

1. Chromosome 11
2. Chromosome 17
3. Chromosome 9
4. Chromosome 19

“Although none of the four loci was essential for the hydrocephalic phenotype, the additive effects of two, three, or four loci increased the penetrance in a linear fashion. It is concluded that hydrocephalus in the H-Tx rat is associated with two, possibly four genetic loci…”

Consequences of Genetic Defects in the Ventricular Walls

Normal

Lining Absent

Immature Neurons Exposed

Gaps

wild type

Hyh (α-SNAP)

Hydrocephalus

Progression

E12.5

E13.5

E14.5

E15.5

Hydrocephalus
Ependymal Denudation Occurs at the Beginning of Neurogenesis

Fewer Neurons ➔ Hydrocephalus *Ex Vacuo*

Functional changes not caused by enlarged ventricles
Ependymal Denudation Observed in Human Fetuses


- Guerra M, Sival D, Jimenez A, Dominguez Pinos MD, den Dunnen W, Bátiz LF, Pérez-Figares JM, Rodríguez E. Defects in cell-cell junctions lead to neuroepithelial-ependymal denudation in the telencephalon of human hydrocephalic foetuses. From 54th Annual Meeting of the Society for Research into Hydrocephalus and Spina Bifida Vancouver, Canada. 7-10 July 2010
Ependymal Denudation May Also Play a Role in Aqueductal Stenosis

Normal H-Tx E21

Hydrocephalic H-Tx E21
Aqueductal Ependymal Denudation Observed in Human Fetuses


♦ Guerra et al. Defects in cell-cell junctions lead to neuroepithelial-ependymal denudation in the telencephalon of human hydrocephalic foetuses. 2010
The early detection of hydrocephalus and of SA stenosis stimulated a close follow up that lead to discover the SA obliteration at PN5.

A ventriculostomy was performed at PN8.
Summary

1. Multiple genes can be involved in hydrocephalus

2. Genetic effects on ventricular walls can cause
   - brain tissue atrophy that allows the ventricles to expand “in a vacuum”
   - Closure/narrowing of the cerebral aqueduct