



Constructing a Quantitative Metric for Evaluating the Clinical Significance of Recurrent Copy Number Variants

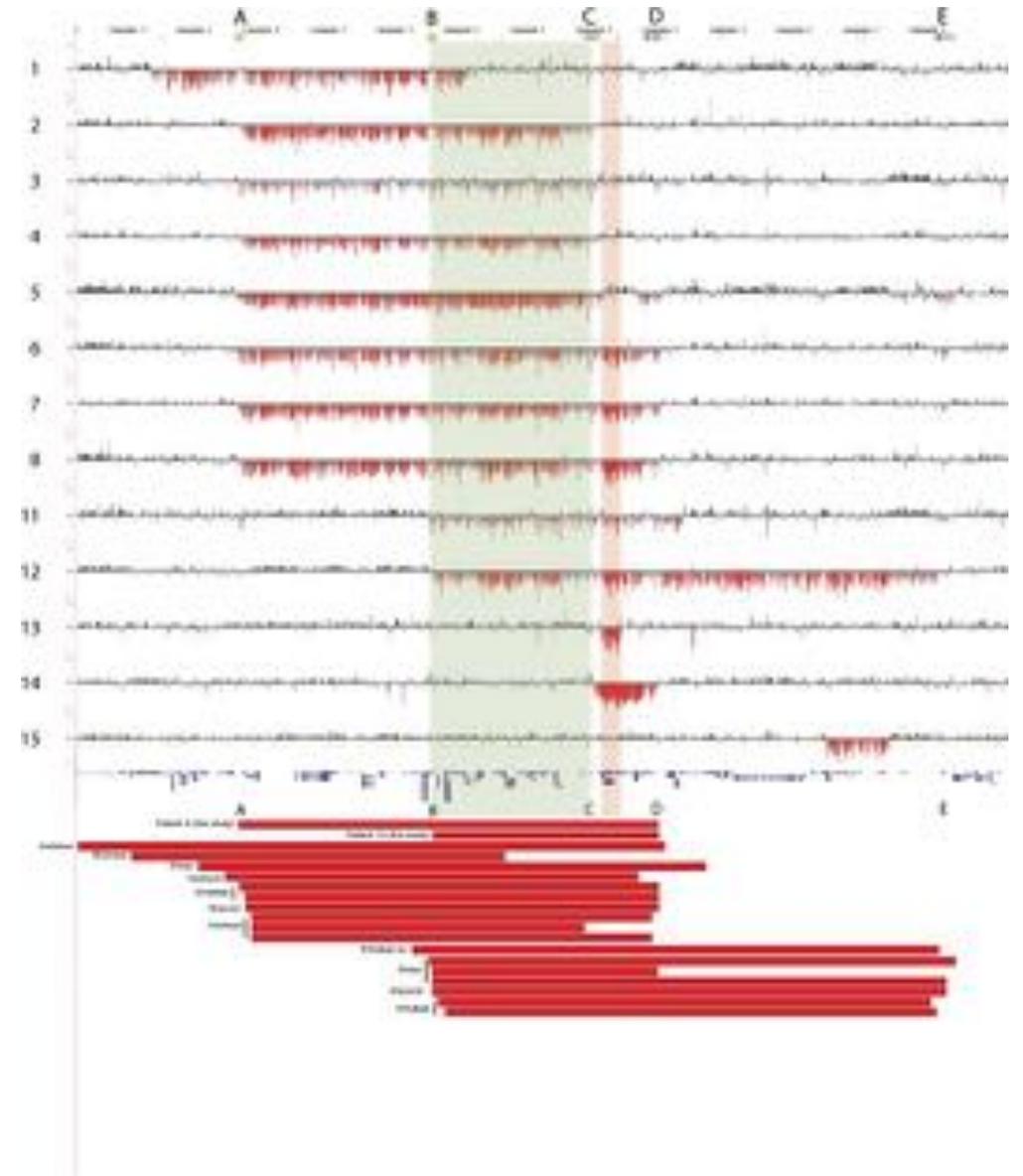
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On behalf of the ClinGen Dosage Sensitivity
Curation (DSC) Working Group

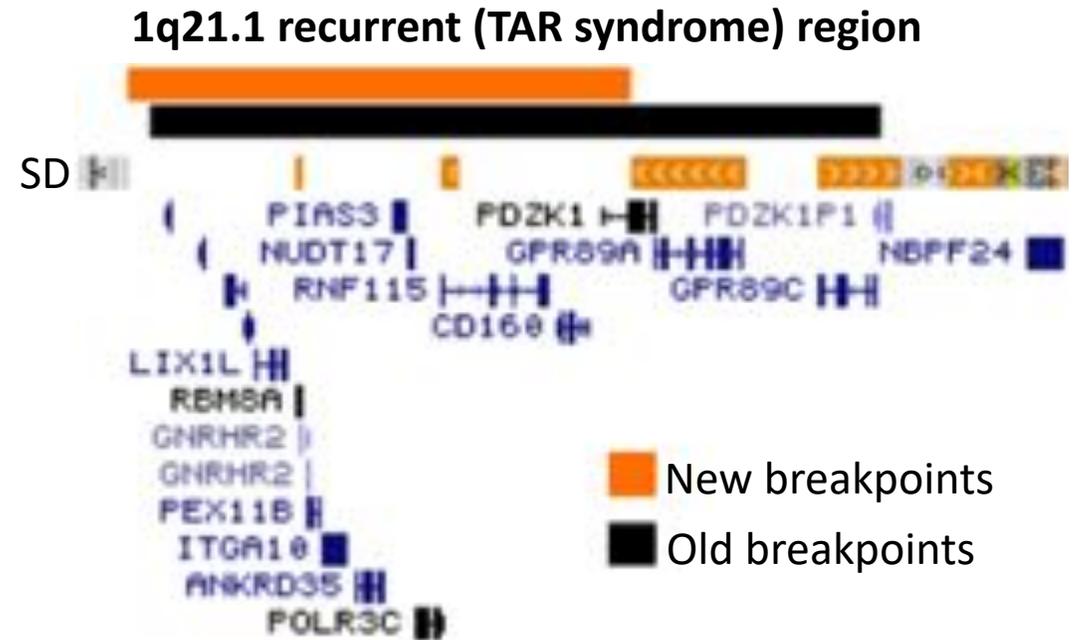
Recurrent CNVs

- One of the most common changes identified during copy number analysis
 - >50 different recurrent CNVs
 - NAHR mediated
- Multi-genic events
- Difficult to interpret clinically
 - Variable/non-specific phenotypes
 - Low penetrance
 - Relatively high prevalence in the general population
 - Ascertainment bias
 - Lack of segregation data
 - Difficulty interpreting statistical studies



History of the recurrent CNV group

- Tasked with curating the recurrent CNV regions and their significance
- Reviewed ~50 regions for their significance using the traditional DSC scoring method
- Developed standardized nomenclature for these events
 - “Cytoband(s)” recurrent (“XXX” syndrome) region (breakpoints, distal/proximal) (includes “candidate/landmark” gene(s))
 - Example - 15q11q13 recurrent (PWS/AS) region (BP1-BP3, Class 1)
- Refined the breakpoints to represent the innermost unique coordinates flanked by segmental duplications (SD)



Traditional dosage sensitivity scoring

Score	Strength of Evidence	Potential Clinical Classification
3	Sufficient evidence for dosage pathogenicity	Pathogenic
2	Emerging/some evidence for dosage pathogenicity	Likely Pathogenic or Uncertain
1	Little/limited evidence for dosage pathogenicity	Uncertain
0	No/insufficient evidence available	Uncertain or Likely Benign
Dosage sensitivity unlikely	Evidence suggests the region is NOT dosage sensitive	Likely Benign or Benign
Autosomal recessive	Gene is associated with autosomal recessive phenotype	Autosomal Recessive

Recurrent CNVs scoring using traditional method

Dosage Sensitivity Score	Haploinsufficiency	Triplosensitivity
3 score	25	18
2 score	8	5
1 score	3	9
0 score	4	6
40 score: DS unlikely	0	3
30: Autosomal recessive phenotype	1	N/A
Under Review		10
Total		51

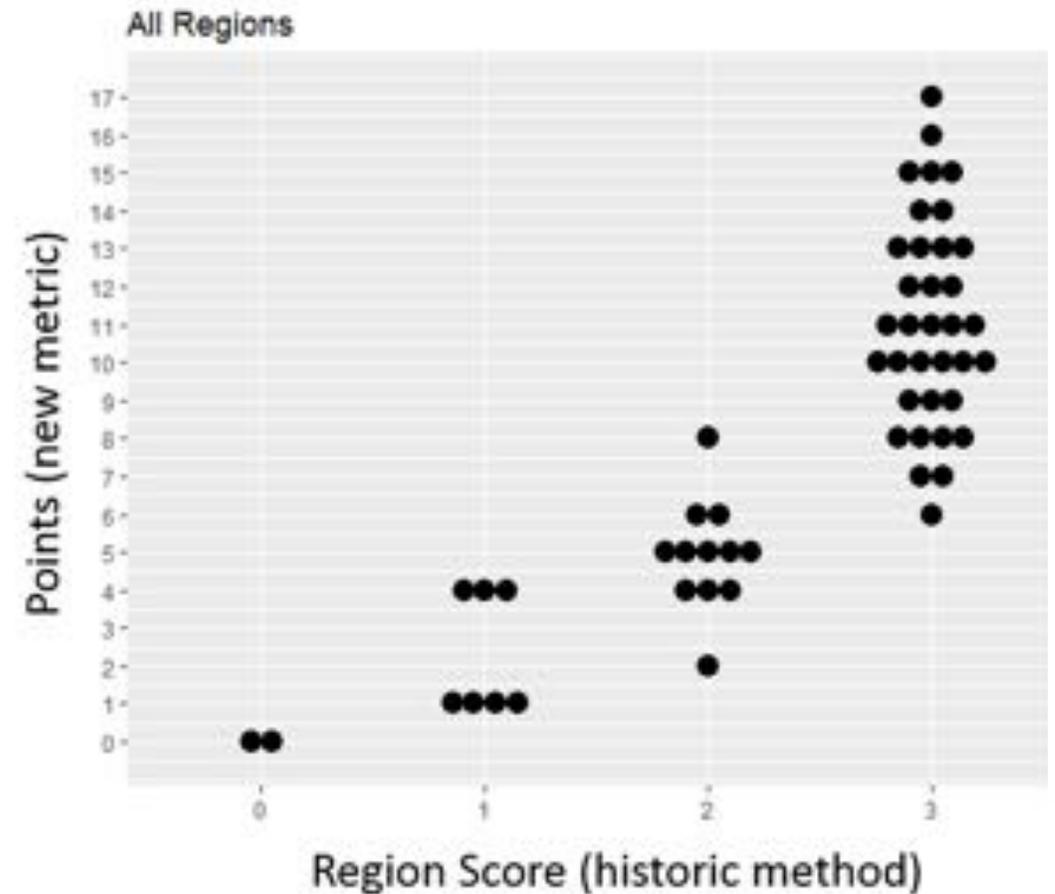
		Suggested Points		
		Default	Range	Max Score
Evidence Type	Evidence	Default	Range	Max Score
1) Number of unrelated probands	More than 2 families reported? (yes =1, no=0). If "no," SKIP to 4	1 or 0	-	1
2) Phenotype (SKIP to 4 if <two unrelated probands)	a) Specific, well-defined OR	4	3->5	5
	b) Non-specific	1	0->2	2
3) Inheritance/ segregation	a) CNV is most often de novo OR	4	3->5	5
	b) CNV is most often inherited, from an <i>affected</i> parent/ CNV segregates with phenotype OR	2	1->2	2
	c) Inheritance is unknown OR	0	-	0
	d) CNV is most often inherited, from an <i>unaffected</i> parent/ CNV does not segregate with phenotype	-1	-1->0	-1
4) Ethnic stratification and/or ascertainment bias	If present, accounted for or corrected? If "no," SKIP sections 5 and 6	-	-	-
5) p-value	p-value <0.05? (yes=1, no=0)	1 or 0	-	1
6) Effect Size	a) LR or OR: Lower 95% CI is greater than 1.00 (+1), 2.00 (+2), or 5.00 (+3)? OR	3, 2, 1, or 0	-	3
	b) Control frequency exceeds 0.1% OR the case frequency? Yes (-1)	-1	-	-1
	Bonus point: LR or OR: Exceeds 5 and lower 95% CI does not include 1? (yes= 1, no= 0)	1 or 0	-	1
7) Contains an established haploinsufficient/triplosensitive gene	Dosage sensitivity scoring has found that an individual gene within the region is either haploinsufficient or triplosensitive	1 or 0	-	1

Scoring Metric -Scale

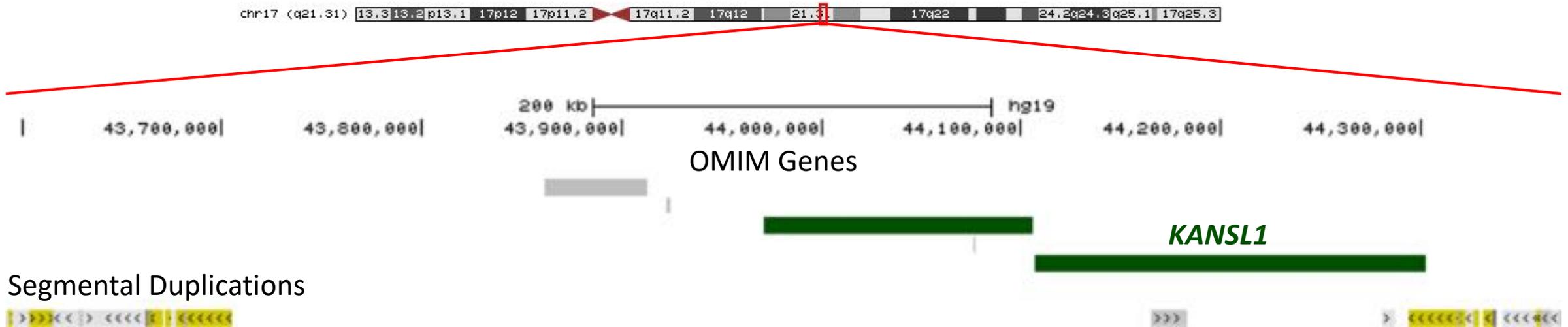
Dosage Sensitivity Scores	Points Range	Traditional Score	Potential Clinical Interpretation
Sufficient Evidence (3)	10->17	3	Pathogenic
Emerging Evidence (2)	5->9	2	Likely Pathogenic
Little Evidence (1)	1->4	1	VUS
No Evidence (0)	0	0	VUS/ VUS-Likely Benign
Dosage Sensitivity Unlikely	-2->-1	-	VUS-Likely Benign/Benign
CNV is Autosomal Recessive	n/a	Associated with recessive condition	Associated with recessive condition

Metric Performance

- Tested on 17 regions
 - Independently by two group members
 - Examined haploinsufficiency (deletion) and triplosensitivity (duplication)
- 75% of the scores agree with historical score
- Independent reviewers had the same score for 94% of the regions



17q21.31 – Deletion



Segmental Duplications

- ~500 kb
- Reported in >20 patients
- Associated with developmental delay, hypotonia, craniofacial abnormalities, friendly/amiable behavior, seizures, and additional clinical findings.
- Almost always *de novo*
- Enriched in the clinical population (p= 1.16E-07)
- Likelihood ratio is Inf (7.51 to Inf)
- Haploinsufficient gene- *KANSL1*

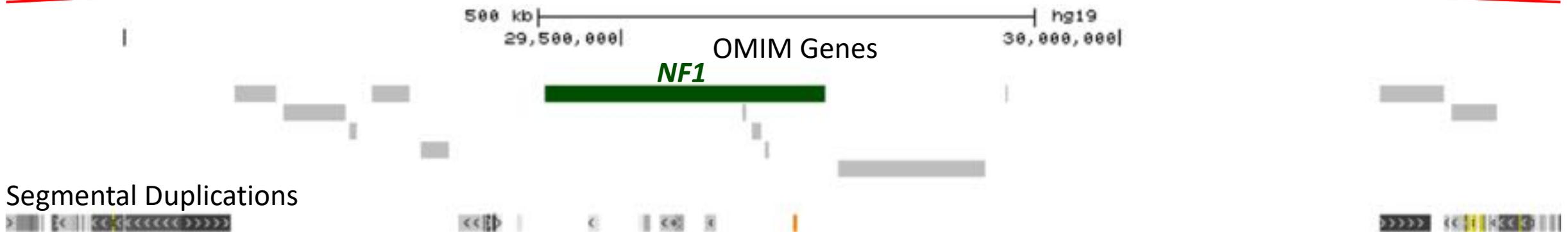
Scoring 17q21.31 - Deletion

Evidence Type	Evidence	Default	Range	Max Score	Deletion Score
1) Number of unrelated probands	More than 2 families reported? (yes =1, no=0). If "no," SKIP to 4	1 or 0	-	1	1
2) Phenotype (SKIP to 4 if <two unrelated probands)	a) Specific, well-defined OR	4	3->5	5	4
	b) Non-specific	1	0->2	2	
3) Inheritance/ segregation	a) CNV is most often de novo OR	4	3->5	5	4
	b) CNV is most often inherited, from an affected parent/ CNV segregates with phenotype OR	2	1->2	2	
	c) Inheritance is unknown OR	0	-	0	
	d) CNV is most often inherited, from an unaffected parent/ CNV does not segregate with phenotype	-1	-1->0	-1	

Evidence Type	Evidence	Default	Range	Max Score	Deletion Score
4) Ethnic stratification and/or ascertainment bias	If present, accounted for or corrected? If "no," SKIP sections 5 and 6	-	-	-	-
5) p-value	p-value <0.05? (yes=1, no=0)	1 or 0	-	1	1
6) Effect Size	a) LR or OR: Lower 95% CI is greater than 1.00 (+1), 2.00 (+2), or 5.00 (+3)? OR	3, 2, 1, or 0	-	3	3
	b) Control frequency exceeds 0.1% OR the case frequency? Yes (-1)	-1	-	-1	
	Bonus point: LR or OR: Exceeds 5 and lower 95% CI does not include 1? (yes= 1, no= 0)	1 or 0	-	1	1
7) Contains an established haploinsufficient gene	Dosage sensitivity scoring has found that an individual gene within the region is either haploinsufficient or triplosensitive	1 or 0	-	1	1
					Sum Points
					15 (DS - 3)

17q11.2 – Duplication

chr17 (q11.2) 13.3 13.2 p13.1 17p12 17p11.2 17q11.2 17q12 21.31 17q22 24.2q24.3q25.1 17q25.3



- ~1.2 Mb
- Reported in ~10 patients
- Highly variable clinical findings including developmental delay/intellectual disability and mild facial dysmorphism
- Inherited from both affected and unaffected parents and found in unaffected relatives
- Enriched in the clinical population ($p= 0.027$)
- Likelihood ratio is Inf (1.23 to Inf)
- No known triplosensitive genes

Scoring 17q11.2 - Duplication

Evidence Type	Evidence	Default	Range	Max Score	Duplication Score
1) Number of unrelated probands	More than 2 families reported? (yes =1, no=0). If "no," SKIP to 4	1 or 0	-	1	1
2) Phenotype (SKIP to 4 if <two unrelated probands)	a) Specific, well-defined OR	4	3->5	5	2
	b) Non-specific	1	0->2	2	
3) Inheritance/ segregation	a) CNV is most often de novo OR	4	3->5	5	1
	b) CNV is most often inherited, from an affected parent/ CNV segregates with phenotype OR	2	1->2	2	
	c) Inheritance is unknown OR	0	-	0	
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4) Ethnic stratification and/or ascertainment bias	If present, accounted for or corrected? If "no," SKIP sections 5 and 6	-	-	-	-
5) p-value	p-value <0.05? (yes=1, no=0)	1 or 0	-	1	1
6) Effect Size	a) LR or OR: Lower 95% CI is greater than 1.00 (+1), 2.00 (+2), or 5.00 (+3)? OR	3, 2, 1, or 0	-	3	1
	b) Control frequency exceeds 0.1% OR the case frequency? Yes (-1)	-1	-	-1	
	Bonus point: LR or OR: Exceeds 5 and lower 95% CI does not include 1? (yes= 1, no= 0)	1 or 0	-	1	1
7) Contains an established triplosensitive gene	Dosage sensitivity scoring has found that an individual gene within the region is either haploinsufficient or triplosensitive	1 or 0	-	1	0
					Sum Points
					7 (DS - 2)

Conclusions

- Preliminary data shows the metric is working to provide an unbiased/standardized approach to curating recurrent CNVs
- Continued work will focus on additional updates to increase confidence in the assigned DS scores.
 - Phenotype specificity scoring
 - Inheritance scoring
- Going forward
 - Review all remaining recurrent CNV regions
 - Move towards the curation of non-recurrent CNVs
 - Curate benign CNV regions

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Questions?