Can zebrafish be autistic?

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What is autism?

- Range of disorders characterized by:
  - Abnormal/decreased social interaction
  - Repetitive Behavior (stereotypies, compulsive behavior, resistance to change, self-injury)
  - Can also involve:
    - Sensory hyper/hyposensitivity
    - Intellectual Disability
    - Seizures
    - Schizophrenia
    - Gastrointestinal symptoms

Incorrect stereotype:

Autism Epidemic?

Autism Prevalence On The Rise*
There has been a 600% increase in prevalence over the last two decades.

*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.
• Now: 3.4 in 1000 children between 3 and 10 years (NIMH)
• 15-fold increase in autism incidence since 1990
  – Broadening of diagnostic criteria
  – New diagnostic tools
  – Awareness
  – Special educational services
  – Reduced stigma
Genetics and Autism

• Autism is the most genetic of neuropsychiatric disorders:
  • ~77% concordance in monozygotic male twins
  • ~30% concordance in dizygotic male twins

• Environmental factors explain about 55% of liability for autism

• Autism is prevalent in boys (4:1) suggesting mutations in X-linked genes as possible causes

Hallmayer et al. 2011 Arch. Gen. Psychiatry
Autism and Synapses

• Many of the genes with mutations found in families with autism have synaptic functions:
  – Neurexins
  – Neuroligins
  – SynCAMs
  – SHANKs
  – GRIK2
What is a synapse?

- Site of communication between neurons
- Signaling occurs in one direction
- A chemical transmits the signal, e.g. glutamate, dopamine
- Some synapses are “excitatory”, whereas others are “inhibitory”
- “Computation” occurs by adding signals from all of the synapses on a single neuron
Why study autism in zebrafish?

- Easier access to study molecular/cellular events during development
- Highly homologous genes to mammals
- Small animals with large numbers of offspring
Why study autism in zebrafish?

• Behaviors relevant to autism?
  – Shoaling (social swimming)
  – Startle response (sensory reflexes)
Neuroligin genes in autism


Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism

Published online 31 March 2003; doi:10.1038/ng1136

Many studies have supported a genetic etiology for autism. Here we report mutations in two X-linked genes encoding neuroligins NLGN3 and NLGN4 in siblings with autism-spectrum disorders. These mutations affect cell-adhesion molecules localized at the synapse and suggest that a defect of synaptogenesis may predispose to autism.
Neuroligins in zebrafish

- 5 genes in humans
  - (1,2,3,4X, 4Y)
- 7 genes in zebrafish
- Only 1 \textit{nlgn1} gene
- Broad neural expression in larva and adult for \textit{nlgn1}

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Davey, Tallafuss and Washbourne, 2010
Davey et al. 2009

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![Image of zebrafish with labels for B, B', m, h, e, d, t, and Vv]

![Diagram of gene locations on Hsa3 and Dre11 chromosomes]
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