SOCIAL DEFICIT IN A MOUSE MODEL OF AUTISM IS TRANSGENERATIONAL

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The prevalence of autism spectrum disorders (ASD) has been dramatically increased over the last two decades.

ASD is highly heritable with the involvement of multiple genes in its pathogenesis.

Environment insults may be involved in the pathogenesis of ASD.
Epigenetics:

Mechanisms causing heritable changes in gene expression or cellular phenotype without changing DNA sequence

- DNA methylation
- Histone modification
- Micro RNA
Hypothesis

Exposure to environmental insults during prenatal or early postnatal development produces epigenetic changes in multiple genes, which can be transferred to next generation.
Vaproic acid (VPA) model

An anticonvulsant and mood stabilizer used to treat psychosis and epilepsy.

A high prevalence of ASD in children from mothers who were treated with VPA during a specific period of mid-gestation (20-24 weeks).

Animals exposed to VPA during mid-gestation showed ASD-like behaviors, abnormal brain structures and altered epigenetic regulation and gene expression.
Prenatal treatment of VPA (E10, 12 d)

F1 Offspring

F2 Offspring

F3 Offspring

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Conclusions

- Prenatal exposure to VPA reduced social activity of F1 and F2 generations of mice.

- The social activity of F3 generation of VPA-treated mice is also reduced, suggesting the VPA-induced alterations in epigenetics are transgenerational.
Current and Future studies

- Identify the genes with epigenetic changes in VPA-treated F1, F2 and F3 generations.
- Test whether similar changes in the behaviors and epigenetics can be observed in other autism models.
- Develop therapeutic approaches to prevent or treat autism.
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Vaproic acid (VPA)

An anticonvulsant and mood stabilizer used to treat psychosis and epilepsy.

An inhibitor of histone deacetylase, an enzyme that alters histone modification.

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