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

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LINDA CRNIC INSTITUTE FOR DOWN SYNDROME™

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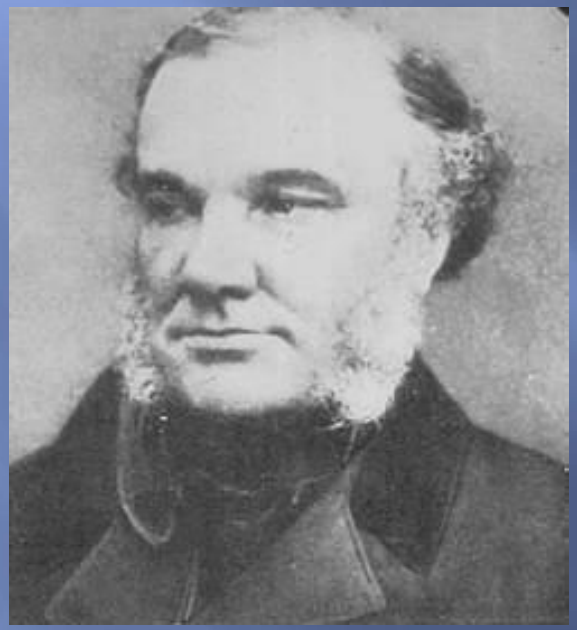
- People with Down Syndrome have very high risk of autoimmune diseases such as autoimmune thyroid disease, celiac disease, and others.
- A gene on chromosome 21, *UBASH3A*, contributes to risk of autoimmune diseases in the general population.
- Our work shows that *UBASH3A* causes the much higher risk of autoimmune disease in Down Syndrome.
- Long-term benefits may include early pre-symptomatic testing and potentially preventive treatment of individuals at highest risk.

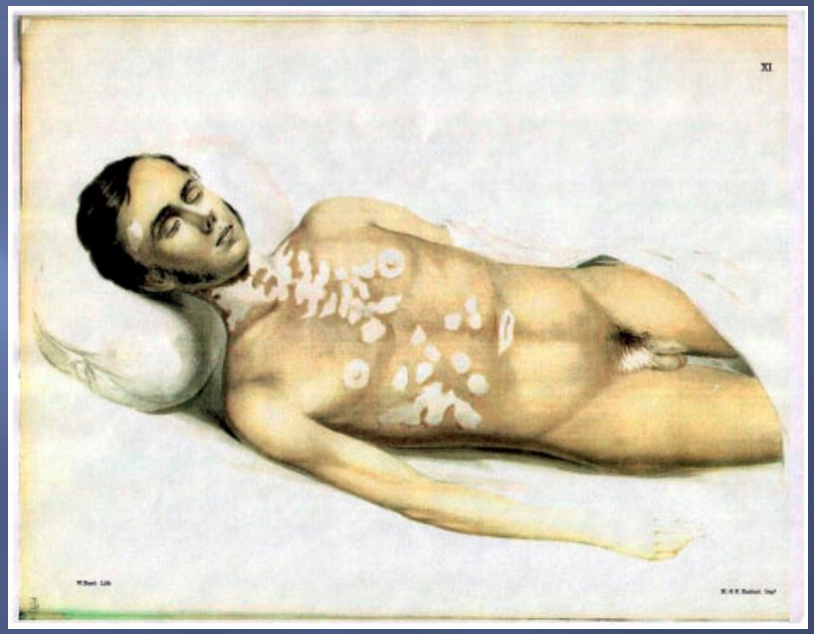
Autoimmune Diseases

- ~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

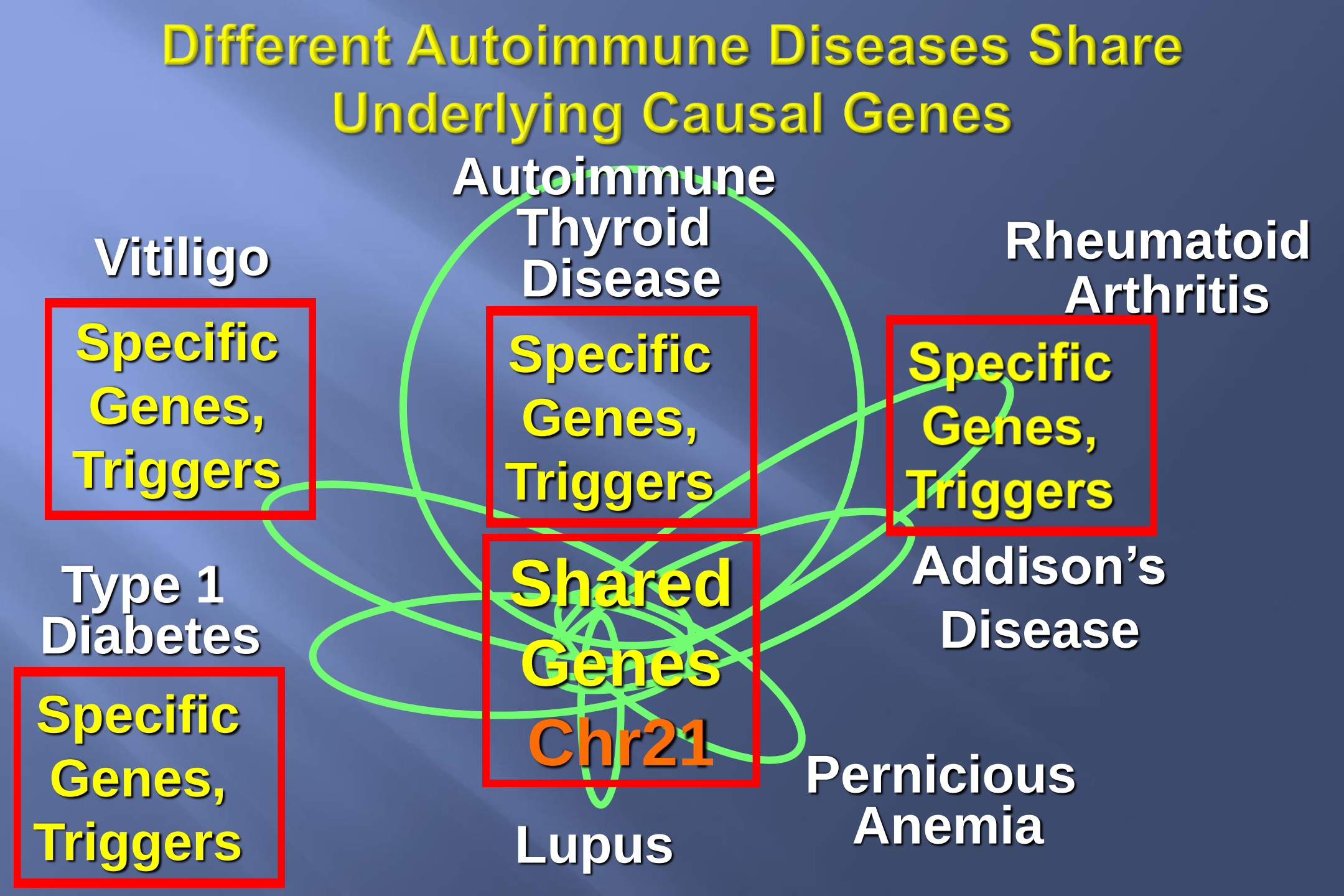




- Autoimmune thyroid disease (Hashimoto's disease, Graves' disease)
- Vitiligo
- Type 1 diabetes
- Rheumatoid arthritis
- Pernicious anemia
- Systemic lupus erythematosus
- Addison's disease

This is also true in people with Down Syndrome

Different Autoimmune Diseases Share Underlying Causal Genes



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

	General Pop.	Down Syndr.
Autoimmune Thyroid Disease (Hashimoto Thyroiditis, Graves' Disease)	~3-5%	~35%
Celiac Disease	1-2% > 0.1%	~5% > 1.4%
Vitiligo	0.4%	3%
Type 1 Diabetes	0.3%	~1%
Rheumatoid Arthritis	~1%	
(Juvenile)	0.14%	0.87%
Systemic Lupus Erythematosus	0.014%	?↑

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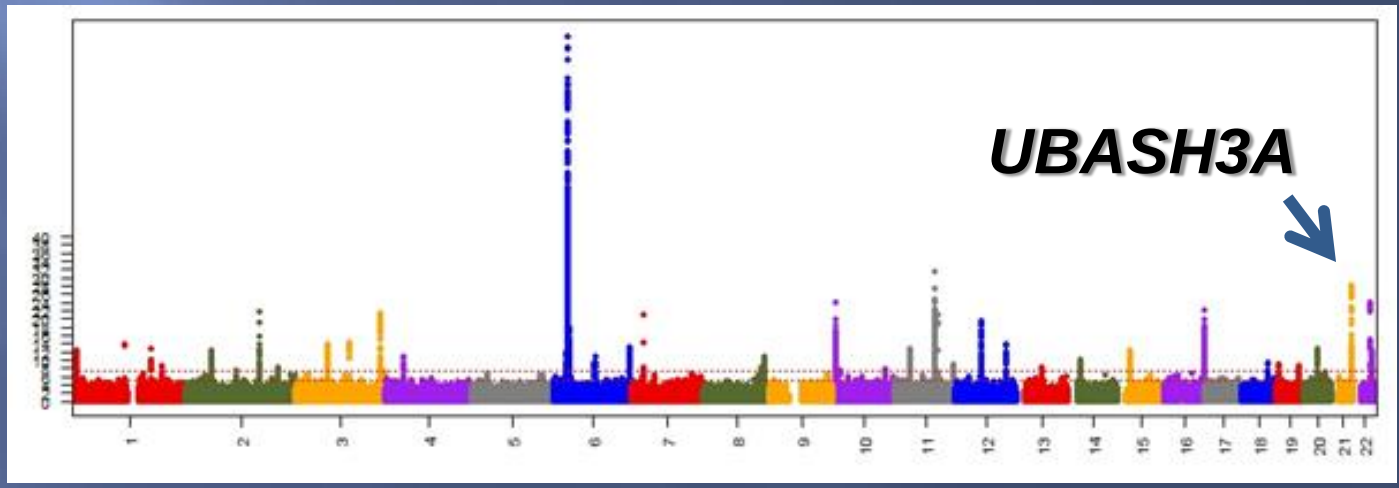
A Generic Autoimmunity Gene on Chr21

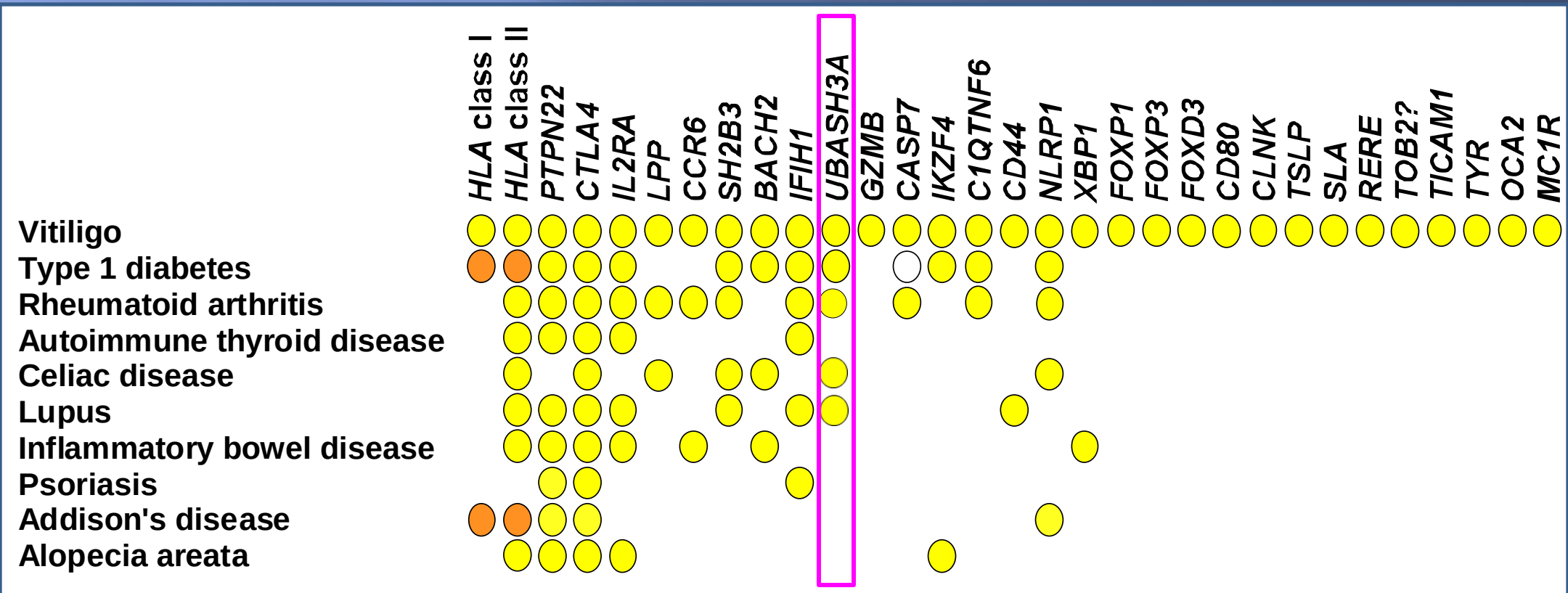
Vitiligo: Anti-Melanocyte Autoimmune Disease

Genomewide association study (GWAS)
4680 EUR cases vs. 39,586 EUR controls



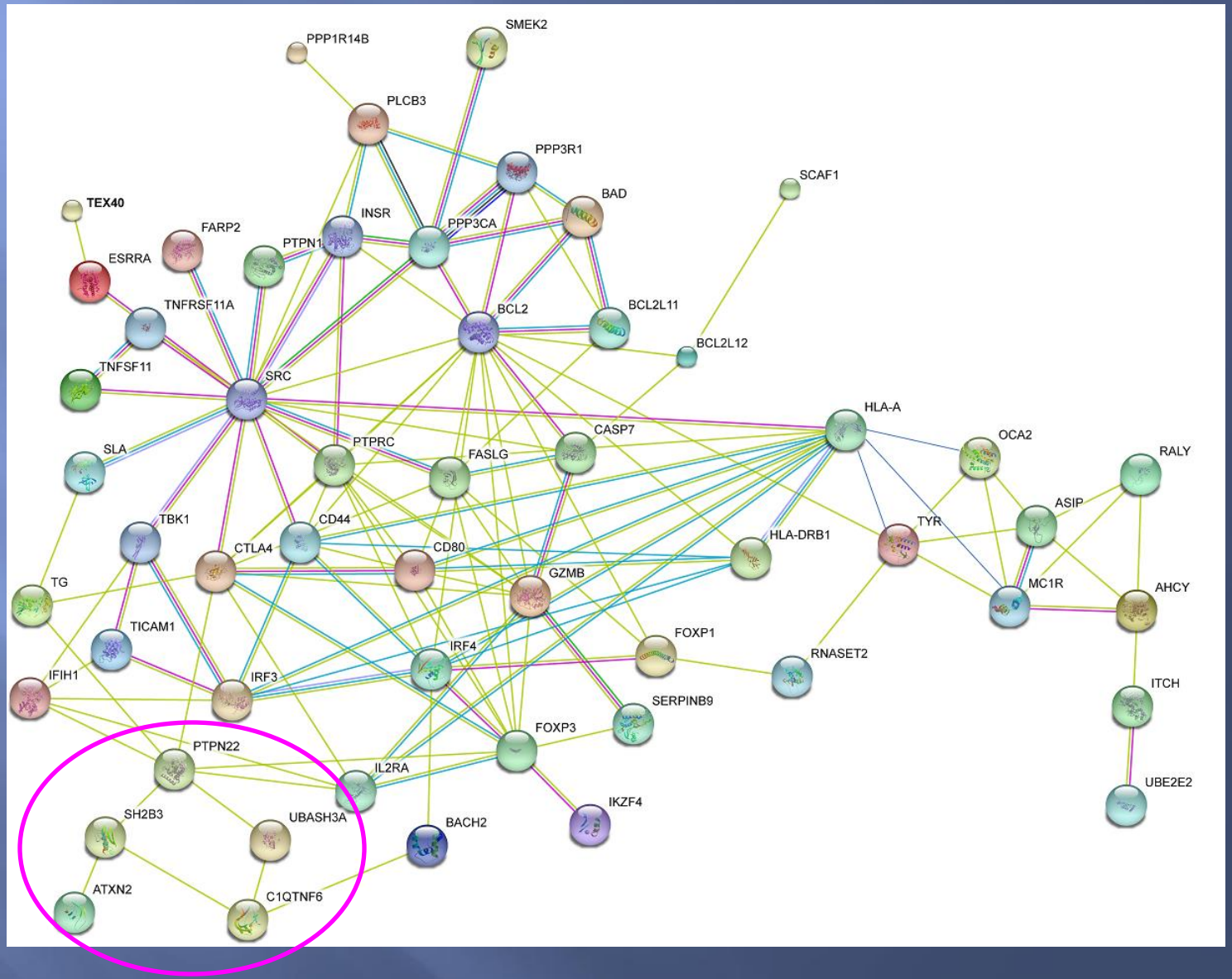
Initial SNP rs2839511
With fine-mapping rs12482904
$P = 5.84 \times 10^{-29}$, OR 1.35, MAF 0.24

UBASH3A is Genetically Associated with Many Autoimmune Diseases



At least in Caucasians, there is a common genetic variation of *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

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Compared *UBASH3A* "SNP" rs2839511 in DS people with AI disease versus "controls without AI disease

Genotyped rs2839511 A/G in:	MAF
140 EUR DS cases	
91 with AI	.28
(64 with AITD)	.27
(27 with AI, without AITD)	.27
49 with no AI	.20
2260 EUR controls with no AI	.22

P = .05

P = .025

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

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Compared frequency of rarer "functional" variation of *UBASH3A* in DS case with versus w/o AI disease

SNP	DS-AI (n=91) versus DS-no AI (n=49)
rs2277798 (S18G)	$P = 0.15$ ($P = 4.70 \times 10^{-5}$ in GWAS)
rs2277800 (L28F)	$P = 0.41$
rs141421753 (V111M)	$P = 1.00$
rs13048049 (R324Q)	$P = 1.00$
rs17114930 (D466E)	$P = 0.50$
rs148149121 (I658V)	$P = 0.26$

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

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Studied AI Disease in DS related to # Copies of High-Risk *UBASH3A* rs2839511-A Allele

	AAA	GAA	GGA	GGG
DS +AI (n=91)	0	23 (.25)	29 (.32)	39 (.43)
DS -AI (n=49)	0	6 (.12)	17 (.35)	26 (.53)

$P = 0.09$

Controls

AA	AG	GG
124	758	1378

AI disease in DS relates to # copies of the high-risk rs2839511-A allele, not just 3 copies of chr21. Both??

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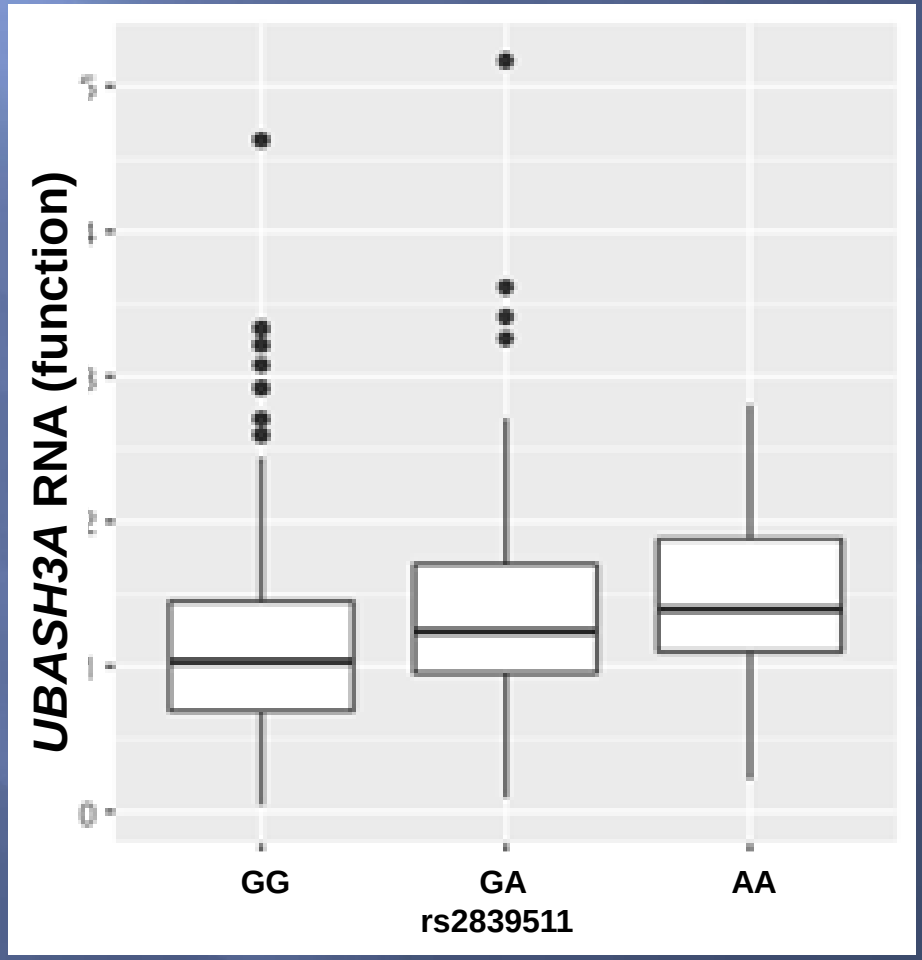
High-Risk *UBASH3A* rs2839511-A Increases Gene Expression (Function)

Immune cells of normal "control" individuals

1.25 -
1.20 -
1.00 -

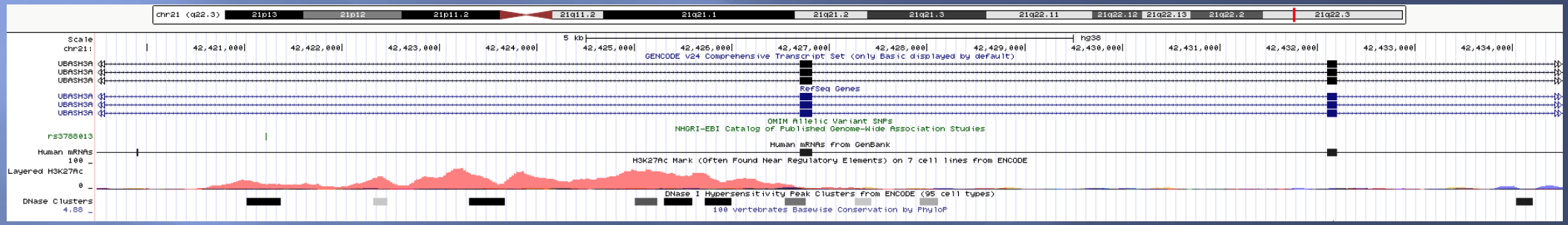


P = 0.000744

Why does rs2839511-A increase *UBASH3A* Expression?

Located near predicted “transcriptional enhancer”

rs9979841 rs2839511 rs12482904



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

rs2839511 genotypes:	UBASH3A function
General population	
GG	100%
GA	120%
AA	~140%
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.

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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.