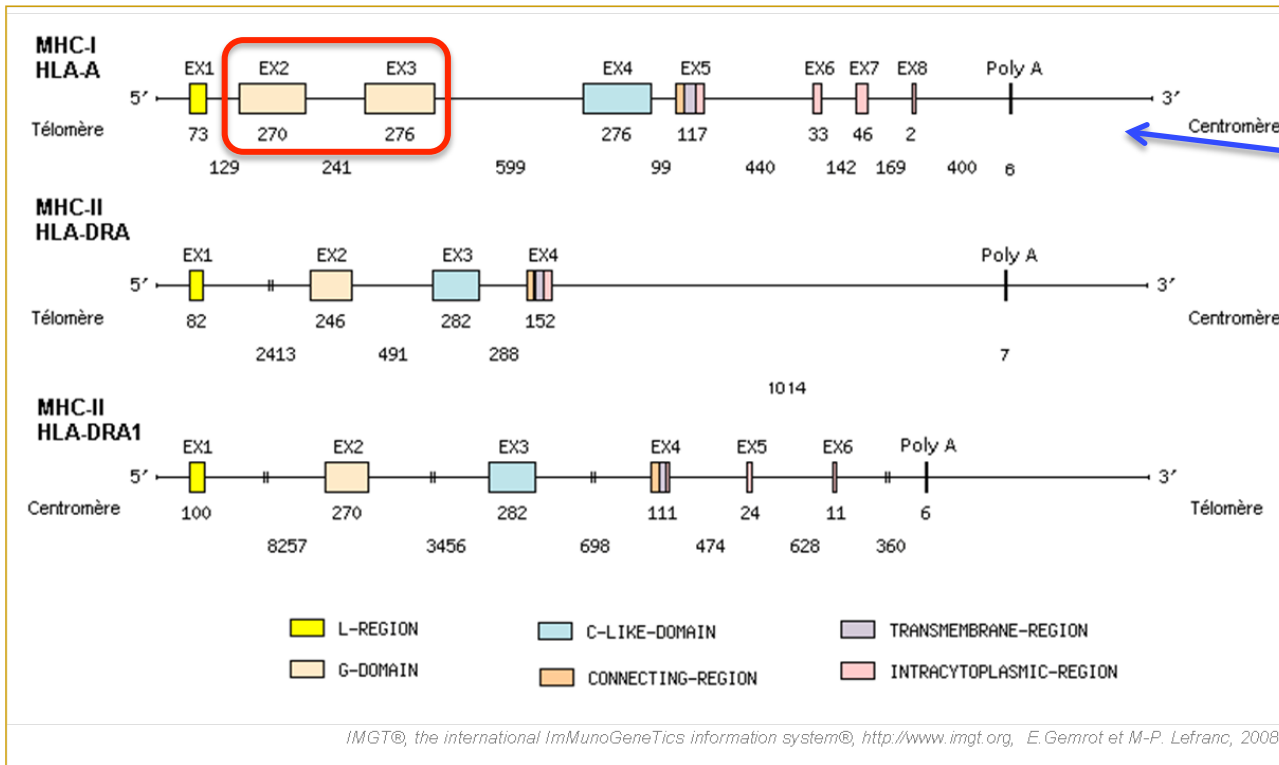




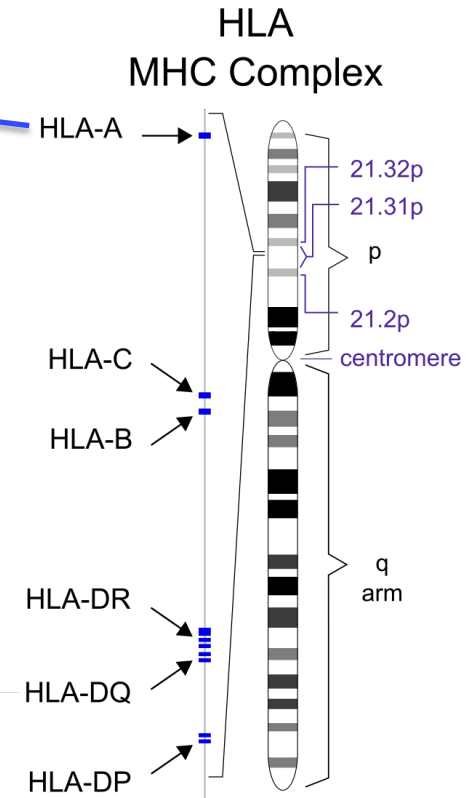
# Chromosomal Phasing of Groups of Sequences

Bob Milius

# HLA



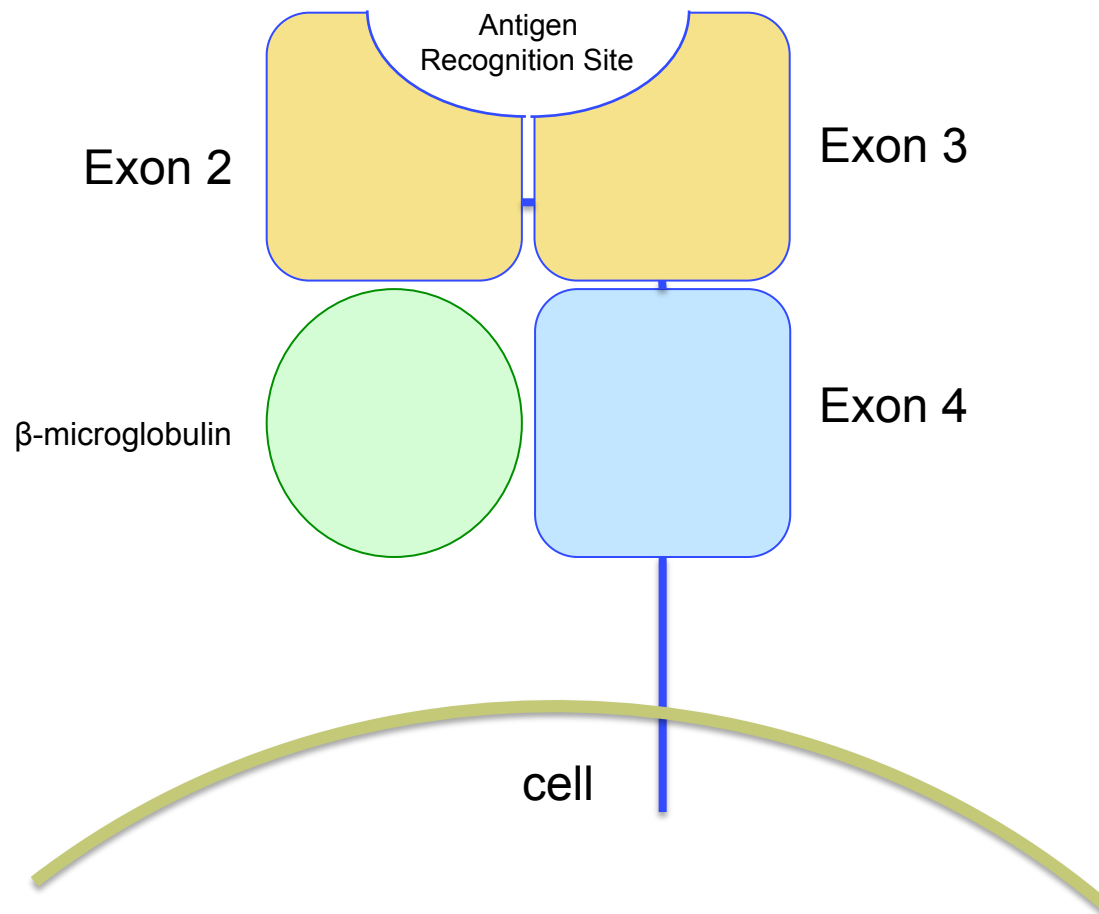
[http://www.imgt.org/IMGTeducation/Tutorials/MHC/\\_FR/Presentation/images/intron\\_exon\\_ADNg.png](http://www.imgt.org/IMGTeducation/Tutorials/MHC/_FR/Presentation/images/intron_exon_ADNg.png)



human chromosome 6

[https://en.wikipedia.org/wiki/Human\\_leukocyte\\_antigen](https://en.wikipedia.org/wiki/Human_leukocyte_antigen)

# HLA Class I



cDNA	80	90	100	110	120	130	140	150	160	170
A*23:29	GCTCCCA	CTCCATGAGG	TATTTCTCCA	CATCCGTGTC	CCGGCCCCGGC	CGCGGGGAGC	CCCCTTCAT	CGCCGTGGGC	TACGTGGACG	ACACGCAGTT
A*23:36	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
A*24:32	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
A*24:128	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
cDNA	180	190	200	210	220	230	240	250	260	270
A*23:29	CGTGCGGTTT	GACAGCGACG	CCGCGAGCCA	GAGGATGGAG	CCGCGGGCGC	CGTGGATGGA	GCAGGAGGGG	CCGGAGTATT	GGGACGAGGA	GACAGGGAAA
A*23:36	-----	-----	-----	-----	-----	-A-	-----	-----	-----	-----
A*24:32	-----	-----	-----	-----	-----	-A-	-----	-----	-----	-----
A*24:128	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
cDNA	280	290	300	310	320	330	340	350	360	370
A*23:29	GTGAAGGCC	ACTCACAGAC	TGACCGAGAG	AACCTGCGGA	TCGCGCTCCG	CTACTACAAC	CAGAGCGAGG	CCG GTTCTCA	CACCCCTCCAG	ATGATGTTTG
A*23:36	-----	-----	-----	-G-	-----	-----	-----	-----	-----	-----
A*24:32	-----	-----	-----	-G-	-----	-----	-----	-----	-----	-----
A*24:128	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
cDNA	380	390	400	410	420	430	440	450	460	470
A*23:29	GCTGCGACGT	GGGGTCGGAC	GGGCGCTTCC	TCCGCGGGTA	CCACCAGTAC	GCCTACGACG	GCAAGGATTA	CATCGCCCTG	AAAGAGGACC	TGCGCTCTTG
A*23:36	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
A*24:32	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
A*24:128	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
cDNA	480	490	500	510	520	530	540	550	560	570
A*23:29	GACCGCGGCG	GACATGGCGG	CTCAGATCAC	CGACGCGAAG	TGGGAGGCGG	CGCGTGTGGC	GGAGCAGTTG	AGAGCCTACC	TGGAGGGCAC	GTGCGTGGAC
A*23:36	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
A*24:32	-----	-----	-----	-A-	-----	-A-	-CA-	-----	-----	-----
A*24:128	-----	-----	-----	-A-	-----	-A-	-CA-	-----	-----	-----
cDNA	580	590	600	610						
A*23:29	GGGCTCCGCA	GATACCTGGA	GAACGGGAAG	GAGACGCTGC	AGCGCACGG					
A*23:36	-----	-----	-----	-----	-----					
A*24:32	-----	-----	-----	-----	-----					
A*24:128	-----	-----	-----	-----	-----					



# Two Possible Genotypes

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A\*23:29 —  —  —

A\*24:32 —  —  —

or

A\*23:36 —  —  —

A\*24:128 —  —  —

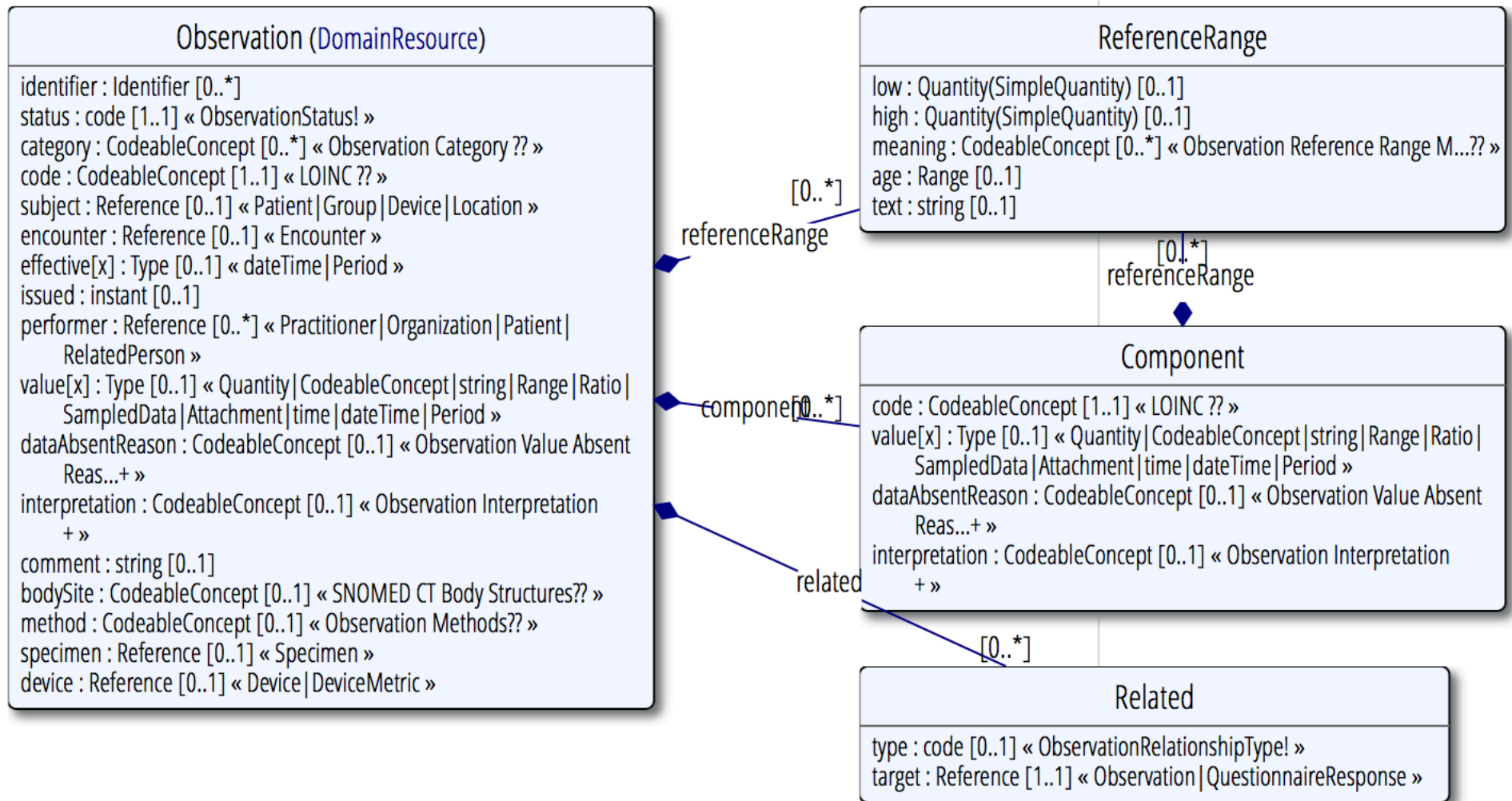
# Grouping Observations

---

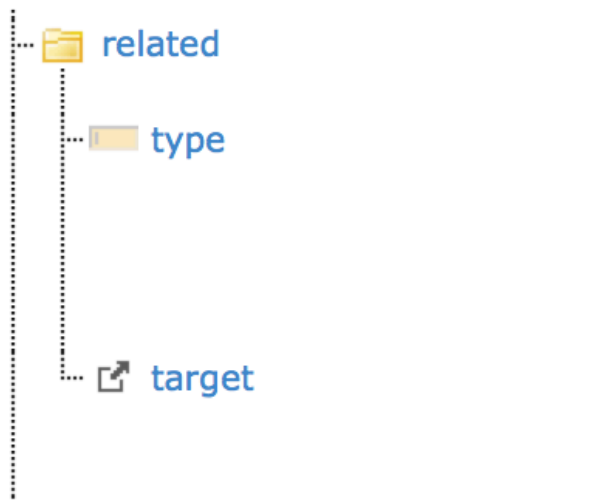
- DiagnosticReport.result
- Observation.related.target
- Observation.component

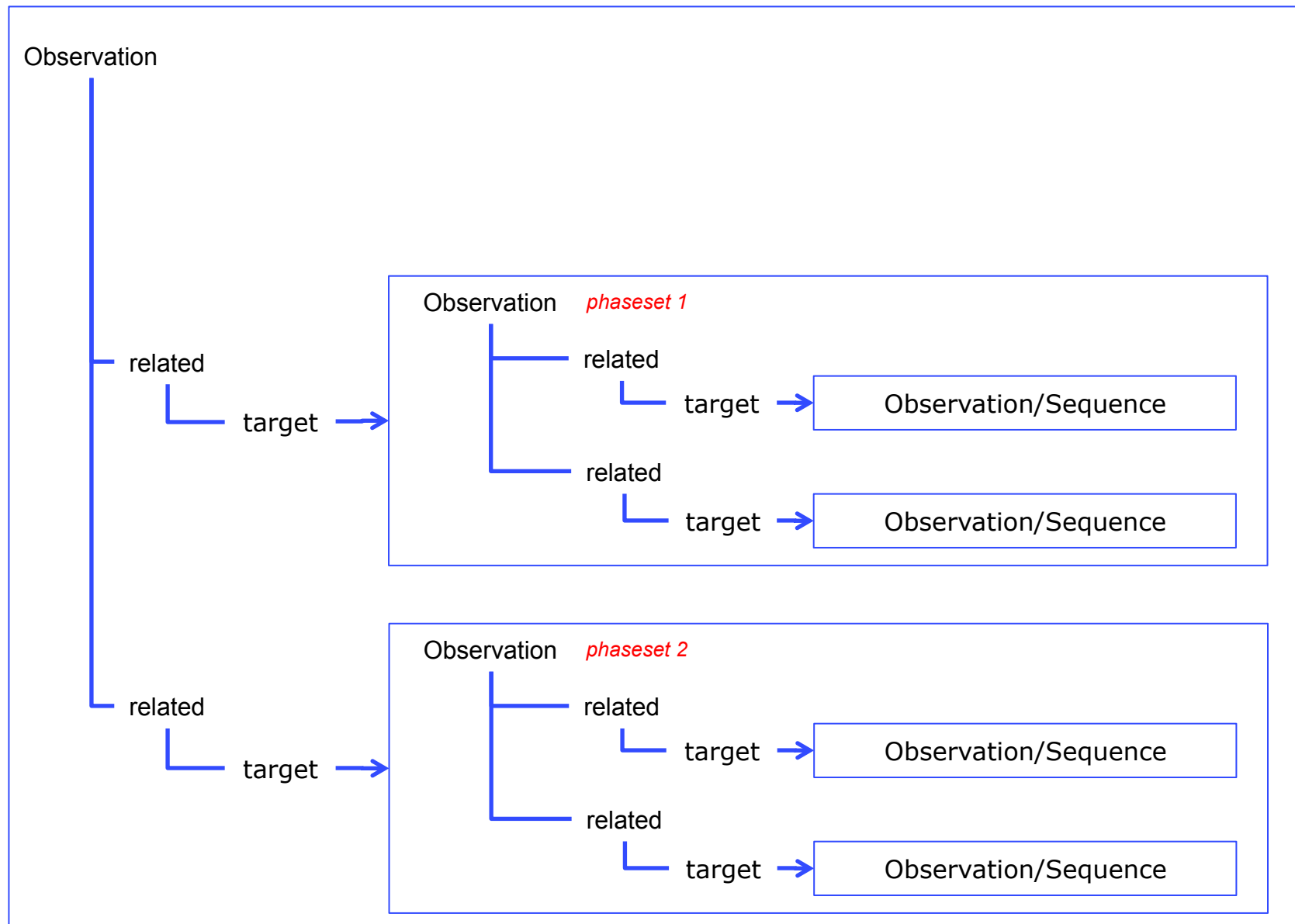
# Observation Resource

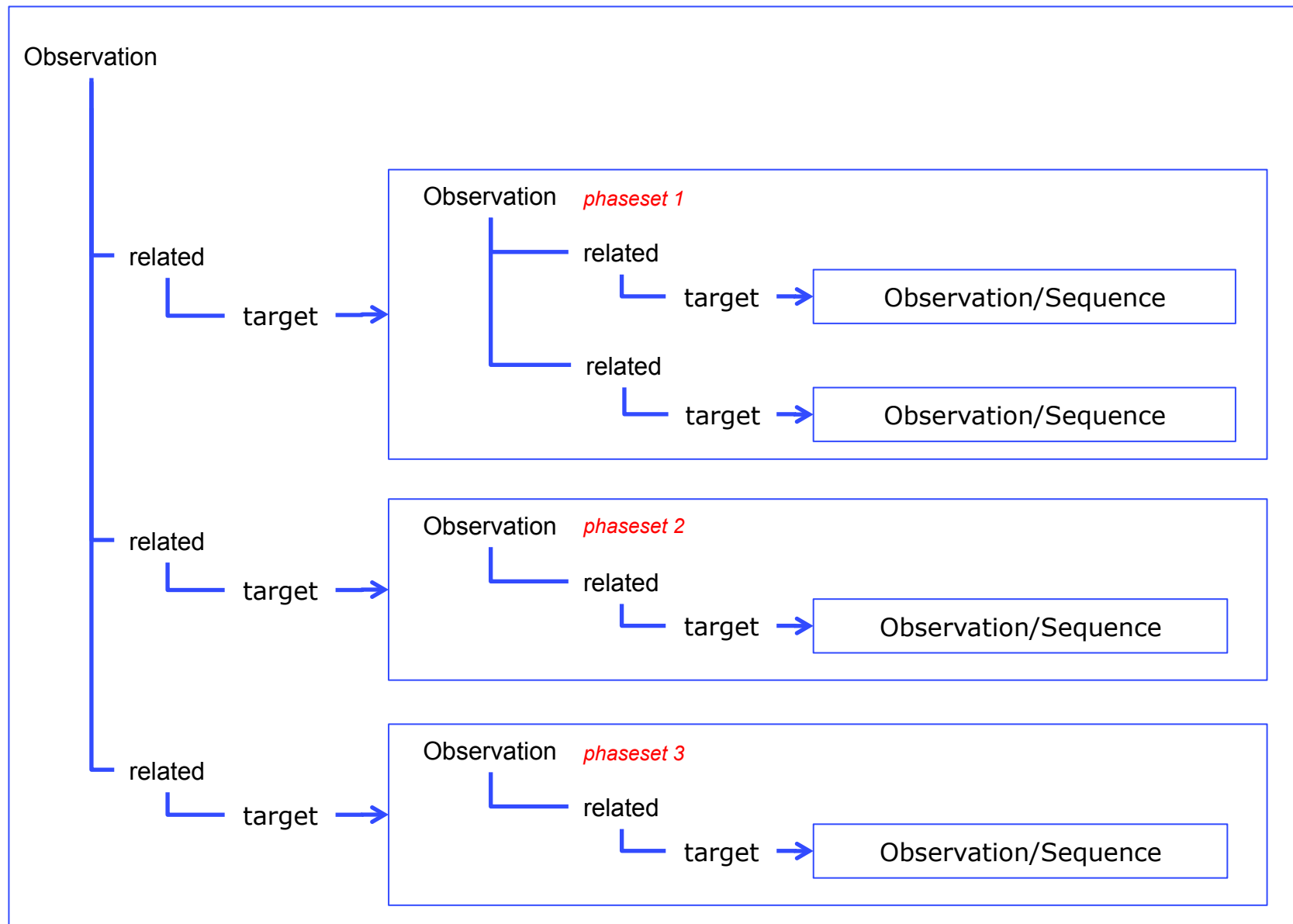
## UML Diagram



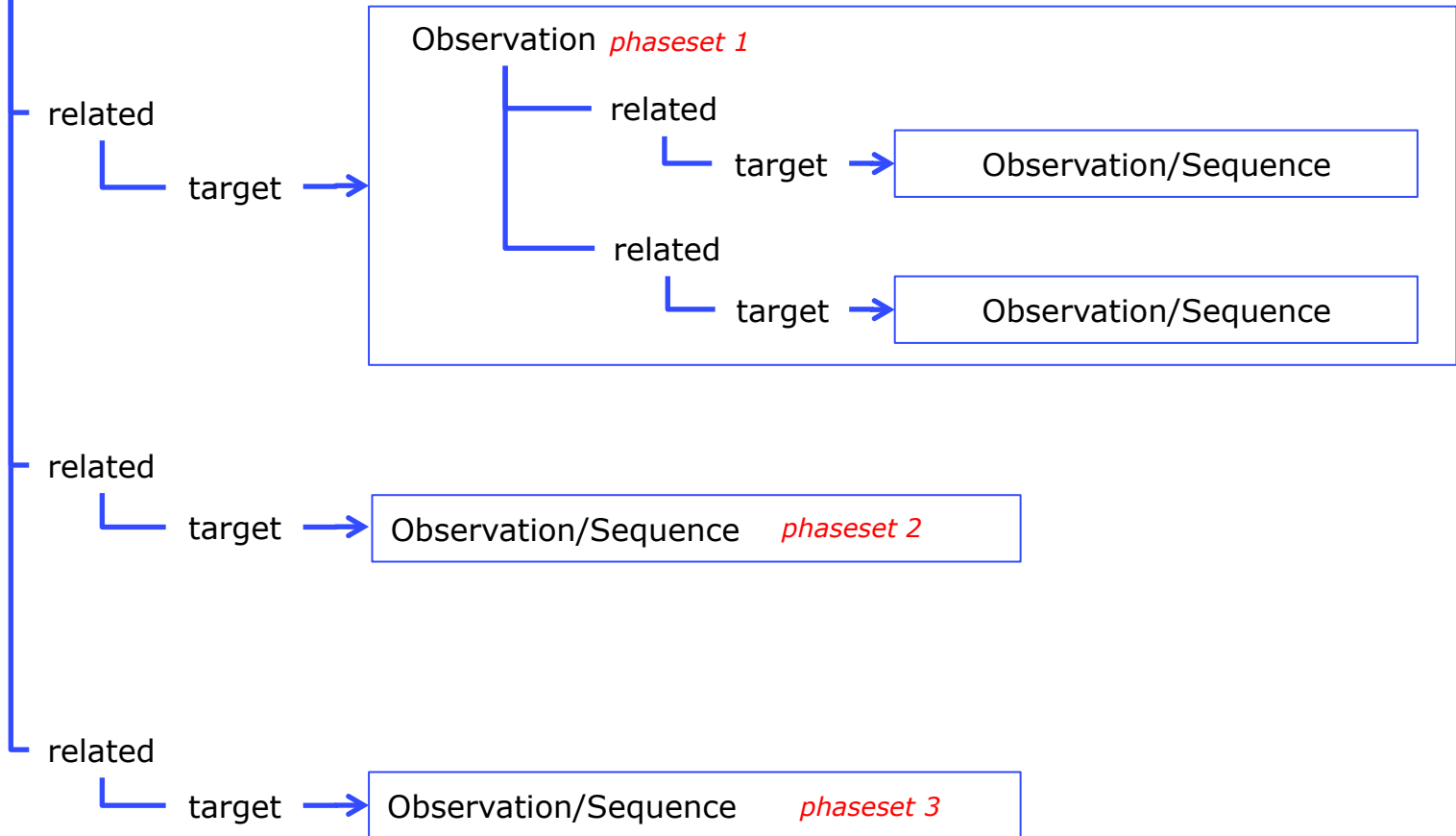
# Observation.related

	$\Sigma$	0..*	BackboneElement	Resource related to this observation
		0..1	code	has-member   derived-from   sequel-to   replaces   qualified-by   interfered-by ObservationRelationshipType (Required)
		1..1	Reference(Observation   QuestionnaireResponse)	Resource that is related to this one





Observation



## Observation

```
<code>  
<coding>  
  <system value="http://loinc.org"/>  
  <code value="57290-9"/>  
  <display value="HLA-A [Type] by High resolution"/>  
</coding>  
</code>  
<valueString value="HLA-A*01:02+HLA-A*01:03"/>
```

related

target

### Observation

*phaseset 1*

*observation-geneticsAlleleName = HLA-A\*01:02*

related

target

Observation/Sequence *exon 2*

related

target

Observation/Sequence *exon 3*

related

target

### Observation

*phaseset 2*

*observation-geneticsAlleleName = HLA-A\*01:03*

related

target

Observation/Sequence *exon 2*

related

target

Observation/Sequence *exon 3*

## chat.fhir.org

### implementers > Observation.related target

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- Kevin Power: That makes sense, but when you have optional nesting like that, it makes implementation more difficult. That isn't a reason not to do it. Just want to make sure we understand the requirements and/or what will we miss out on if we don't represent phasing. I just haven't seen many examples from our clients where they report or send phasing information. But maybe that's because there isn't a good way to do so today. :)
- Bob Milius: @Kevin Power Yes, it would make implementation more complicated. At NMDP, we ask our labs to send us phasing information if they have it. Another way to do it is to add a phaseset element to the sequence resource or observation for genetics profile and use a unique label (e.g., uuid) to tag those sequences that are in phase with each other. Just need to make sure they aren't used outside of the lab result.
- Kevin Power: I like the additional phaseset element, as long as we don't lose something important.

Observation

related

target

Observation/Sequence  
*phaseSet 1*

related

target

Observation/Sequence  
*phaseSet 1*

related

target

Observation/Sequence  
*phaseSet 2*

related

target

Observation/Sequence  
*phaseSet 3*

## Observation

related

target

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:56078a59-9c8a-4f50-a06a-7d628c2a3dac"/>*

related

target

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:56078a59-9c8a-4f50-a06a-7d628c2a3dac"/>*

related

target

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:9c68c1be-2f3c-44b3-b3a3-d745e785b4c5"/>*

related

target

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:189994f7-6fb5-445a-a1e7-3b8077aa0863"/>*

## DiagnosticReport

result

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:56078a59-9c8a-4f50-a06a-7d628c2a3dac"/>*

result

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:56078a59-9c8a-4f50-a06a-7d628c2a3dac"/>*

result

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:9c68c1be-2f3c-44b3-b3a3-d745e785b4c5"/>*

result

Observation for Genetics > Sequence

*<phaseSet value="urn:uuid:189994f7-6fb5-445a-a1e7-3b8077aa0863"/>*

# chat.fhir.org

## implementers > Observation.related target

---

- Simone Heckmann

Concerning Observation.related, please check [GF#9970](#)

The use of a "code + reference" pattern is discouraged, particularly where the number of relationships is low. The rationale is as follows:

- it creates more complex instances
- it requires slicing to apply constraints to what relationships are supported, what cardinalities are allowed, which resource types are permitted, etc.
- it creates the possibility of ambiguity as to what's in core. Relationships that aren't part of core shouldn't be included as part of core whether explicit relationships or the code+reference approach is used

code + reference is appropriate if the number of "core" relationship types is large (>~5) and the referenced type choices make sense for all of the relationship types. Should ideally be consistent across resources from the same "families" as per QA rules.

## chat.fhir.org implementers > Observation.related target

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- Lloyd McKenzie: The proposal that OO is considering would eliminate Observation.related and instead add Observation.component and a few others, as well as some extensions.
- Eric Haas: Lloyd is partially correct. We already have Observation.component. There are many possible ways to express an interpretation including and inline interpretation code element in Observation, or simply grouping an interpretation observation along with the others within a diagnostic report kind of like is done in V2 messaging. 'derived-from' is can also be to say that the interpretation value was deduced or inferred from the target Observation(s).  
I don't know what direction the WG is going to go on this, but I think if we choose to inline with the related we would have a .member and .derivedFrom elements.

# Where to put phaseset?

---

- In the Sequence Resource?
  - Sequence.phaseset
- Or in a Profile?
  - Sequence > Consensus-Sequence-Block (currently)
    - sequence-consensus-sequence-blockPhaseset
  - Observation > ObservationForGenetics
    - observation-geneticsPhaseset

# phaseset is currently in consensus-sequence-block

## 4.36.10 Profile for Consensus Sequence Block 🌐

### 4.36.10.1 Content 🌐

#### Profiles:

Consensus-sequence-block

Describes consensus sequence block used in HLA typing report

#### Extensions:

sequence-consensus-sequence-blockPhaseSet

#### Phase Set :

A phase set identifier to associate different consensussequence-blocks.

sequence-consensus-sequence-blockExpectedCopyNumber

#### Expected Copy Number :

To indicated how many copies of the sequence block was expected.

sequence-consensus-sequence-blockContinuity

#### Continuity :

A continuity flag to indicate whether a gap exists between blocks.

sequence-consensus-sequence-blockStrand

#### Strand :

Strand.

## Extension: Phase Set

URL for this extension:

<http://hl7.org/fhir/StructureDefinition/sequence-consensus-sequence-blockPhaseSet>

Status: draft. Extension maintained by: Health Level Seven International (Clinical Genomics)

A phase set identifier to associate different consensussequence-blocks.

Context of Use: Use on element: Sequence

usage info: insert a list of places where this extension is used

## Extension Content

### Summary

### Full Structure

### XML

### JSON

### All

### Summary

Name	Flags	Card.	Type	Description & Constraints
★ extension		0..1	integer	URL = <a href="http://hl7.org/fhir/StructureDefinition/sequence-consensus-sequence-blockPhaseSet">http://hl7.org/fhir/StructureDefinition/sequence-consensus-sequence-blockPhaseSet</a> Phase Set: A phase set identifier to associate different consensussequence-blocks. Use on element: Sequence



? [Documentation for this format](#)

change to uri

# Sequence.phaseSet

---

- Mock up in staging site
  - <http://genomics-advisor.smartplatforms.org:4000/sequence.html>

  phaseSet	0..1	uri	Phase set identifier (UUID/OID)
--	------	-----	---------------------------------------

```

<Sequence>
  <text>
    <div>
      <pre>"HLA-A*01:01:01:01, exon 2"</pre>
    </div>
  </text>
  <type value="DNA"/>
  <patient>
    <reference value="Patient/98944/_history/1"/>
  </patient>
  <specimen>
    <reference value="Specimen/98945/_history/1"/>
  </specimen>
  <phaseSet value="urn:uuid:56078a59-9c8a-4f50-a06a-7d628c2a3dac"/>
  <referenceSeq>
    <referenceSeqId>
      <coding>
        <system value="http://www.ebi.ac.uk/ipd/imgt/hla"/>
        <version value="3.23"/>
        <code value="HLA00001"/>
      </coding>
      <text value="HLA-A*01:01:01:01"/>
    </referenceSeqId>
    <windowStart value="0"/>
    <windowEnd value="3503"/>
  </referenceSeq>
  <observedSeq
value="GCTCCCACTCCATGAGGTATTTCTTCACATCCGTGTCCCGGCCCGGCCGCGGGGAGCCCCGCTTCATCGCCGTGGGCTACGTGGACGAC
ACGCAGTTCGTGCGGTTTCGACAGCGACGCCGCGAGCCAGAAGATGGAGCCGCGGGCGCCGTGGATAGAGCAGGAGGGGCCGGAGTATTGGGACCAG
GAGACACGGAATATGAAGGCCCACTCACAGACTGACCGAGCGAACCTGGGGACCCTGCGCGGCTACTACAACCAGAGCGAGGACG"/>
</observedSeq>
</Sequence>

```