Neurodevelopmental Disabilities in Kabuki Syndrome

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Overview

- Intro to Neurodevelopmental Disabilities
- Specific Neurodevelopmental Disabilities in KS
- Current Research
- Potential Clinical and Educational Strategies for Right Now

Overview of Neurodevelopmental Disabilities

- Intellectual disability
- ADHD
- Autism spectrum disorder
- Specific learning disabilities
- Cerebral palsy
- Language disorder
- Anxiety
- Epilepsy
- And More…..

Overlap and Multiple Disabilities are the Rule Not the Exception

Certain Patterns of Cognitive Strengths and Weaknesses Have Been Associated with Specific Genetic Syndromes

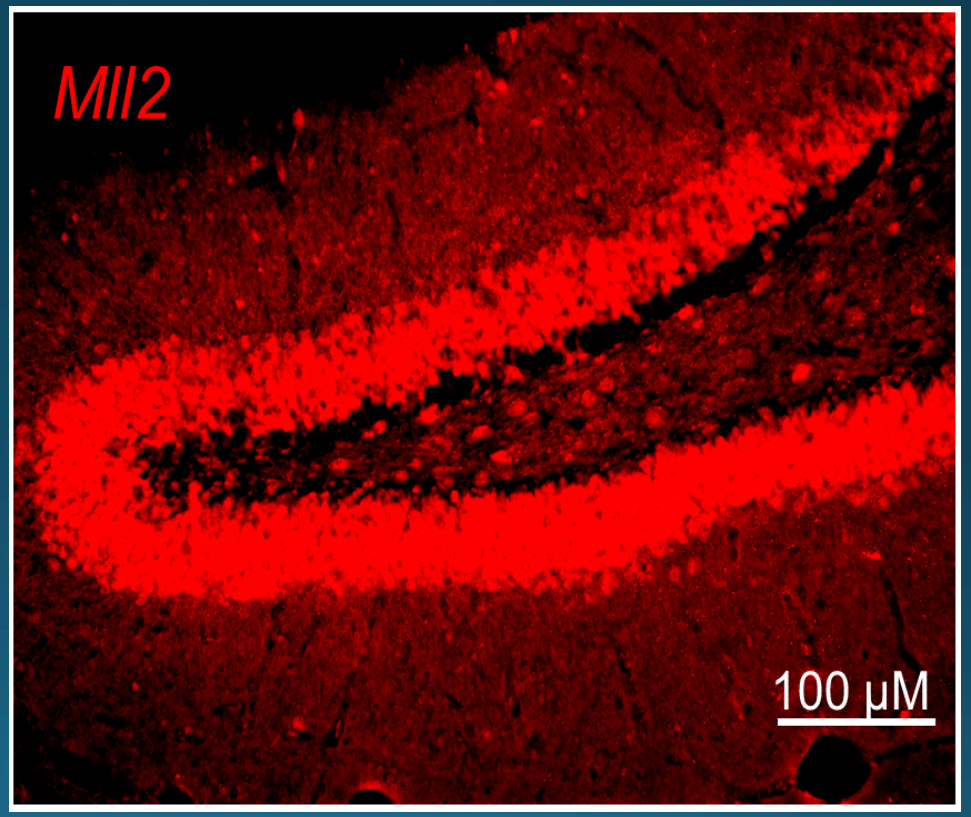
	Intellectual Disability	Language Disability	Visual-Spatial Problems	ADHD	Anxiety	Autistic Features	Seizures
Williams Syndrome	+	-	+	+/-	+	-	-
Angelman Syndrome	+	+	-	-	-	+/-	+
Rett Syndrome	+	+	-	-	+	+	+
Down Syndrome	+	+	-	-	-	+/-	-
16p11.2 deletion	+/-	+	-	+/-	+/-	+	+/-

Does Kabuki Syndrome have a Particular Cognitive Profile?

- Previously reported as mild-moderate ID with 10% normal IQ and some scattered into severe ID
- Weakness in visuospatial construction with strengths in verbal reasoning
- Possible trend toward improvement over time
- Most extensive data from Mervis et al 2005

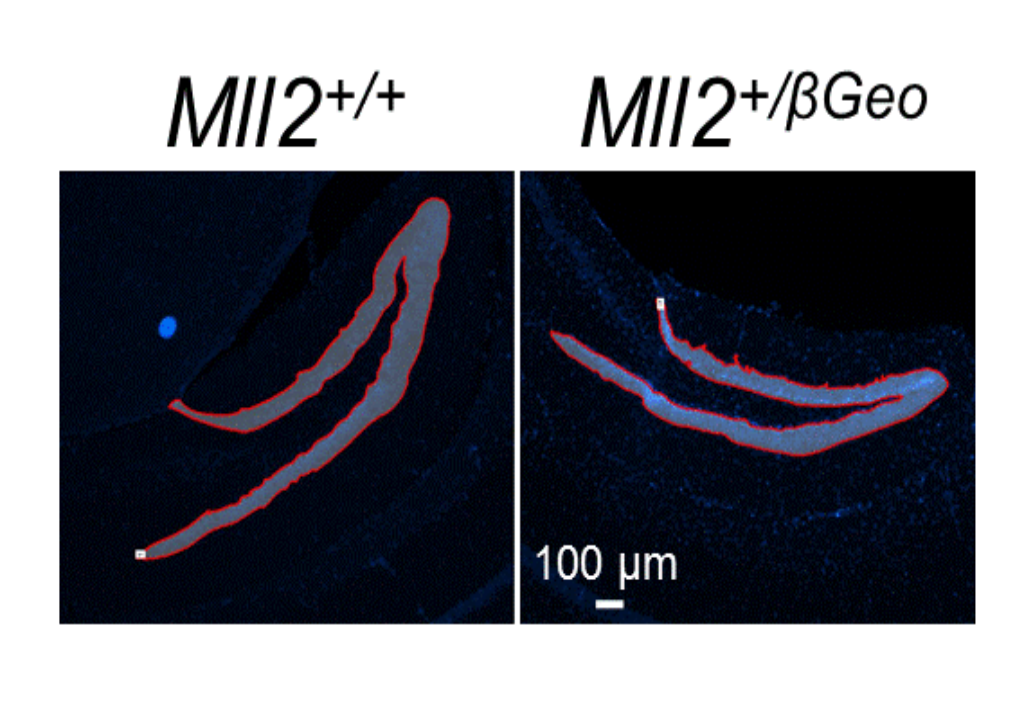
Mll2 is highly expressed in Granule Cell Layer (GCL) of the dentate gyrus

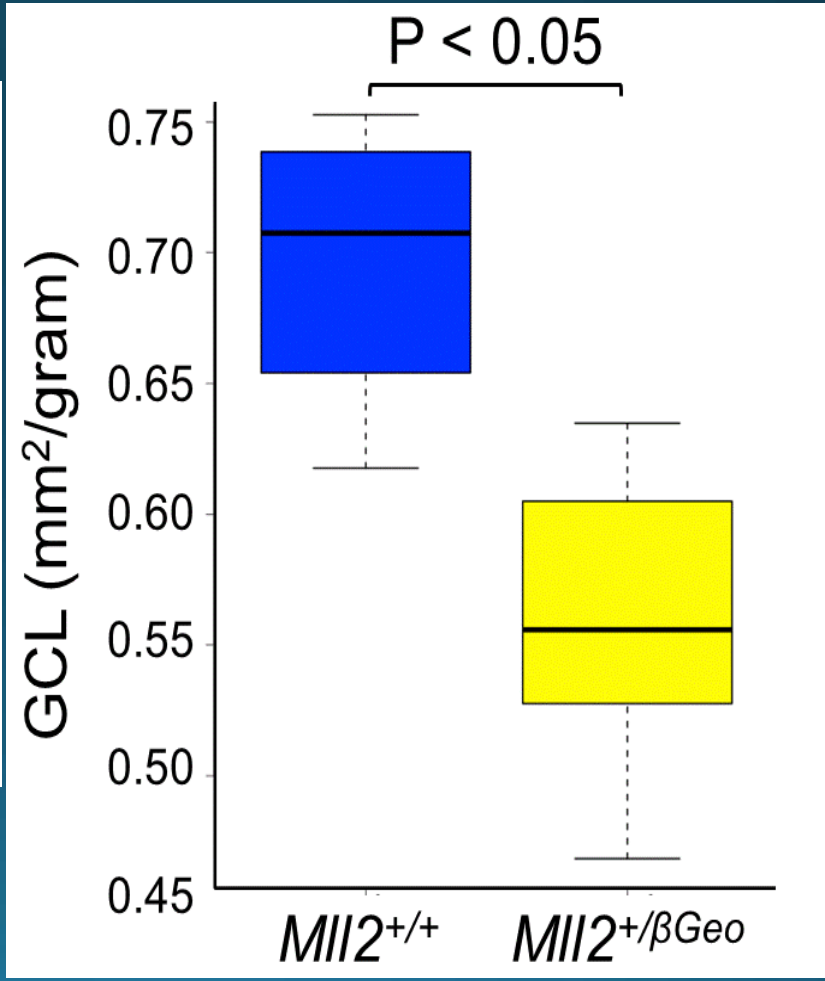
- Dentate gyrus is part of hippocampus;
- Strongest expression in Granule Cell Layer (GCL);
- Adult neurogenesis occurs in subgranular zone (SGZ);
- Defects of adult neurogenesis lead to hippocampal memory defects.



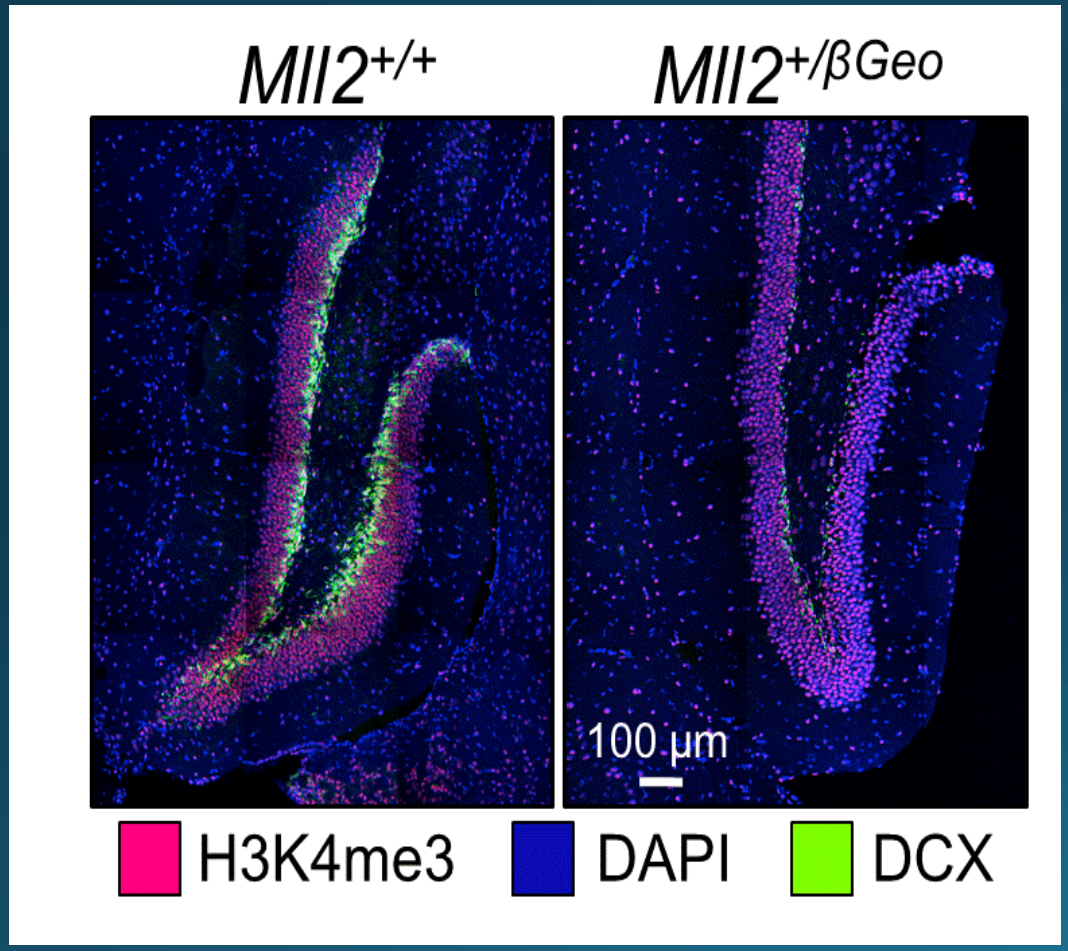
Immunofluorescence against *Mll2* (WT)

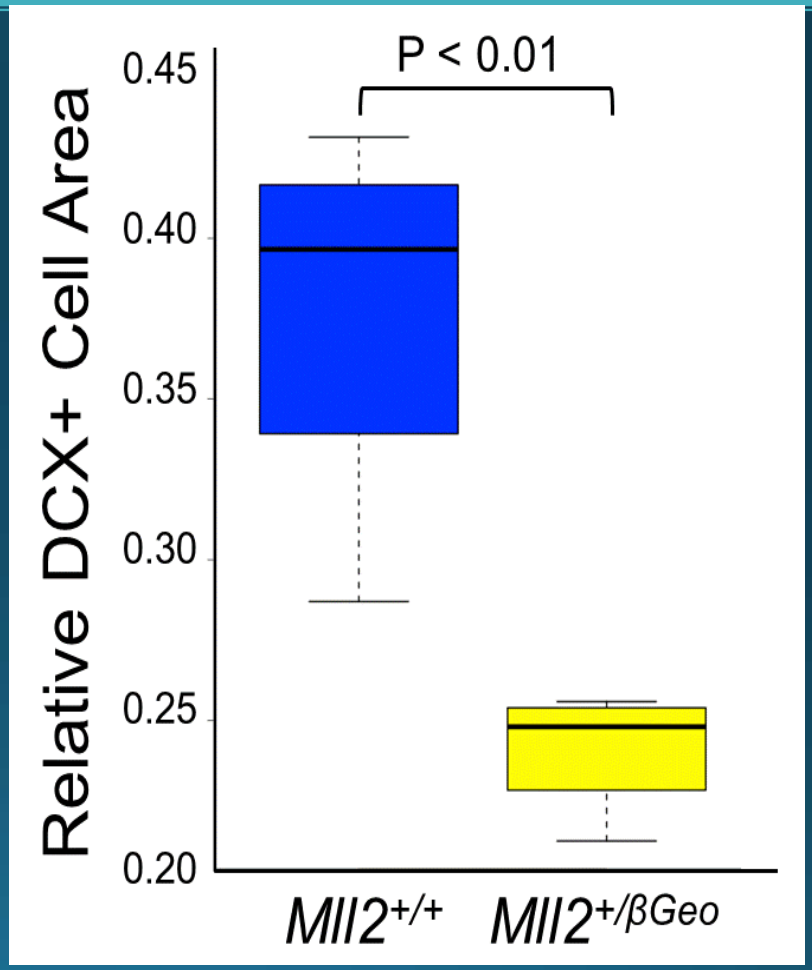
Mll2$^{+/\beta Geo}$ mice have a thinner GCL layer





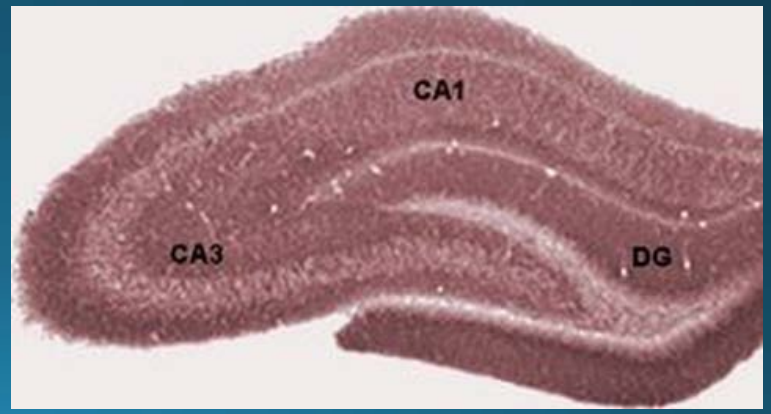
Mll2$^{+/\beta Geo}$ mice have a deficiency of neurogenesis





What does the dentate gyrus do?

- Integration of sensory inputs to determine a spatial representation
- Pattern separation of spatial (especially metric) information
  - reduction of interference between similar spatial locations
- Pattern separation of context
- Importance of context in object recognition
- Temporal integration and remote memory (visual/spatial) and spatial pattern separation
  - Based in part on neurogenesis
- Mnemonic processing of odor information



Defect in DG Neurogenesis
Visuospatial Deficits
Cognitive Profile Seen in KS????

Neuropsychologic process/function	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	28 yrs	7 yrs	15 yrs	11 yrs	14 yrs
	Female	Male	Female	Female	Male
Full Scale IQ	87	N/A	84	71	66
Perceptual or Non-verbal Reasoning*	↓	N/A	↓	↓	↓
Verbal Reasoning/ Comprehension	Normal	Normal	Normal	Normal	↓
Expressive Language	↓	↓	Normal	Normal	Normal
Processing Speed	↓	N/A	↓	↓	↓
Basic Math Calculation	Normal	↓	↓	N/A	N/A
Visual Selective Attention*	↓	N/A	↓	↓	N/A
Visual Working Memory*	↓	N/A	↓	↓	↓
Verbal Working Memory*	Normal	Normal	Normal	Normal	↓
Visual Delayed Memory*	↓	N/A	↓	N/A	↓
Verbal Delayed Memory*	↓	↓	↓	Normal	Normal
Switching/ Inhibition	↓	N/A	↓	Normal	N/A
Verbal Organization	Normal	N/A	Normal	Normal	N/A
Visual Organization*	↓	N/A	↓	N/A	↓
Fine Motor	↓	↓	↓	↓	↓

N/A = not adequately tested with testing regimen;

↓ = *deficient area (defined as >1 SD below test mean + lower than full scale IQ or if that is unavailable, highest individual test score)*

Yellow = function has been linked to dentate gyrus;
** = Function has been linked to hippocampus;*

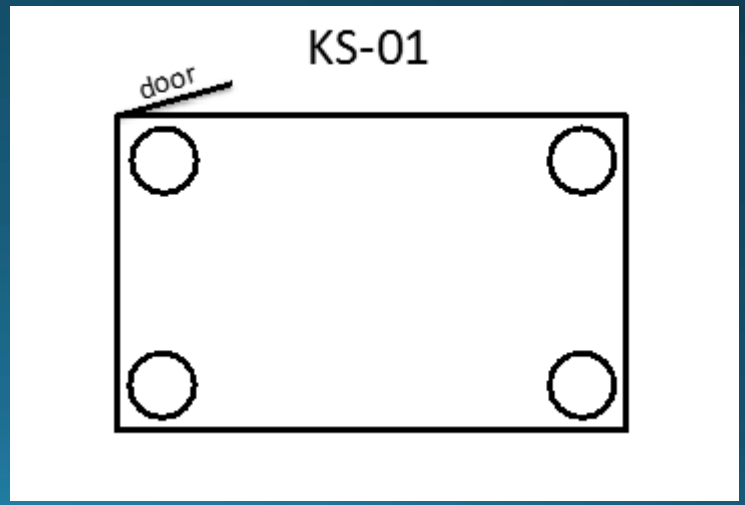
Maybe we are on to something…

Prospective Neuropsych Study

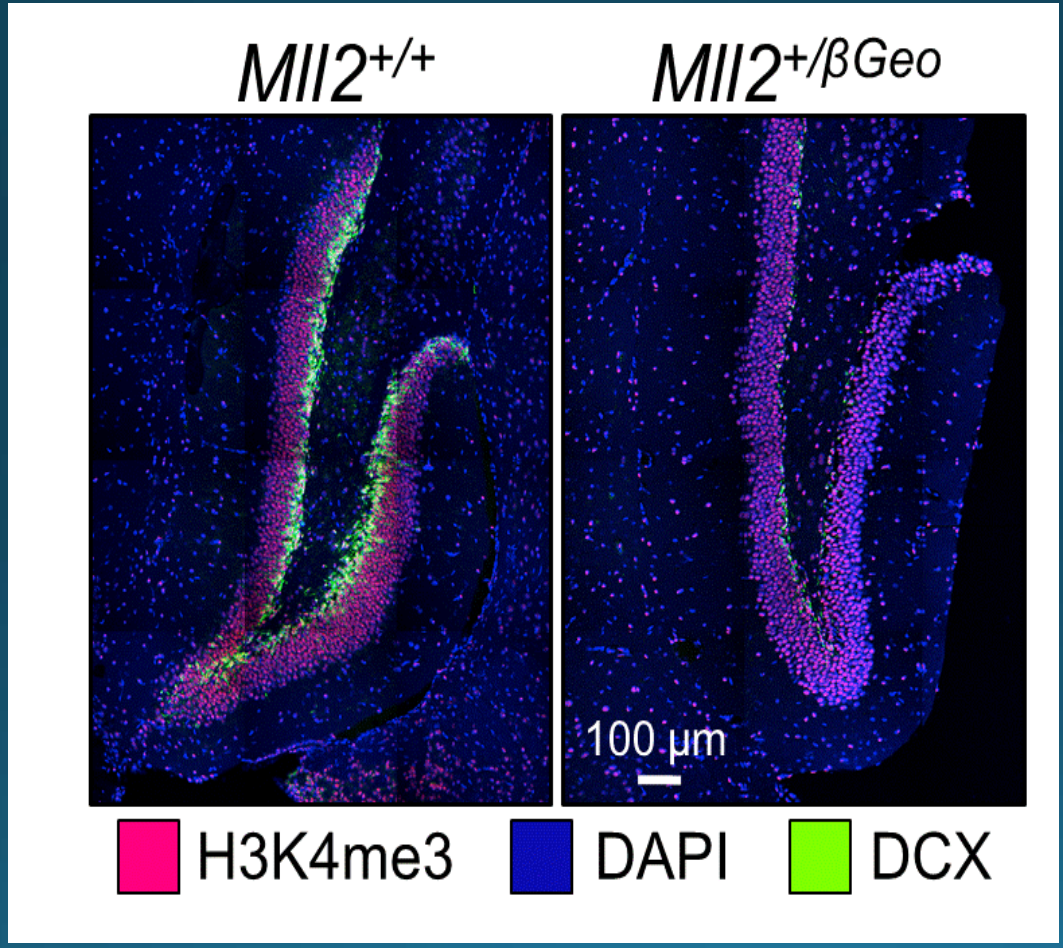
- 20-25 genetically-defined KS patients and controls (ages 7 and older) given a neuropsych battery
- Battery specifically designed to look at potential areas of difficulty specific to KS
- Easy to administer and portable
- < 1 hour in length
- Eventual goal to use as outcome measure in a clinical trial
- This study is actively enrolling

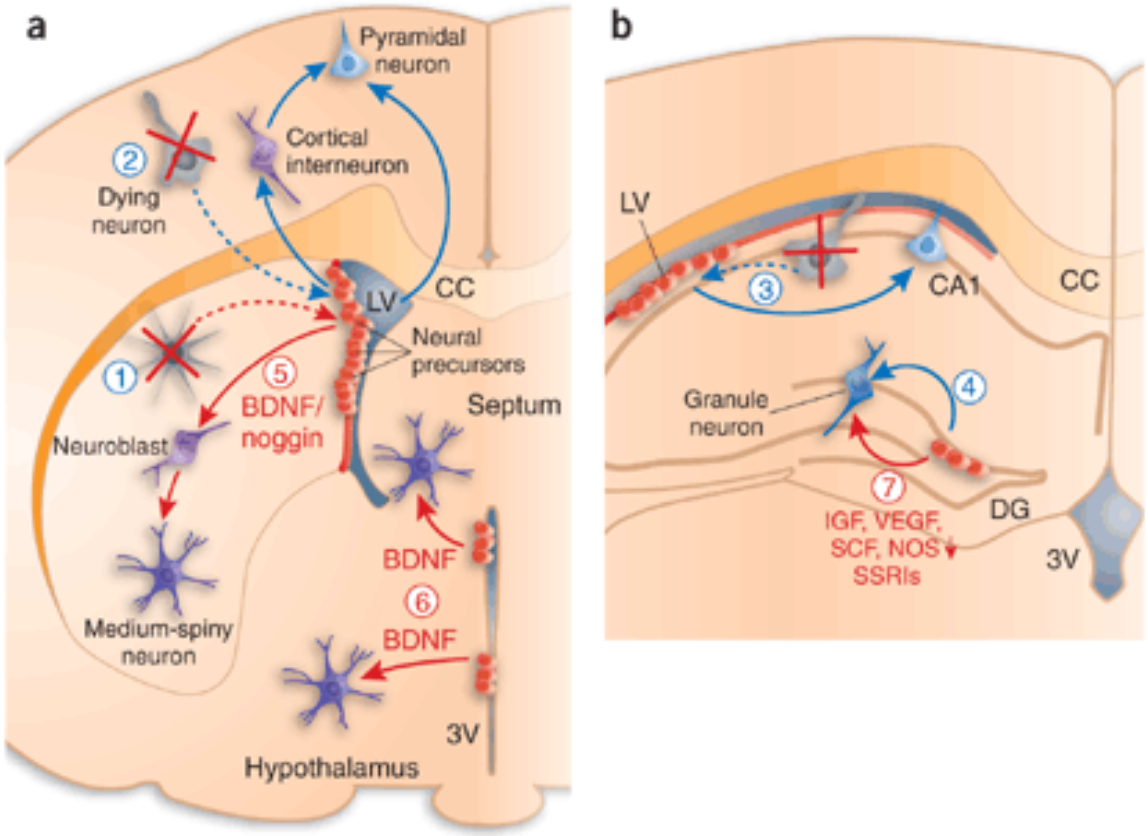
Reorientation Paradigm

- Already used in Williams syndrome
- Similar in concept to Morris Water Maze used with mice
- Further evidence for the visual spatial weakness and another potential outcome measure for a clinical trial
- Collecting pilot data



What About Neurogenesis?

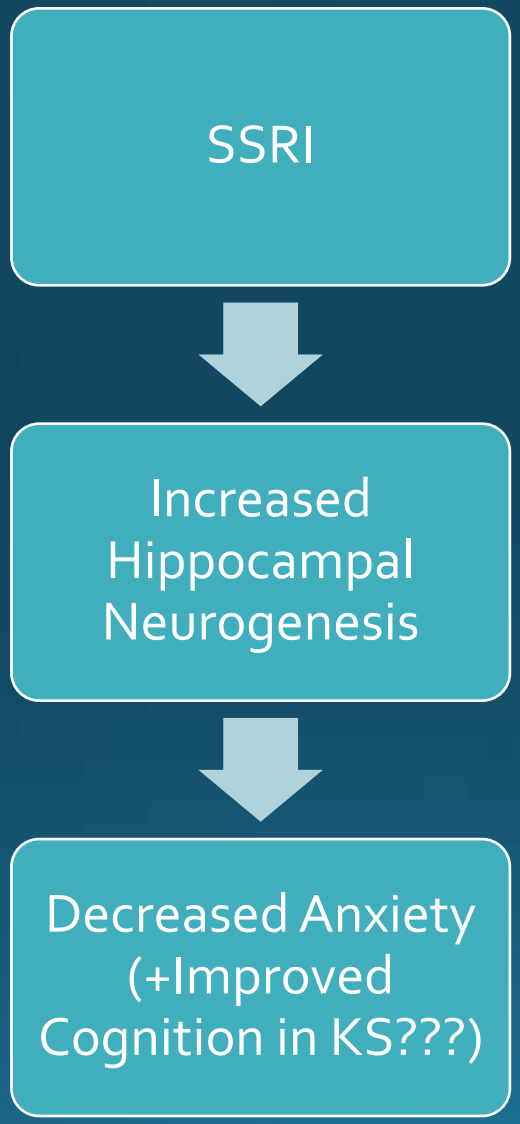




From Goldman *Nat Biotech* 2005

One thing we have found… Anxiety

- Anxiety seems (anecdotally) to be very prevalent in patients with Kabuki syndrome, particularly as they get older
- SSRIs have proven effective for treatment of anxiety
- SSRIs increase neurogenesis and most now believe that this contributes to the anti-anxiety effect
- COULD ANXIETY BE A PROXY FOR NEUROGENESIS IMPROVEMENT IN KABUKI SYNDROME?


SSRI
Increased Hippocampal Neurogenesis
Decreased Anxiety (+Improved Cognition in KS???)

Pediatric Anxiety Rating Scale (PARS)

PEDIATRIC ANXIETY RATING SCALE (PARS)

SYMPTOM CHECKLIST
Instructions: Fill in the blanks with "1" (yes), "2" (no), or "9" (other, e.g., unable or unwilling to answer)

SOCIAL INTERACTIONS or PERFORMANCE SITUATIONS	**Parent**	**Child**	**Rater**
1. Has fear of and/or avoids participating in group activities.	_____	_____	_____
2. Has fear of and/or avoids going to a party or social event.	_____	_____	_____
3. Has fear of and/or avoids talking with a stranger.	_____	_____	_____
4. Has fear of and/or avoids talking on the phone.	_____	_____	_____
5. Reluctant or refuses to talk in front of a group.	_____	_____	_____
6. Reluctant or refuses to write in front of other people.	_____	_____	_____
7. Reluctant or refuses to eat in public.	_____	_____	_____
8. Reluctant or refuses to use a public bathroom.	_____	_____	_____
9. Reluctant or refuses to change into gym clothes or bathing suit with others present.	_____	_____	_____
SEPARATION			
10. Worry about harm happening to attachment figures.	_____	_____	_____
11. Worry about harm befalling self, including the fear of dying.	_____	_____	_____
12. Distress when separation occurs or is anticipated.	_____	_____	_____
13. Fear or reluctance to be alone.	_____	_____	_____
14. Reluctance or refusal to go to school or elsewhere.	_____	_____	_____
15. Complaints of physical symptoms when separation occurs or is anticipated.	_____	_____	_____
16. Reluctance or refusal to go to sleep alone.	_____	_____	_____
17. Reluctance or refusal to sleep away from home.	_____	_____	_____
18. Nightmares with a separation theme.	_____	_____	_____
19. Clings to parent, or follows parent around the house.	_____	_____	_____

PARS

SEVERITY ITEMS
Instructions: For each item circle the number that best characterizes the patient during the past week.

1. Overall Number of Anxiety Symptoms (Circle code for past week only)	**Code**
Not applicable	8
Does not know	9
No symptoms	0
1 symptom	1
2-3 symptoms	2
4-6 symptoms	3
7-10 symptoms	4
More than 10 symptoms	5

2. Overall Frequency of Anxiety Symptoms	
Not applicable	8
Does not know	9
No symptoms	0
1 or 2 days a week	1
3 or 4 days a week	2
5 or 6 days a week	3
Daily	4
Several hours every day	5

PARS and FXS

- Fragile X is a disorder that has some similarities to KS
- In FXS, PARS:
  - High inter-rater reliability
  - High test-retest reliability
  - High cross-site reliability
  - Good clinical validity

Anxiety Study

- 15 minute video chat (or in person) interviews with child with KS, parents or guardians and unaffected sibling
- PARS and CBCL administered
- Actively recruiting/enrolling
- Could also lead to future therapeutic trial

So What Might the Neurodevelopmental Profile Look Like in KS?

	Intellectual Disability	Language Disability	Visual-Spatial Problems	ADHD	Anxiety	Autistic Features	Seizures	Hypotonia
Kabuki Syndrome	+ (not always present and often mild)	-	+	+/- (often present in early life and disappears later)	+ (often appears later like in preteen years)	-	+/- (10-40%)	+ (usually profound in early life and mild later)

- Problems creating new memories (particularly visuospatial) but good retention once memory created
- Memory may be able to be formed and retained with frequent repetition

What Can I Do Now For My Child's Neurodevelopmental Issues?

Educational

- Develop a good IEP targeting areas of weakness – for most KS, ID should be the IEP diagnosis
- KS patients often have specific difficulties with visuospatial memory and problem solving but obtain good neuropsych testing specific to your child to tailor an education program
- Handwriting circumvention
- Appropriate hearing impaired curriculum if that is an issue
- Educational program focused on safety in the community (eg, stranger danger)
- More repetition of the same concepts may be particularly beneficial in KS

Therapies

- Early involvement with Infants and Toddlers
- Physical therapy if necessary, particularly with early hypotonia
- OT to help with ADLs and fine motor tasks
- Feeding program if necessary
- Always have good balance – therapy is good but also need to maintain family sanity and allow children to be children and development to take its course

Neurologic/Medical

- High suspicion for seizures and treat if present – may discuss with your neurologist if Depakote or the ketogenic diet are good options
- If anxiety is present and impairing, consider treatment with SSRI
- Treat ADHD with typical ADHD therapies (stimulants first, possibly atomoxetine or alpha-adrenergics)
- Consider cochlear implant early if this is warranted

Thank You To…

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