Ibuprofen slows migration of enteric nervous system precursor cells increasing the risk of Hirschsprung-like disease in animal models

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Still nothing to disclose. . .
except that this is work of

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Nandor Nagy
Allan Goldstein
Olga Tusheva
Brittany Graham
Rajarshi Sengupta

Ellen Merrick Schill

Robert Heuckeroth
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Hypothesis

Hirschsprung disease might be preventable in some cases
Hirschsprung disease (HSCR)
(No neurons in distal bowel)
1:5000 live births
Chronic severe constipation
Growth failure
Bilious emesis
Abdominal distension
Enterocolitis (35%)
Death (3-6%)


ENS Morphogenesis

Human bowel neurons and nerve fibers
Fixed tissue: 300 micron section; PGP9.5 staining;
16 stitched confocal images

Rajarshi Sengupta
Dilated bowel containing enteric neurons

Missing nerve cells only here!

Just a bit more ENS precursor migration

Healthy

Hirschsprung disease: Complex genetics and partial penetrance

Population prevalence

Male Sex RET +9.7 T allele Down Syndrome

ENSCoding ZFHX1B SOX10 PHOX2B

Environmental risk factors

HD Risk

Low

High

Threshold

Hirschsprung-like disease is exacerbated by reduced de novo GMP synthesis

Jonas G. Lake, Opa A. Tishans, Brittany L. Graham, and Robert O. Heuckeroth

Thanks: Steve Johnson and Matt Goldsmith
~25% of women use ibuprofen during early pregnancy

Ibuprofen reduces bowel colonization by ENS precursors in live fish

In vitro culture

Ibuprofen prevents bowel colonization by ENS precursors in chick

Nandor Nagy
Allan Goldstein
Ibuprofen reduces bowel colonization by ENS precursors in Ret+/- mice

Ellen Merrick Schill

Ibuprofen slows ENS precursor migration

Ibuprofen reduces lamellipodia in migrating ENS precursors

Active RAC1, F-actin also reduced
Some cases of Hirschsprung disease may be preventable

Population risk 1:5000
RET heterozygosity 1:2
Down syndrome 1:50-100
Male sex increases risk 4-fold
1:3125 male 1:12,500 female

Ibuprofen during early pregnancy??

Heuckeroth Lab
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Rajeshi Sengupta
Amanda Lemke
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Saya Bery
Christina Wright
Sabine Schneider

National Institute of Diabetes and Digestive and Kidney Diseases
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Children's Discovery Institute of Washington-University and St. Louis Children's Hospital
Irma and Norman Braman Endowment for Research in GI Motility Disorders
Suzi and Scott Lustgarten Endowment
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Human Development

Pregnancy recognition
Prenatal care initiation

Day: 1 8 22 26 29 37 42 47 53
Week: 0 1 2 3 4 5 6 7 8

Ayoola et al. (2010) Birth 37(1), 37-43
HealthyPeople.gov (2020 objectives)
Table 1. Genetic risk for Hirschsprung disease (Sorted by risk factor prevalence in children with HD)

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<thead>
<tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>Y-chromosome</td>
<td></td>
<td>2 to 4-fold</td>
<td>80% (80%)</td>
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<tr>
<td>Non-syndromic</td>
<td>RET</td>
<td>intronic enhancer +9.7 T (SNP rs2435357)</td>
<td>5.3-fold TT 2.4-fold TC</td>
<td>60% of affected Caucasians have the T allele</td>
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<tr>
<td>Non-syndromic</td>
<td>RET</td>
<td>coding mutation</td>
<td>&gt;2500-fold</td>
<td>50% of familial 20% of sporadic</td>
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<tr>
<td>Down syndrome</td>
<td>Trisomy 21</td>
<td></td>
<td>1/800</td>
<td>50-fold 8%</td>
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<tr>
<td>Mowat-Wilson</td>
<td>ZFHX1B</td>
<td>Syndromic</td>
<td>3000-fold 6%</td>
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<tr>
<td>Shah-Waardenburg (WS4)*</td>
<td>EDNRB</td>
<td>Syndromic</td>
<td>5-fold 5%</td>
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<tr>
<td>Other chromosomal</td>
<td>Deletions, duplications,</td>
<td>Varies</td>
<td>4%</td>
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<tr>
<td>anomaly (non-Down)</td>
<td>and translocations</td>
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<tr>
<td>Shah-Waardenburg (WS4)*</td>
<td>SOX10</td>
<td>Syndromic</td>
<td>&gt;4000-fold 4%</td>
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<tr>
<td>Smith-Lemli-Opitz</td>
<td>DHCR7</td>
<td>Syndromic</td>
<td>50-fold 1%</td>
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<tr>
<td>HCSAS**</td>
<td>L1CAM</td>
<td>Syndromic</td>
<td>40-fold 0.8%</td>
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<tr>
<td>Bardet Biedl</td>
<td>BBS 1-11 (eleven different genes)</td>
<td>Syndromic</td>
<td>30-fold 0.6%</td>
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<tr>
<td>Congenital Central</td>
<td>PHOX2B</td>
<td>Syndromic</td>
<td>1000-fold 0.5%</td>
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<td>Hypoventilation</td>
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<tr>
<td>Cartilage Hair</td>
<td>RMRP</td>
<td>Syndromic</td>
<td>25-fold 0.5%</td>
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<td>Hypoplasia</td>
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<tr>
<td>Goldberg-Shprintzen</td>
<td>KIAA1279</td>
<td>Syndromic</td>
<td>Unknown</td>
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<tr>
<td>Rarely identified</td>
<td>EDN3, ECE1, GDNF, NRTN,</td>
<td>10 cases total</td>
<td>Unknown Unknown</td>
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<tr>
<td>mutations</td>
<td>GFRA1</td>
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<td>Unknown gene 3p21</td>
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<td>4-fold</td>
<td>Common variant</td>
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<tr>
<td>Unknown gene 19q12</td>
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<td>5-fold</td>
<td>Common variant</td>
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<td>Other loci 9q31, 16q23, 4q31-32</td>
<td>Unknown Unknown</td>
<td>Unknown Unknown</td>
<td>Unknown Unknown</td>
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</tbody>
</table>

These data are based on the following manuscripts: (10, 27-32)

All HSCR mutations are partially penetrant

Enteric Nervous System Development

Cell Biology of ENS Development

Ras
pERK
Neuritogenesis

pAKT
Survival

RAC1-GTP
Lamellipodia
Actin Polymerization
Migration

RET
GDNF
GFRα1
Submucosal Neurons

Myenteric Neurons