Genetic Role of **UBASH3A** in Autoimmune Disease in Down Syndrome

Richard A. Spritz, M.D.
Professor and Director,
Human Medical Genetics and Genomics Program
University of Colorado Denver School of Medicine
Aurora, CO 80045
• People with Down Syndrome have very high risk of autoimmune diseases such as autoimmune thyroid disease, celiac disease, and others.

• A gene on chromosome 21, *UBASH3A*, contributes to risk of autoimmune diseases in the general population.

• Our work shows that *UBASH3A* causes the much higher risk of autoimmune disease in Down Syndrome.

• Long-term benefits may include early presymptomatic testing and potentially preventive treatment of individuals at highest risk.
Autoimmune Diseases

• ~50-80 different disorders in which one’s own immune/inflammatory cells recognize and attack “self” cells and tissues

• Examples: Type 1 diabetes, autoimmune thyroid disease, vitiligo, celiac disease, rheumatoid arthritis

• “Complex traits”: caused by multiple genes + environmental triggers

• AI diseases rank among top 10 causes of death in ♀

• Prevalence of autoimmune diseases greatly elevated among people with Down Syndrome
Patients with one Autoimmune Disease are at Higher Risk of Others

1855: Addison’s Disease, Vitiligo, Pernicious Anemia

- Autoimmune thyroid disease (Hashimoto’s disease, Graves’ disease)
- Vitiligo
- Type 1 diabetes
- Rheumatoid arthritis
- Pernicious anemia
- Systemic lupus erythematosus
- Addison’s disease

This is also true in people with Down Syndrome
Different Autoimmune Diseases Share Underlying Causal Genes

Vitiligo
- Specific Genes, Triggers

Type 1 Diabetes
- Specific Genes, Triggers

Autoimmune
- Thyroid Disease
- Specific Genes, Triggers

Lupus
- Shared Genes
- Chr21

Addison’s Disease
- Specific Genes, Triggers

Rheumatoid Arthritis
- Specific Genes, Triggers

Pernicious Anemia
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.

2. A chromosome 21 gene, UBASH3A, contributes to autoimmune diseases in the general population.

3. Does UBASH3A cause the even higher frequency of autoimmune diseases in people with Down Syndrome?

4. Is there anything “special” about UBASH3A in Down Syndrome?

5. Is the problem 3 copies of UBASH3A (increased function), 3 chances to carry common UBASH3A high-risk variations, or a combination of the two?

6. So, is the basic mechanism increased UBASH3A function?
# High Frequency of Autoimmune Diseases in People with Down Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>General Pop.</th>
<th>Down Syndr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Thyroid Disease</td>
<td>~3-5%</td>
<td>~35%</td>
</tr>
<tr>
<td>(Hashimoto Thyroiditis, Graves’ Disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>1-2% &gt; 0.1%</td>
<td>~5% &gt; 1.4%</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>0.4%</td>
<td>3%</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>0.3%</td>
<td>~1%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>~1%</td>
<td></td>
</tr>
<tr>
<td>(Juvenile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>0.014%</td>
<td>0.87%</td>
</tr>
</tbody>
</table>
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.

2. A chromosome 21 gene, **UBASH3A**, contributes to autoimmune diseases in the general population.

3. Does **UBASH3A** cause the even higher frequency of autoimmune diseases in people with Down Syndrome?

4. Is there anything “special” about **UBASH3A** in Down Syndrome?

5. Is the problem 3 copies of **UBASH3A** (increased function), 3 chances to carry common **UBASH3A** high-risk variations, or a combination of the two?

6. So, is the basic mechanism **increased** **UBASH3A** function?
Genomewide association study (GWAS)  
4680 EUR cases vs. 39,586 EUR controls

Initial SNP rs2839511  
With fine-mapping rs12482904  
$P = 5.84 \times 10^{-29}$, OR 1.35, MAF 0.24
At least in Caucasians, there is a common genetic variation of \textit{UBASH3A} that predisposes to many different autoimmune diseases.
UBASH3A regulates the function of T-Cells

T-cells are the immune cells that attack “self” tissues
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.

2. A chromosome 21 gene, UBASH3A, contributes to autoimmune diseases in the general population.

3. Does UBASH3A cause the even higher frequency of autoimmune diseases in people with Down Syndrome?

4. Is there anything “special” about UBASH3A in Down Syndrome?

5. Is the problem 3 copies of UBASH3A (increased function), 3 chances to carry common UBASH3A high-risk variations, or a combination of the two?

6. So, is the basic mechanism increased UBASH3A function?
Compared *UBASH3A* “SNP” rs2839511 in DS people with AI disease versus “controls without AI disease

Genotyped rs2839511 A/G in:

<table>
<thead>
<tr>
<th>MAF</th>
<th>140 EUR DS cases</th>
<th>2260 EUR controls with no AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>91 with AI</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>(64 with AITD)</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>(27 with AI, without AITD)</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>49 with no AI</td>
<td>.20</td>
<td></td>
</tr>
</tbody>
</table>

1. Yes; *UBASH3A* AI disease high-risk SNP is associated with AI disease in DS cases with AI disease versus controls w/o AI disease

2. Yes, *UBASH3A* AI disease high-risk SNP is associated with AI disease in DS cases with AI disease versus DS cases w/o AI disease

So yes, *UBASH3A* apparently is the cause of AI disease in DS
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.
2. A chromosome 21 gene, UBASH3A, contributes to autoimmune diseases in the general population.
3. Does UBASH3A cause the even higher frequency of autoimmune diseases in people with Down Syndrome?
4. Is there anything “special” about UBASH3A in Down Syndrome?
5. Is the problem 3 copies of UBASH3A (increased function), 3 chances to carry common UBASH3A high-risk variations, or a combination of the two?
6. So, is the basic mechanism increased UBASH3A function?
Compared frequency of rarer “functional” variation of **UBASH3A** in DS case with versus w/o AI disease

<table>
<thead>
<tr>
<th>SNP</th>
<th>DS-Al (n=91) versus DS-no Al (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2277798 (S18G)</td>
<td>$P = 0.15$ ($P = 4.70 \times 10^{-5}$ in GWAS)</td>
</tr>
<tr>
<td>rs2277800 (L28F)</td>
<td>$P = 0.41$</td>
</tr>
<tr>
<td>rs141421753 (V111M)</td>
<td>$P = 1.00$</td>
</tr>
<tr>
<td>rs13048049 (R324Q)</td>
<td>$P = 1.00$</td>
</tr>
<tr>
<td>rs17114930 (D466E)</td>
<td>$P = 0.50$</td>
</tr>
<tr>
<td>rs148149121 (I658V)</td>
<td>$P = 0.26$</td>
</tr>
</tbody>
</table>

Without going into details, none of these seem to matter at all. So, there is nothing “special” about the “flavor” of **UBASH3A** in DS with AI disease.
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.
3. Does *UBASH3A* cause the even higher frequency of autoimmune diseases in people with Down Syndrome?
4. Is there anything “special” about *UBASH3A* in Down Syndrome?
5. Is the problem 3 copies of *UBASH3A* (increased function), 3 chances to carry common *UBASH3A* high-risk variations, or a combination of the two?
6. So, is the basic mechanism increased *UBASH3A* function?
Studied AI Disease in DS related to # Copies of High-Risk *UBASH3A* rs2839511-A Allele

<table>
<thead>
<tr>
<th></th>
<th>AAA</th>
<th>GAA (n=91)</th>
<th>GGA (n=91)</th>
<th>GGG (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS +AI</td>
<td>0</td>
<td>23 (.25)</td>
<td>29 (.32)</td>
<td>39 (.43)</td>
</tr>
<tr>
<td>DS -AI</td>
<td>0</td>
<td>6 (.12)</td>
<td>17 (.35)</td>
<td>26 (.53)</td>
</tr>
</tbody>
</table>

Controls

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>124</td>
<td>758</td>
<td>1378</td>
<td></td>
</tr>
</tbody>
</table>

\[ P = 0.09 \]

AI disease in DS relates to # copies of the high-risk rs2839511-A allele, not just 3 copies of chr21. Both??
So, what is going on in Down Syndrome?

1. Autoimmune diseases in people with Down Syndrome are not different than in the general population.
3. Does *UBASH3A* cause the even higher frequency of autoimmune diseases in people with Down Syndrome?
4. Is there anything “special” about *UBASH3A* in Down Syndrome?
5. Is the problem 3 copies of *UBASH3A* (increased function), 3 chances to carry common *UBASH3A* high-risk variations, or a combination of the two?
6. So, is the basic mechanism increased *UBASH3A* function?
High-Risk UBASH3A rs2839511-A Increases Gene Expression (Function) Immune cells of normal “control” individuals

\[ P = 0.000744 \]
This segment specifically controls expression of UBASH3A in immune cells

rs9979841 eliminates a binding site for “AIRE”

AIRE is a master controller of T cells; elimination of AIRE function causes: AUTOIMMUNE DISEASES
New Hypothesis

• rs2839511-A is just a “tag” for rs9979841-A
• rs9979841-A eliminates binding of AIRE to the *UBASH3A* “enhancer”
• That elevates expression of *UBASH3A* RNA in immune cells ~1.2X per variant copy
• People with DS (trisomy 21) have 3 copies of *UBASH3A* and have at least 1.5X normal UBASH3A function
• Therefore, all people with trisomy 21 have elevated function of *UBASH3A* (3 copies)
• If they carry rs2839511-A, level of UBASH3A function (and AI disease risk) can be even higher!
## New Hypothesis

<table>
<thead>
<tr>
<th>rs2839511 genotypes:</th>
<th>UBASH3A function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General population</strong></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>100%</td>
</tr>
<tr>
<td>GA</td>
<td>120%</td>
</tr>
<tr>
<td>AA</td>
<td>~140%</td>
</tr>
</tbody>
</table>

| **Down Syndrome** |                  |
| GGG                | 150%             |
| GGA                | 170%             |
| GAA                | 190%             |
| AAA                | 210%             |
Conclusions

• A specific gene, *UBASH3A*, on chromosome 21 is responsible for high risk of AI disease in Down Syndrome
• It does this by increasing UBASH3A function
• Genetic variation in UBASH3A can increase function beyond the 150% due to trisomy 21, increasing risk even further.
• Future steps are to determine how increased UBASH3A function increases AI risk, and whether risk could be reduced by targeted treatment.
• Long-term benefits may include pre-symptomatic testing and AI disease prevention.
Thanks to

Linda Crnic Institute for Down Syndrome for funding

Sheri Riccardi
Tracey Ferrara
Songtao Ben
Ellen Elias

Stephanie Santorico

Especially, thanks to DS patients and their parents
Conclusions

1. UBASH3A AI disease high-risk SNP rs2839511-A is associated with AI disease in DS versus non-DS controls with no AI disease.

2. There is nothing else special about the version of UBASH3A in DS patients with AI; similar to patients in general population with AI disease.

3. It is not just that AI disease risk in DS results from three copies of chr21 and thus elevated function of UBASH3A. It is clear that AI disease risk also relates at least in part to the 1.5X risk of carrying high-risk AI alleles.