

A formalization of one of the main claims of “FTO Obesity Variant Circuitry and Adipocyte Browning in Humans” by Claussnitzer et al. 2015¹

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Abstract. Claussnitzer et al. claimed in previous work that a regulatory element within the first intron of FTO affects IRX3 and IRX5 expression during early adipogenesis. We present here a formalization of that claim, stating that all things of class “early human adipogenesis” that are in the context of a thing of class “regulatory element within the first intron of FTO” generally have a relation of type “affects” to a thing of class “expression of genes IRX3 and IRX5” in the same context.

Keywords: Early human adipogenesis, regulatory element within the first intron of FTO, expression of genes IRX3 and IRX5

1. Introduction

Claussnitzer et al. [1] state that “The rs1421085 T-to-C single-nucleotide variant disrupts a conserved motif for the ARID5B repressor, which leads to derepression of a potent preadipocyte enhancer and a doubling of IRX3 and IRX5 expression during early adipocyte differentiation.”. We present here a formalization of the main scientific claim from this quote by using a semantic template called the super-pattern [2].

2. Formalization

Our formalization looks as follows:

¹As RDF/nanopublication: http://purl.org/np/RAXBBJ2WkonyQNIXfdCAOaCi64J_xqgVGeaLjVQow9M88

CONTEXT-CLASS (“in the context of all ...”):	early human adipogenesis
SUBJECT-CLASS (“things of type ...”):	regulatory element within the first intron of FTO
QUALIFIER:	generally
RELATION-TYPE (“have a relation of type...”):	affects
OBJECT-CLASS (“to things of type...”):	expression of genes IRX3 and IRX5

In the context class we use a new minted class “early human adipogenesis” that is a subclass of “adipogenesis” (Q2824461) from Wikidata. In the subject class, we use a new minted class “regulatory element within the first intron of FTO” that is related to the class “FTO” (Q14912501) and “intron” (Q207551) from Wikidata. In the object class we minted a new class “expression of genes IRX3 and IRX5” that is a subclass of “gene expression” (Q26972) from Wikidata and is related to the class “IRX5” (Q18035174) and “IRX3” (Q18046058) from Wikidata.

3. RDF Code

This is our formalization as a nanopublication in TriG format:

```
@prefix this: <http://purl.org/np/RAXBBJ2WkonyQNLXfdCAOaCi64J_xqgVGealJVQow9M88> .
@prefix sub: <http://purl.org/np/RAXBBJ2WkonyQNLXfdCAOaCi64J_xqgVGealJVQow9M88#> .
@prefix np: <http://www.nanopub.org/nschema#> .
@prefix dct: <http://purl.org/dc/terms/> .
@prefix nt: <https://w3id.org/np/o/ntemplate/> .
@prefix npx: <http://purl.org/nanopub/x/> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#> .
@prefix orcid: <https://orcid.org/> .
@prefix prov: <http://www.w3.org/ns/prov#> .
@prefix sp: <https://w3id.org/linkflows/superpattern/terms/> .

sub:Head {
  this: np:hasAssertion sub:assertion ;
  np:hasProvenance sub:provenance ;
  np:hasPublicationInfo sub:pubinfo ;
  a np:Nanopublication .
}
sub:assertion {
  sub:spi a sp:SuperPatternInstance ;
  rdfs:label "A regulatory element within the first intron of FTO affects IRX3 and IRX5 expression during early
adipogenesis" ;
  sp:hasContextClass <http://purl.org/np/RAtsHwzNs36rGrLnoSbGrPD351Qw033Acoe4zmdXhsYlM#early-human-adipogenesis> ;
  sp:hasSubjectClass <http://purl.org/np/RAXLYvJ1JrRf2JAowYgBgJleQPMqtpXnXsIvse7GmLeT8#regulatory-element-within-the-first
-intron-of-FTO> ;
  sp:hasQualifier sp:generallyQualifier ;
  sp:hasRelation sp:affects ;
  sp:hasObjectClass <http://purl.org/np/RAwXITv7qCtqOYz1R6ozZRGLRtG6mlogrYdRQ1E4dRDg#expression-of-genes-IRX3-and-IRX5> .
}
sub:provenance {
  sub:activity a sp:FormalizationActivity ;
  prov:used sub:quote , <https://doi.org/10.1056/NEJMoa1502214> ;
  prov:wasAssociatedWith orcid:0000-0003-2432-4125 .
  sub:assertion prov:wasGeneratedBy sub:activity .
  sub:quote prov:value "The rs1421085 T-to-C single-nucleotide variant disrupts a conserved motif for the ARID5B repressor,
which leads to derepression of a potent preadipocyte enhancer and a doubling of IRX3 and IRX5 expression during
early adipocyte differentiation." ;
  prov:wasQuotedFrom <https://doi.org/10.1056/NEJMoa1502214> .
}
sub:pubinfo {
  sub:sig npx:hasAlgorithm "RSA" ;
  npx:hasPublicKey "MIGfMA0GCsGqSIb3DQEBAQUAA4GNADCBiQKBgQCS1s10iABv1mrDnFWp9ecwHdQ+U1Jn6JCDYXspRsbZgsm2QAiofbnVvf6gfkcjj
Scd5fQ3sW/W8r/o7bdafVSD6xuTG/vHrO9Ax/guPij6O/Z57Hk0nQy6c+171HpaJ2BPPWKogYiFZ/8eulmuM6BJ8TDKxcoBtcqP5QbvN9KYj1QIDAQAB" ;
  npx:hasSignature "MUs9dML4QrzQVnft2hqnfkif+lpusIVT0o4c74M69kgNQmA0CXVRzUZIHcvavS/pMlobVFBhfktQ7kHs5a0CZGvrvtOhQJYD17eXzg
6dwD/LqdYNYErVwxduyvWInXMasXpDzdYkFtddAft/5Vny6BSBo1IzclnGFgwhZhFmpg=" ;
  npx:hasSignatureTarget this: .
  this: dct:created "2021-10-27T10:22:03.671-07:00"^^xsd:dateTime ;
  dct:creator orcid:0000-0003-2432-4125 ;
  npx:introduces sub:spi ;
  <https://w3id.org/linkflows/reviews/isUpdateOf> <http://purl.org/np/RAXxJWyH80dTJLs-ZY1q5jVq10WFNoLFvWecUFyR8EEo> ;
  nt:wasCreatedFromProvenanceTemplate <http://purl.org/np/RAB_oy10D3XUP-zY1qGz7Uj58AsUXhEKeGmRFg5LsgDM> ;
}
```

```

nt:wasCreatedFromPubinfoTemplate <http://purl.org/np/RAA2MfqdBczmz9yVWjKLXNbyfBNcwsMmOqcNuxkk1maIM> ,
<http://purl.org/np/RAOGu9Lh0BD4tbIRB9RG6RGRA_ObDh75NTbIqaWgxxs8M> ;
nt:wasCreatedFromTemplate <http://purl.org/np/RAV68imZrEjfcP2rnEglhzoBqEvc0cQMtp9_1za0BxNM4> .
}

```

The following nanopublications introduce the newly minted classes in TriG format.
This is the class definition of “early human adipogenesis”:

```

@prefix this: <http://purl.org/np/RAtsHwzNs36rGrLnoSbGrPD351Qw033Acoe4zmdXhsYlM> .
@prefix sub: <http://purl.org/np/RAtsHwzNs36rGrLnoSbGrPD351Qw033Acoe4zmdXhsYlM#> .
@prefix np: <http://www.nanopub.org/nschema#> .
@prefix dct: <http://purl.org/dc/terms/> .
@prefix nt: <https://w3id.org/np/o/ntemplate/> .
@prefix npx: <http://purl.org/nanopub/x/> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#> .
@prefix orcid: <https://orcid.org/> .
@prefix prov: <http://www.w3.org/ns/prov#> .
@prefix skos: <http://www.w3.org/2004/02/skos/core#> .

sub:Head {
  this: np:hasAssertion sub:assertion ;
  np:hasProvenance sub:provenance ;
  np:hasPublicationInfo sub:pubinfo ;
  a np:Nanopublication .
}
sub:assertion {
  sub:early-human-adipogenesis a <http://www.w3.org/2002/07/owl#Class> ;
  rdfs:label "early human adipogenesis" ;
  rdfs:subClassOf <http://www.wikidata.org/entity/Q2824461> ;
  skos:definition "early human adipogenesis" .
}
sub:provenance {
  sub:assertion prov:wasAttributedTo orcid:0000-0003-2432-4125 .
}
sub:pubinfo {
  sub:sig npx:hasAlgorithm "RSA" ;
  npx:hasPublicKey
  "MIGfMA0GCSqGSIb3DQEBAQUAA4GNADCBiQKBgQCS1s10iABv1mrDnFWp9ecwHdQ+U1Jn6JCDYXspRsbZgsm2QAiofbnVvf6gfkckjScd5f3sW/W8r/
  o7bdafVsd6xUTG/vHr09Ax/guPiJ6O/Z57Hk0nQy6c+l71HpaJ2BPPWkOgYiFZ/8eulmuM6BJ8TDKxoBtcqP5QbvN9KYj1QIDAQAB" ;
  npx:hasSignature
  "eiaG+BcxTl6aKpKUpVosKrOxB6PON3szX55WGjEnlAwV87u5m44huRHXOoDdC/4XgPvT40woR34zhB+VqVlJoiZmk6rTPEVRENSG8vdxq3Wdbj6W4qJszB1mxb
  +XFw2Awdj/4IzNIzK1/at9WQvIE5rV8tkYIvSnmLFWTxKvL/A=" ;
  npx:hasSignatureTarget this: .
  this: dct:created "2021-06-21T16:44:19.998-07:00"^^xsd:dateTime ;
  dct:creator orcid:0000-0003-2432-4125 ;
  npx:introduces sub:early-human-adipogenesis ;
  nt:wasCreatedFromProvenanceTemplate <http://purl.org/np/RANwQa4ICWS5SOjw7gp99nBpXBasapwtZF1fIM3H2gYTM> ;
  nt:wasCreatedFromPubinfoTemplate <http://purl.org/np/RAA2MfqdBczmz9yVWjKLXNbyfBNcwsMmOqcNuxkk1maIM> ;
  nt:wasCreatedFromTemplate <http://purl.org/np/RADpgrpigXtt8iPV9uOPf3wIT3qzOI8Sg2Q72CNV8g-Yo> .
}

```

This is the class definition of “regulatory element within the first intron of FTO”:

```

@prefix this: <http://purl.org/np/RAXLYvJlJrRf2JAowYGbGJleQPmqtPxnXsIvse7GmLeT8> .
@prefix sub: <http://purl.org/np/RAXLYvJlJrRf2JAowYGbGJleQPmqtPxnXsIvse7GmLeT8#> .
@prefix np: <http://www.nanopub.org/nschema#> .
@prefix dct: <http://purl.org/dc/terms/> .
@prefix nt: <https://w3id.org/np/o/ntemplate/> .
@prefix npx: <http://purl.org/nanopub/x/> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#> .
@prefix orcid: <https://orcid.org/> .
@prefix prov: <http://www.w3.org/ns/prov#> .
@prefix skos: <http://www.w3.org/2004/02/skos/core#> .

sub:Head {
  this: np:hasAssertion sub:assertion ;
  np:hasProvenance sub:provenance ;
  np:hasPublicationInfo sub:pubinfo ;
  a np:Nanopublication .
}
sub:assertion {
  sub:regulatory-element-within-the-first-intron-of-FTO a <http://www.w3.org/2002/07/owl#Class> ;
  rdfs:label "regulatory element within the first intron of FTO" ;
  skos:definition "a regulatory element present within the first intron of the human gene FTO" ;
  skos:relatedMatch <http://www.wikidata.org/entity/Q14912501> , <http://www.wikidata.org/entity/Q207551> .
}
sub:provenance {

```

```

    sub:assertion prov:wasAttributedTo orcid:0000-0003-2432-4125 .
  }
  sub:pubinfo {
    sub:sig npx:hasAlgorithm "RSA" ;
    npx:hasPublicKey
    "MIGfMA0GCSqGSIb3DQEBAQUAA4GNADCBiQKBgQCS1s10iABv1mrDnFWp9ecwHdQ+U1Jn6JCDYXspRsbZgsm2QAiofbnVvf6gfkckjScd5fq3sW/W8r/
    o7bdafVsd6xutG/vHrO9Ax/guPiJ6O/Z57Hk0nQy6c+17lHpaJ2BPPWKogYiFZ/8eulmuM6BJ8TDKxoBtcqP5QbvN9KYj1QIDAQAB" ;
    npx:hasSignature
    "M8cVwUkflLauLgLUm+ul7EgLSXQhcSsberJUCBwTF2Ri78XD6JNdHsF5+Qekg3xefqy7d8530m2RHPxjSkooNi3XAOZwsd2T6OziZ0lSmAIsaRarmsnHbl/
    GDF00S40iqCLljVFNXMosdVd9runltov655znbpiFBjxmMd66+v0=" ;
    npx:hasSignatureTarget this: .
    this: dct:created "2021-10-27T10:04:01.217-07:00"^^xsd:dateTime ;
    dct:creator orcid:0000-0003-2432-4125 ;
    npx:introduces sub:regulatory-element-within-the-first-intron-of-FTO ;
    npx:supersedes <http://purl.org/np/RANaxL2OxGmP9VAN6cUi_0KEK0rJb9bPn411A5HquXKrI> ;
    <https://w3id.org/linkflows/reviews/isUpdateOf> <http://purl.org/np/RANaxL2OxGmP9VAN6cUi_0KEK0rJb9bPn411A5HquXKrI> ;
    nt:wasCreatedFromProvenanceTemplate <http://purl.org/np/RANwQa4ICWS5SOjw7gp99nBpXBasapwtZF1fIM3H2gYTM> ;
    nt:wasCreatedFromPubinfoTemplate <http://purl.org/np/RAA2MfqdBczmz9yVWjKLXNbyfBNcwsMmOqcNUxkk1maIM> ,
    <http://purl.org/np/RAOGu9Lh0BD4tbIRB9RG6RGRA_ObDh75NTbIqaWgxxs8M> ,
    <http://purl.org/np/RAjpBMLw3owYhJUBo3DtSuDlXsNAJ8cnGeWAutDVjuAuI> ;
    nt:wasCreatedFromTemplate <http://purl.org/np/RADpgRpigXtt8iPV9uOf3wIT3qzOI8Sg2Q72CNV8g-Yo> .
  }

```

This is the class definition of “expression of genes IRX3 and IRX5”:

```

@prefix this: <http://purl.org/np/RAwXiTv7qCtqOYz1R6ozZRGLRtG6mlogrYdRQ1E4dRDg> .
@prefix sub: <http://purl.org/np/RAwXiTv7qCtqOYz1R6ozZRGLRtG6mlogrYdRQ1E4dRDg#> .
@prefix np: <http://www.nanopub.org/nschema#> .
@prefix dct: <http://purl.org/dc/terms/> .
@prefix nt: <https://w3id.org/np/o/ntemplate/> .
@prefix npx: <http://purl.org/nanopub/x/> .
@prefix xsd: <http://www.w3.org/2001/XMLSchema#> .
@prefix rdfs: <http://www.w3.org/2000/01/rdf-schema#> .
@prefix orcid: <https://orcid.org/> .
@prefix prov: <http://www.w3.org/ns/prov#> .
@prefix skos: <http://www.w3.org/2004/02/skos/core#> .

sub:Head {
  this: np:hasAssertion sub:assertion ;
  np:hasProvenance sub:provenance ;
  np:hasPublicationInfo sub:pubinfo ;
  a np:Nanopublication .
}
sub:assertion {
  sub:expression-of-genes-IRX3-and-IRX5 a <http://www.w3.org/2002/07/owl#Class> ;
  rdfs:label "expression of genes IRX3 and IRX5" ;
  rdfs:subClassOf <http://www.wikidata.org/entity/Q26972> ;
  skos:definition "Expression of the human genes IRX3 and IRX5" ;
  skos:relatedMatch <http://www.wikidata.org/entity/Q18035174> , <http://www.wikidata.org/entity/Q18046058> .
}
sub:provenance {
  sub:assertion prov:wasAttributedTo orcid:0000-0003-2432-4125 .
}
sub:pubinfo {
  sub:sig npx:hasAlgorithm "RSA" ;
  npx:hasPublicKey
  "MIGfMA0GCSqGSIb3DQEBAQUAA4GNADCBiQKBgQCS1s10iABv1mrDnFWp9ecwHdQ+U1Jn6JCDYXspRsbZgsm2QAiofbnVvf6gfkckjScd5fq3sW/W8r/
  o7bdafVsd6xutG/vHrO9Ax/guPiJ6O/Z57Hk0nQy6c+17lHpaJ2BPPWKogYiFZ/8eulmuM6BJ8TDKxoBtcqP5QbvN9KYj1QIDAQAB" ;
  npx:hasSignature
  "kT9nlq5nE5y03RkSemozUyzyNgdKTIpY7WlwiDD2ZlRrHlOxQpbq+VPME6Ay3oEgTi/WuE5o6AY+dGK4V6eLcVnDQ1xqC7GanaD5JGL89a5Z/
  oBkHf1JG8fHQFOATrg4n62hcjGeRZOZrZLjdnAozGdDQf19gxq78E4QTYo=" ;
  npx:hasSignatureTarget this: .
  this: dct:created "2021-10-27T09:44:46.276-07:00"^^xsd:dateTime ;
  dct:creator orcid:0000-0003-2432-4125 ;
  npx:introduces sub:expression-of-genes-IRX3-and-IRX5 ;
  npx:supersedes <http://purl.org/np/RANjcIDg1VkgWDSqxkFyVn__2UEbR-V7y81qtV4rxcLJk> ;
  <https://w3id.org/linkflows/reviews/isUpdateOf>
  <http://purl.org/np/RAY3LaUoVtBLj9CN36wyyvTIjSMsACerVtEApnA12zjy0> ;
  nt:wasCreatedFromProvenanceTemplate <http://purl.org/np/RANwQa4ICWS5SOjw7gp99nBpXBasapwtZF1fIM3H2gYTM> ;
  nt:wasCreatedFromPubinfoTemplate <http://purl.org/np/RA2vCBXZf-icEcvRGhu1JXugTGxpsV5Yr9yqCI1bQh4A> ,
  <http://purl.org/np/RAA2MfqdBczmz9yVWjKLXNbyfBNcwsMmOqcNUxkk1maIM> ,
  <http://purl.org/np/RAjpBMLw3owYhJUBo3DtSuDlXsNAJ8cnGeWAutDVjuAuI> ;
  nt:wasCreatedFromTemplate <http://purl.org/np/RADpgRpigXtt8iPV9uOf3wIT3qzOI8Sg2Q72CNV8g-Yo> .
}

```

References

- [1] M. Claussnitzer, S.N. Dankel, K.-H. Kim, G. Quon, W. Meuleman, C. Haugen, V. Glunk, I.S. Sousa, J.L. Beaudry, V. Puv-

- indran, N.A. Abdennur, J. Liu, P.-A. Svensson, Y.-H. Hsu, D.J. Drucker, G. Mellgren, C.-C. Hui, H. Hauner and M. Kellis, FTO Obesity Variant Circuitry and Adipocyte Browning in Humans, *New England Journal of Medicine* **373**(10) (2015), 895–907. doi:[10.1056/NEJMoa1502214](https://doi.org/10.1056/NEJMoa1502214).
- [2] C.I. Bucur, T. Kuhn, D. Ceolin and J. van Ossenbruggen, Expressing high-level scientific claims with formal semantics, in: *Proceedings of the 11th Knowledge Capture Conference 2021*. doi:[10.1145/3460210.3493561](https://doi.org/10.1145/3460210.3493561).