Diagnosis of Vascular Ehlers Danlos Syndrome (VEDS)

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Disclosures

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An academic diagnostic laboratory

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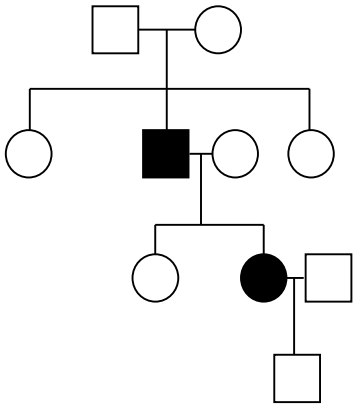
https://thevedsmovement.org/

https://translucentone.blog/2020/02/29/the-movement/

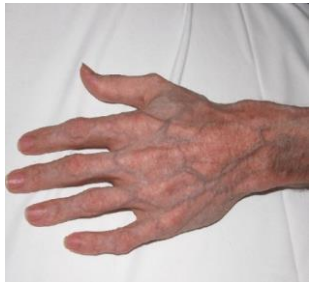
Context of Diagnosis

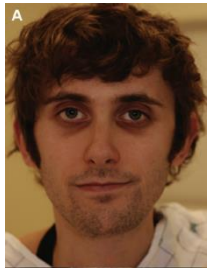
- Immediate need—acute patient presentation with major vascular event
- Follow up of referral from another provider to develop a care plan
- Request from a patient with a “diagnosis” of VEDS to act as part of a care team

Immediate need



- Past medical history
  - Pneumothorax, vascular events, bowel rupture, bruising
- Genetic testing
- Family history
- Genetic testing in the family and results
- Physical exam

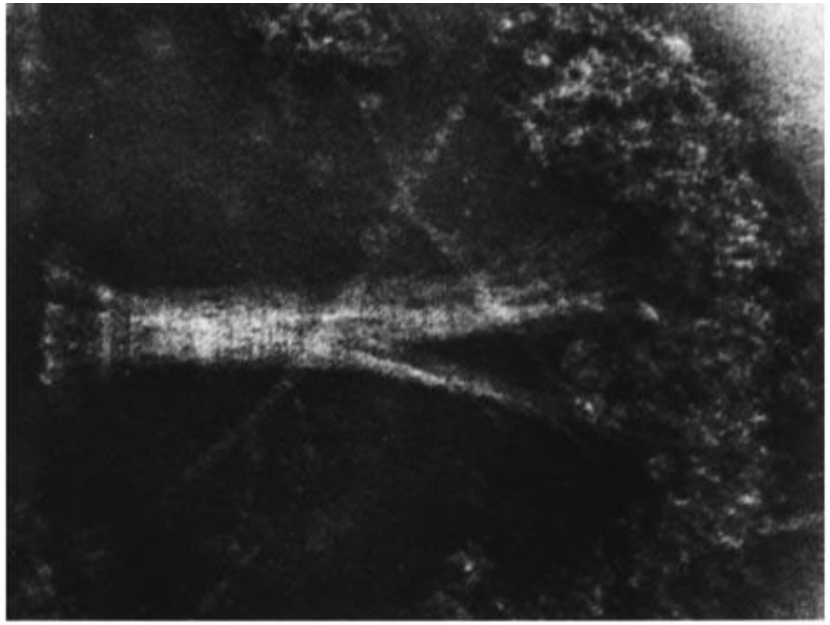


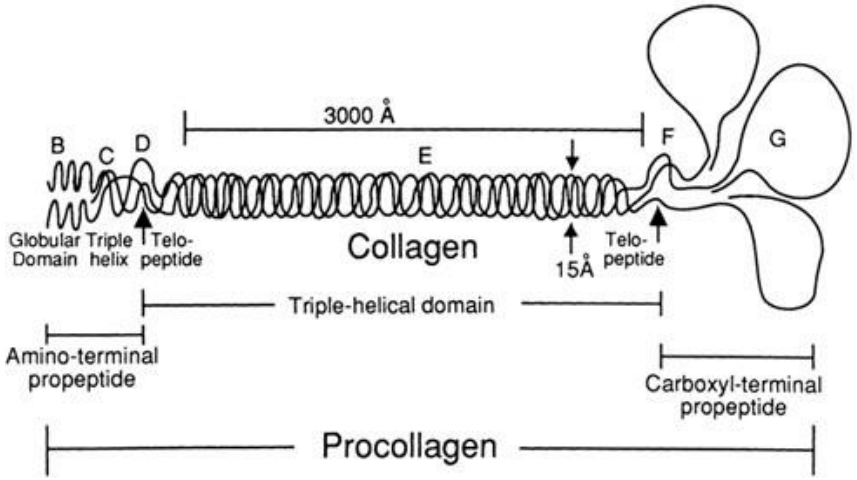


Non-urgent

- Has genetic testing been done
- If yes, what does the report say
- What does the report mean

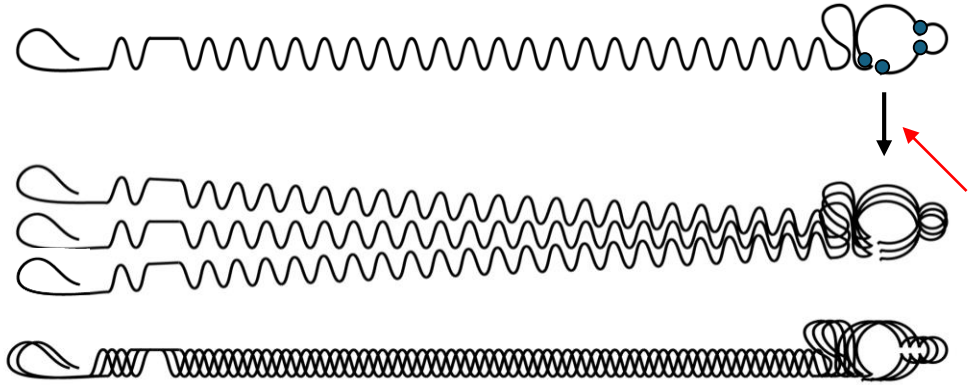
Approaching the 45th Anniversary of the Discovery of Type III Collagen





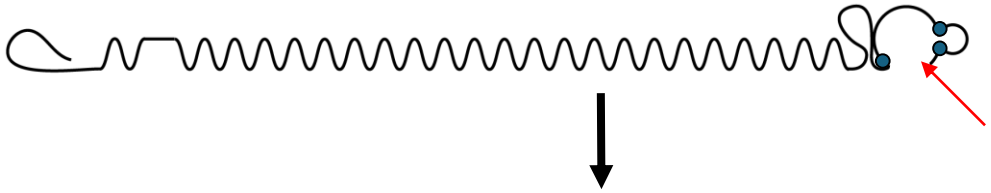
Half-normal amounts of type III procollagen molecules despite mutant mRNA stability

50% normal
proα1(III) chains



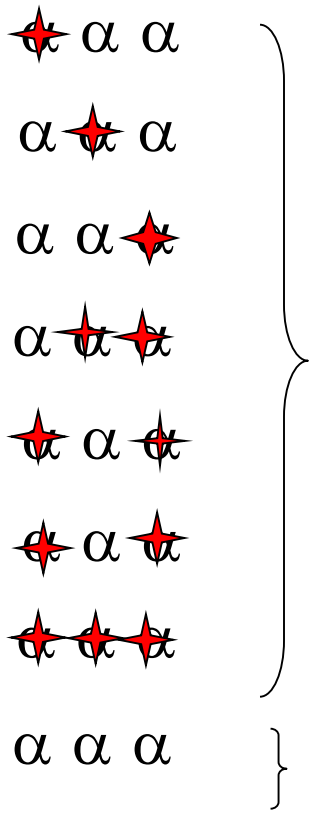
50% normal type III
procollagen

50% truncated
proα1(III) chains



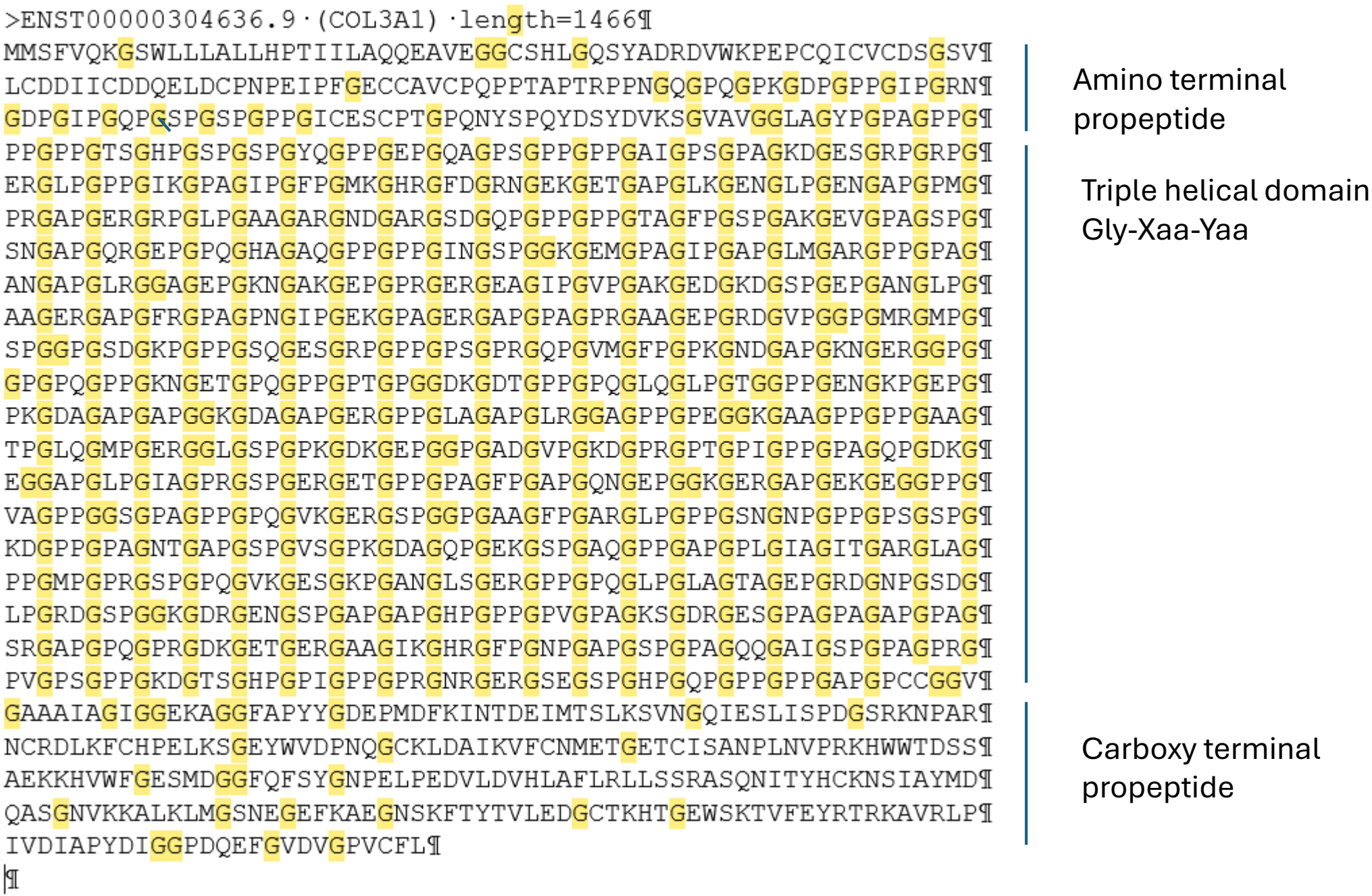
proα1(III) degraded

Dominant negative effect of structurally abnormal proα1(III) chains



7/8 of type III procollagen molecules are **abnormal**

1/8 of type III procollagen molecules are **normal**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LCDDIICDDQELDCPNPEIPFGECCAVCPQPPTAPTRPPNGQGPQGPKGDPGPPGIPGRN¶
GDPGIPGQPGSPGSPGPPGICESCPTGPQNYSPQYDSYDVKSGVAVGGLAGYPGPAGPPG¶
PPGPPGTSGHPGSPGSPGYQGPPGEPGQAGPSGPPGPPGAIGPSGPAGKDGESGRPGRPG¶
ERGLPGPPGIKGPAGIPGFPGMKGHRGFDGRNGEKGETGAPGLKGENGLPGENGAPGPMG¶
PRGAPGERGRPGLPGAAGARGNDGARGSDGQPGPPGPPGTAGFPGSPGAKGEVGPAGSPG¶
SNGAPGQRGEPGPQGHAGAQGPPGPPGINGSPGGKGEMGPAGIPGAPGLMGARGPPGPAG¶
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GPGPQGPPGKNGETGPQGPPGPTGPGGDKGDTGPPGPQGLQGLPGTGGPPGENGKPGEPG¶
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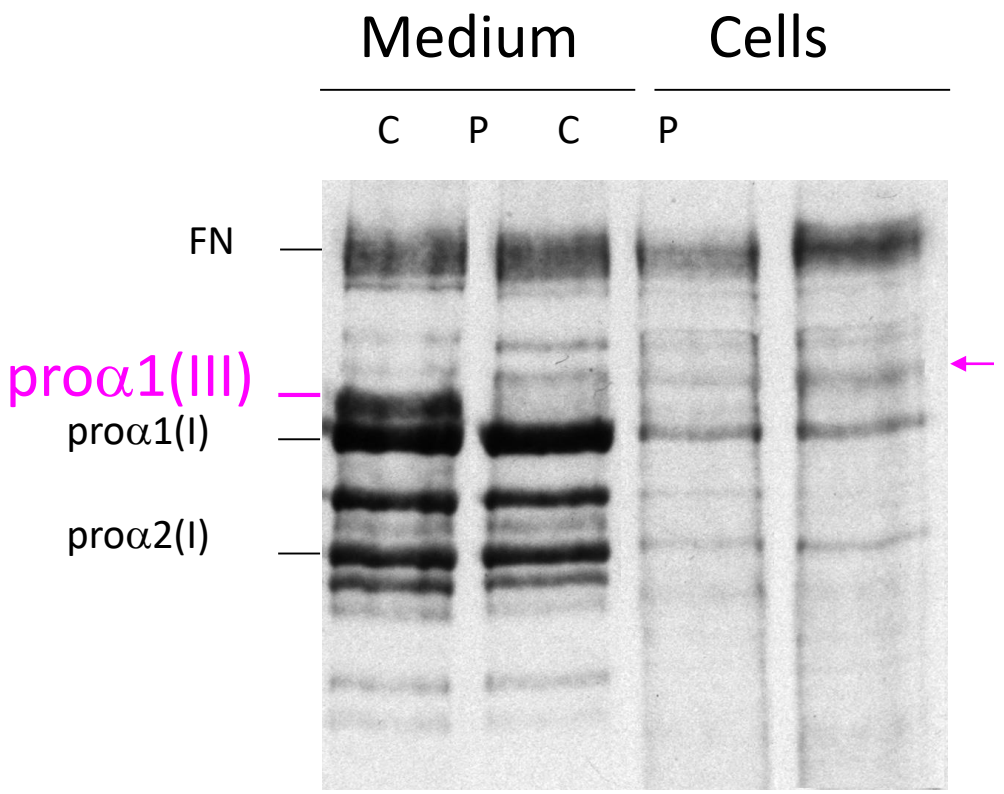
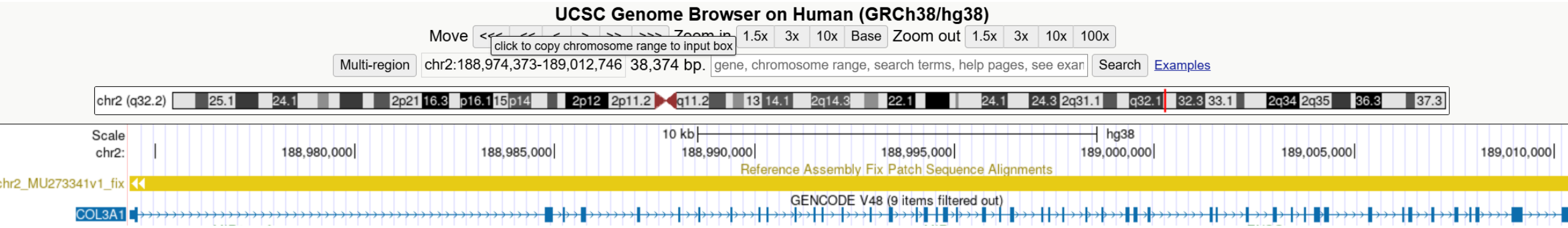
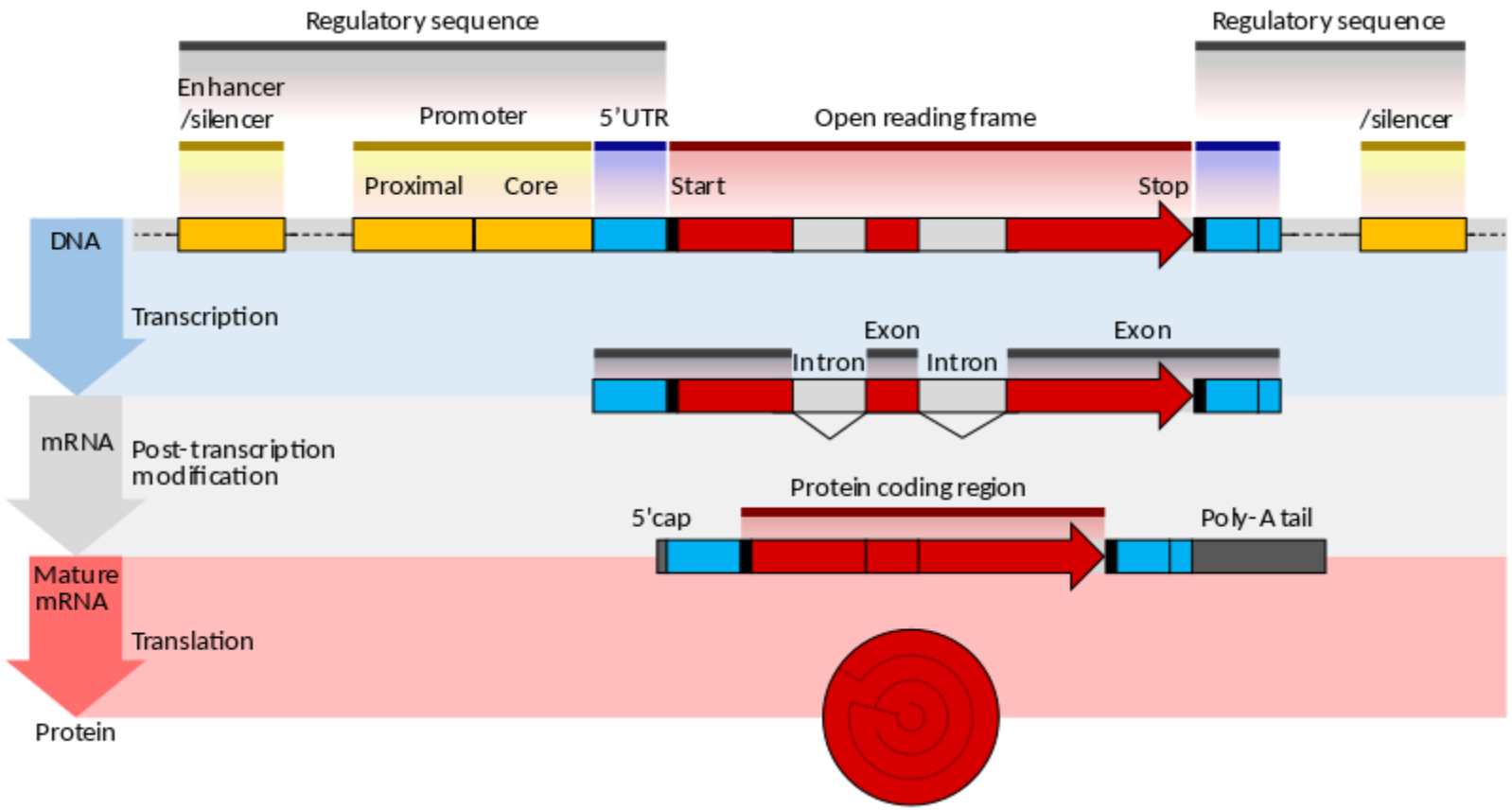
TPGLQGMPGERGGLGSPGPKGDKGEPGGPGADGVPGKDGPRGPTGPIGPPGPAGQPGDKG¶
EGGAPGLPGIAGPRGSPGERGETGPPGPAGFPGAPGQNGEPGGKGERGAPGEKGEGGPPG¶
VAGPPGGSGPAGPPGPQGVKGERGSPGGPGAAGFPGARGLPGPPGSNGNPGPPGPSGSPG¶
KDGPPGPAGNTGAPGSPGVSGPKGDAGQPGEKGSPGAQGPPGAPGPLGIAGITGARGLAG¶
PPGMPGPRGSPGPQGVKGESGKPGANGLSGERGPPGPQGLPGLAGTAGEPGRDGNPGSDG¶
LPGRDGSPGGKGDRGENGSPGAPGAPGHPGPPGPVGPAGKSGDRGESGPAGPAGAPGPAG¶
SRGAPGPQGPRGDKGETGERGAAGIKGHRGFPGNPGAPGSPGPAGQQGAIGSPGPAGPRG¶
PVGPSGPPGKDGTSGHPGPIGPPGPRGNRGERGSEGSPGHPGQPGPPGPPGAPGPCCGGV¶
GAAAIAGIGGEKAGGFAPYYGDEPMDFKINTDEIMTSLKSVNGQIESLISPDGSRKNPAR¶
NCRDLKFCHPELKSGEYWVDPNQGCKLDAIKVFCNMETGETCISANPLNVPRKHWWTDSS¶
AEKKHVWFGESMDGGFQFSYGNPELPEDVLDVHLAFLRLLSSRASQNITYHCKNSIAYMD¶
QASGNVKKALKLMGSNEGEFKAEGNSKFTYTVLEDGCTKHTGEWSKTVFEYRTRKAVRLP¶
IVDIAPYDIGGPDQEFGVDVGPVCFL¶
¶
Amino terminal propeptide
Triple helical domain Gly-Xaa-Yaa
Carboxy terminal propeptide

Analysis of type III collagen production by fibroblasts

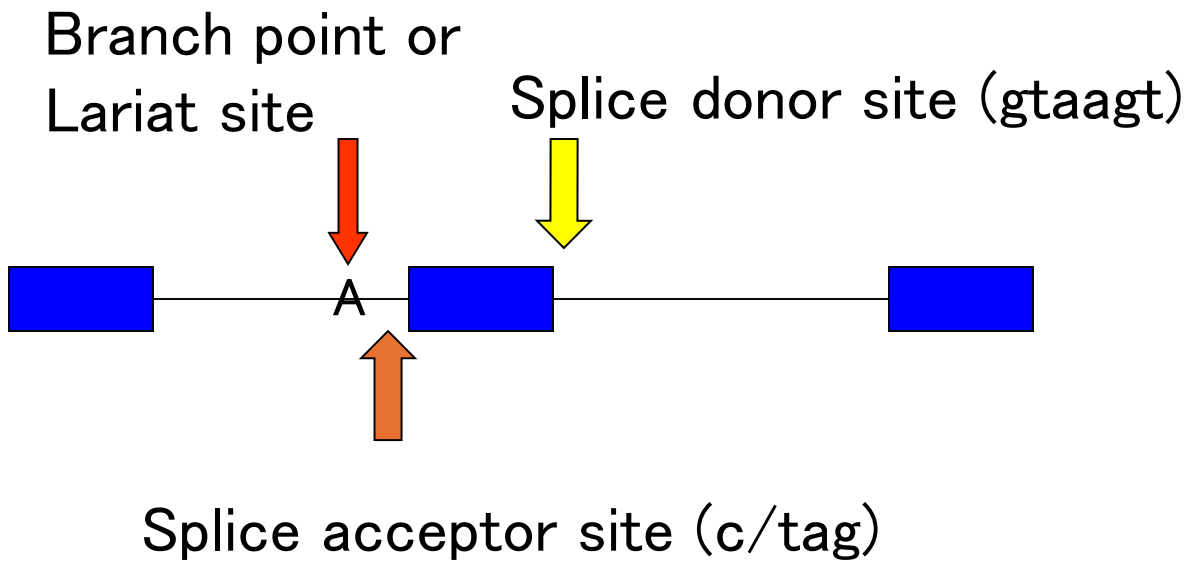
Procollagens




UCSC Genome Browser on Human (GRCh38/hg38)
Move
click to copy chromosome range to input box
1.5x
3x
10x
Base
Zoom out
1.5x
3x
10x
100x
Multi-region
chr2:188,974,373-189,012,746
38,374 bp.
gene, chromosome range, search terms, help pages, see exar
Search
Examples
chr2 (q32.2)
Scale
chr2:
10 kb
hg38
188,980,000
188,985,000
188,990,000
188,995,000
189,000,000
189,005,000
189,010,000
Reference Assembly Fix Patch Sequence Alignments
hr2_MU273341v1_fix
GENCODE V48 (9 items filtered out)
COL3A1


Regulatory sequence
Regulatory sequence
Enhancer
/silencer
Promoter
5'UTR
Open reading frame
/silencer
Proximal
Core
Start
Stop
DNA
Transcription
Exon
Exon
Intron
Intron
mRNA
Post-transcription
modification
Protein coding region
5'cap
Poly-A tail
Mature
mRNA
Translation
Protein

Important Elements of Splice Sites



Gene

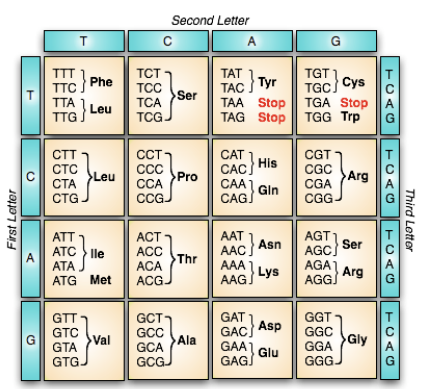
agagtggcaagagagcagcccgttcactaacacctttgtcctgggttctc
cgtctctgatcttagagtcctgatcattgctctcctgtccctgtctcccc
ttcctcctgccatcccgagaggcaaggttgggtttcccagggtggcttct
gatatgtcctttcttctgatt**cag**GGTGAAGCTGGTCCCCAAGGGCCCCG
AGGCTCTGAAGGTCCCCAGGGTGTGCGTGGTGAGCCTGGCCCCCCTGGCC
CTGCTGGTGCTGCTGGCCCTGCT**gtaagt**gtccccgactcagtgtcccct
ttgccactttctaacctcagagtccttgcctgttgctgacac

Transcription and splicing:

A>A, C>C, G>G, T>U

mRNA

GGUGAAGCU**GGU**CCCCAA**GGG**CCCCGA**GGC**UCUGAA**GGU**CCCCA**GGG**U
GUGCGU**GGU**GAGCCU**GGC**CCCCCU**GGC**CCUGCU**GGU**GCUGCU**GGC**CCU
GCU



Translation

Protein

GlyGluAla**Gly**ProGln**Gly**ProArg**Gly**SerGlu**Gly**ProGln**Gly**ValArg
GlyGluPro**Gly**ProPro**Gly**ProAla**Gly**AlaAla**Gly**ProAla

Missense/nonsense mutation

Single nucleotide substitutions in codons

GGT>CGT (Gly>Arg)

GGA>TGA (Gly>Ter)

COL3A1:c.1816G>C, p.Gly606Arg

COL3A1:c.3847C>T, p.Gln1283Ter(*)

Splice site mutation

cagGGTCCTCGTgtaagt

-321 +12345

COL3A1:c.997-1G>C, p.Gly333Lys_350del

COL3A1:c.2824-1G>A, p.Gln942fs*294

COL3A1:c.1662+1G>T, p.Gly537_Pro554del

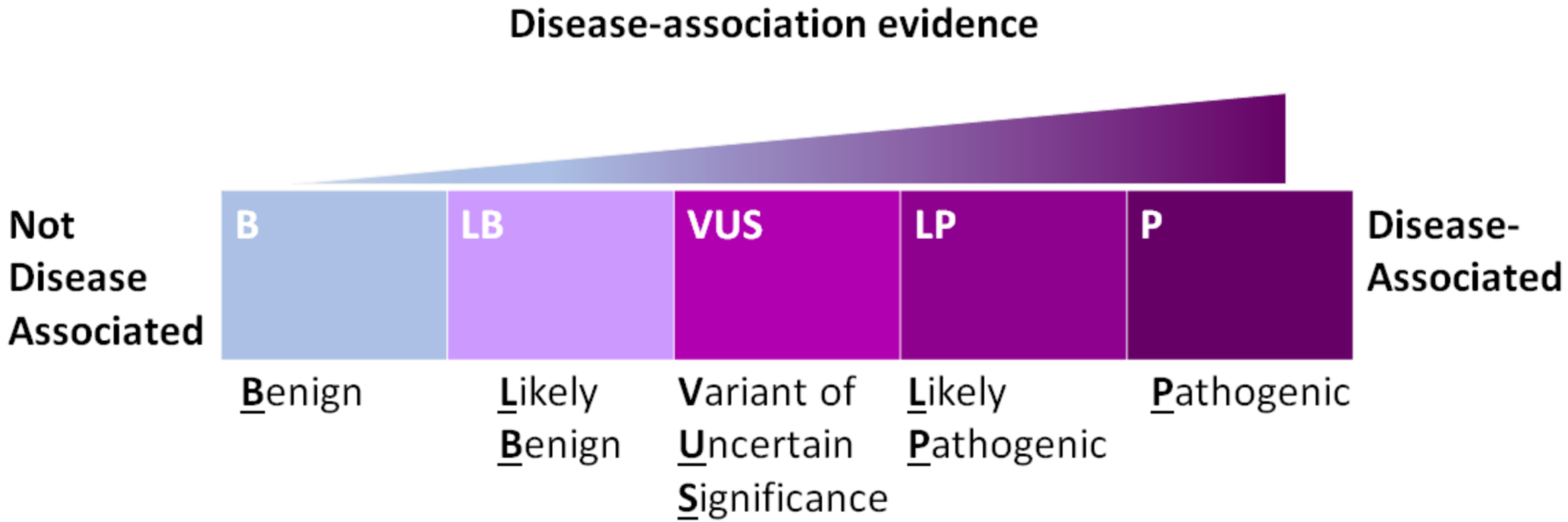
COL3A1:c.789+1G>A, p.Phe268Leu*10

Frame shift mutation (insertion/deletion)

GGT CCT CGT>GTC CTC GT.....TGA

COL3A1:c.776delA, p.Ile256Tyr*7

Gene variants were classified based on ACMG guidelines.



Time to diagnosis

Proteins: 4-6 weeks
Next generation sequence: 3-4 days, usually 7-10 days
Sanger sequence for known mutation: <1day

Future
Targeted long read sequencing: 6-10 hours

Thank you

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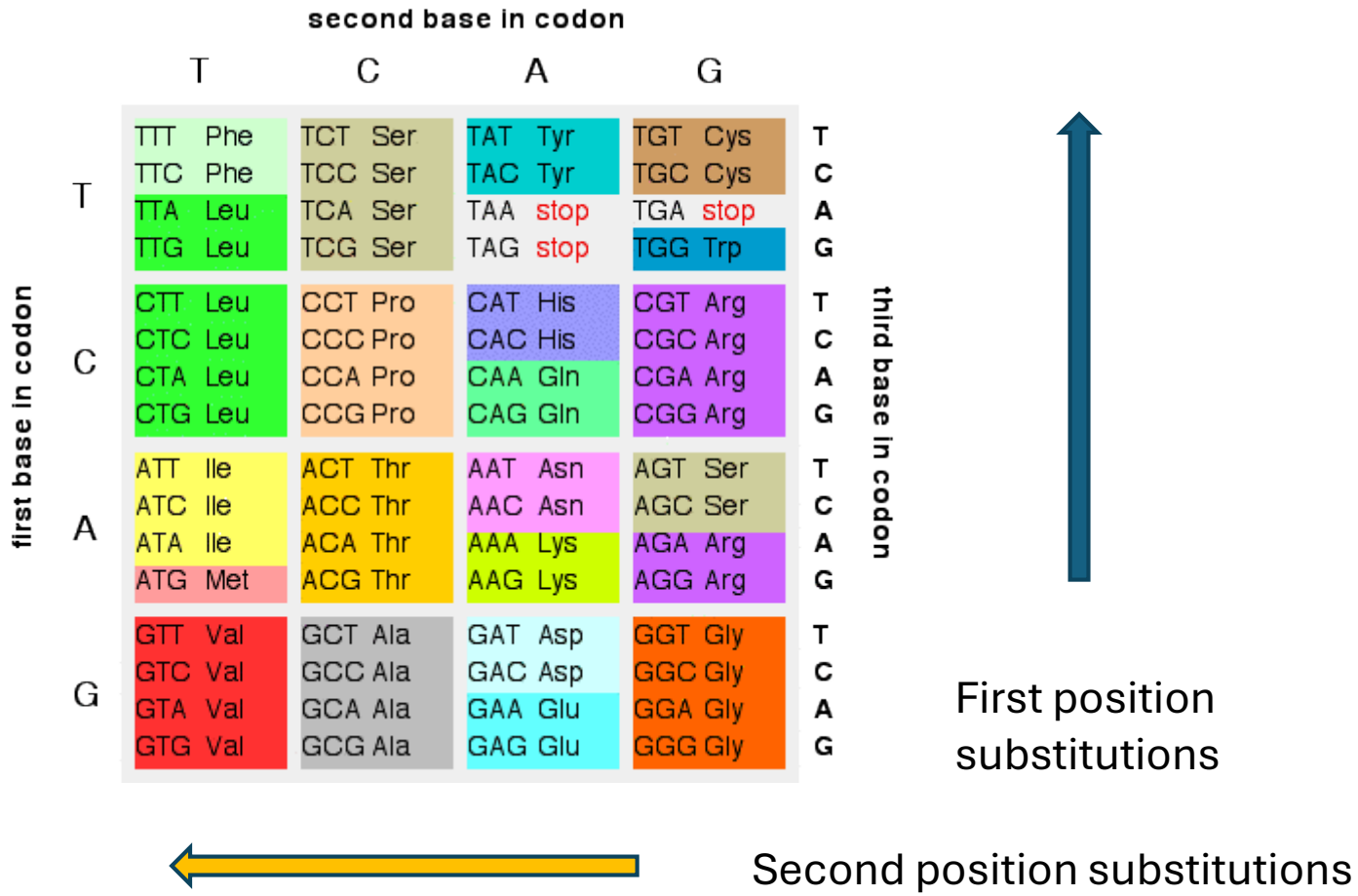
second base in codon
T
C
A
G
first base in codon
third base in codon
T
C
A
G
TTT Phe
TTC Phe
TTA Leu
TTG Leu
TCT Ser
TCC Ser
TCA Ser
TCG Ser
TAT Tyr
TAC Tyr
TAA stop
TAG stop
TGT Cys
TGC Cys
TGA stop
TGG Trp
CTT Leu
CTC Leu
CTA Leu
CTG Leu
CCT Pro
CCC Pro
CCA Pro
CCG Pro
CAT His
CAC His
CAA Gln
CAG Gln
CGT Arg
CGC Arg
CGA Arg
CGG Arg
ATT Ile
ATC Ile
ATA Ile
ATG Met
ACT Thr
ACC Thr
ACA Thr
ACG Thr
AAT Asn
AAC Asn
AAA Lys
AAG Lys
AGT Ser
AGC Ser
AGA Arg
AGG Arg
GTT Val
GTC Val
GTA Val
GTG Val
GCT Ala
GCC Ala
GCA Ala
GCG Ala
GAT Asp
GAC Asp
GAA Glu
GAG Glu
GGT Gly
GGC Gly
GGA Gly
GGG Gly
First position substitutions
Second position substitutions