RECURRENT LUNG INFECTIONS IN A HETEROZYGOUS CARRIER OF NOVEL NSMCE3 MUTATION

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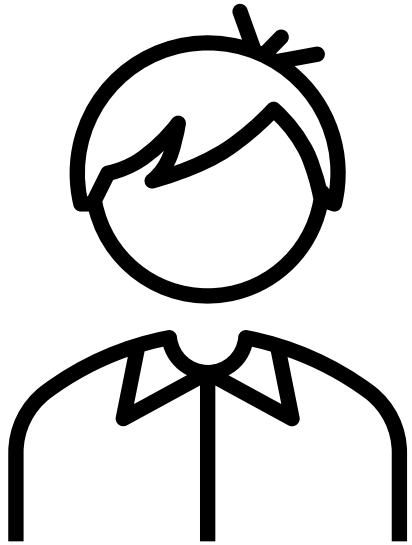
Case

- 5-year-old boy with history of atopic dermatitis and asthma.
- Over the past 4 years, he has had recurrent febrile episodes with more than 5 episodes of otitis media and more than 10 episodes of viral upper respiratory infections (URIs)--most complicated by bacterial pneumonia requiring treatment with oral antibiotics.
- He has not required IV antibiotics to clear the infections.

Case

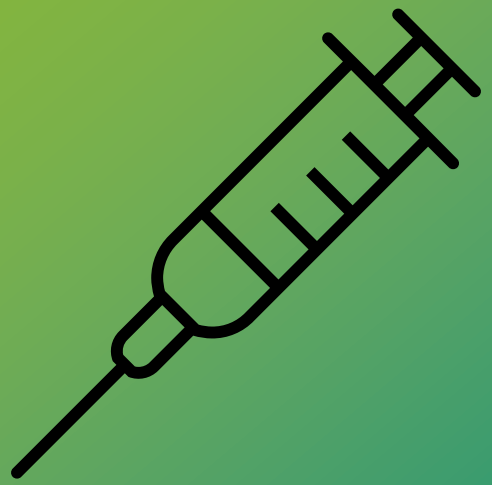
- He has no history of skin infections, internal organ abscess, thrush or fungal skin infections, failure to thrive.
- There is no family history of immunodeficiency.
- Despite his recurrent URIs, he has continued to thrive and meet his developmental millstones.



Labs

CBC	
WBC Count	6.40
RBC Count	4.71
Hgb	13.3
HCT	40.7
MCV	86.4
MCH	28.2
RDW	14.2
Platelet Count	214
Mean Platelet Volume	11.7
Neutrophil #	2.64
Immature Gran #	0.02
Lymphocyte #	3.11
Monocyte #	0.49
Eosinophil #	0.15
Basophil #	0.01

CMP	
Sodium	138
Potassium	4.4
Chloride	107
CO2 Total	23
Anion Gap	8
BUN	8
Creatinine	0.52
BUN/Cr Ratio	15.4
Glucose	86
Total Protein	7
Albumin	4.1
Calcium	9.7
Bilirubin Total	0.4
Alk Phos	209
AST	24
ALT	16



- Initial immunologic workup showed CD3+CD8+ T cells that were initially low, but upon repeat normalized. He also initially had marginally-low IgM level that normalized.

- He showed great response to HiB and pneumovax vaccines.

Labs

Streptococcus Pneumoniae IgG Ab (23 Serotypes)	
SEROTYPE 1 (1)	9.4
SEROTYPE 2 (2)	7.6
SEROTYPE 3 (3)	30.9
SEROTYPE 4 (4)	25.2
SEROTYPE 5 (5)	19.3
SEROTYPE 8 (8)	74.4
SEROTYPE 9 (9N)	2.7
SEROTYPE 12 (12F)	<0.4
SEROTYPE 14 (14)	21
SEROTYPE 17 (17F)	35.9
SEROTYPE 19 (19F)	25.8
SEROTYPE 20 (20)	0.8
SEROTYPE 22 (22F)	14
SEROTYPE 23 (23F)	7.7
SEROTYPE 26 (6B)	38.2
SEROTYPE 34 (10A)	3
SEROTYPE 43 (11A)	4.4
SEROTYPE 51 (7F)	8.9
SEROTYPE 54 (15B)	0.5
SEROTYPE 56 (18C)	23.4
SEROTYPE 57 (19A)	15.9
SEROTYPE 68 (9V)	99
SEROTYPE 70 (33F)	3.2

IMMUNODEFICENCY PROFILE		
WBC	5 - 15 10*3/uL	7.5
% Lymphs	49 - 73 %	49.9
Abs Lymph Count	{cells}/uL	3,742
CD19 PERCENT	14 - 33 %	27
REABCD19	720 - 2,600 {cells}/uL	1,010
%CD3, T CELLS	56 - 75 %	**52 Low**
CD3 ABS COUNT	2,100 - 6,200 {cells}/uL	**1,946 Low**
%CD4, T HELPER	28 - 47 %	35
CD4 ABS COUNT	1,300 - 3,400 {cells}/uL	1,310
%CD8, T SUPRES	16 - 30 %	**13 Low**
CD8 ABS COUNT	620 - 2,000 {cells}/uL	**487 Low**
RECD56%	4 - 17 %	10
REABCD56	180 - 920 {cells}/uL	374

Labs

QUANTITATIVE IMMUNOGLOBULINS		
IMMUNOGLOBULIN G	452 - 1,207 mg/dL	1,076
IMMUNOGLOBULIN A	21 - 128 mg/dL	111
IMMUNOGLOBULIN M	43 - 173 mg/dL	69
IMMUNOGLOBULIN E	14 - 710 IU/mL	36

OTHER LABS		
RHEUMATOID FACTOR	0 - 29 IU/mL	<15
ANA SCREEN		Negative
ESR	0 - 15 mm/hr	2
CRP	0.0 - 8.0 mg/L	<5.0

Other Labs		
DIP TOX IGG AB	0.10 IU/mL or greater IU/mL	0.26
TETANUS TOX IGG	0.10 IU/mL or greater IU/mL	1.37
H INFLUEN B IGG AB	mcg/mL	>9.00
CH50(HEMOLYTIC)	31 - 60 U/mL	45
MANNOSE BINDING LECTIN	NORMAL: > =100	173

- Genetic testing (Invitae Primary Immunodeficiency Panel and Primary Ciliary Dyskinesia and Cystic Fibrosis panel) for this patient showed a heterozygous variant of uncertain significance (VUS) in the NSMCE3 gene.

- Interestingly, biallelic missense mutations in the NSMCE3 gene have been associated with a DNA breakage syndrome.

- Chromosomal breakage syndromes are rare.

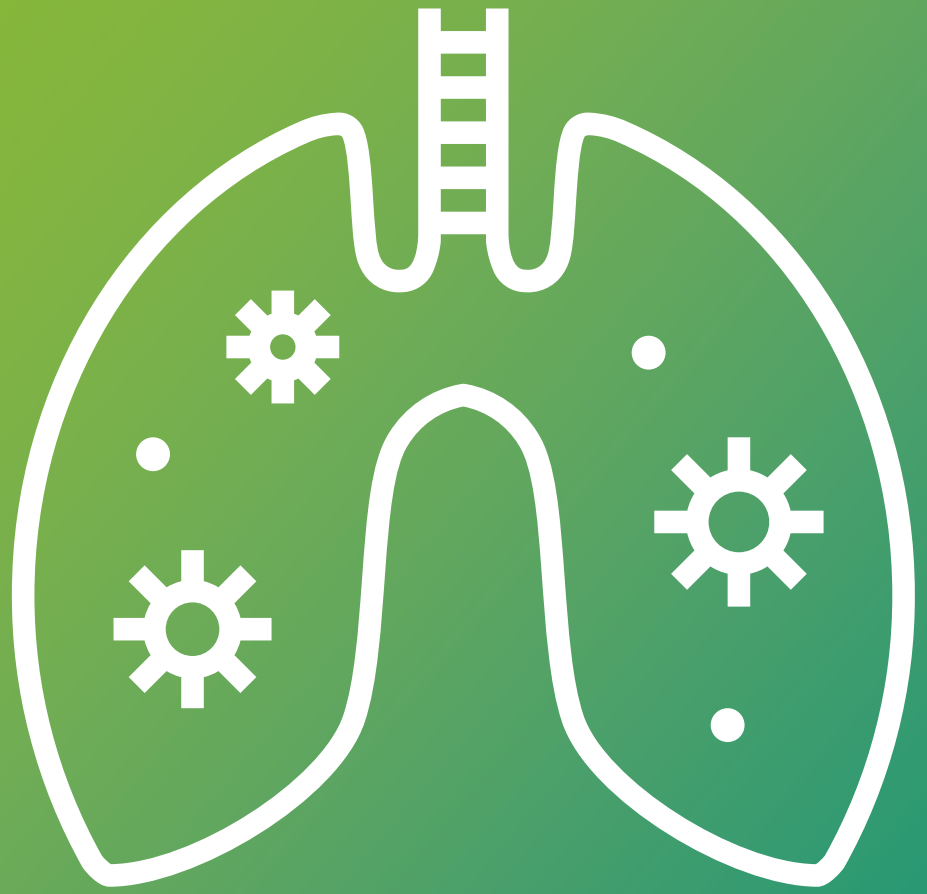
- They are characterized by defective DNA repair mechanisms and chromosomal instability leading to high frequency chromosomal breakage and unbalanced rearrangements.

- Examples of disorders in this category include Ataxia telangiectasia, Bloom syndrome, Fanconi anemia and Xeroderma pigmentosum.

LICS

- In 2016 biallelic missense mutations in the NSMCE3 gene were proposed as a new autosomal recessive lung disease immunodeficiency and chromosome breakage syndrome (LICS).
- LICS usually presents with early-onset lung disease, pneumonia, B- and T- cell dysfunction and resultant death in early childhood.
- Children may also experience feeding difficulties, weight loss, failure to thrive, hypotonia, in addition to increased infection susceptibility.

Van der Crabben SN, Hennus MP, McGregor GA, et al. Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. J Clin Invest. 2016;126(8):2881-2892. doi:10.1172/JCI82890

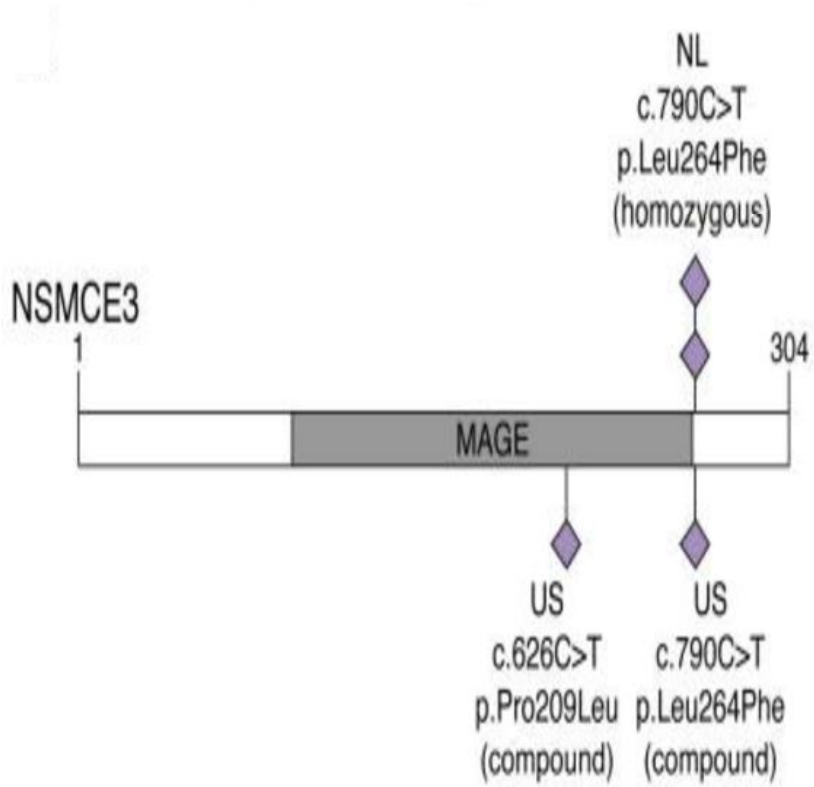


- Not all affected children have abnormal B and T cell numbers and responses, indicating that there may possibly be a variable phenotype of the same syndrome. **However, all of them had lung disease** (such as ILD, pneumonia).

Willemse BWM, van der Crabben SN, Kerstjens-Frederikse WS, et al. New insights in phenotype and treatment of lung disease immuno-deficiency and chromosome breakage syndrome (LICS). Orphanet J Rare Dis. 2021;16(1):137. Published 2021 Mar 19. doi:10.1186/s13023-021-01770

LICS

- Biallelic missense mutations leading to LICS are associated with the coding DNA sequence **c.790C>T** of the NSMCE3 gene that substitutes the nucleotide cytosine (C) at position c.790 by thymine (T).
- This mutation is associated with homozygous protein variant **p.Leu264Phe** (substitution of the amino acid leucine for phenylalanine at position 264).
- This mutation is also associated with compound heterozygote variant **p.Leu264Phe**, **p.Pro209Leu** that additionally substitutes proline for leucine at position 209.



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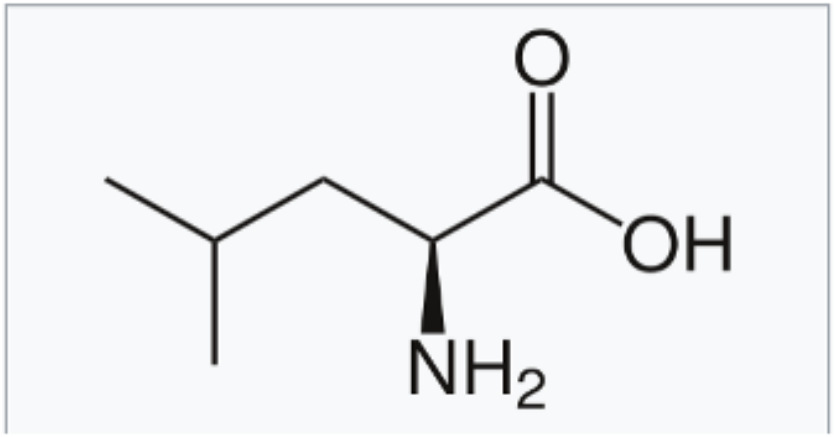
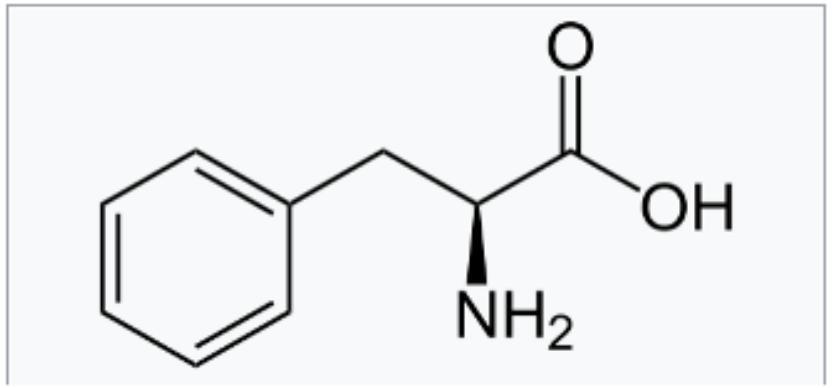
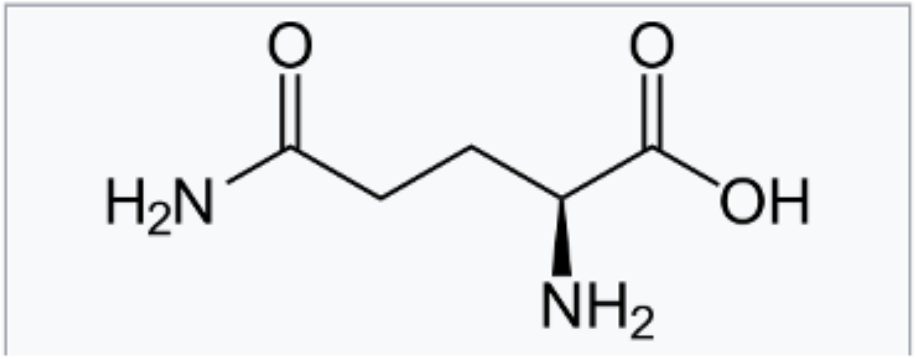
Leucine



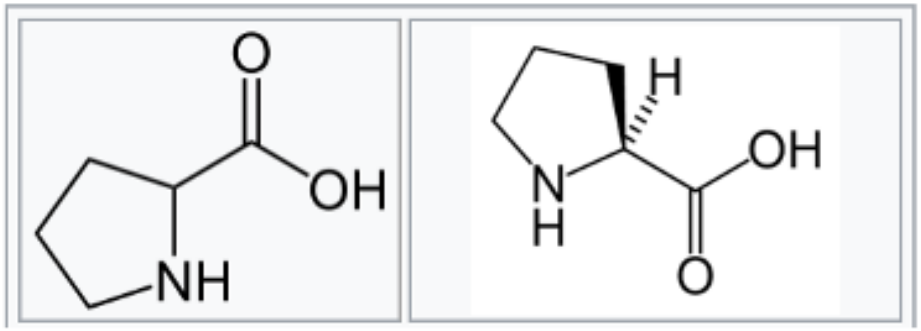
Phenylalanine

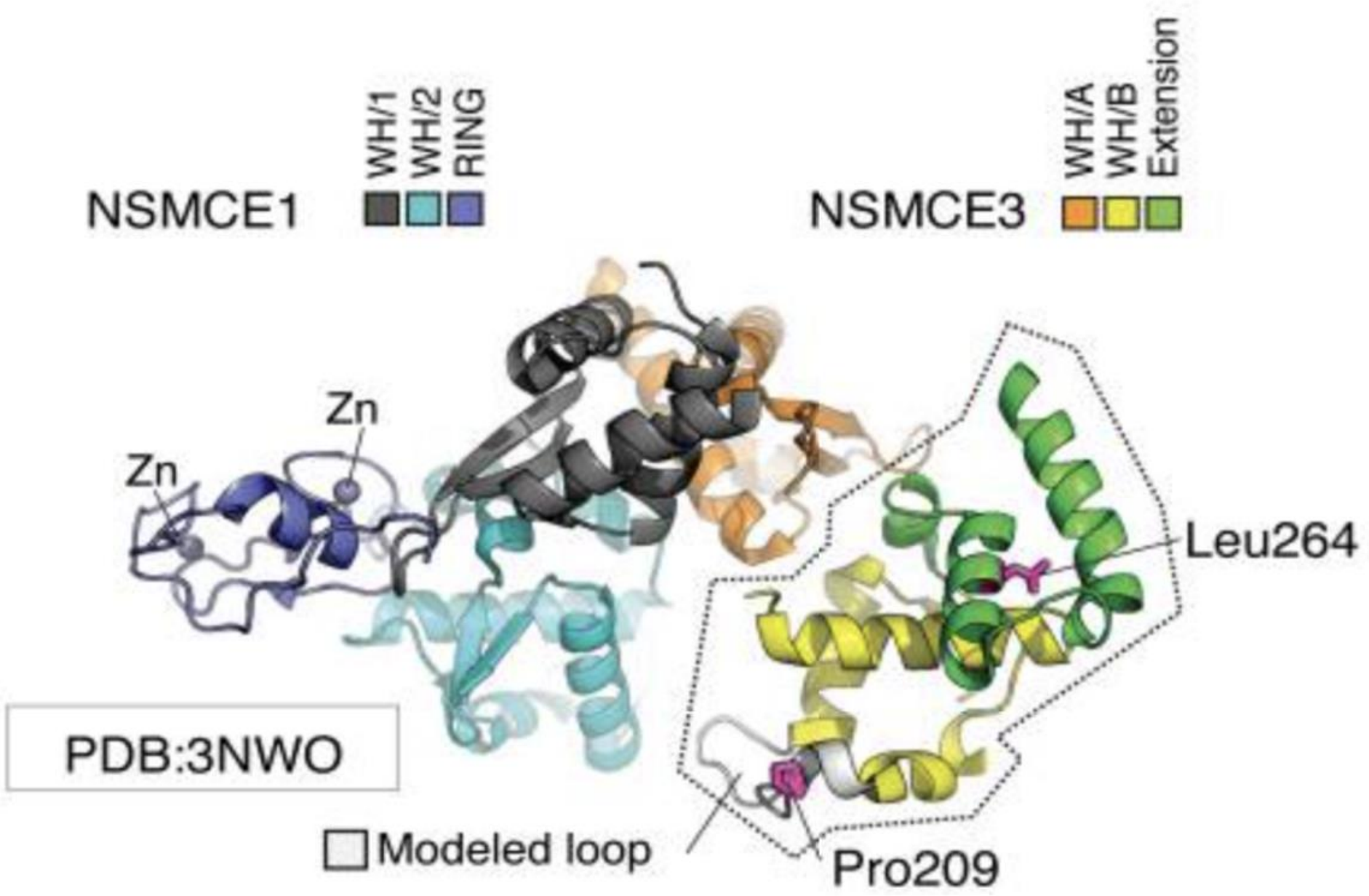


Glutamine



Proline





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LICS

- The **p.Leu264Phe** and **p.Pro209Leu variants** disrupt the structure of the NSMCE3 protein.

- Laboratory models and computational analyses of these protein product variants have shown reduced binding of NSMCE3 to NSMCE4 leading to disruption of the SMC5 and SMC6 complex and decreased levels of these subunits in cells.

- As a result, during critical illness, increased chromosomal abnormalities (such as de novo supernumerary marker chromosomes) have been noted in peripheral blood lymphocytes of affected individuals.

Van der Crabben SN, Hennus MP, McGregor GA, et al. Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. J Clin Invest. 2016;126(8):2881-2892. doi:10.1172/JCI82890

NSMCE3

- NSMCE3 stands for "*NSE3 Homolog, SMC5-SMC6 Complex Component*" and is also known as NDNL2 (Necdin-Like Protein 2) or MAGEG1 (melanoma-associated antigen G1).

- The NSMCE3 gene is located on the long arm of chromosome 15 at position 13 (15q13).

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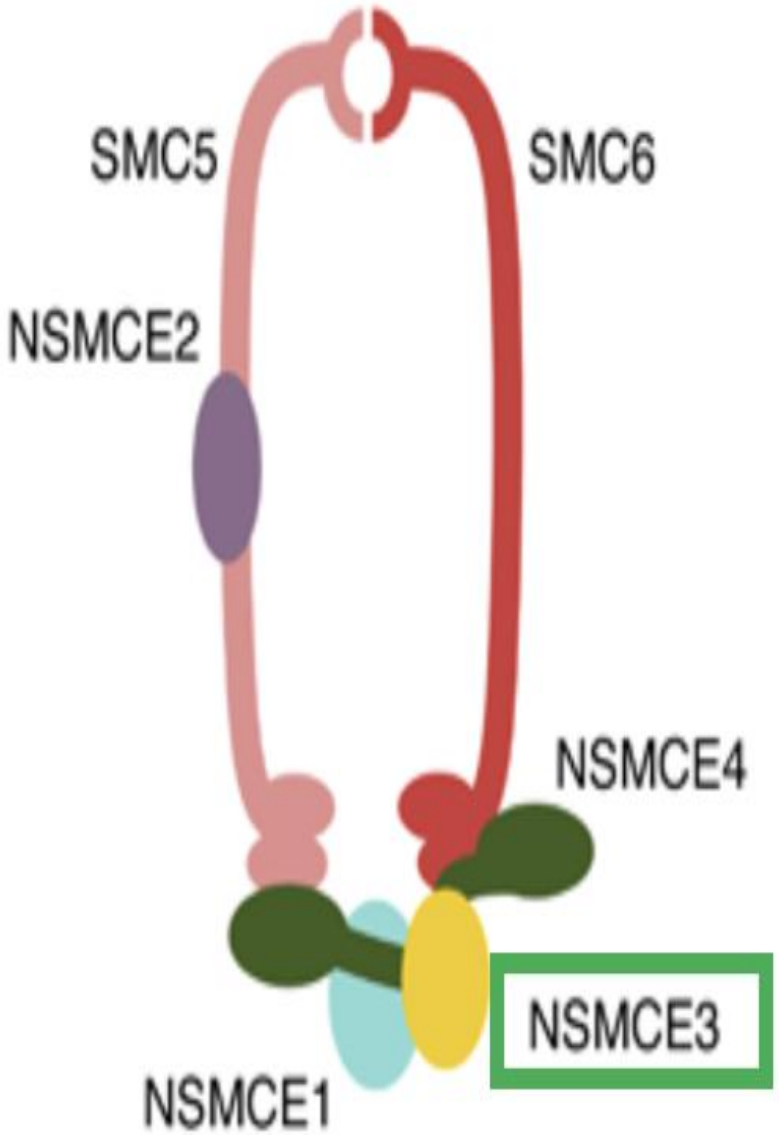
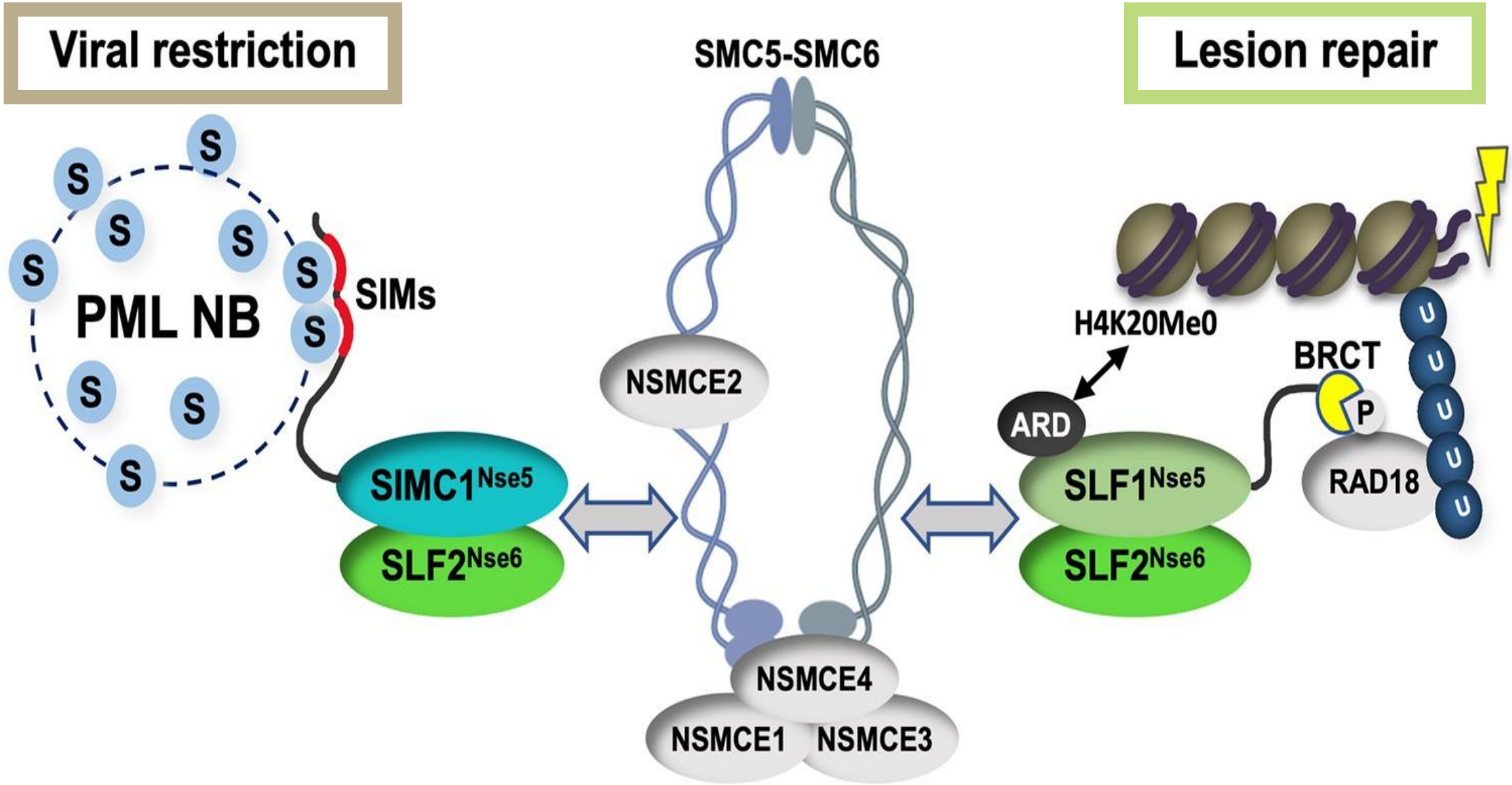


- The protein product of NSMCE3 helps bridge and stabilize the SMC5/6 complex, which is made of SMC5, SMC6, and NSMCE1 to 6.
- NSMCE3 interacts with both NSMCE1 and NSMCE4
- The SMC5/6 complex plays a crucial role in genome integrity and stability and is directly involved in DNA repair and chromosome segregation during cell division. It is also thought to help suppress viral infections.

Van der Crabben SN, Hennus MP, McGregor GA, et al. Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. J Clin Invest. 2016;126(8):2881-2892. doi:10.1172/JCI82890



Oravcová M, Nie M, Zilio N, et al. The Nse5/6-like SIMC1-SLF2 complex localizes SMC5/6 to viral replication centers. *Elife*. 2022;11:e79676. Published 2022 Nov 14. doi:10.7554/eLife.79676

Back to Our Patient…

- 5-year-old boy with recurrent ear and lung infections and febrile episodes who is heterozygous for a variant of uncertain significance (VUS) in the NSMCE3 gene.
- This variant is different from the known pathogenic variant **c.790C>T** associated with LICS-autosomal recessive disease.
- Our patient was found to have deletion-insertion mutation **c.41_42delinsCC** in the NSMCE3 gene (i.e., nucleotides 41 and 42 of the coding DNA sequence are deleted and two cytosines inserted).
- This results in **p. Gln14Pro** protein product which changes glutamine (neutral and polar) to proline (neutral and non-polar) at the 14th amino acid position in the protein product.

Discussion

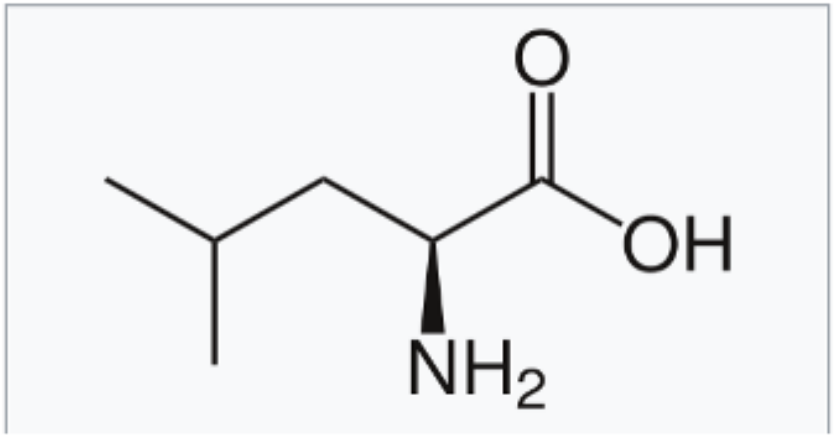
- In most cases, heterozygous carriers can compensate for a defective allele.
- Our patient has a deletion-insertion variant in one NSMCE3 allele, which may affect the protein product's conformation.
- In this patient, a proline (neutral, non-polar) residue replaced the normally occurring glutamine (neutral, polar) amino acid in the NSMCE3 protein.

Discussion

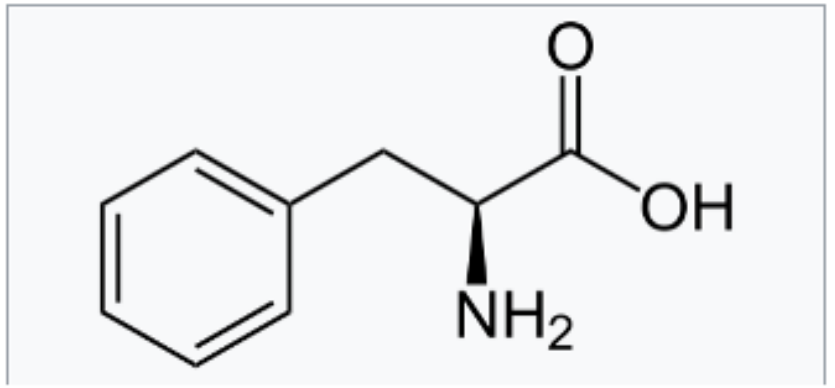
- Proline and glutamine are metabolically related. However, unlike glutamine that has no ring, proline is made of a rigid ring structure that can facilitate the folding of many naturally occurring proteins.

- However, with its constrained ring, proline is also a structural disruptor that can introduce kinks and bends that disturb the normal folding of protein chains, creating conformational restrictions that decrease stability.

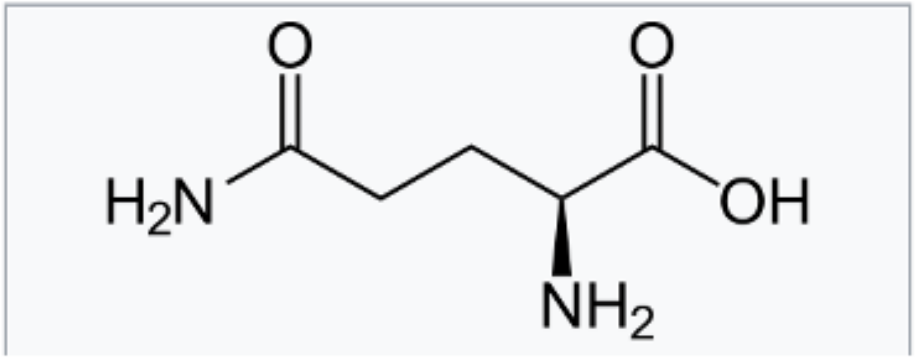
Leucine



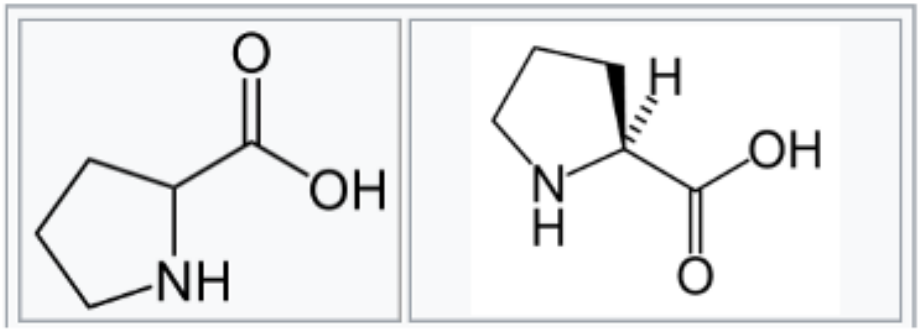
Phenylalanine



Glutamine



Proline



Discussion

- Since the NSMCE3 protein functions in DNA repair and known mutations have been associated with pneumonia and viral infections, we hypothesize that our patient's reduced level of normal protein may underlie his recurrent sinopulmonary infections.

- However, it is not known at this time if heterozygous carriers of NSMCE3 mutations have a clinical phenotype associated with pathologic mechanisms in lung disease and immune deficiency.

Discussion

- In the Netherlands, heterozygous individuals for the disease-causing variant c.790C>T variant are not uncommon, but so far there has not been reports of recurrent sinopulmonary infections in carriers of this variant allele. There is low awareness of the disease at this time.

- Visited several online databases including OMIM, Mastermind, gnomAD, Uniprot, Varsome and ClinVar had an entry for this specific mutation in the NSMCE3 gene that our patient has.

NM_138704.4(NSMCE3):c.41_42delinsCC (p.Gln14Pro)

Cite this record

Interpretation: Uncertain significance

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts
Submissions: 2
First in ClinVar: Mar 22, 2021
Most recent Submission: Dec 31, 2022
Last evaluated: Apr 13, 2022
Accession: VCV001043795.3
Variation ID: 1043795
Description: 2bp indel

Variant details | Conditions | Gene(s)

NM_138704.4(NSMCE3):c.41_42delinsCC (p.Gln14Pro)

Allele ID: 1031883
Variant type: Indel
Variant length: 2 bp
Cytogenetic location: 15q13.1
Genomic location: 15: 29269664-29269665 (GRCh38) GRCh38 UCSC
15: 29561868-29561869 (GRCh37) GRCh37 UCSC

HGVS:

Nucleotide	Protein	Molecular consequence
NM_015307.2:c.277-17187_277-17186delinsCC MANE SELECT		
NM_138704.4:c.41_42delinsCC MANE SELECT	NP_619649.1:p.Gln14Pro	missense
NM_001387214.1:c.277-17187_277-17186delinsCC		

... more HGVS

Protein change: Q14P
Other names: -
Canonical SPDI: NC_000015.10:29269663:CT:GG
Functional consequence: -
Global minor allele frequency (GMAF): -
Allele frequency: -
Links: dbSNP: rs2043569702
VarSome

Conclusion

- More remains to be learned about the NSMCE3 gene, the protein it encodes, and its role in stabilizing the SMC5-6 chromatin reorganizing complex.

- At this time, the clinical significance of this missense mutation c.41_42delinsCC (p.Gln14Pro) in one NSMCE3 allele remains unclear.

- In vitro studies, laboratory models, and computation analyses could help further elucidate this.

References

1. Van der Crabben SN, Hennus MP, McGregor GA, et al. Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. J Clin Invest. 2016;126(8):2881-2892. doi:10.1172/JCI82890

2. Willemse BWM, van der Crabben SN, Kerstjens-Frederikse WS, et al. New insights in phenotype and treatment of lung disease immuno-deficiency and chromosome breakage syndrome (LICS). Orphanet J Rare Dis. 2021;16(1):137. Published 2021 Mar 19. doi:10.1186/s13023-021-01770

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THANK YOU

QUESTIONS