Understanding the Report

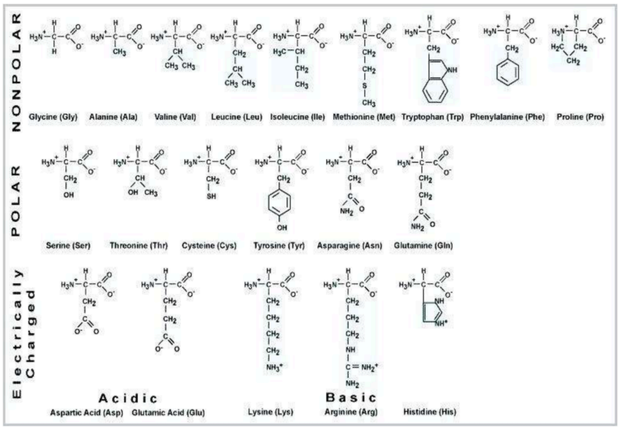
Describe the type of genetic report and what the result is indicating:

1. arr[hg19]2q33.1(198,356,789-203,491,035)X1
2. c.346G>C (p.G116R)
3. c.1945dupT (p.S649FfsX40)
4. c.847C>T (p.R283X)
5. c.487+1G>T

So, You Found a VUS…

- For copy number variants:
  - What genes are included in the area?
  - How big is the area?
  - Is it inherited or de novo?
  - Is it a deletion or duplication?
- For single nucleotide changes:
  - What type of change is it?
  - Is an amino acid changed?
  - How similar is the amino acid?
  - Is it conserved?
  - Does it occur in an important part of the protein?
  - Is it found in population databases? (ExAC, 1000 genomes)
  - Has it been shown to segregate with disease?
  - Have there been any functional studies?

Physiochemical Properties of Amino Acids



Histone H1 (residues 120-180)

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HUMAN  KKASKPKKAASKAPTKKPKATPVKKAKKKLAATPKKAKKPKTVKAKPVKASKPKKAKPVK
MOUSE  KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKAKKPKVVKVKPVKASKPKKAKTVK
RAT    KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKAKKPKIVKVKPVKASKPKKAKPVK
COW    KKAAKPKKAASKAPSKKPKATPVKKAKKKPAATPKKTKKPKTVKAKPVKASKPKKTKPVK
CHIMP  KKASKPKKAASKAPTKKPKATPVKKAKKKLAATPKKAKKPKTVKAKPVKASKPKKAKPVK
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NON-CONSERVED AMINO ACIDS: Conservative, Conservative, Non-conservative, Conservative, Non-conservative, Semi-conservative, Conservative, Non-conservative

ACMG 2015 Guidelines for Variant Classification

	Benign: Strong	Benign: Supporting	Pathogenic: Supporting	Pathogenic: Moderate	Pathogenic: Strong	Pathogenic: Very strong
Population data	MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data – benign BP6	Reputable source – pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			