EMR GHENT

Ectopic Mineralization research Ghent

OLIVIER VANAKKER | ECTOPIC CALCIFICATION

A prevalent multifaceted condition influencing healthy aging

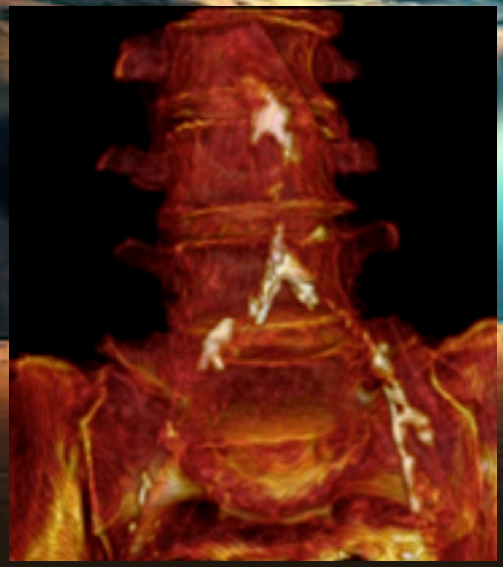
MANAMA Clinical Genetics | 12.XI.2024

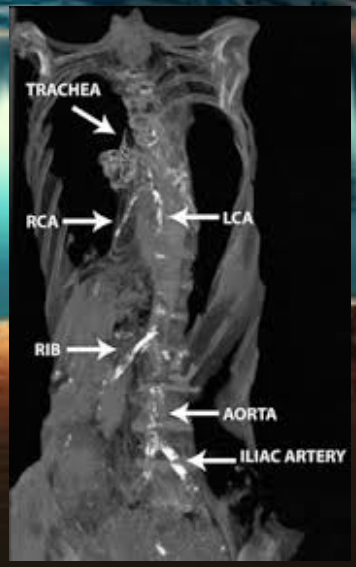
200 JAAR UNIVERSITEIT GENT

INTEC
International Network on Ectopic Calcification

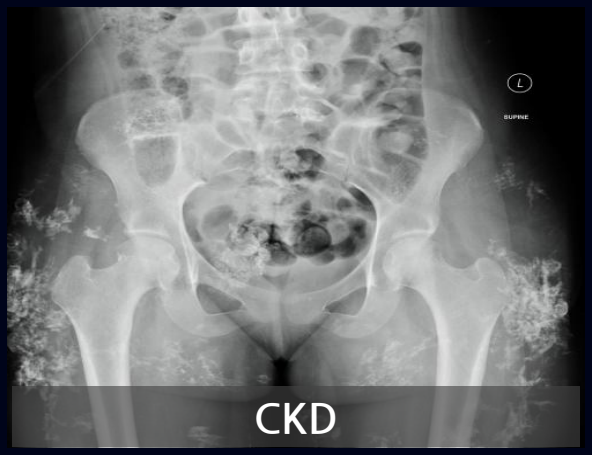
May 6th 1203 BC

2008 AD

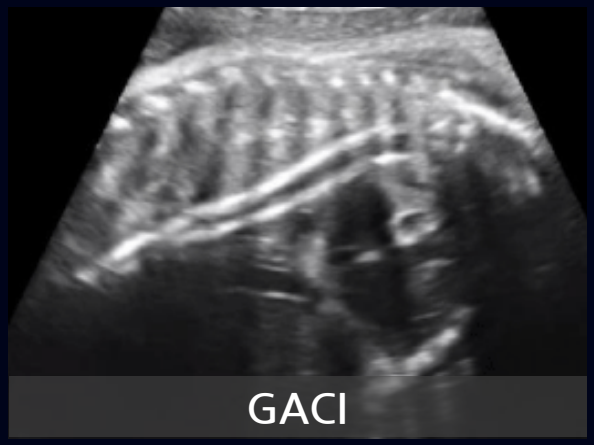




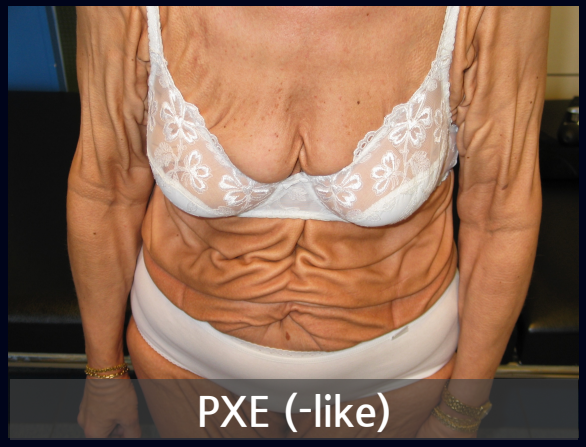
Lithopedion



CKD



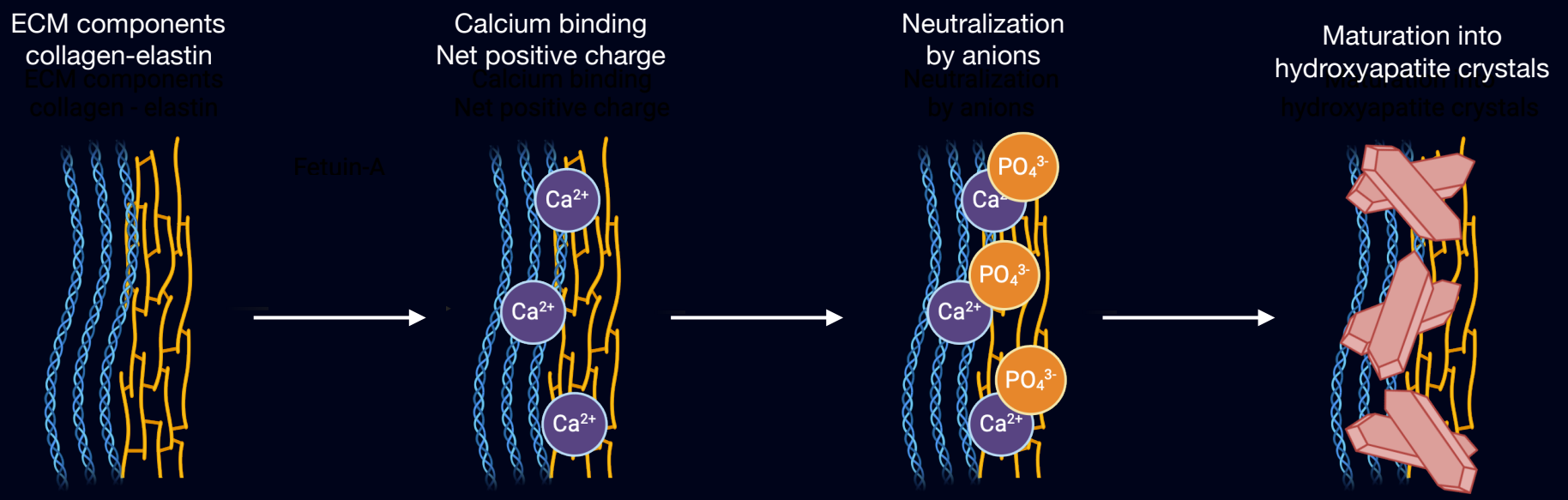
GACI



PXE (-like)

Aging

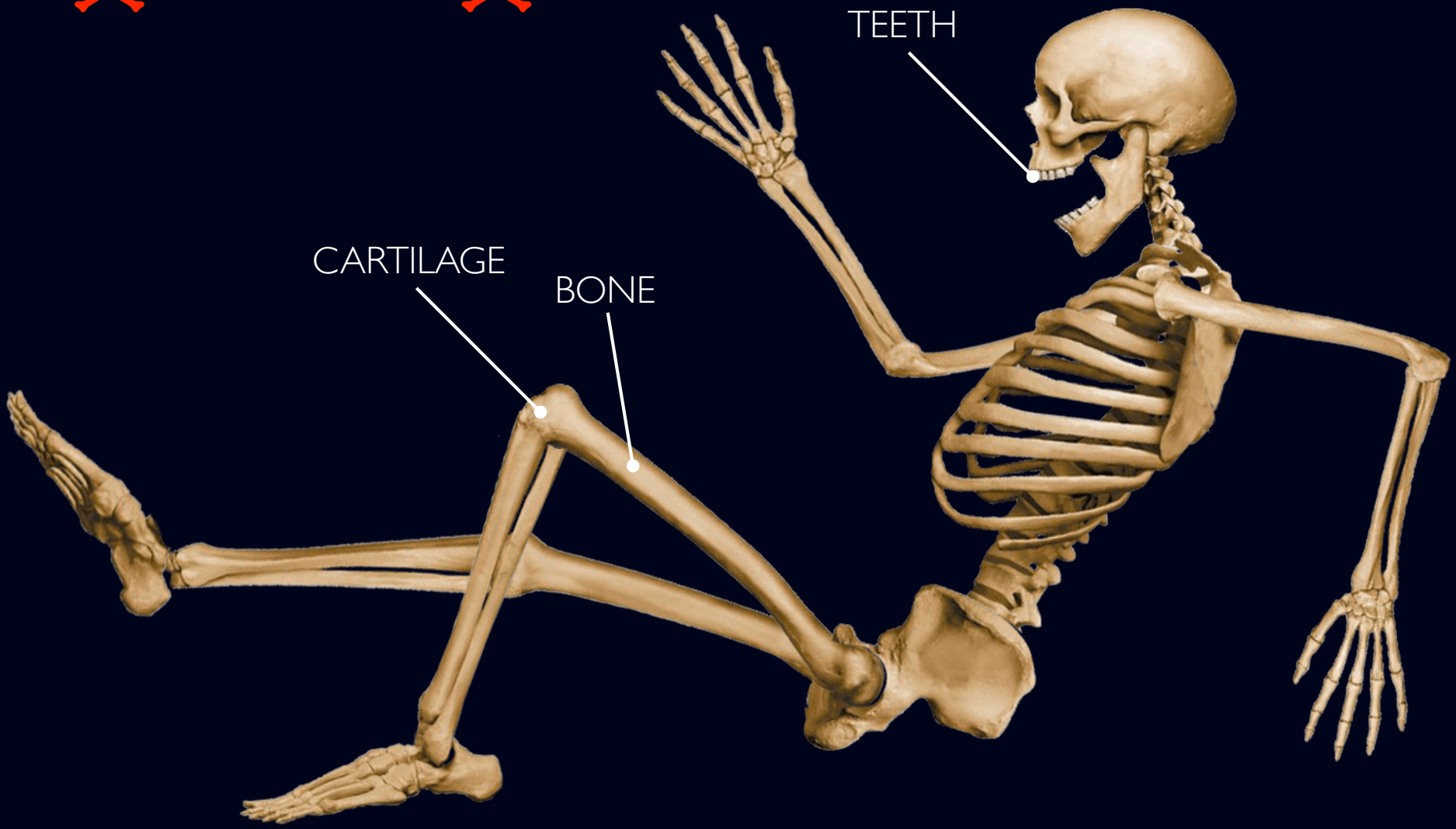
CALCIFICATION | MULTISTEP PROCESS



Humans are supersaturated for calcium and phosphate

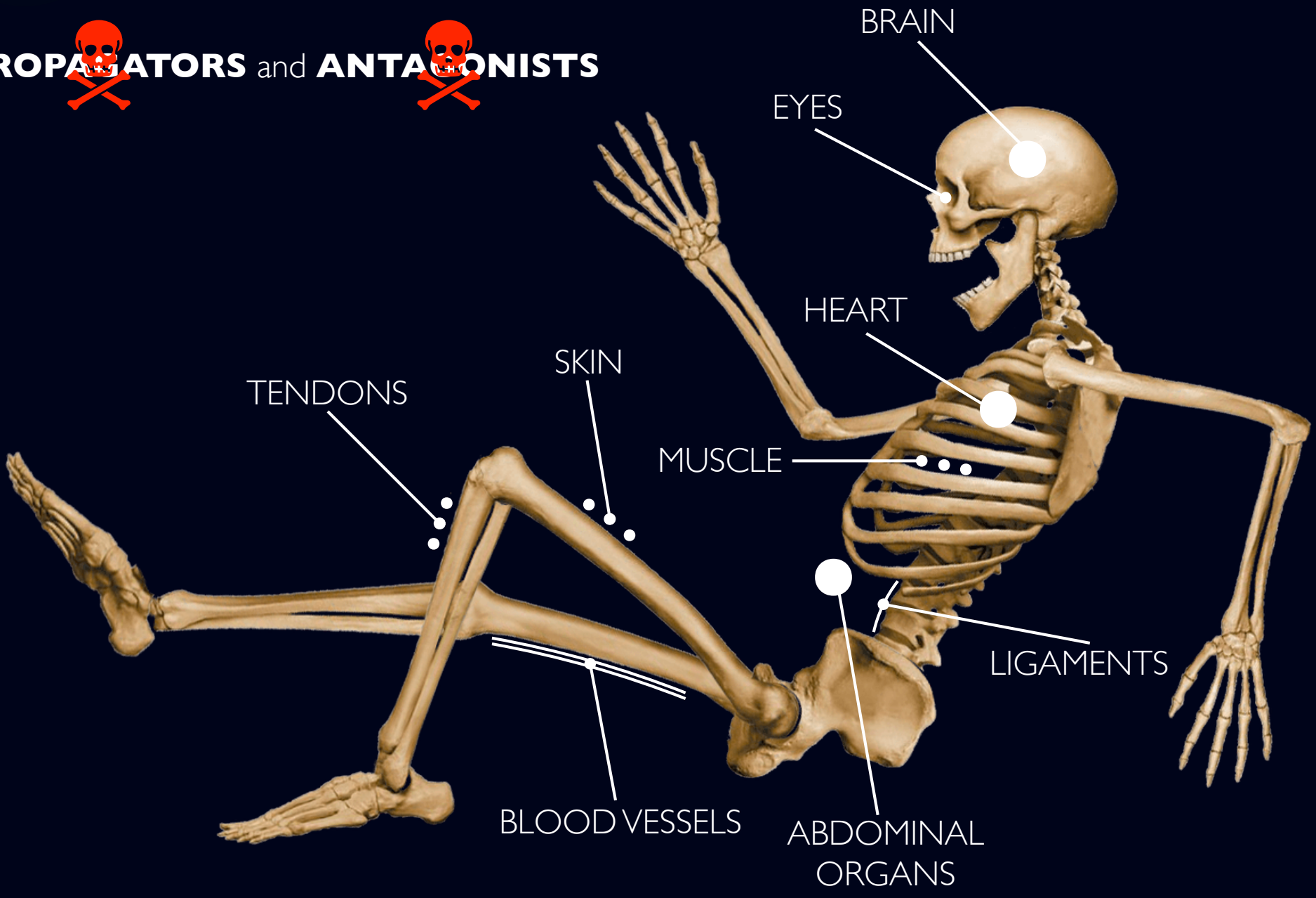
NORMAL MINERALIZATION | ACTIVELY REGULATED

PROPAGATORS and **ANTAGONISTS**

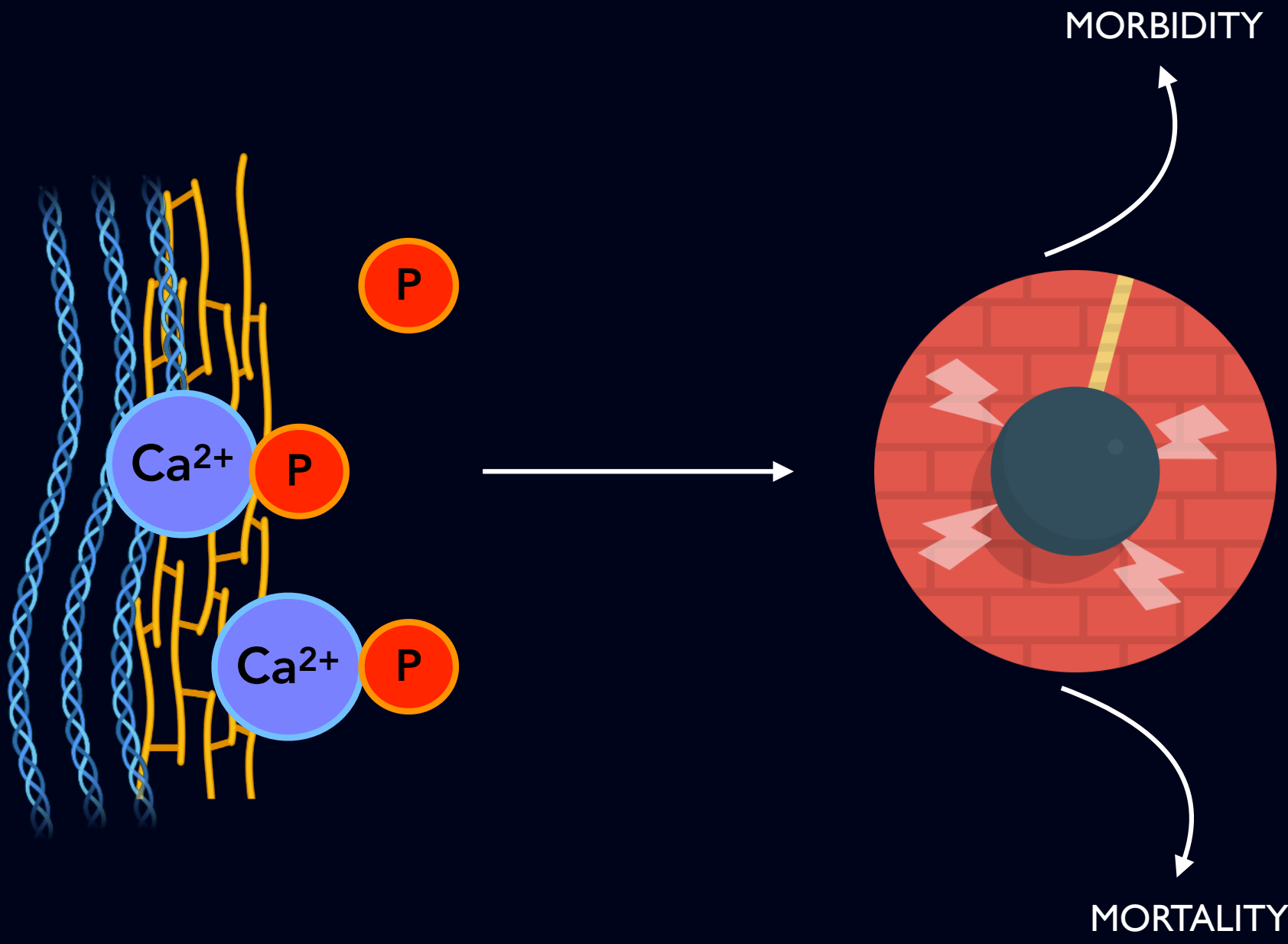


ECTOPIC MINERALIZATION | DYSREGULATION

PROPAGATORS and ANTAGONISTS



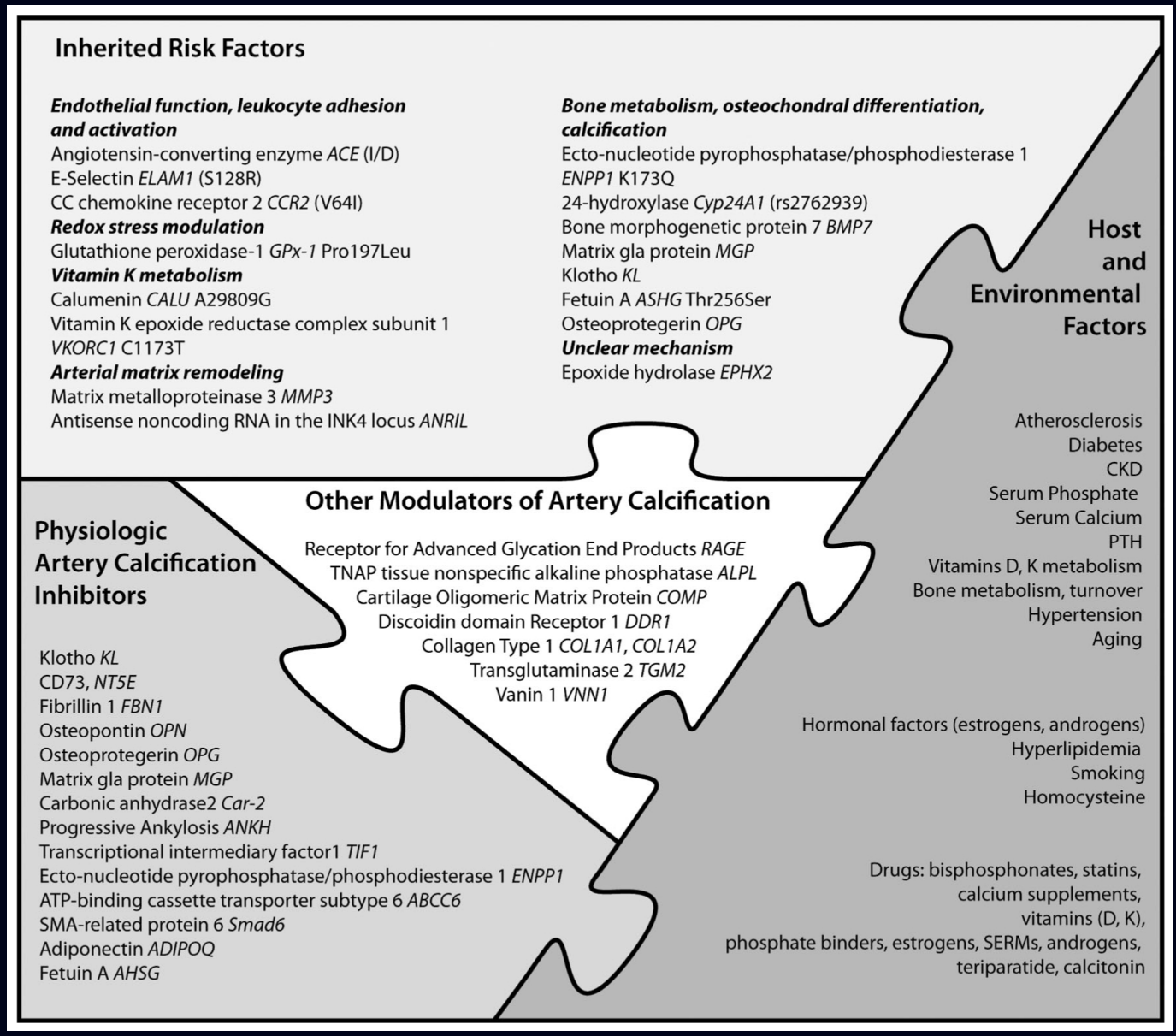
ECTOPIC MINERALIZATION | DYSREGULATION



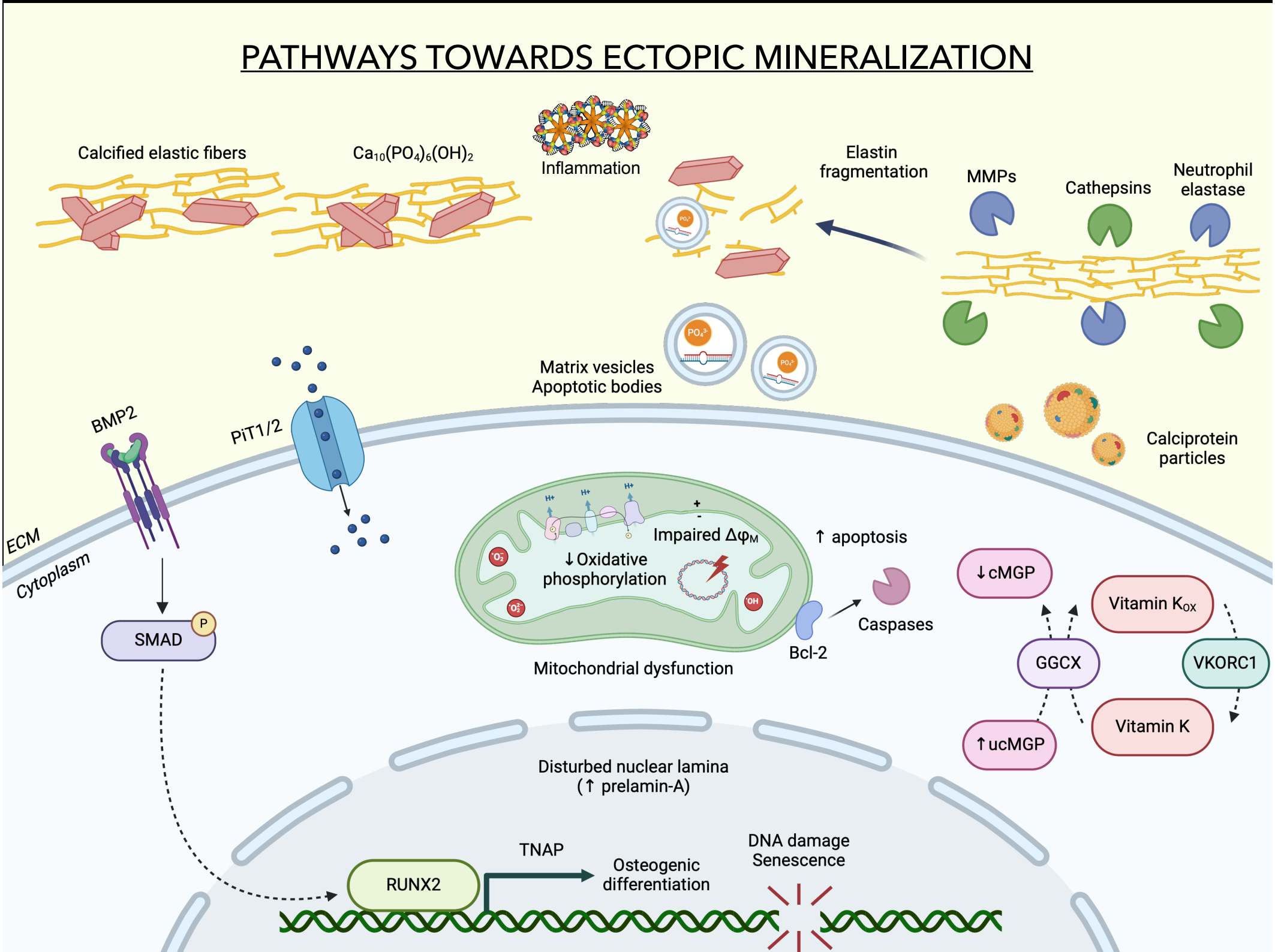
ECTOPIC CALCIFICATION | OUTLINE

- **MECHANISMS** OF ECTOPIC CALCIFICATION
- ECTOPIC CALCIFICATION IN **RARE (AND COMMON) DISEASES**
- **GENETICS** OF ECTOPIC CALCIFICATION
- **DIAGNOSIS AND MANAGEMENT** OF ECTOPIC CALCIFICATION
- **TREATMENT** OF ECTOPIC CALCIFICATION
- NEED FOR **INTEGRATIVE MANAGEMENT** OF ECTOPIC CALCIFICATION

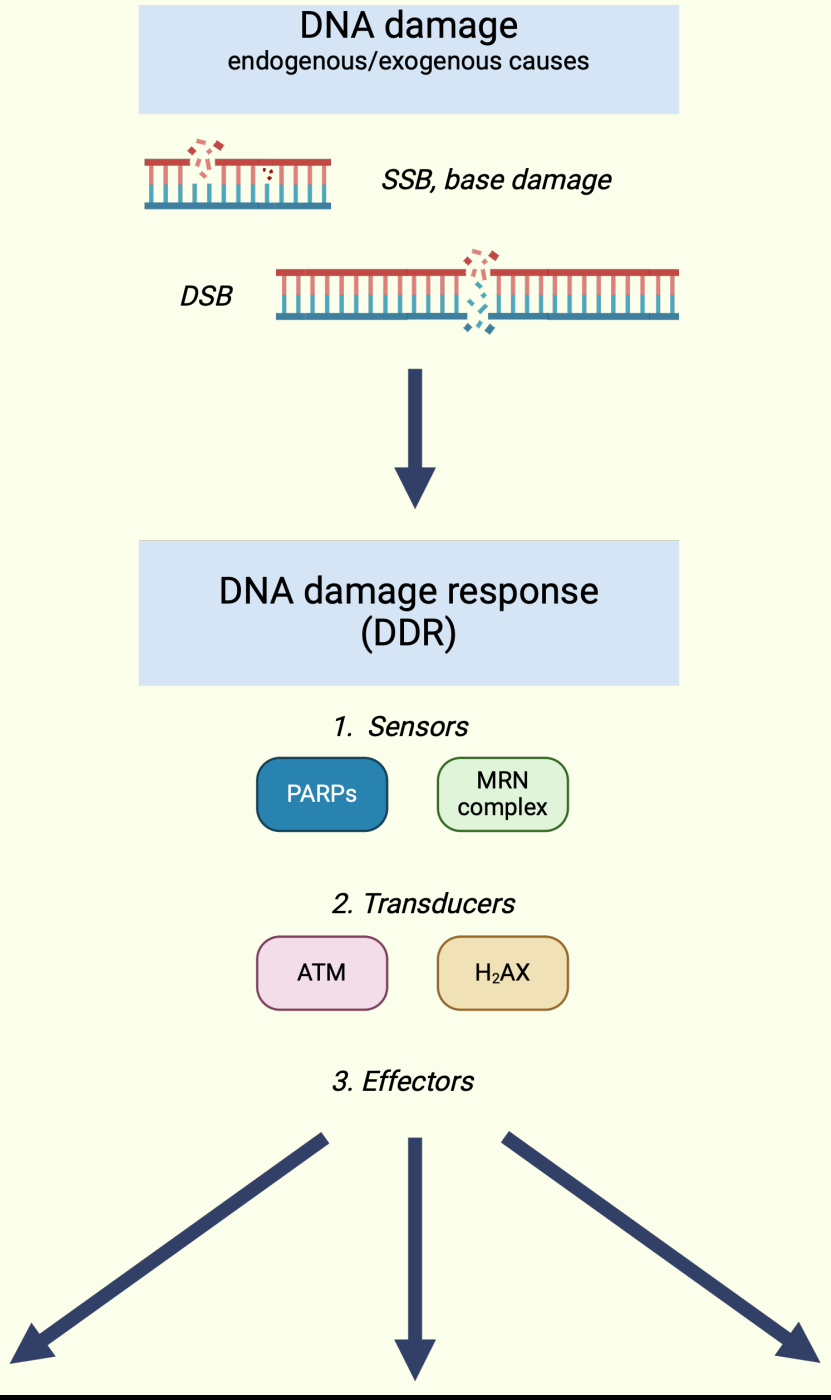
MECHANISMS OF MINERALIZATION | MULTIFACTORIAL

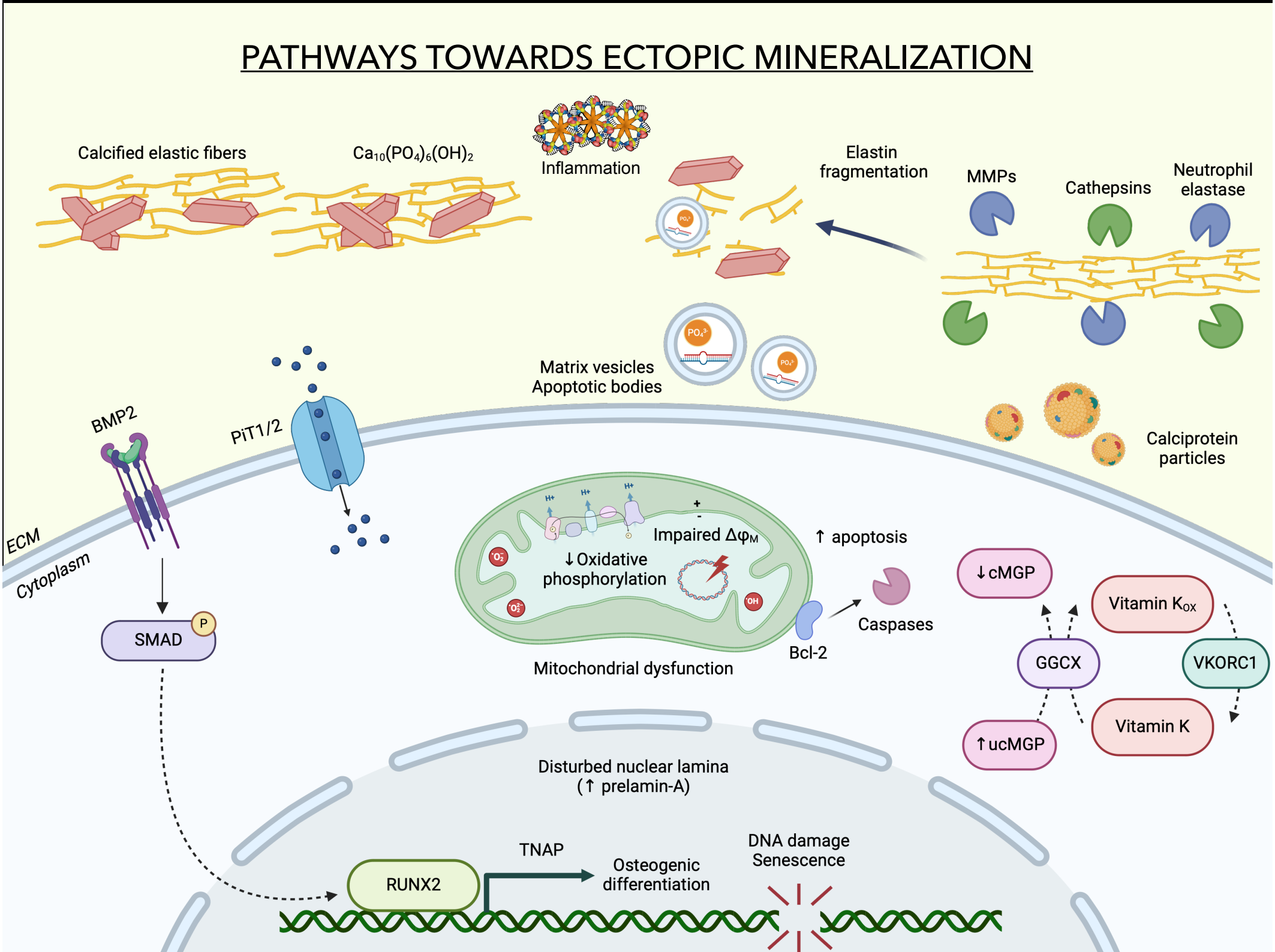


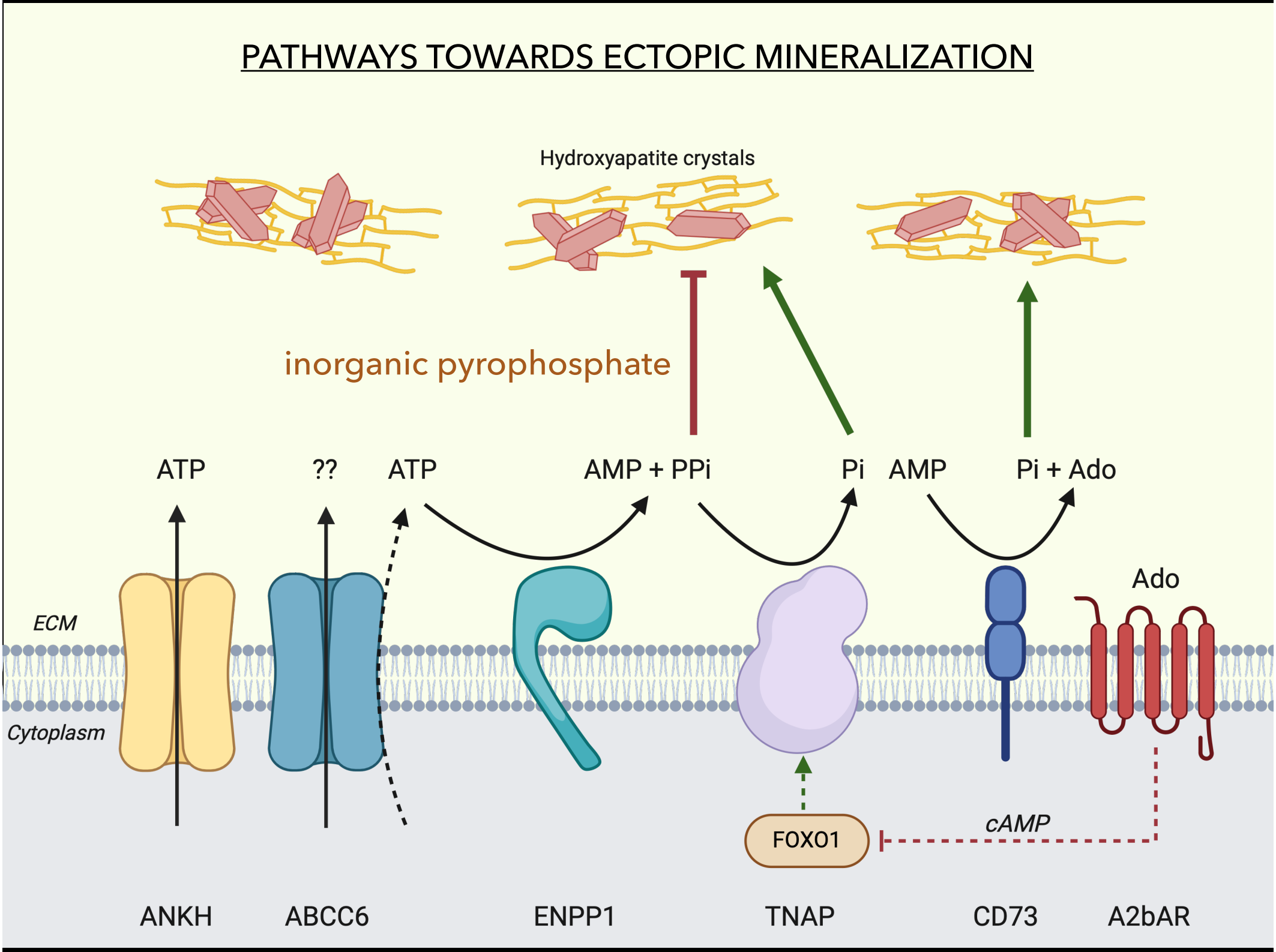
Rutsch et al., *Circ Res*, 2011


PATHWAYS TOWARDS ECTOPIC MINERALIZATION
Calcified elastic fibers
$Ca_{10}(PO_4)_6(OH)_2$
Inflammation
Elastin fragmentation
MMPs
Cathepsins
Neutrophil elastase
Matrix vesicles
Apoptotic bodies
Calciprotein particles
BMP2
PiT1/2
ECM
Cytoplasm
SMAD
P
Impaired $\Delta\varphi_M$
↓Oxidative phosphorylation
↑ apoptosis
Caspases
Bcl-2
Mitochondrial dysfunction
↓cMGP
Vitamin K_{OX}
GGCX
VKORC1
Vitamin K
↑ucMGP
Disturbed nuclear lamina
(↑ prelamin-A)
RUNX2
TNAP
Osteogenic differentiation
DNA damage
Senescence

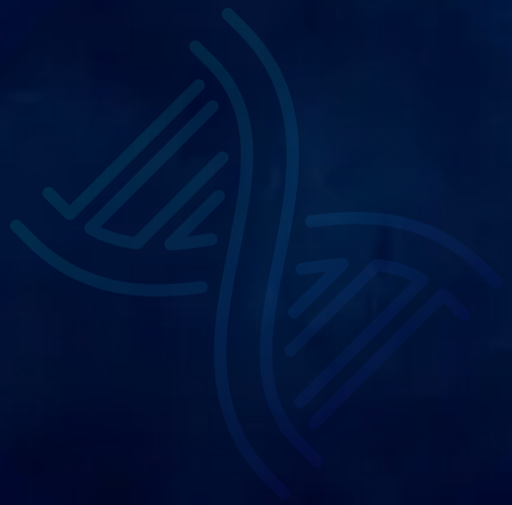
PATHWAYS TOWARDS ECTOPIC MINERALIZATION




PATHWAYS TOWARDS ECTOPIC MINERALIZATION
Calcified elastic fibers
$Ca_{10}(PO_4)_6(OH)_2$
Inflammation
Elastin fragmentation
MMPs
Cathepsins
Neutrophil elastase
Matrix vesicles
Apoptotic bodies
Calciprotein particles
BMP2
PiT1/2
ECM
Cytoplasm
SMAD
P
Impaired $\Delta\varphi_M$
↓Oxidative phosphorylation
↑ apoptosis
Caspases
Bcl-2
Mitochondrial dysfunction
↓cMGP
Vitamin K_{OX}
GGCX
VKORC1
Vitamin K
↑ucMGP
Disturbed nuclear lamina
(↑ prelamin-A)
RUNX2
TNAP
Osteogenic differentiation
DNA damage
Senescence


PATHWAYS TOWARDS ECTOPIC MINERALIZATION
Hydroxyapatite crystals
inorganic pyrophosphate
ATP
??
ATP
AMP + PPi
Pi
AMP
Pi + Ado
Ado
ECM
Cytoplasm
FOXO1
cAMP
ANKH
ABCC6
ENPP1
TNAP
CD73
A2bAR

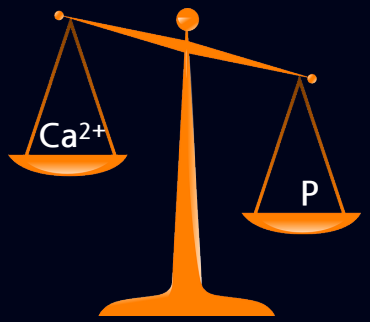
ECTOPIC CALCIFICATION | HEREDITARY DISORDERS



RARE & COMMON DISORDERS | VARIABILITY

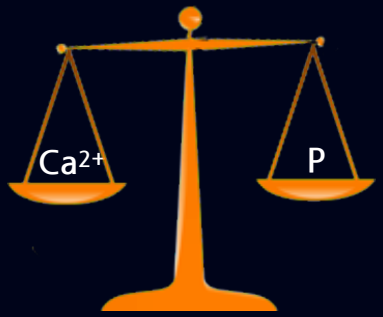
	Hereditary diseases	Acquired diseases
Neurology	COATSplus syndrome; Leuko-encefalopathy with calcifications and cysts; Primary familial brain calcification	Alzheimer disease; Brain tumors; Down syndrome; Lewy body disease; Parkinson disease; Vascular dementia
Cardiology & vascular disease	Generalised arterial calcification of infancy (GACI); Pseudoxanthoma elasticum (PXE); Singleton-Merten syndrome	Heart failure; Valve calcification; Vascular calcification (coronary, peripheral art.); Metabolic syndrome
Endocrinology	Hypophosphatasia; (pseudo)Hypoparathyroidism	Diabetes mellitus; Metabolic syndrome
Nephrology	Gitelman syndrome; PXE	Chronic kidney disease; Nephrocalcinosis, kidney stones
Dermatology	Calcinosis cutis; Calcinosis universalis; Calciphylaxis; PXE; PXE-like syndrome; Tumoral calcinosis	Dermatomyositis; Myositis ossificans; Polymyositis
Rheumatology	Chondrocalcinosis; Hereditary calcification of joints and arteries (ACDC)	CREST syndrome; Osteoarthritis; Scleroderma; Systemic lupus erythematosus
Orthopaedics & physiotherapy	Fibrodysplasia ossificans progressiva; Progressive osseous heteroplasia	Degenerative disease of intervertebral disk; Scoliosis
Ophthalmology	PXE	Age-related macular degeneration (ARMD)
Pneumology	Keutel syndrome	Chronic obstructive lung disease
Generalized	Progeroid syndromes	Sarcoidosis; Systemic sclerosis

RARE CALCIFICATION DISEASES | CLASSIFICATION 1



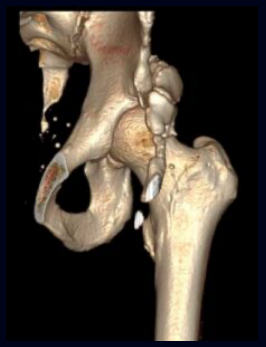
METASTATIC

- Tumoral calcinosis
- Primary hyperparathyroid.
- Second. hyperparathyroid.
- Sarcoidosis
- Vitamin D intoxication
- Milk-Alkali syndrome
- Renal failure
- Tumor lysis syndrome



DYSTROPHIC

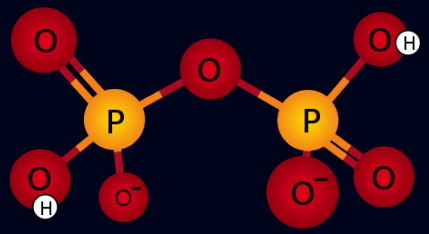
- Systemic sclerosis
- Scleroderma
- (Hutchinson-Gilford) progeria
- ACDC-related arterial calcif.
- Pseudoxanthoma Elasticum
- GACI
- Keutel syndrome
- Basal ganglia calcification



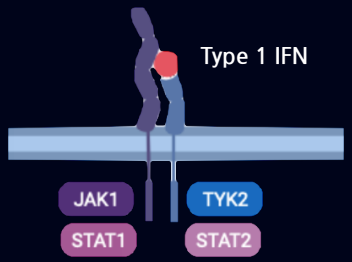
OSSIFICATION

- Myositis ossificans
- Fibrodysplasia ossificans progressiva
- Primary Hypertrophic osteo-arthropathy

RARE CALCIFICATION DISEASES | CLASSIFICATION 2



INORGANIC PYROPHOSPHATE DEFICIENCY

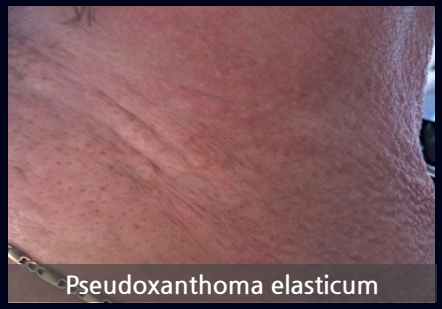


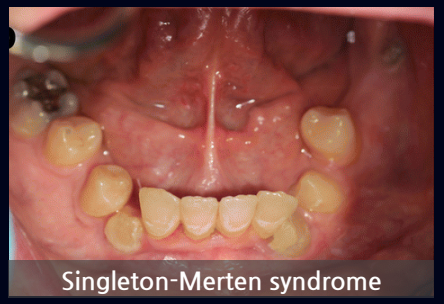
INTERFERONOPATHY

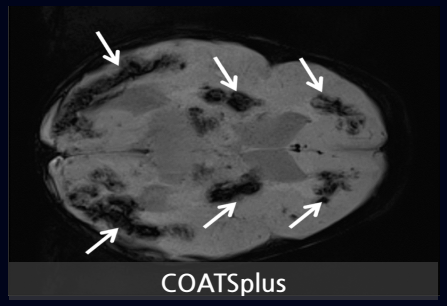
GGCX

VK-DEPENDENT DISEASES

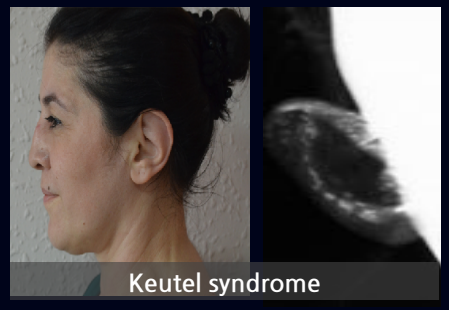
all the rest

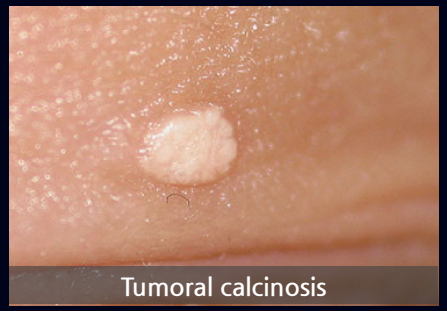

Pseudoxanthoma elasticum

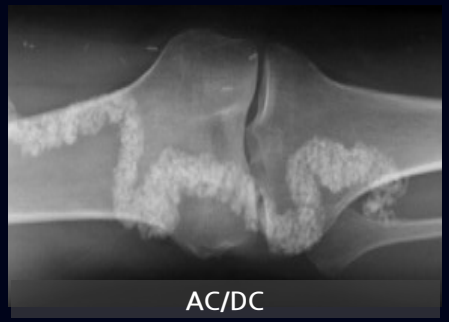

Singleton-Merten syndrome


COATSplus

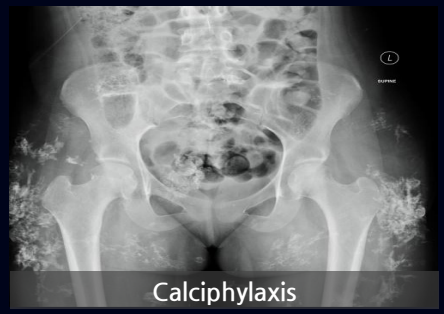

Gen. arterial calcification of inf.


Keutel syndrome

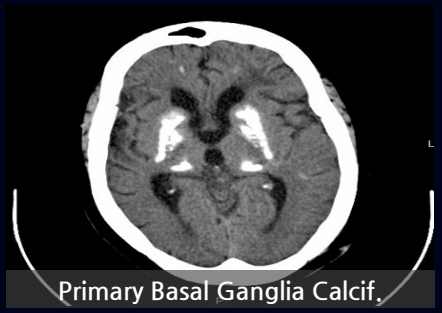

Tumoral calcinosis


AC/DC

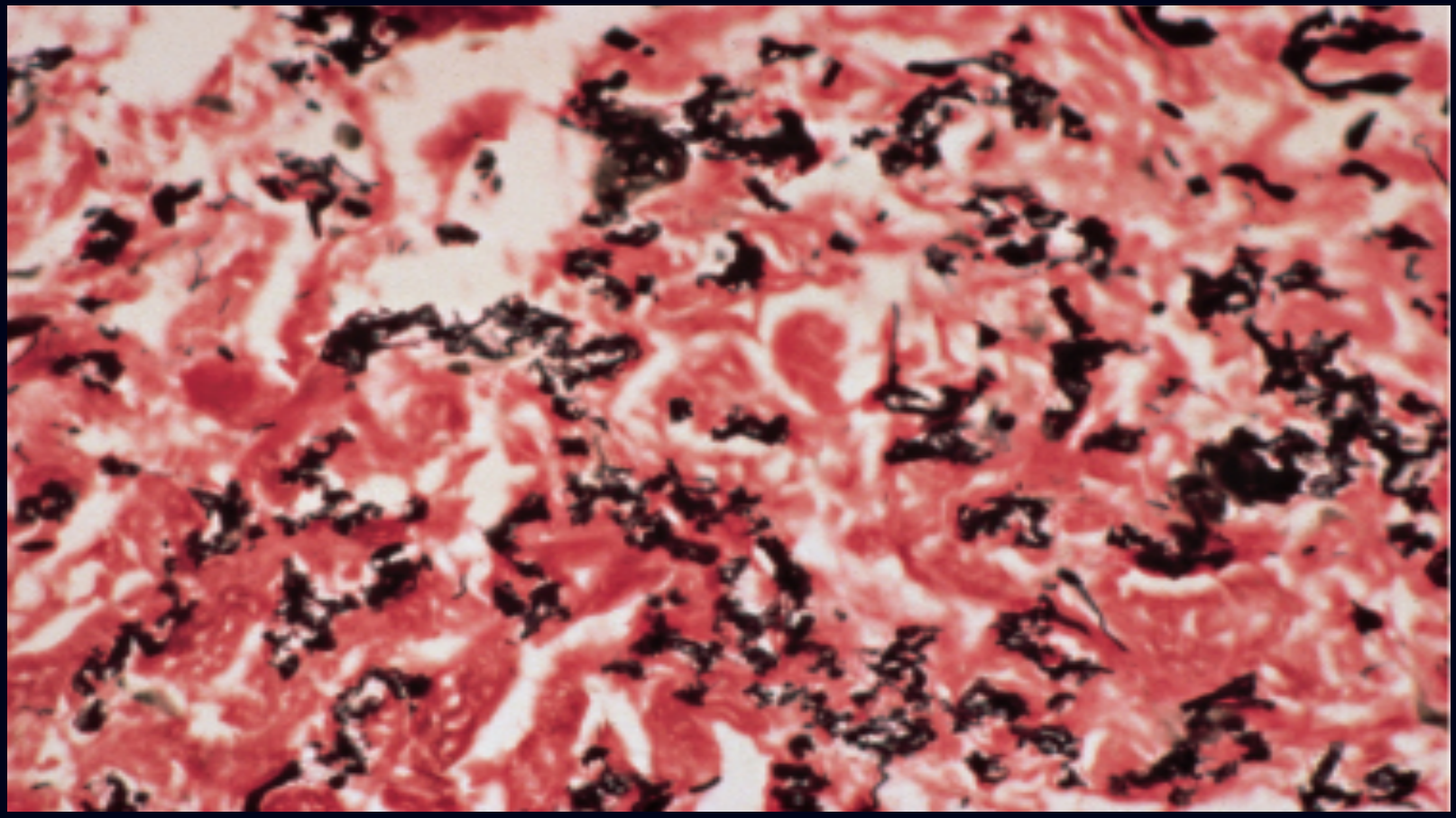

PXE-like with coagulopathy


Calciphylaxis


Hutchinson-Gilford


Primary Basal Ganglia Calcif.

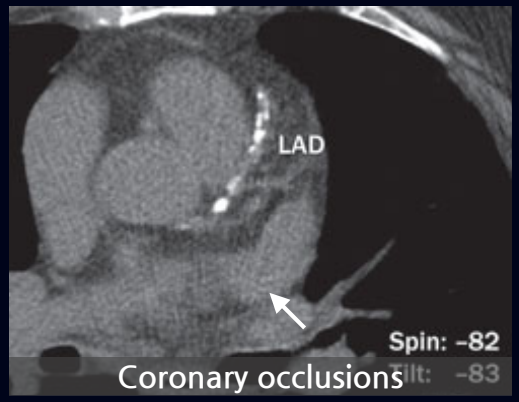

Fibrodysplasia Prog. Ossif.



PXE affects the skin, eyes and cardiovascular system

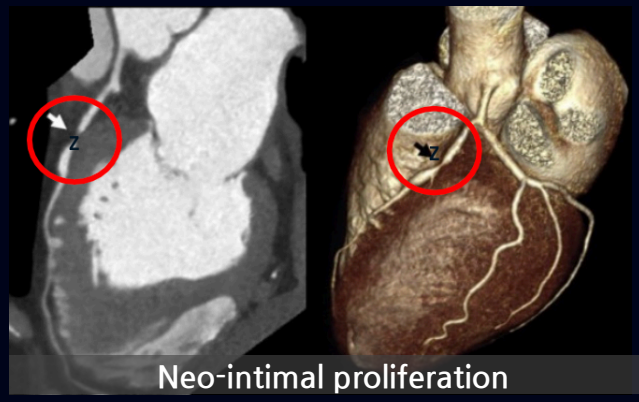
PPi DEFICIENCY | PSEUDOXANTHOMA ELASTICUM (PXE)

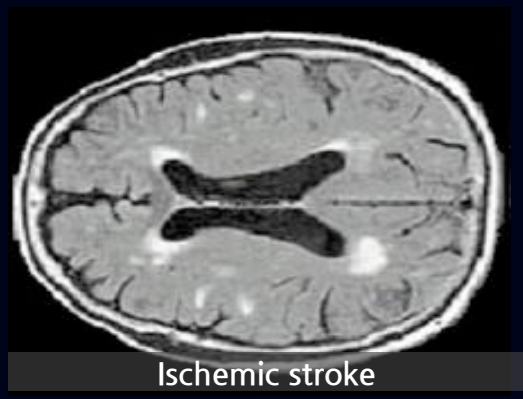
Calcification-related



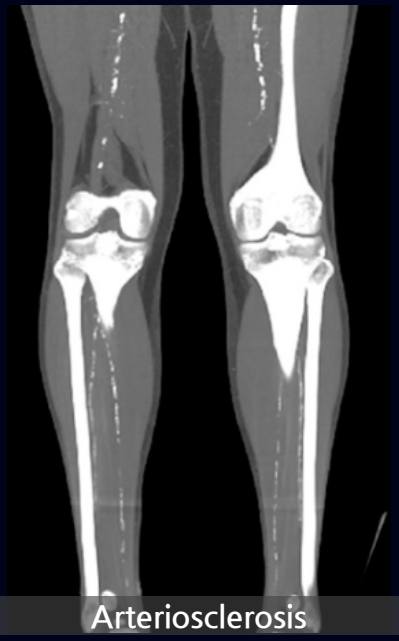
Coronary occlusions

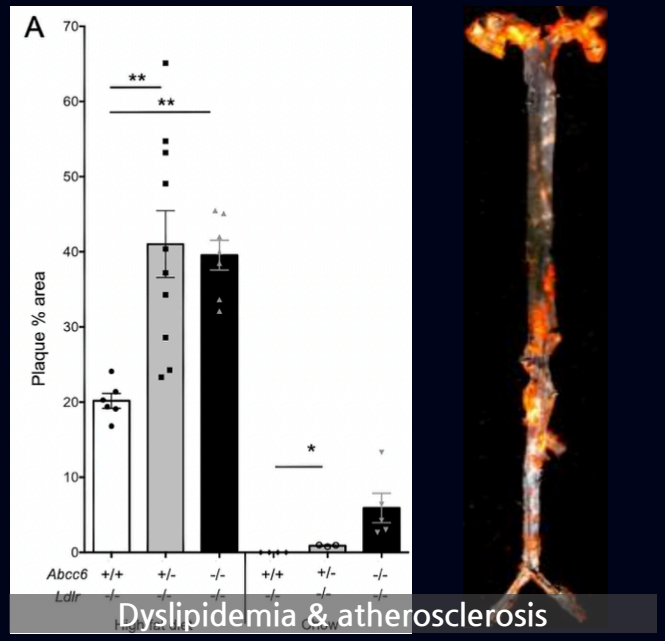
Calcification-unrelated


Neo-intimal proliferation

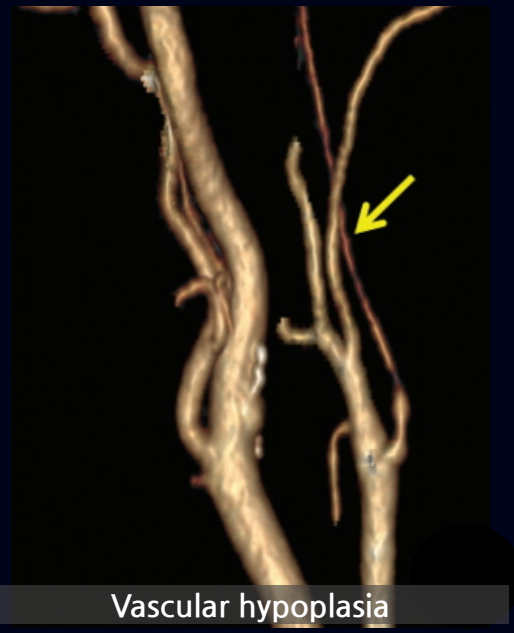

Ischemic stroke

Karam et al, 2015


Arteriosclerosis



Dyslipidemia & atherosclerosis

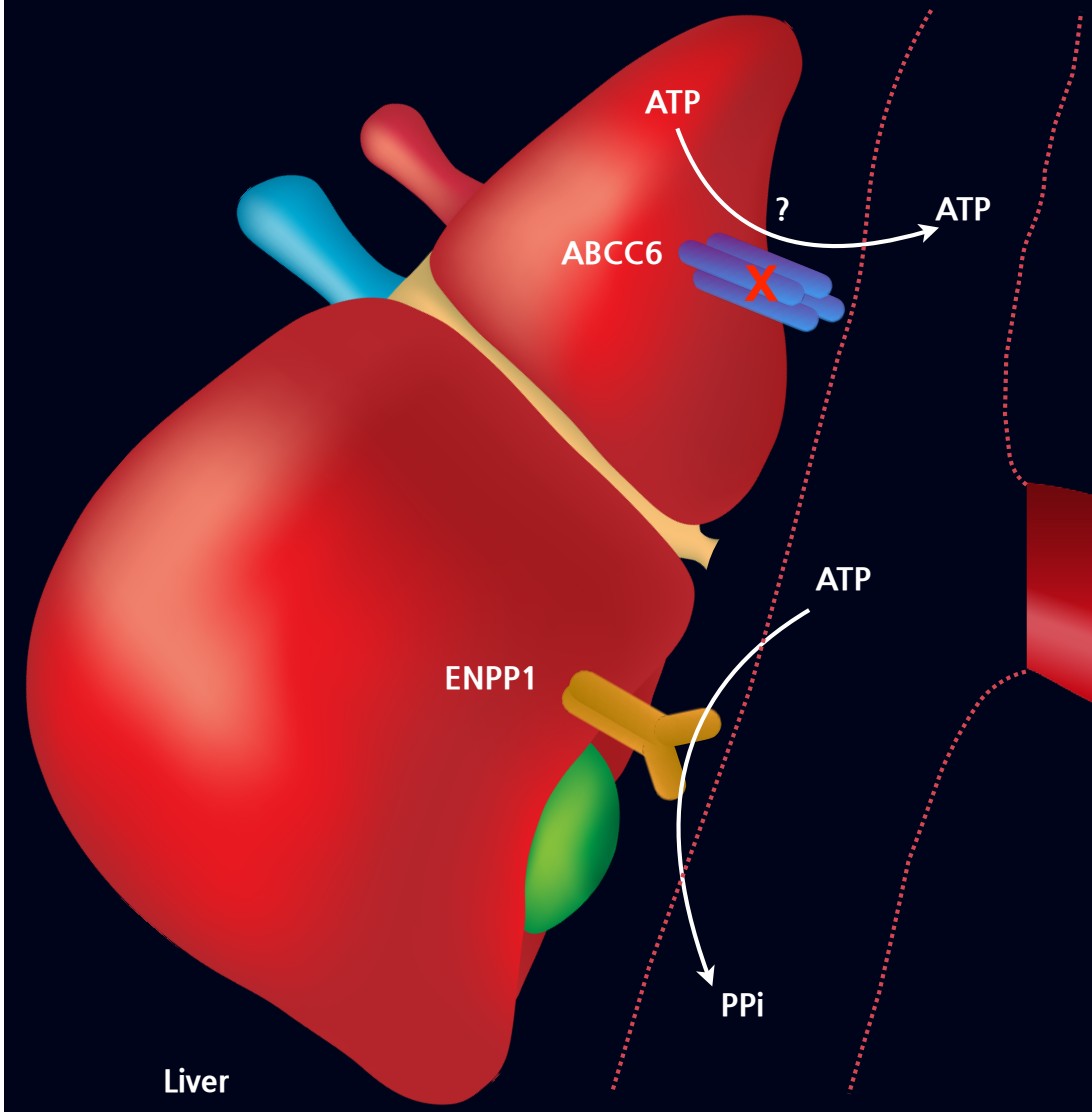

Vascular hypoplasia

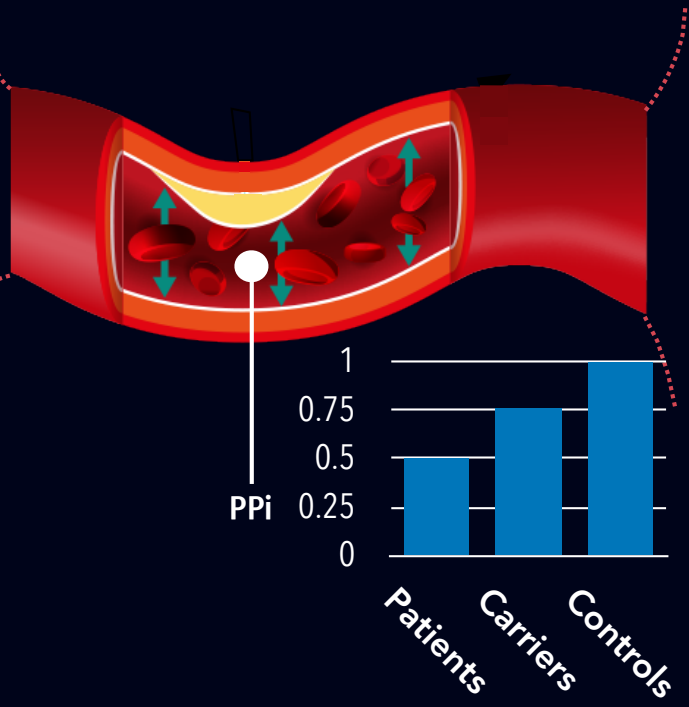
A METABOLIC DISORDER | ABCC6 DEFICIENCY

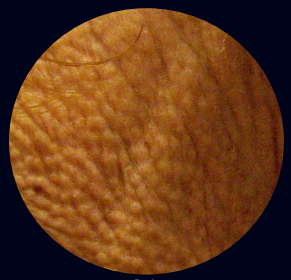
DEFICIENT CALCIFICATION INHIBITORS (MGP, FETUIN-A)

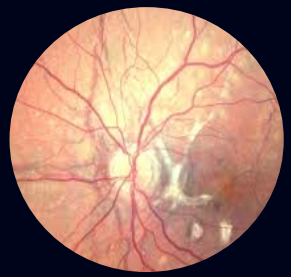
INCREASED OXIDATIVE STRESS

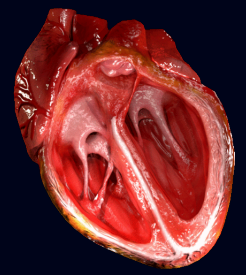
ACTIVATED DNA DAMAGE RESPONSE






Skin

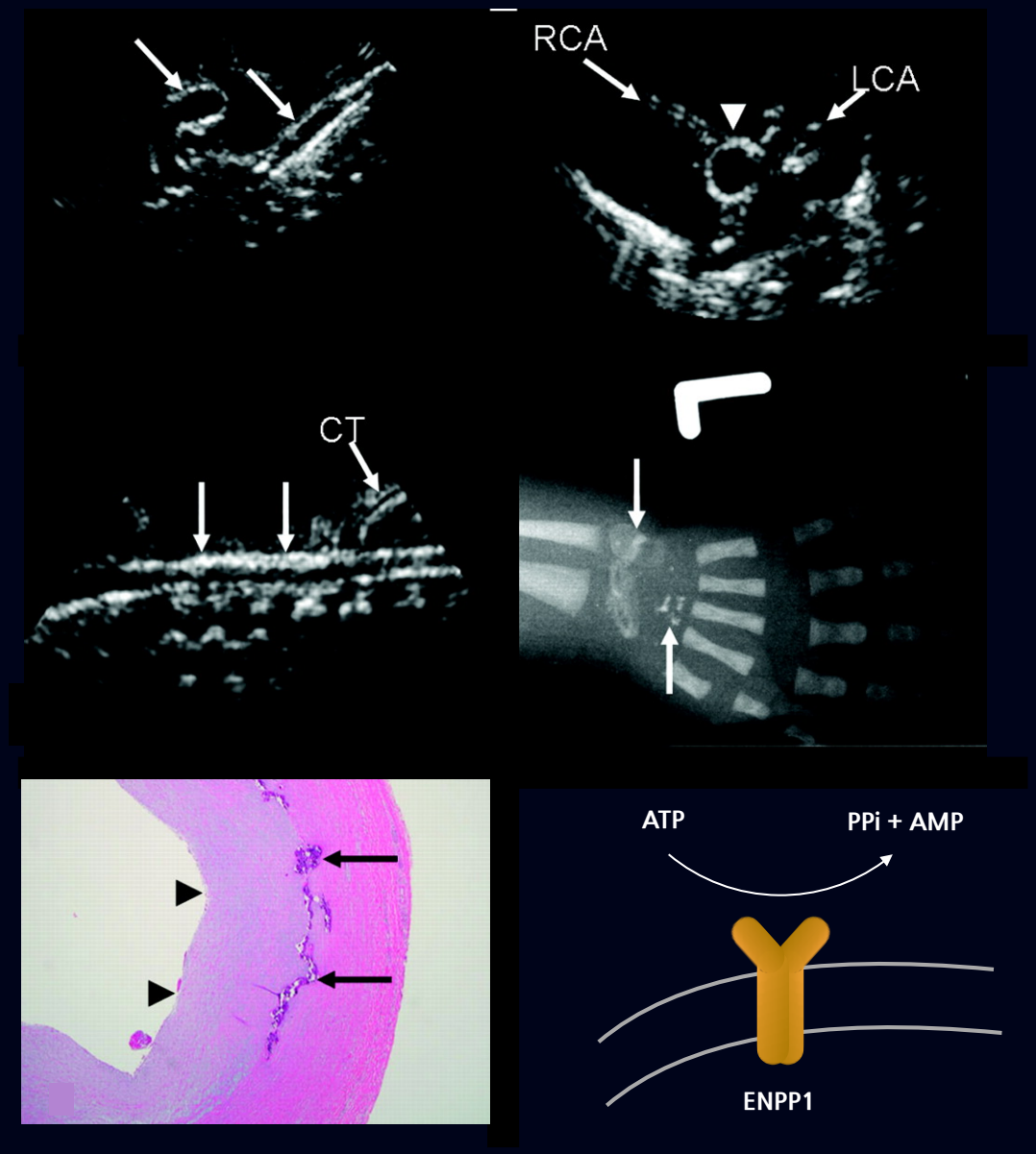

Eyes


Heart & vessels

Van Gils et al, J Clin Med, 2023

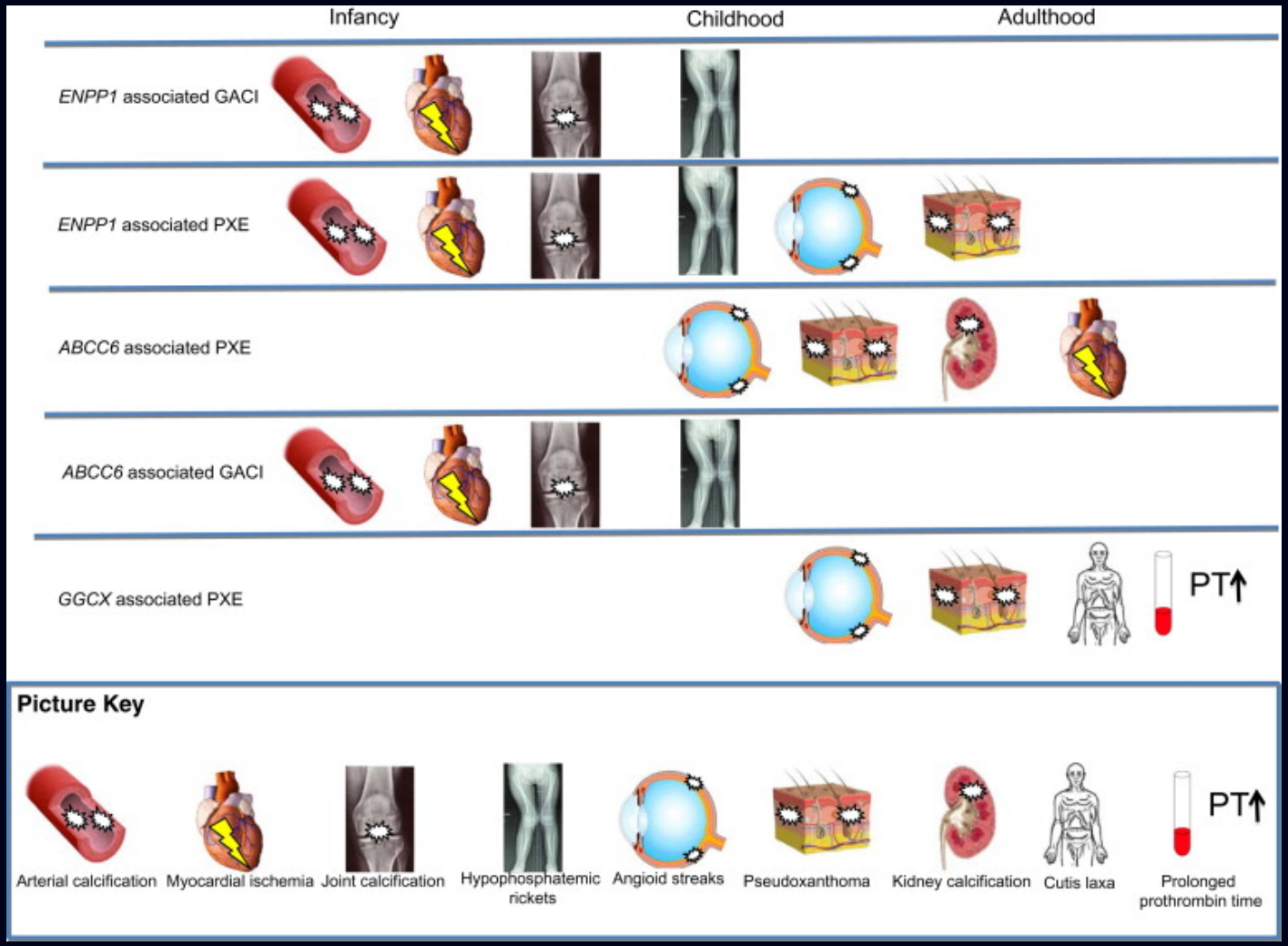
PPi correction does not completely alleviate calcification in animal models

PPi DEFICIENCY | GENERALIZED ARTERIAL CALCIFICATION OF INFANCY



In utero ectopic calcification of bloodvessels and hypertrophia of the vessel wall

PPi DEFICIENCY | THE PXE - GACI SPECTRUM

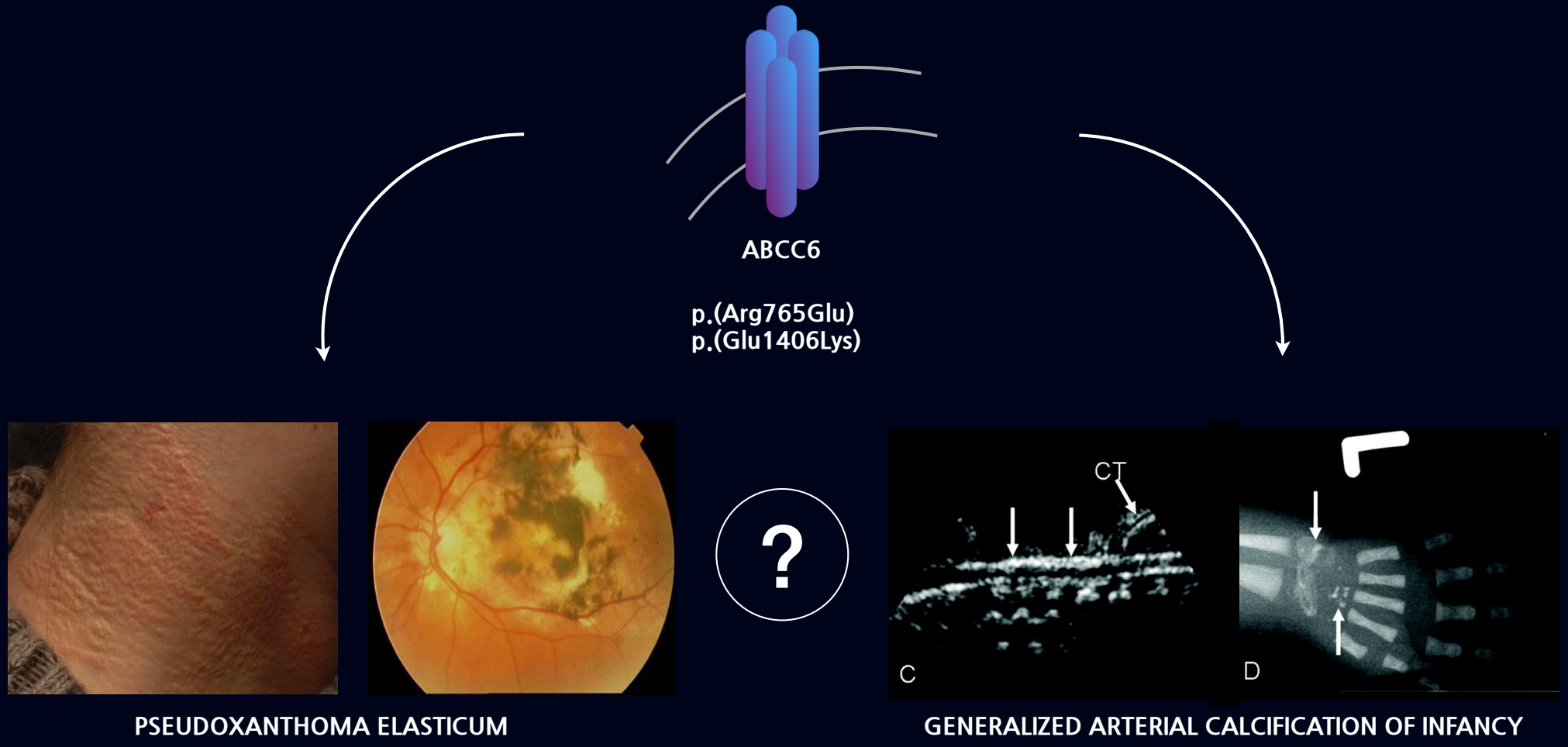


Nitschke et al., 2012

PXE can also be caused by mutations in the ENPP1 gene

GACI can also be caused by mutations in the ABCC6 gene

PPi DEFICIENCY | ROLE OF DISEASE MODIFYING FACTORS

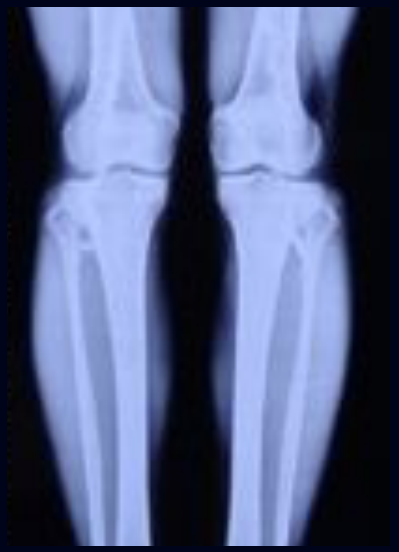


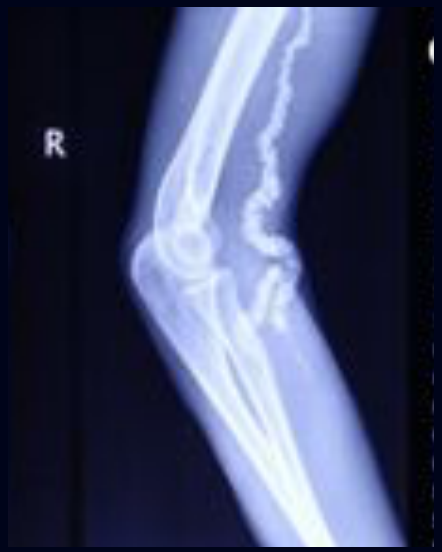
PSEUDOXANTHOMA ELASTICUM

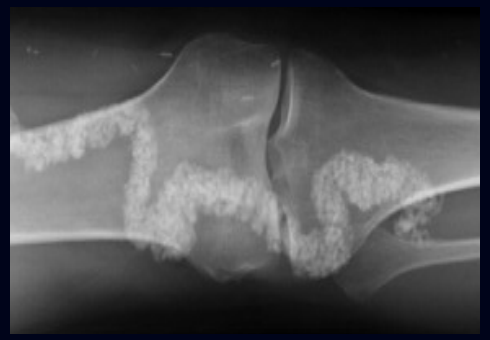
GENERALIZED ARTERIAL CALCIFICATION OF INFANCY

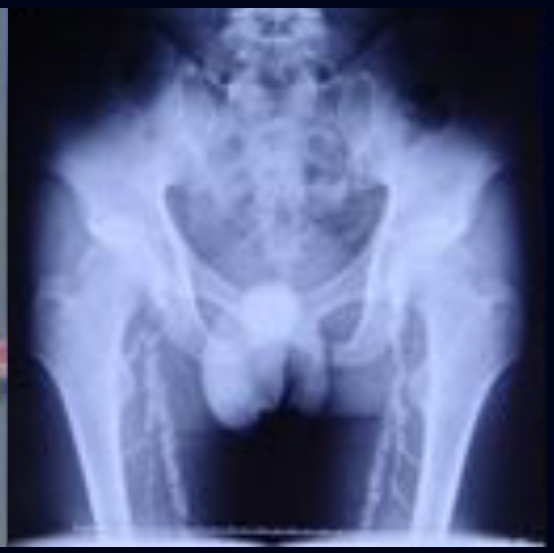
Identical ABCC6 mutations can cause either PXE or GACI

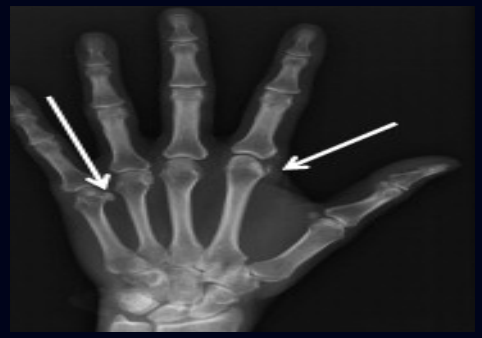
PPi DEFICIENCY | ARTERIAL CALCIFICATION D/T CD73 DEFICIENCY

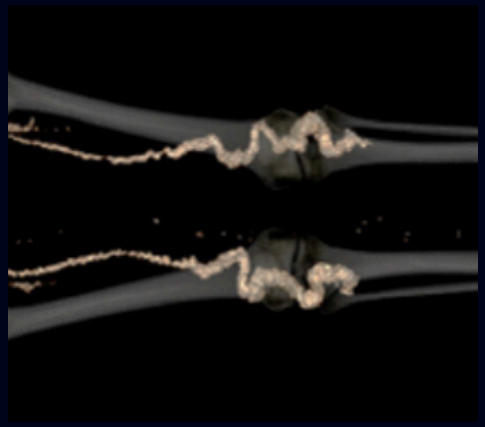


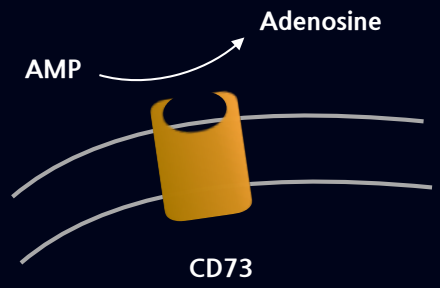




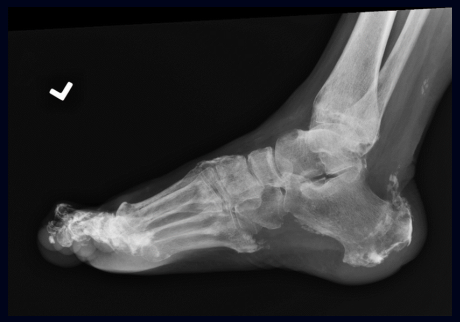


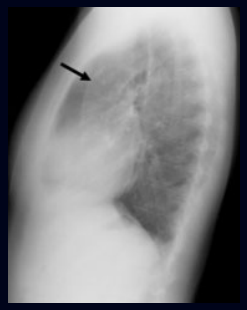


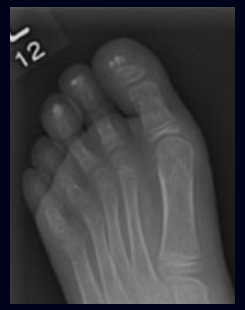


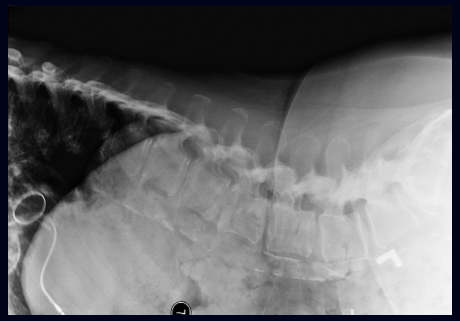


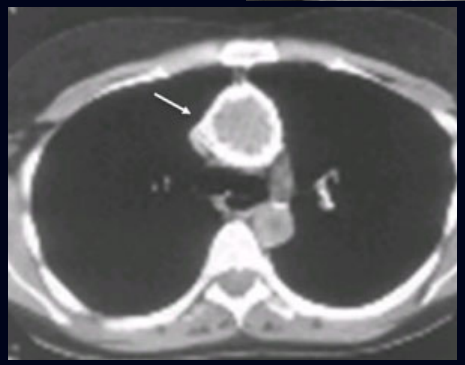
INTERFERONOPATHY | SINGLETON-MERTEN SYNDROME

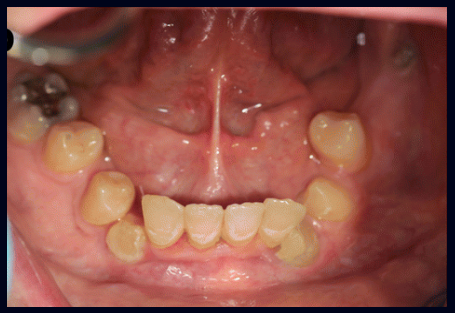


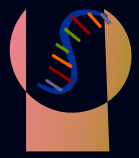




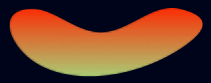








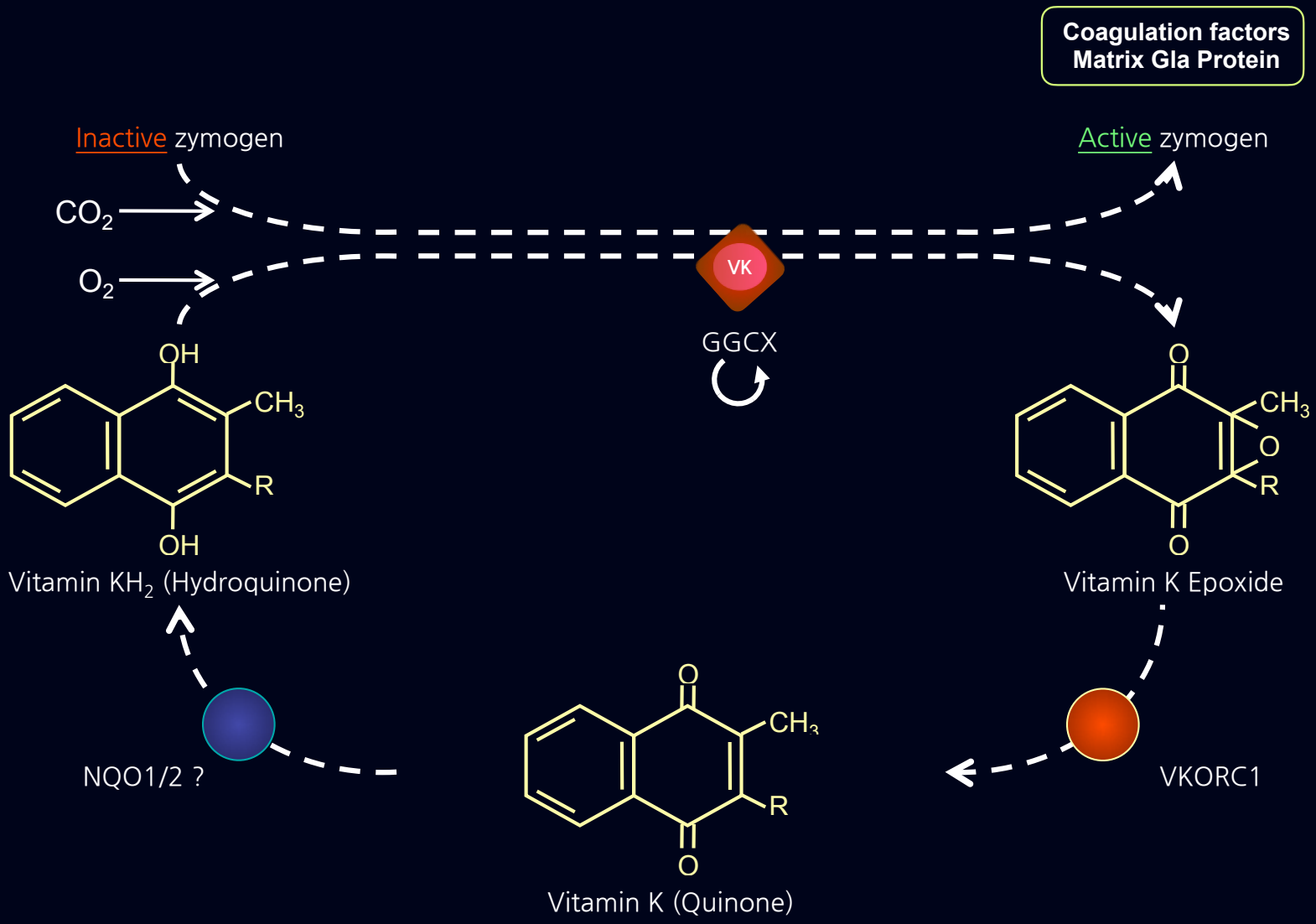
IFIH1



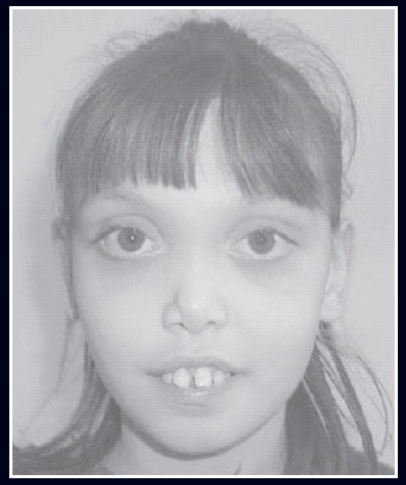
DDX58

Autosomal dominant short stature, bone dysplasia and heart failiure

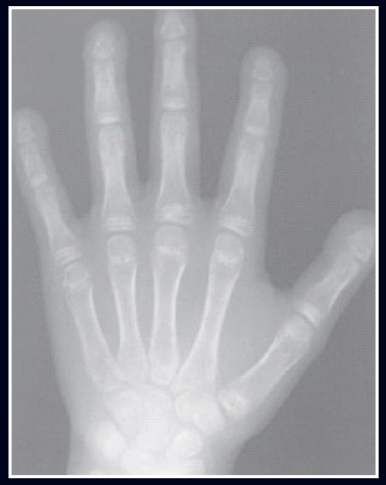
VK-DEPENDANT DISEASES | VITAMIN K CYCLE



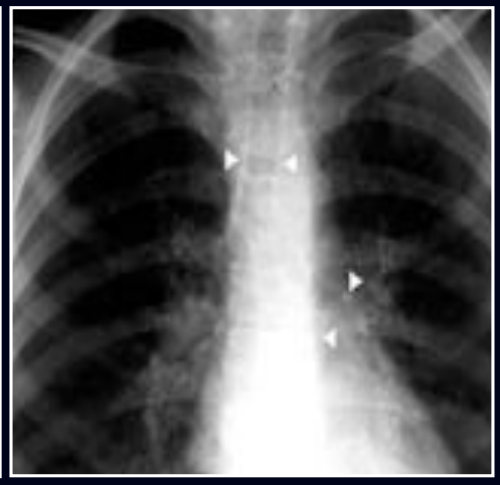
CARDINAL FEATURES

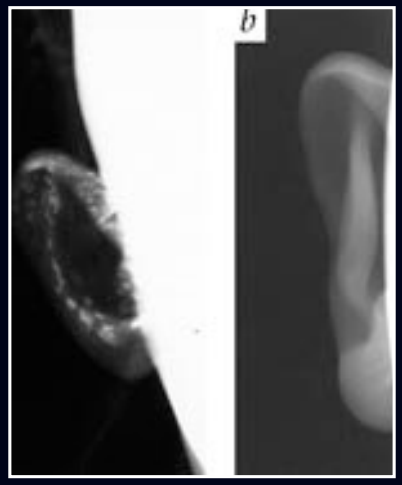


Facial dysmorphia:
long face
midface hypoplasia
small alae



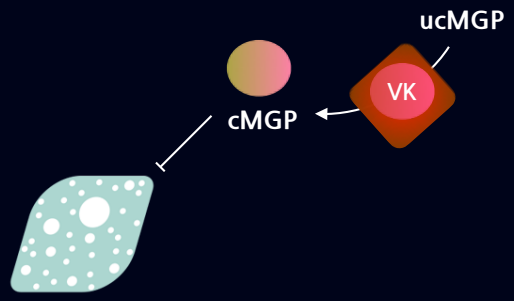
Brachytelephalangism



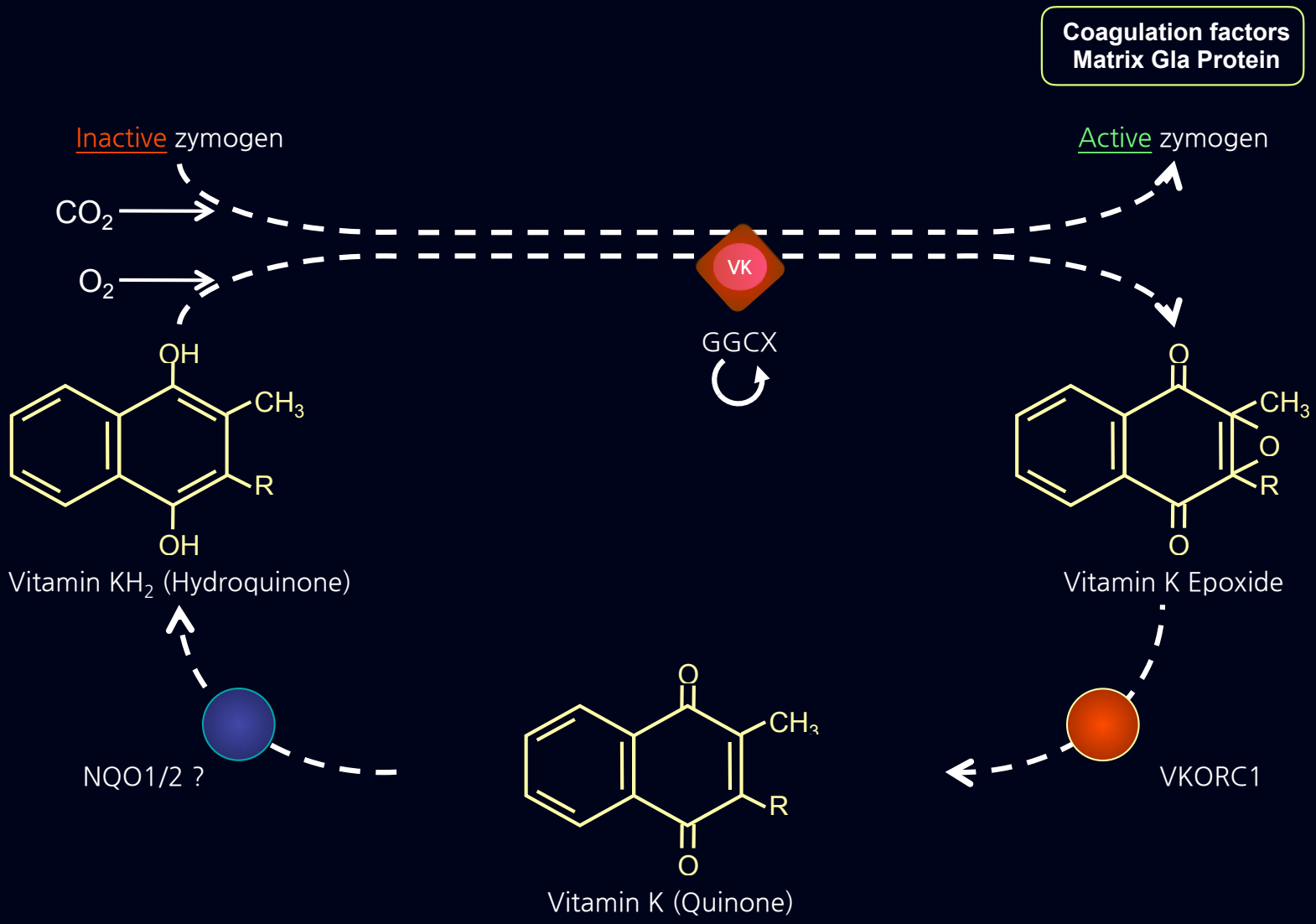


Cartilaginous calcification
(Peripheral pulmonary stenosis)

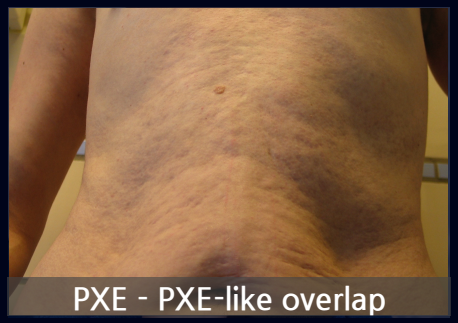
7 pathogenic variants in the MGP gene

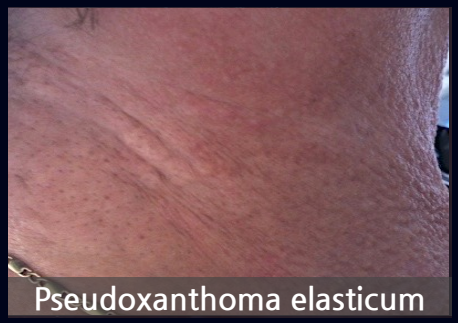


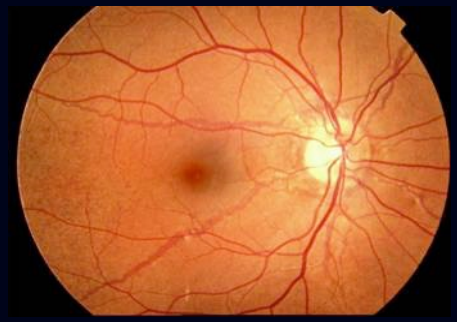
VK-DEPENDANT DISEASES | VITAMIN K CYCLE

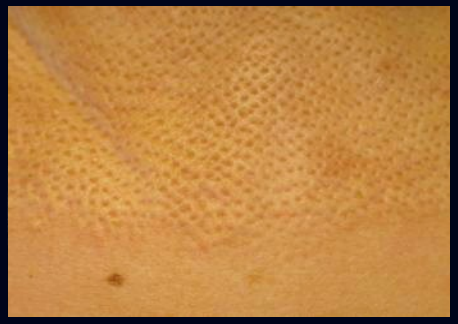


VK-DEPENDENT DISEASES | PXE-LIKE DISORDER WITH COAGULOPATHY

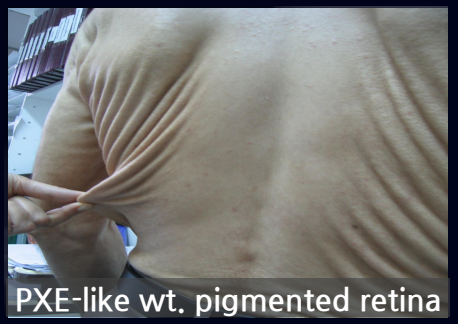

PXE - PXE-like overlap

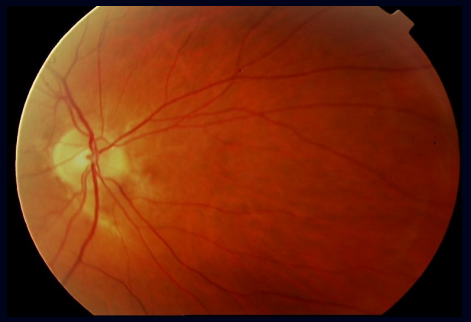

Pseudoxanthoma elasticum

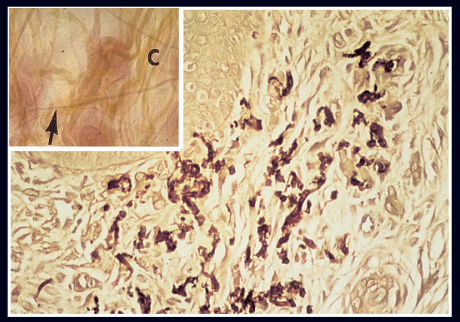


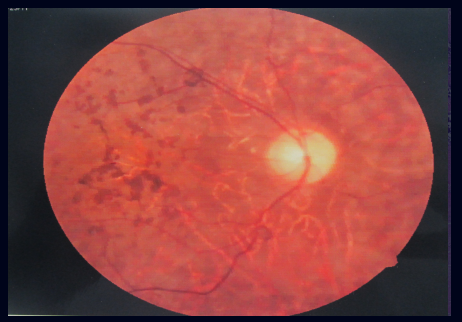



PXE-like with coagulopathy


PXE-like wt. pigmented retina

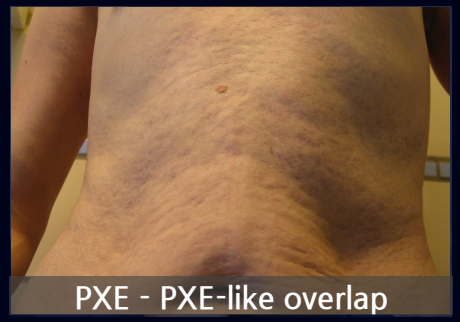


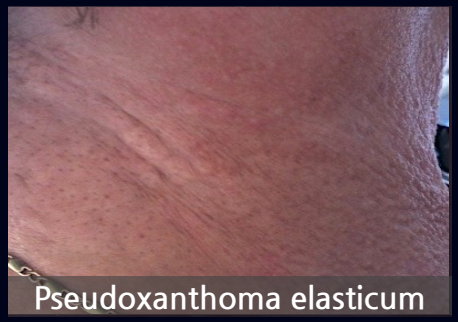


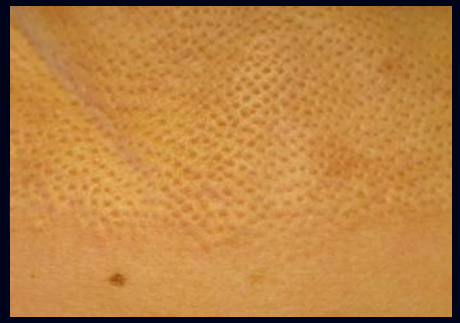


Vanakker et al, J Invest Dermatol, 2007

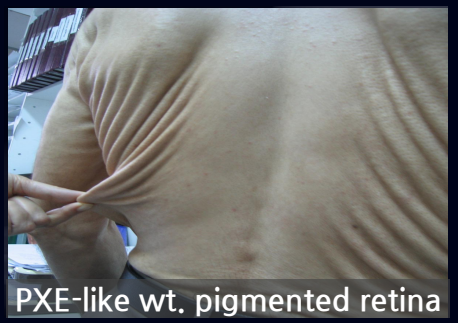
VK-DEPENDENT DISEASES | PXE-LIKE W/ PIGMENTED RETINOPATHY

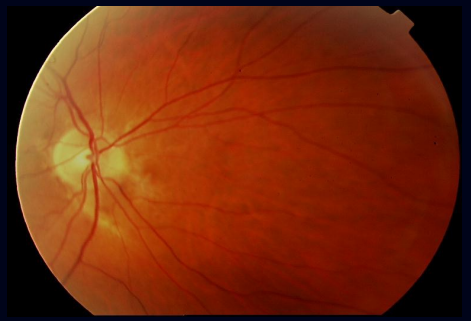

PXE - PXE-like overlap

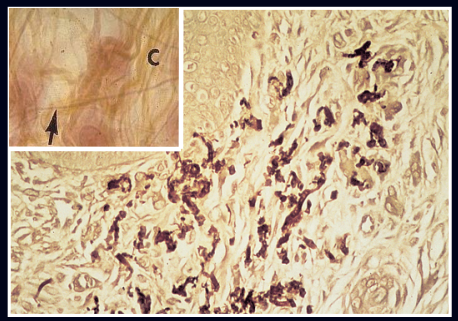

Pseudoxanthoma elasticum

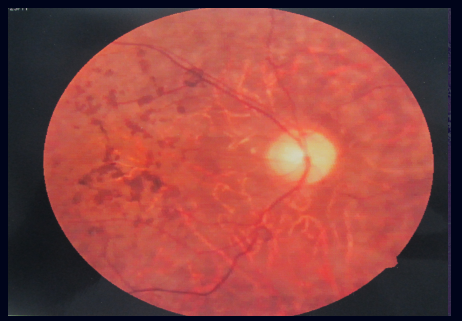



PXE-like with coagulopathy


PXE-like wt. pigmented retina

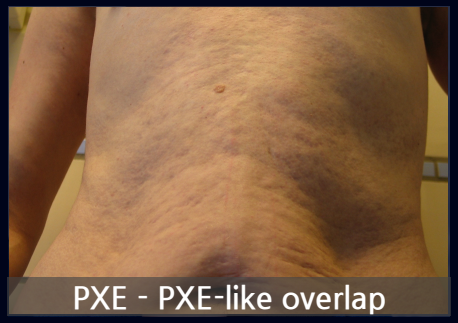


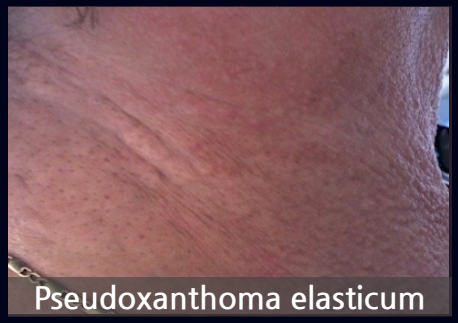


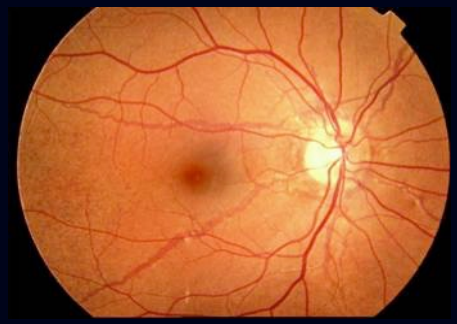


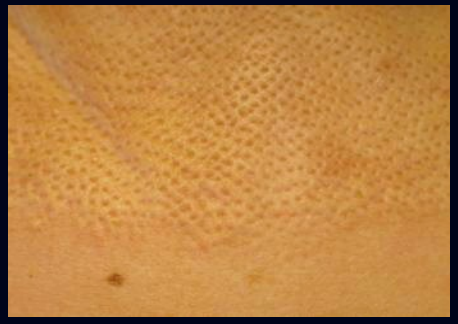
Kariminedjad, Vanakker et al, J Invest Dermatol, 2014

GGCX | DISEASE MODIFYING CAPACITIES

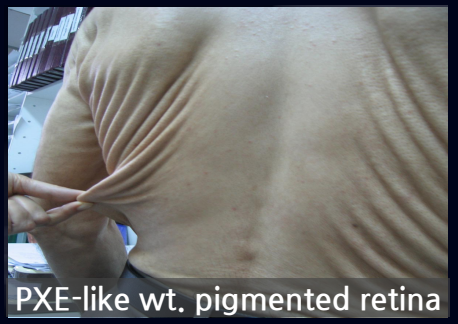

PXE - PXE-like overlap

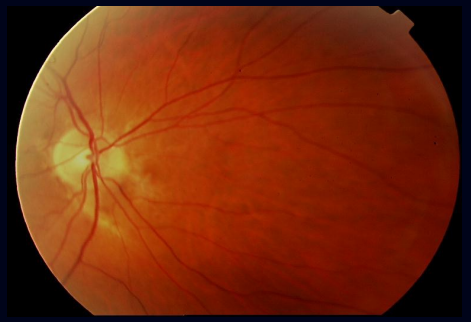

Pseudoxanthoma elasticum

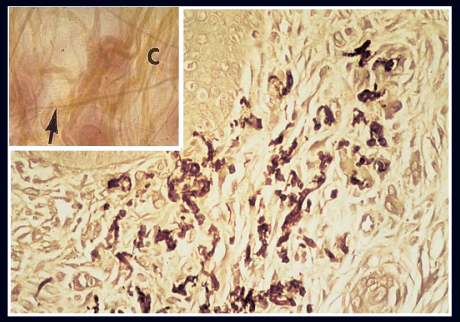


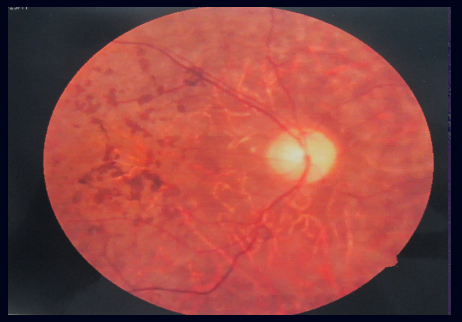



PXE-like with coagulopathy


PXE-like wt. pigmented retina



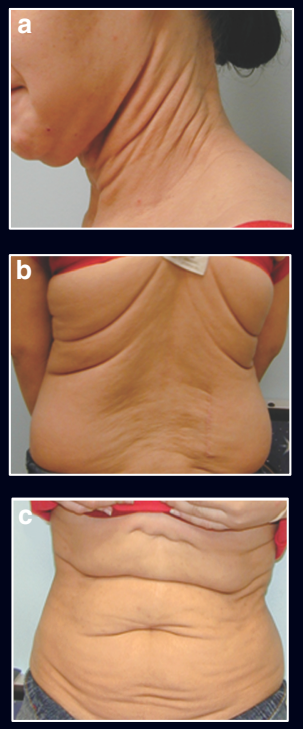




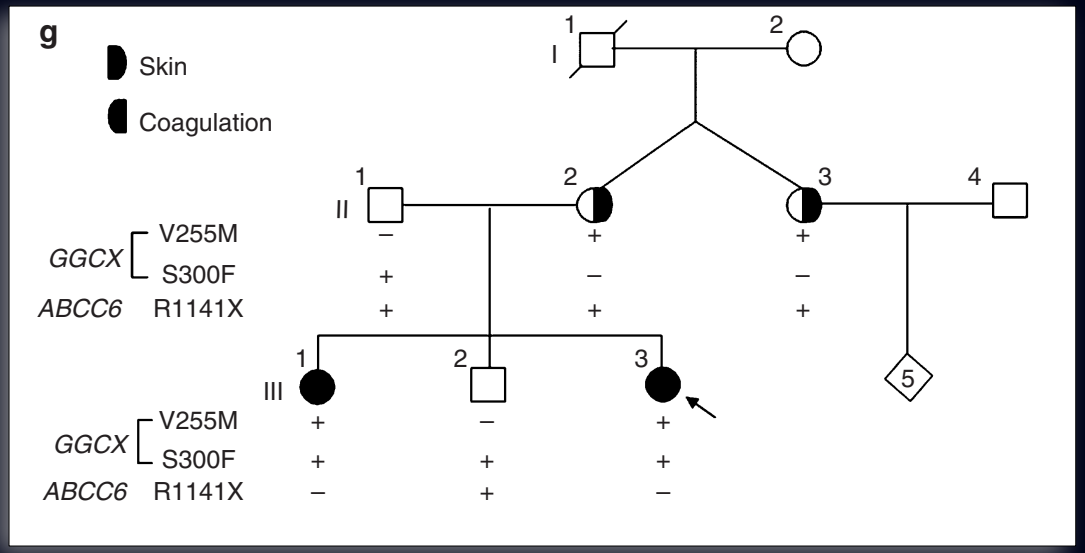
Vanakker et al, Am J Med Genet, 2011

ABCC6 + GGCX | DIGENIC INHERITANCE

Patient III-3

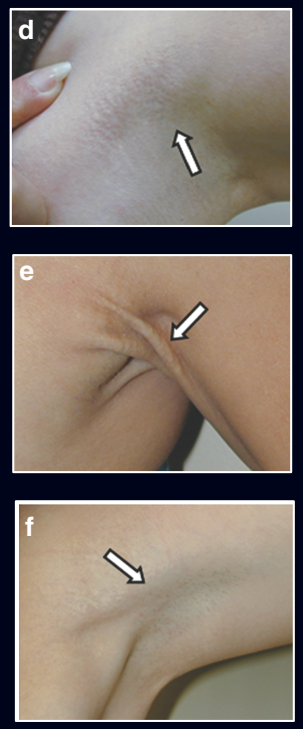


Coagulation disorder



Li et al, 2009

Patient II-2



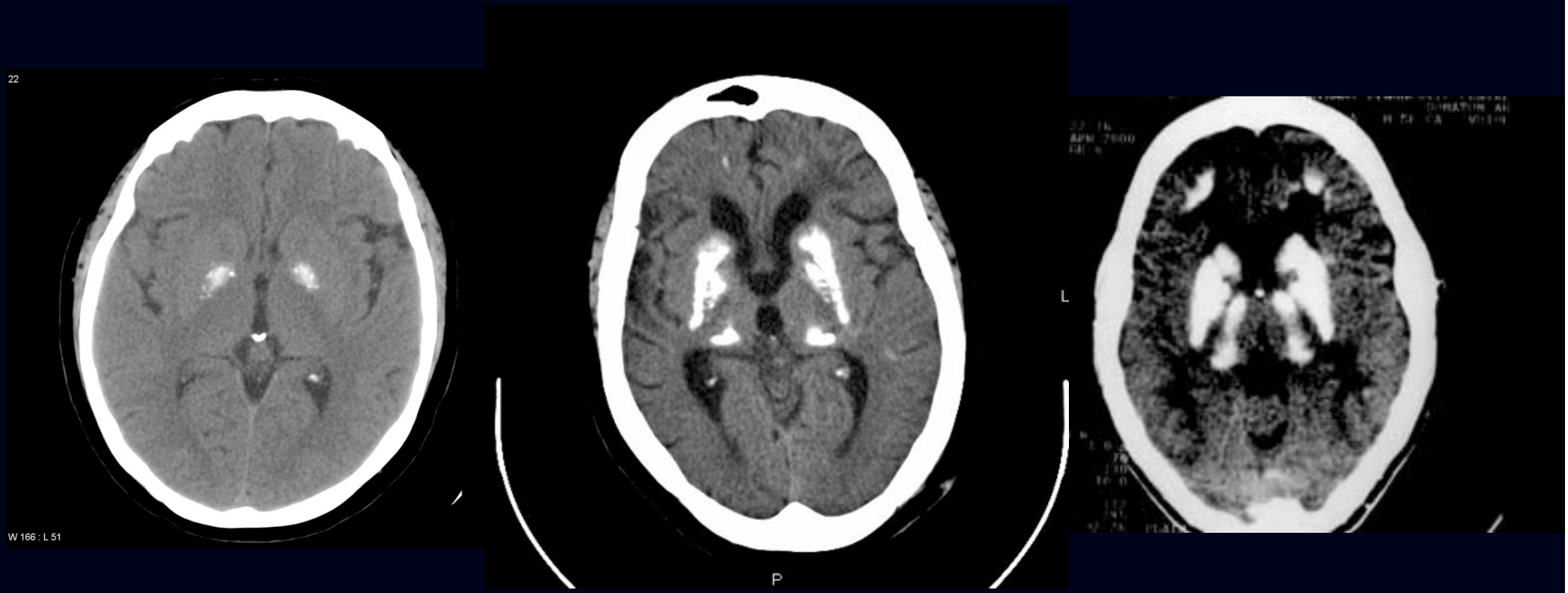
No coagulation disorder

BRAIN CALCIFICATIONS| BASAL GANGLIA CALCIFICATIONS

As a group not considered a rare disorder

Part of normal aging process

Variety of acquired etiologies



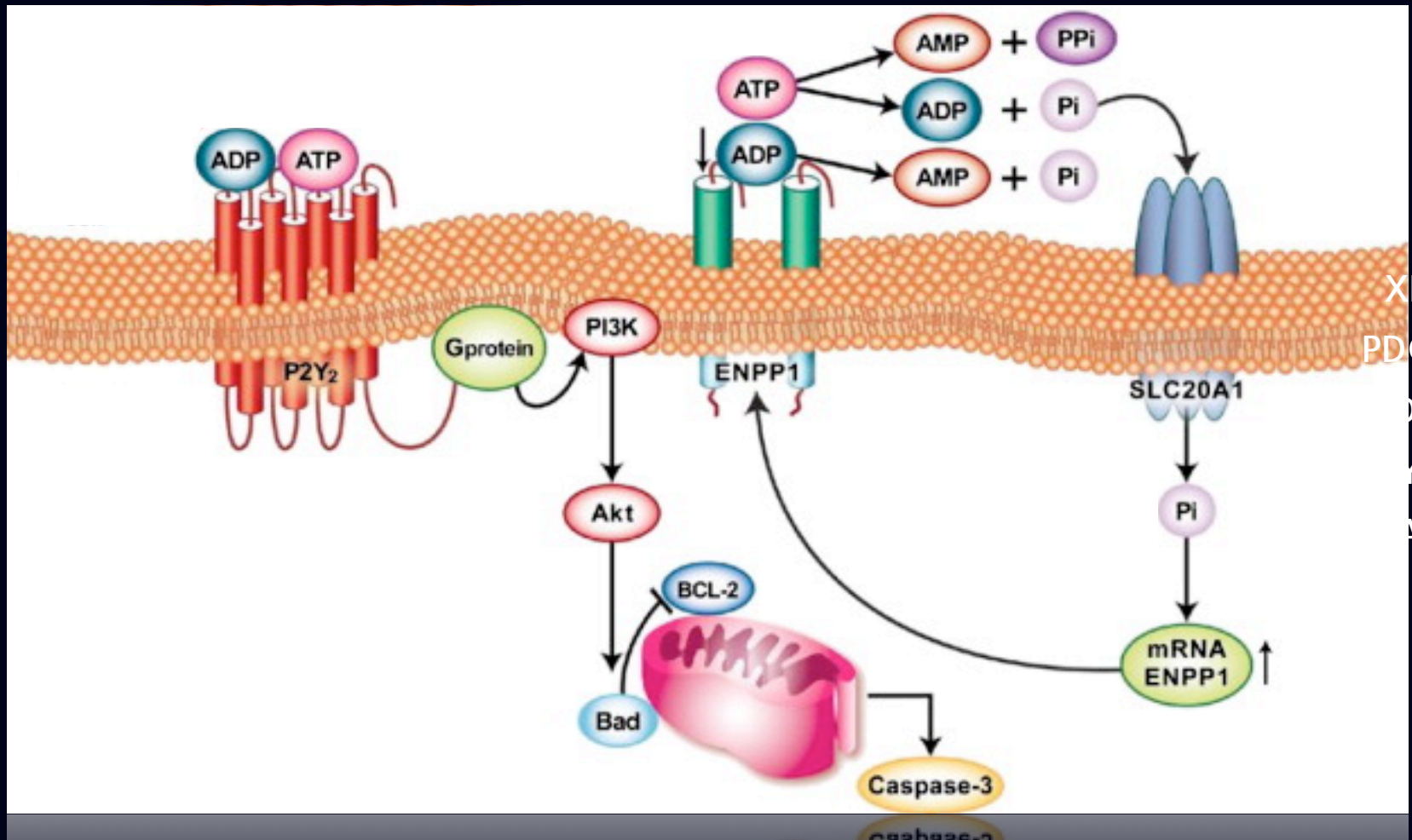
PFBC | PRIMARY FAMILIAL BASAL GANGLIA CALCIFICATIONS

Rare neurodegenerative disorder

Early onset basal ganglia calcification

Neuropsychiatric and movement disorders in 3rd-5th decade

No other mineralisation phenotypes



XPR1 (AD)

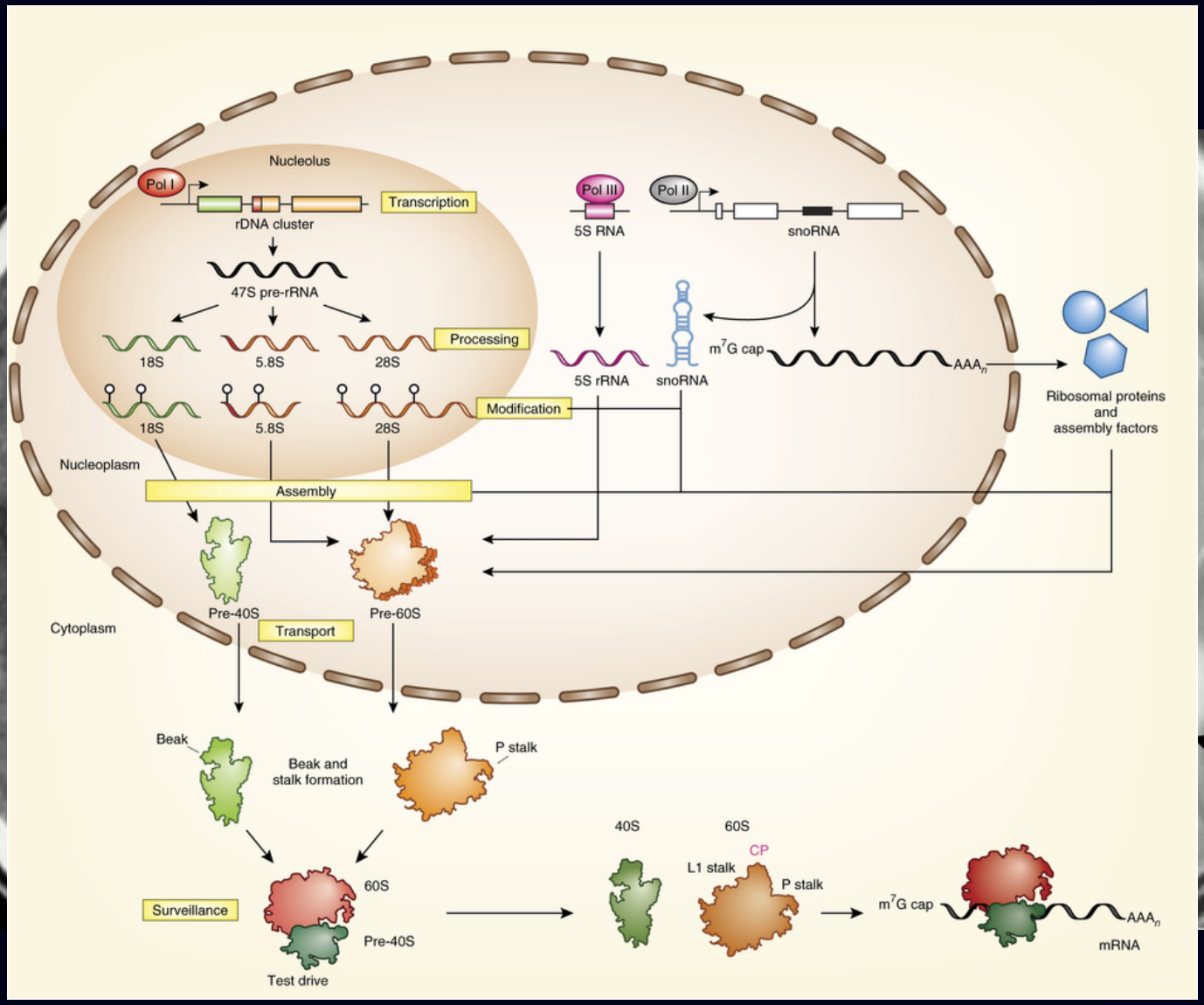
PDGFRB (AD)

GFB (AD)

YORG (AR)

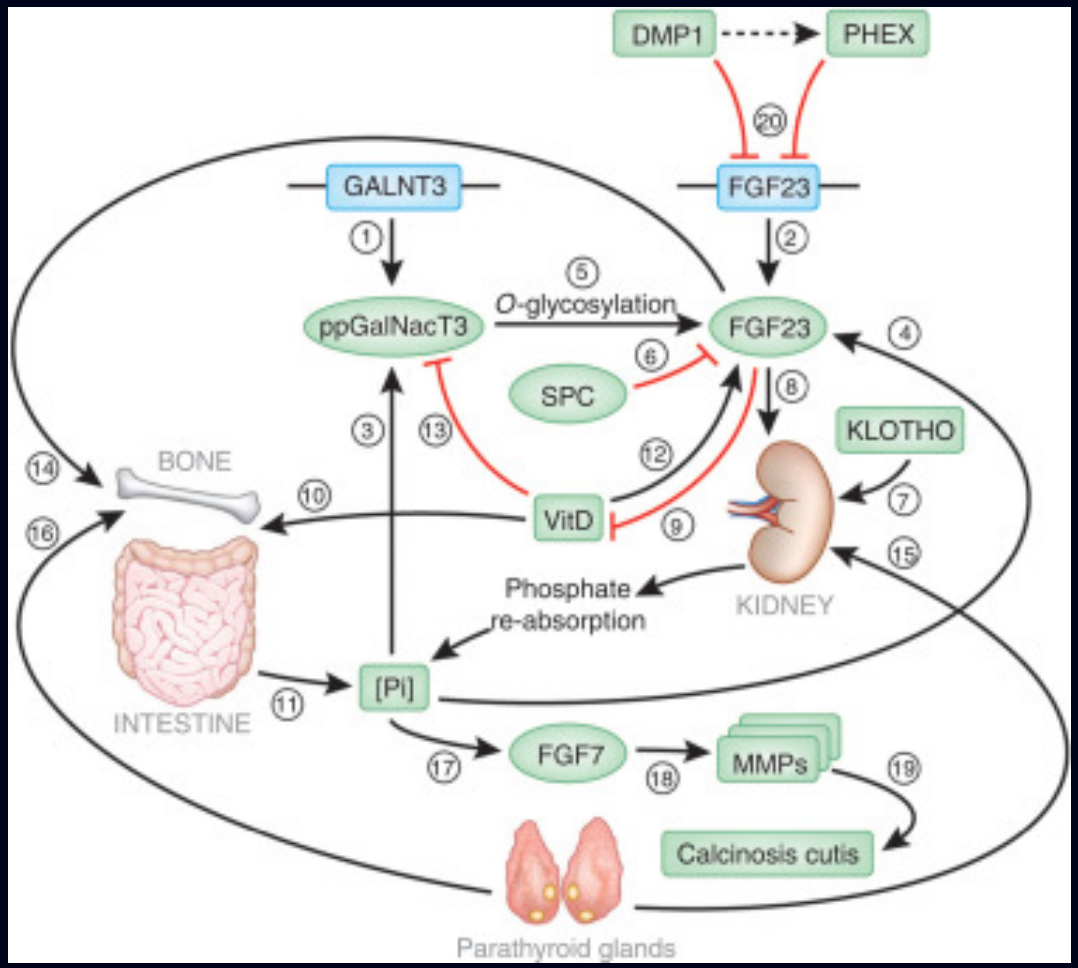
AM2 (AR)

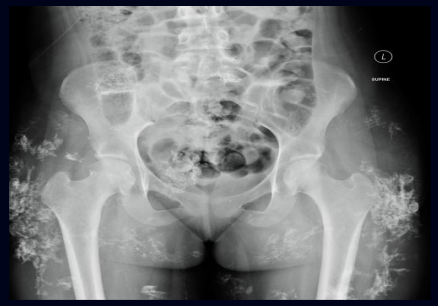
BRAIN | LEUCO-ENCEFALOPATHY WITH C & C

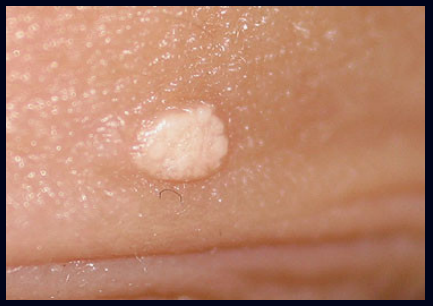


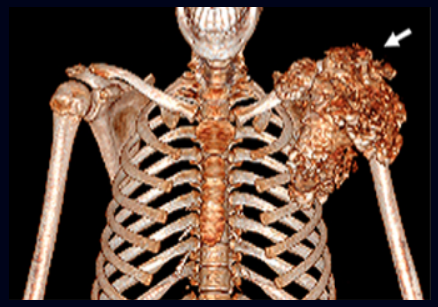
SNORD118: box C/D snoRNA U8

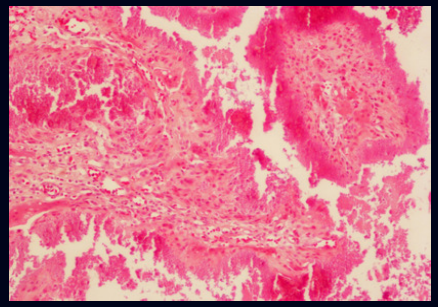
TUMORAL CALCINOSIS | SYMPTOMS AND PATHOPHYSIOLOGY

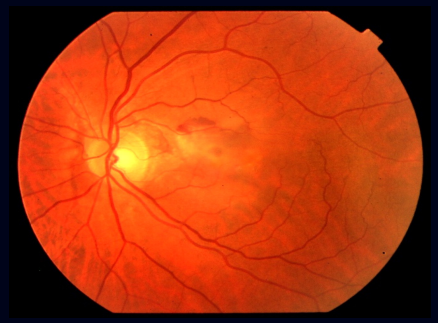


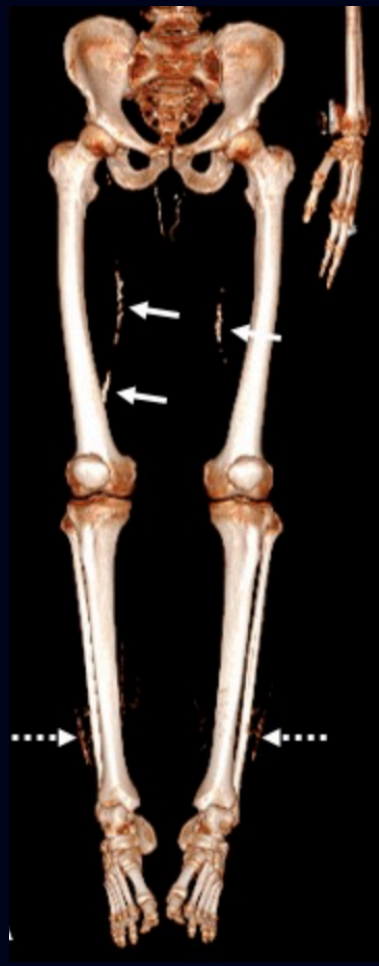






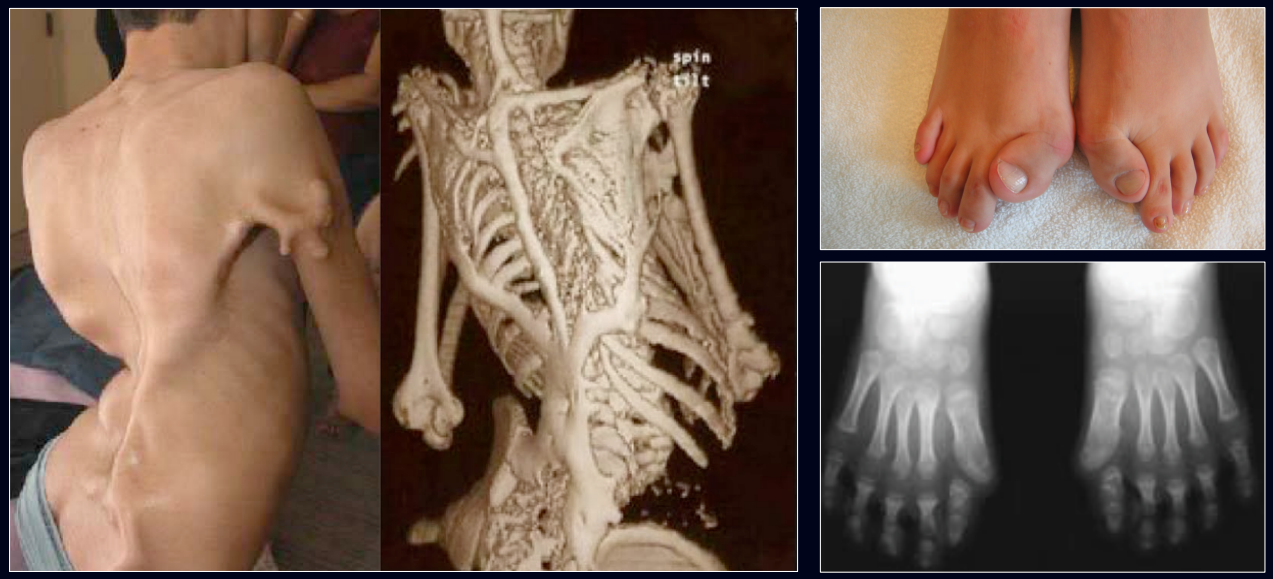




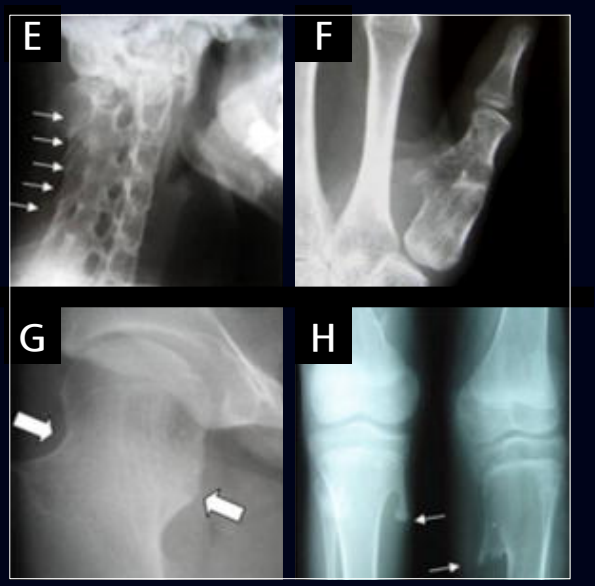


OSSIFICATION | FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

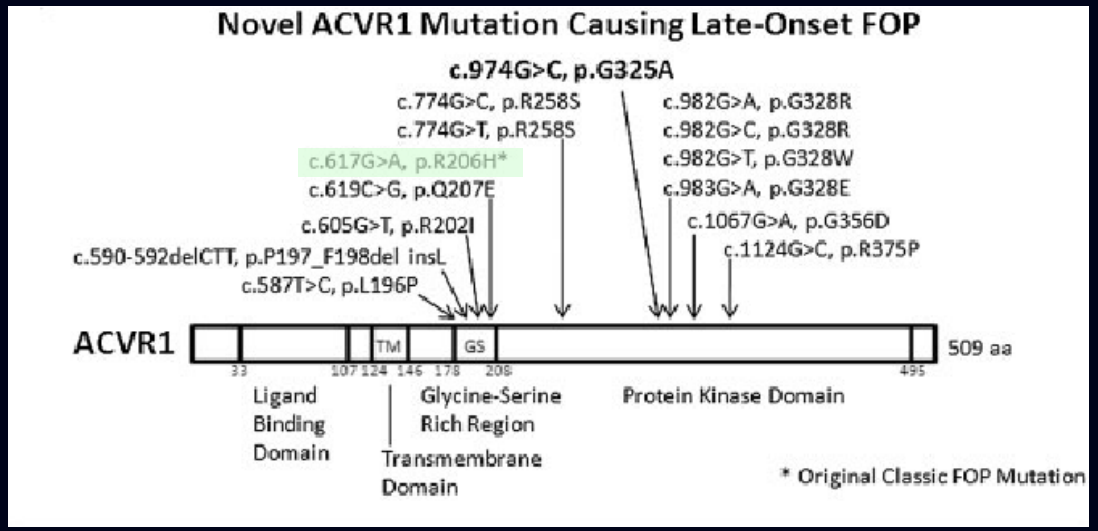
TYPICAL FOP



ATYPICAL FOP-Plus



Kaplan et al., 2009



Dandara et al., 2012

OSSIFICATION | FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Birth

1st DECADE

2nd D.

4th D.

Normal (except for congenital malformation of toes)

Flare-ups
(episodes of painful soft tissue swellings)

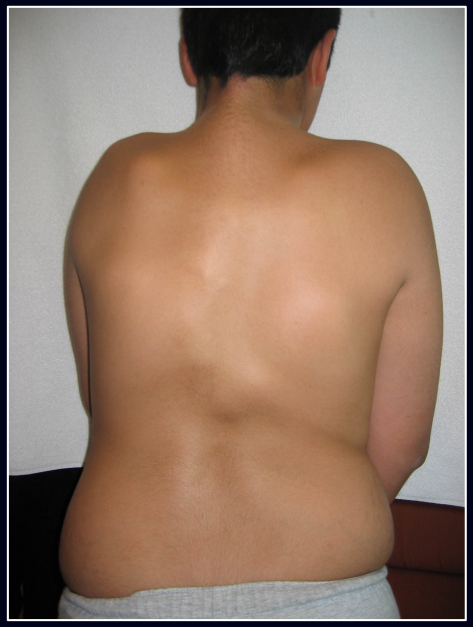
Initially some flare-ups may regress

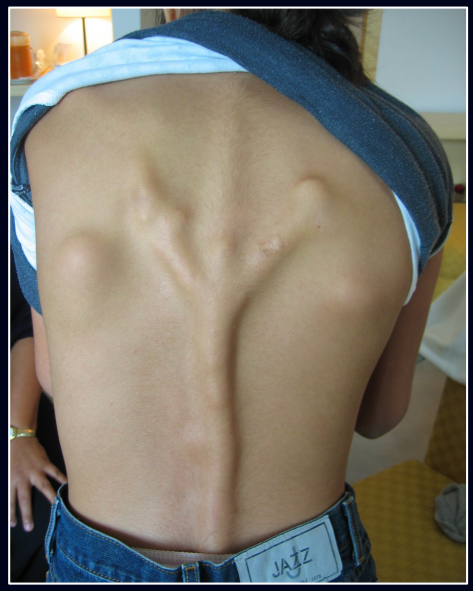
Transformation of skeletal muscle, tendons, ligaments, fascia, aponeuroses into heterotopic bone

NO skin involvement
(DD Progressive osseous heteroplasia)

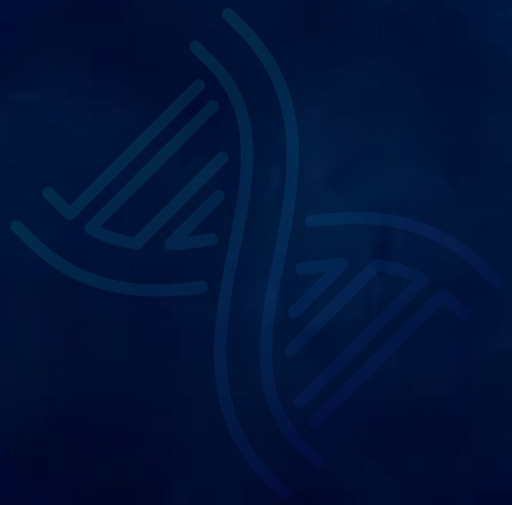
Limitations in mobility

Demise
- Thoracic ossification
- Severe weight loss (jaw ossification)
- Spinal ossification

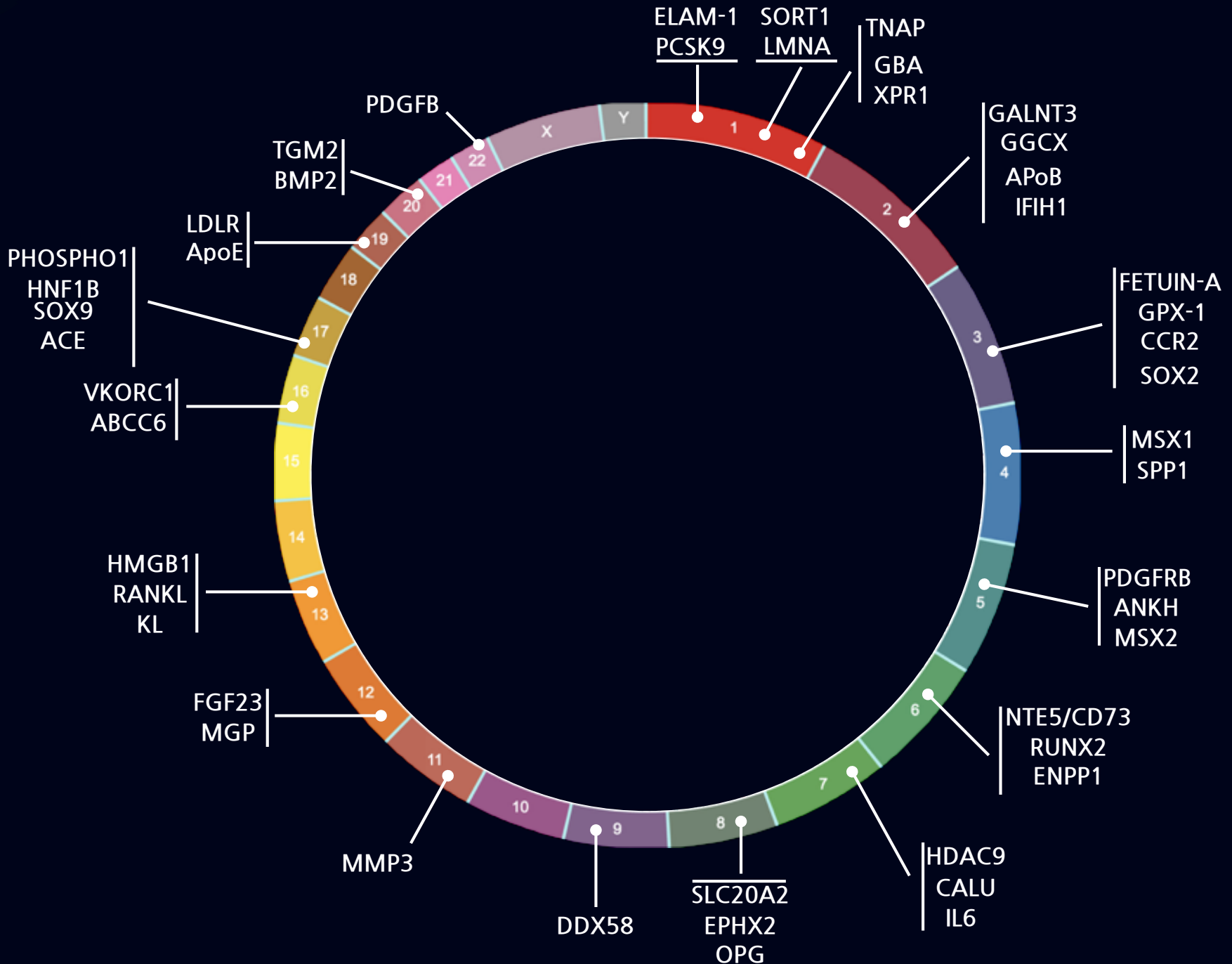


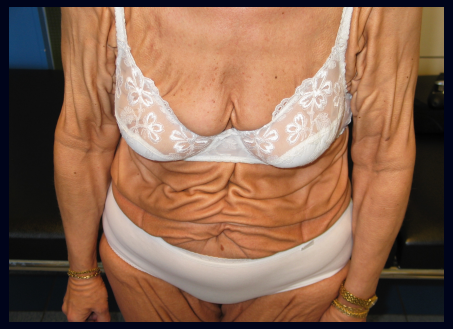


ECTOPIC CALCIFICATION | GENETICS



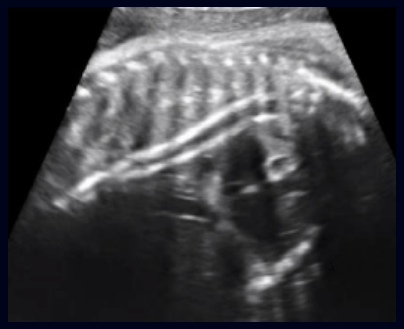
ECTOPIC CALCIFICATION | GENOMIC ARCHITECTURE



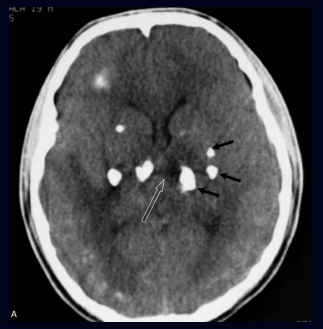


Pseudoxanthoma elasticum(-like)

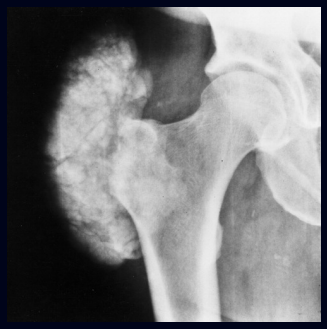
Progeria syndromes



Arterial calcification of infancy



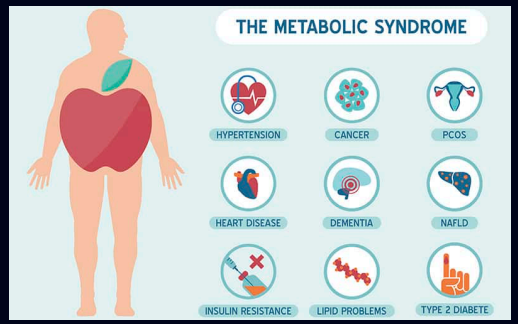
Familial brain calcification



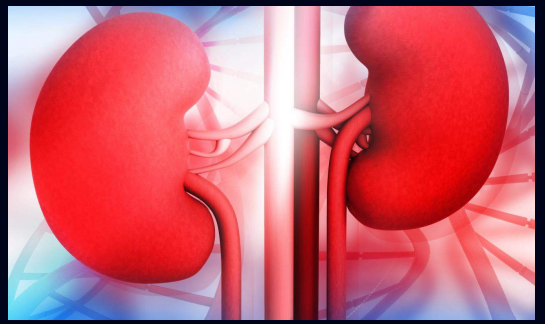
Tumoral calcinosis

PREDICT MONITOR PREVENT TREAT

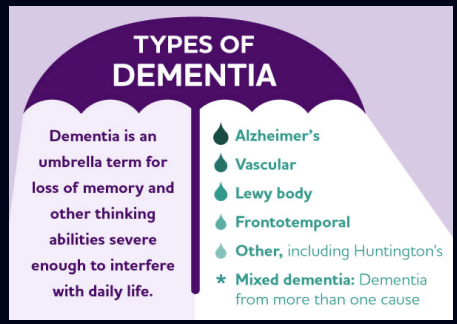
Diabetes mellitus



Metabolic syndrome



Chronic kidney disease



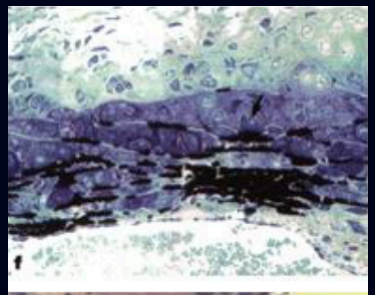
Dementia

FROM RARE TO COMMON | CLINICAL EXAMPLES

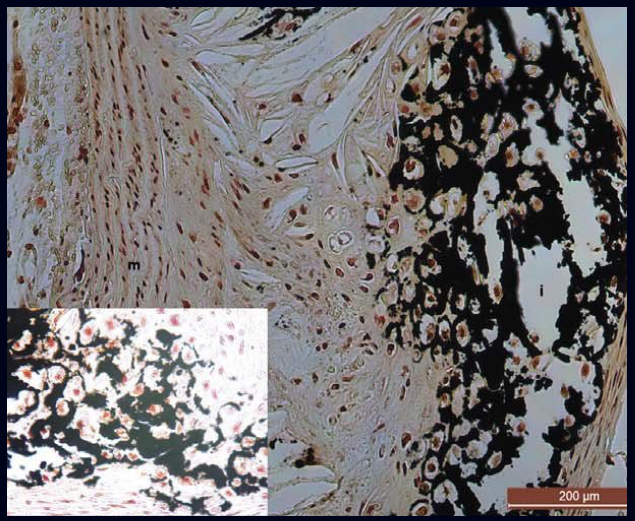
MGP

MGP null

Wild-Type

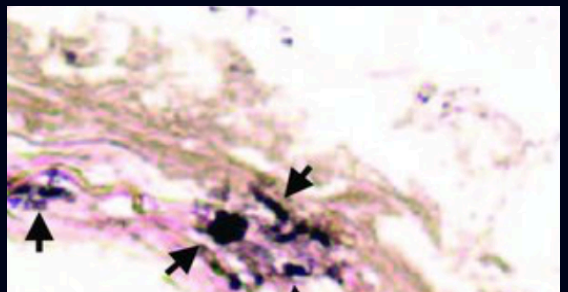


Keutel syndrome

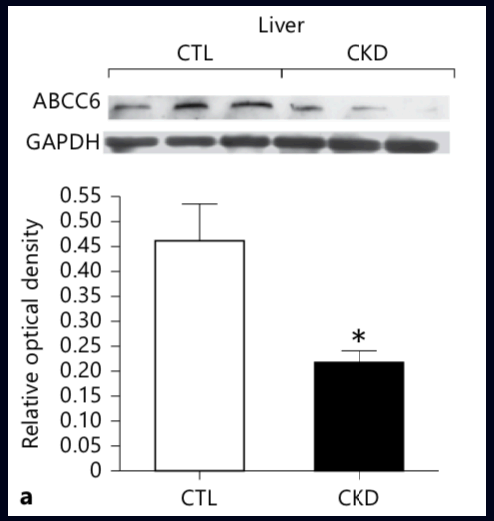


WARFARIN-INDUCED MINERALIZATION

ABCC6

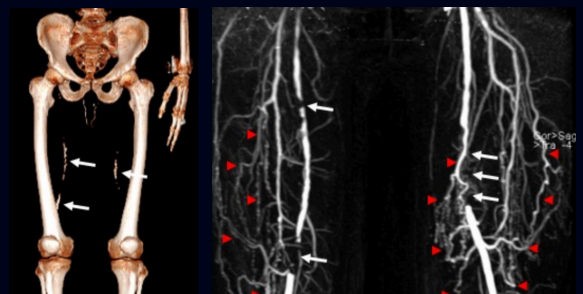


Pseudoxanthoma elasticum

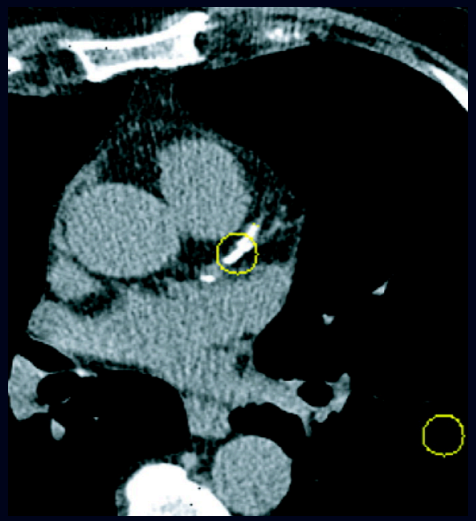


CKD-INDUCED MINERALIZATION

FGF23



Tumoral calcinosis



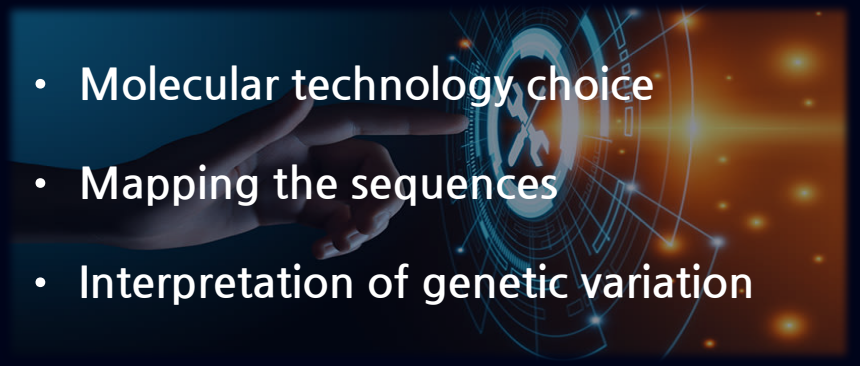
CORONARY ARTERY MINERALIZATION

GENOMICS OF CALCIFICATION | CHALLENGES

TECHNICAL

OBTAIN

INTERPRET

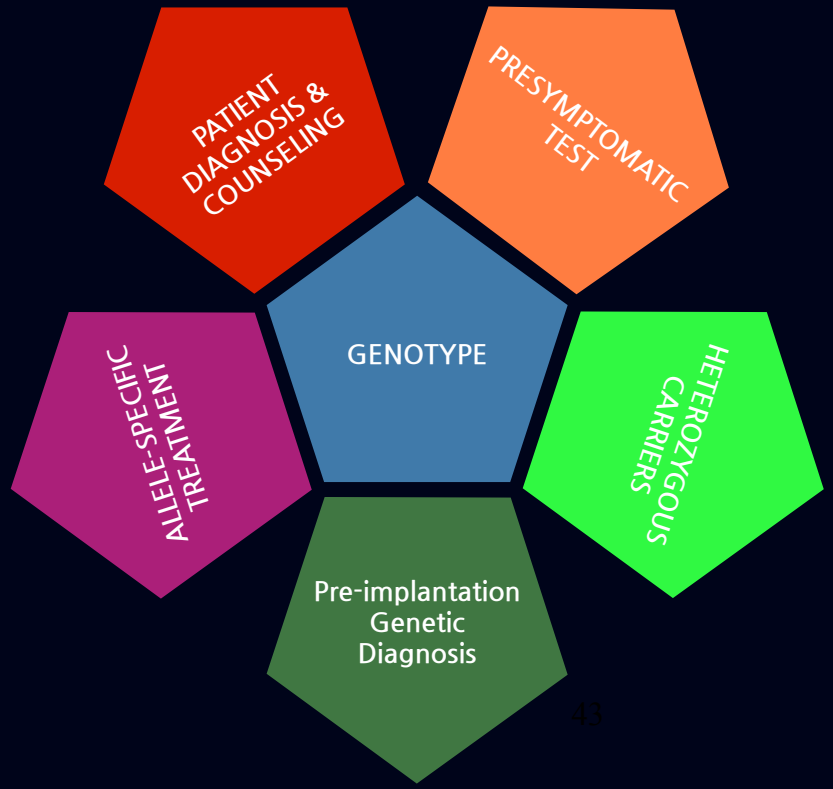


- Molecular technology choice
- Mapping the sequences
- Interpretation of genetic variation

CLINICAL

USE

ETHICAL



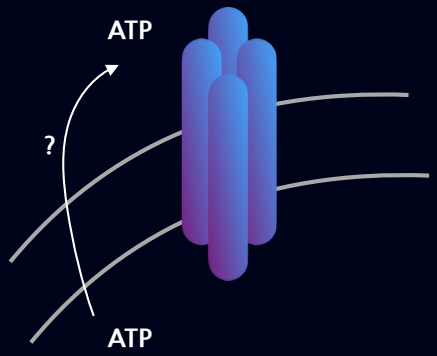
PXE | THE ABCC6 GENOMIC LOCUS

nature genetics

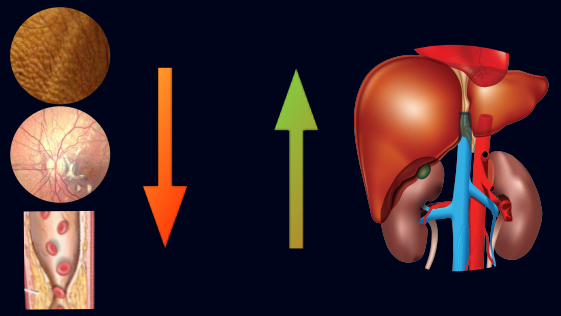
nature genetics • volume 25 • june 2000

Mutations in a gene encoding an ABC transporter cause pseudoxanthoma elasticum

Olivier Le Saux[1], Zsolt Urban[1], Cordula Tschuch[1], Katalin Csiszar[1], Barbara Bacchelli[2], Daniela Quaglino[2], Ivonne Pasquali-Ronchetti[2], F. Michael Pope[3,4], Allan Richards[4], Sharon Terry[5], Lionel Bercovitch[6], Anne de Paepe[7] & Charles D. Boyd[1]

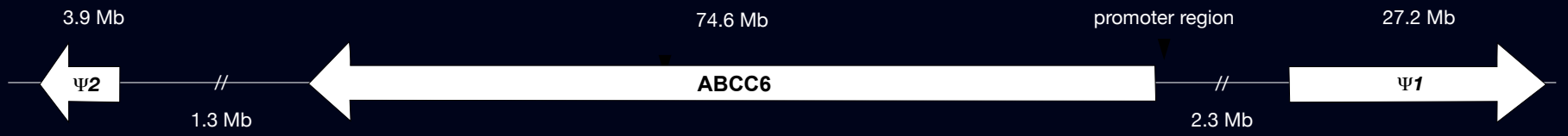


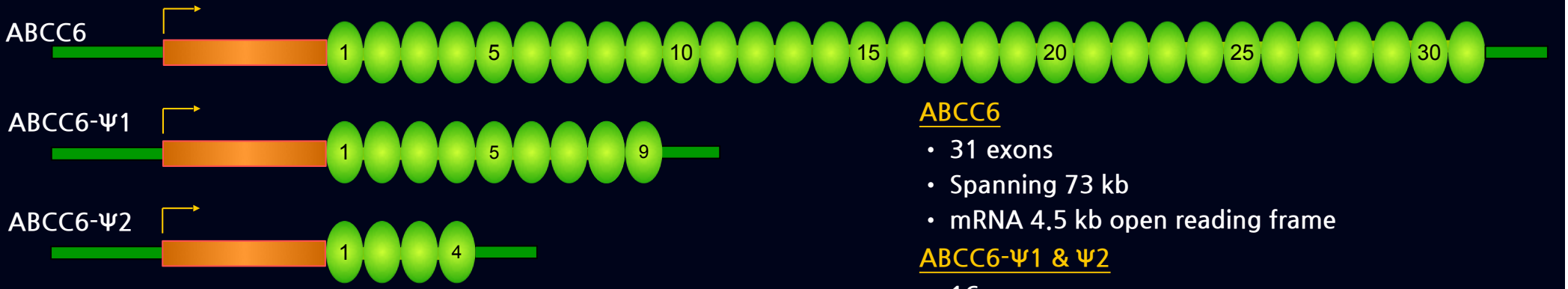
ABCC6



Expression profile

ABCC6 LOCUS: 16p13.11





ABCC6

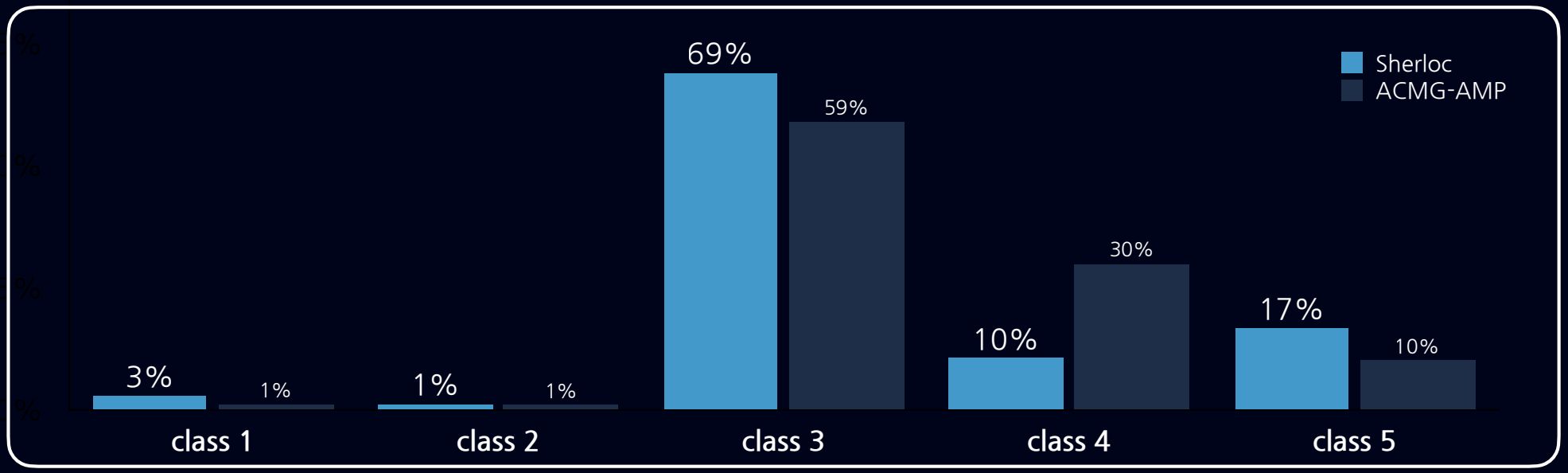
- 31 exons
- Spanning 73 kb
- mRNA 4.5 kb open reading frame

ABCC6-Ψ1 & Ψ2

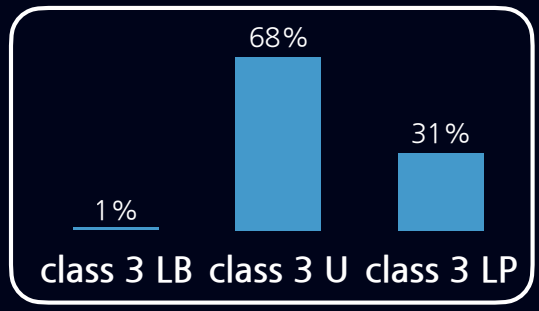
- 16p
- 99.995% homology

PXE | ABCC6 MISSENSE VARIANT INTERPRETATION

N = 286 missense variants



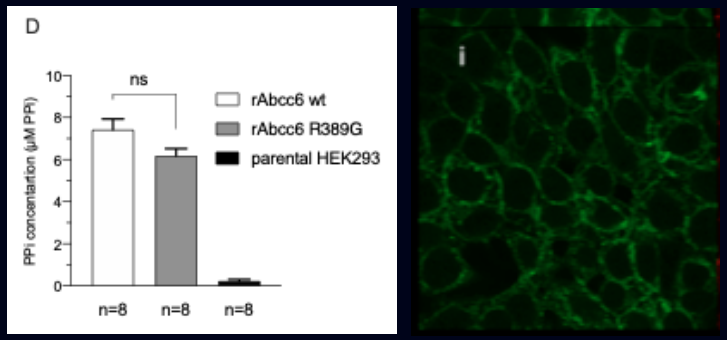
VARIANTS OF UNKNOWN SIGNIFICANCE



133 out of 286 missense variants (47%) are (likely) pathogenic

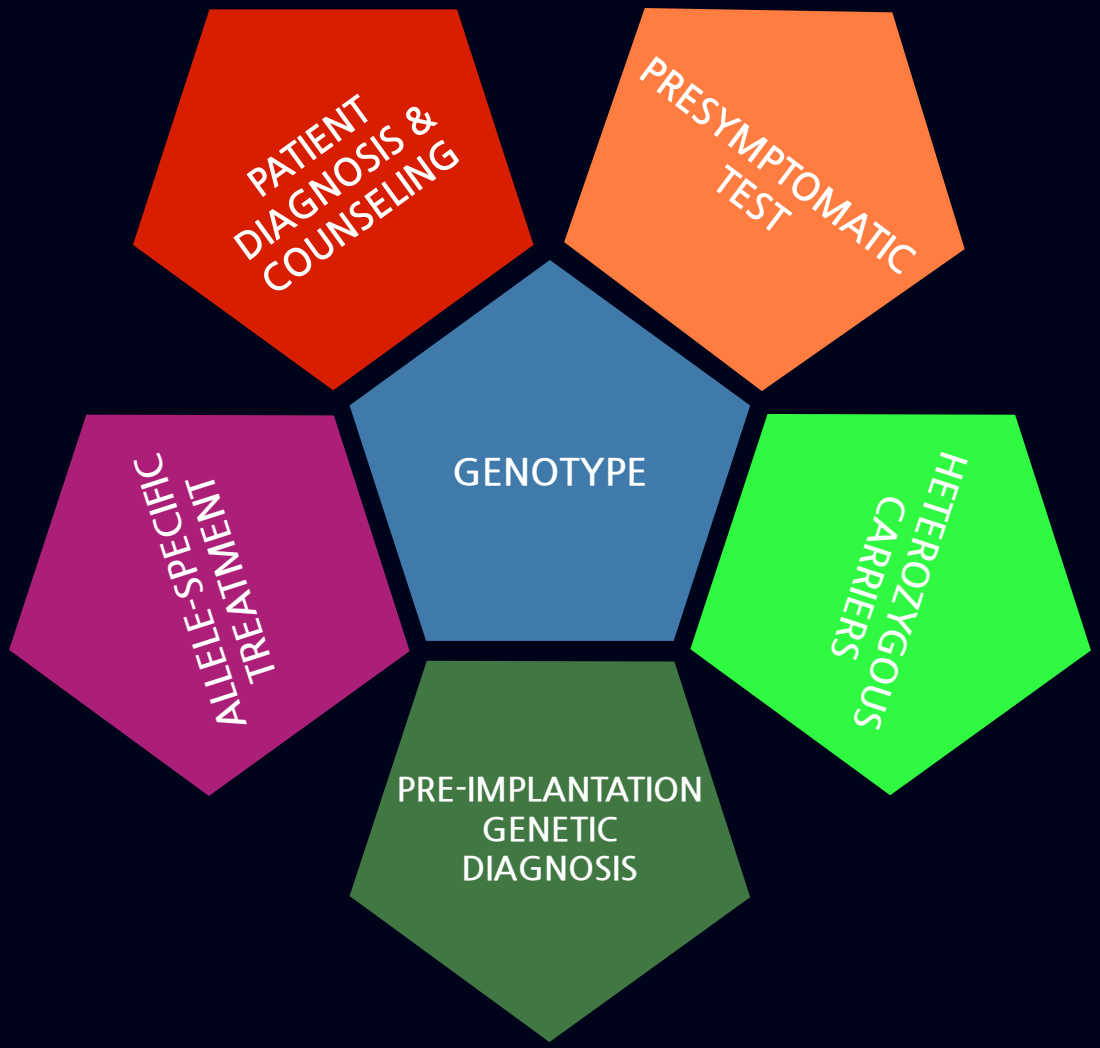
Verschuere et al. GIM, 2020

PXE | INCOMPLETE PENETRANT ABCC6 ALLELES

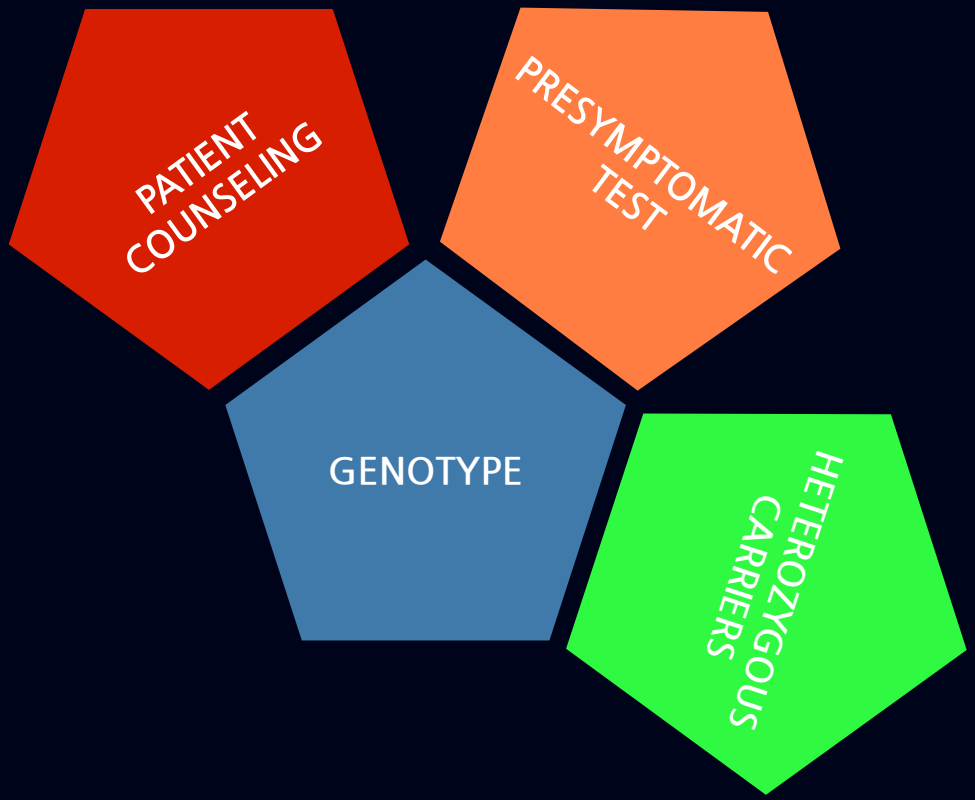
	p.(R391G)	p.(V787I)
POPULATION GENETICS	AF: 0.0078 Enrichment: 2.89 $p=5x10^{-4}$	AF: 0.00057 Enrichment: 9.53 p=0.02
ESTIMATED PENETRANCE	20%	10%
FUNCTIONAL VALIDATION		
UNDERLYING MECHANISM	Third ABCC6 variant in cis Second ABCC6 variant in trans	

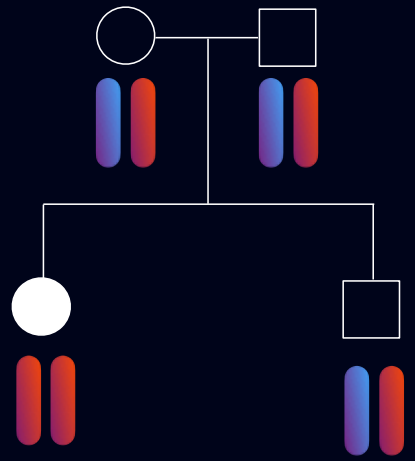
Szeri et al. Hum. Mutat., 2022

GENOMICS | CLINICAL APPLICATIONS



GENOMICS | TESTING FAMILY MEMBERS OF A PROBAND





Heterozygous carriers have a higher cardio- & cerebrovascular risk[48]

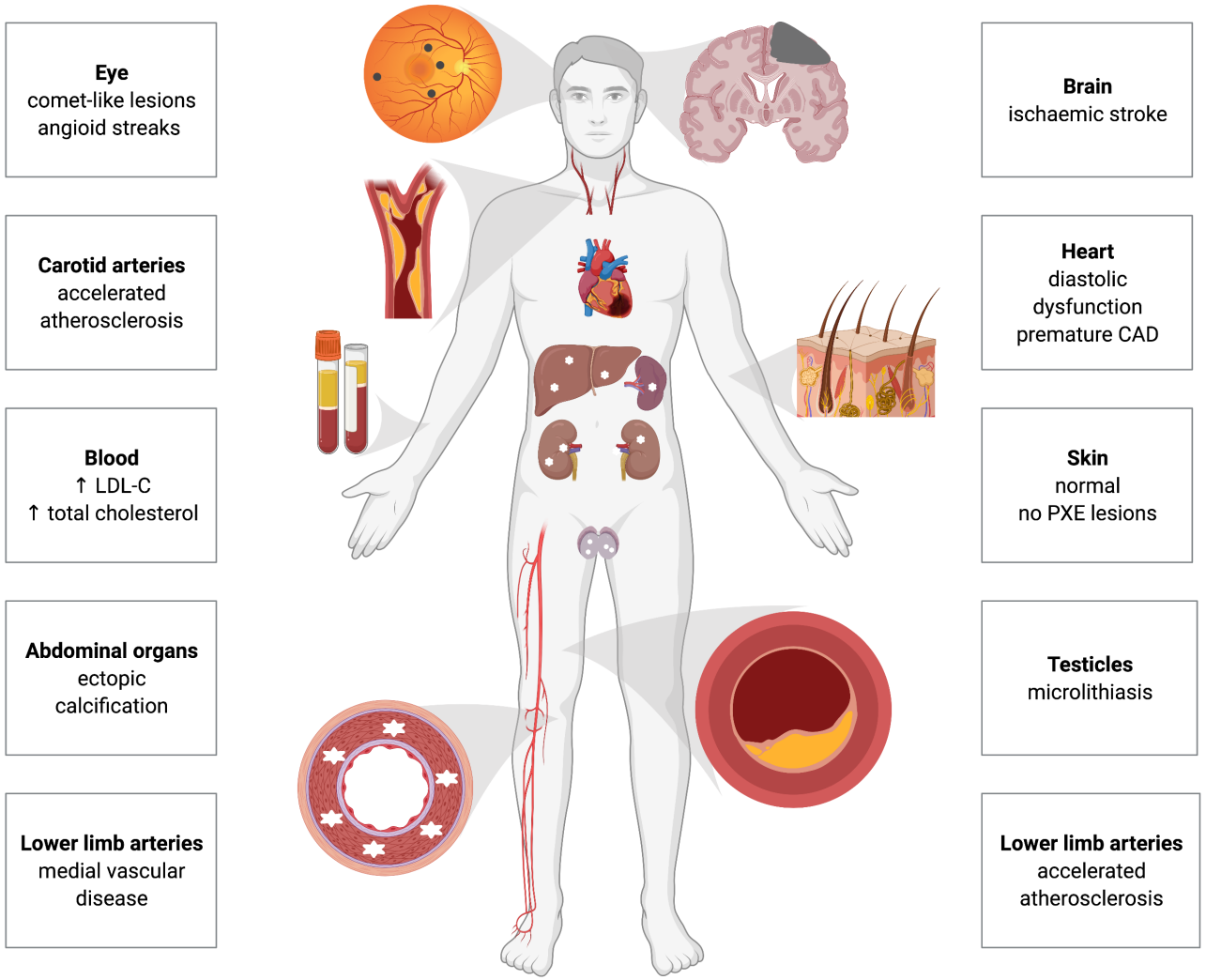
Journal of Medical Genetics

To cite: Nollet L, Campens L, De Zaeytijd J, *et al*. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmedgenet-2020-107565

Original research

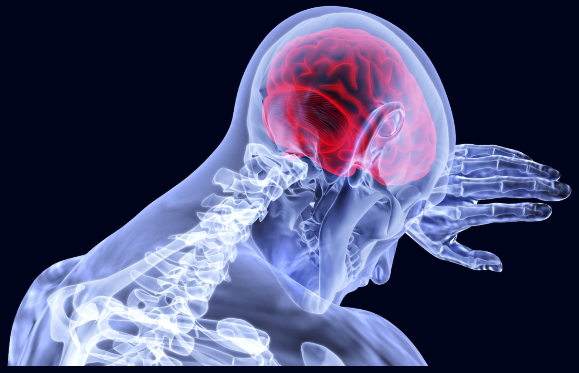
Clinical and subclinical findings in heterozygous *ABCC6* carriers: results from a Belgian cohort and clinical practice guidelines

Lukas Nollet ,[1,2] Laurence Campens,[3] Julie De Zaeytijd,[4] Bart Leroy,[4,5] Dimitri Hemelsoet,[6] Paul J Coucke,[1,2] Olivier M Vanakker[1,2]

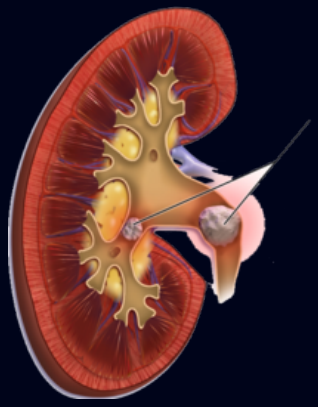


GENOMICS | FINDING ABCC6 PATHOGENIC VARIANTS

ABCC6 BEYOND PXE



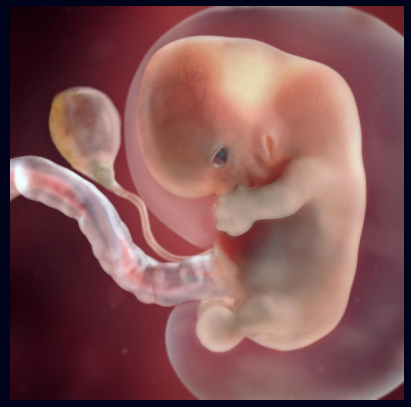
De Vilder et al.



Letavernier et al.

SECONDARY FINDING

Untargeted exome analysis



prenatal (ultra-fast) Mendeliome analysis

EXPANDED CARRIER SCREENING

AR
X-L

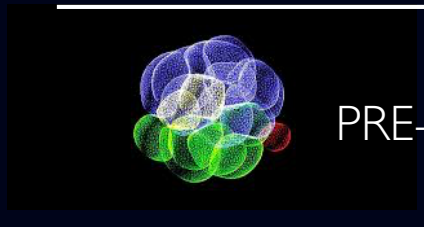
EasyDN

Genepath
LABORATORIES

CoreBiome

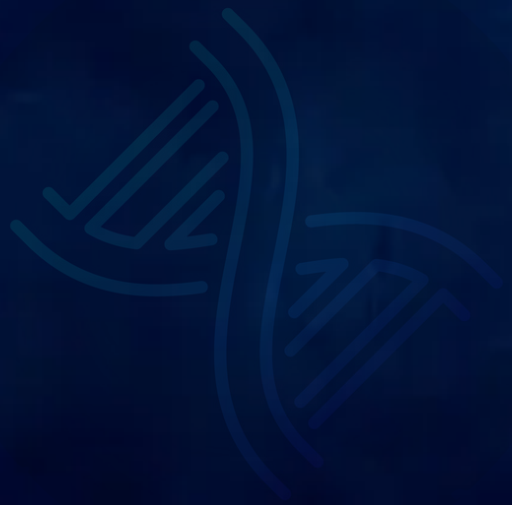
Genetix23

GENETIC SOLUTIONS
A BETTER LIFE FOR YOU



PRE-IMPLANTATION GENETIC DIAGNOSIS

ECTOPIC CALCIFICATION | MANAGEMENT

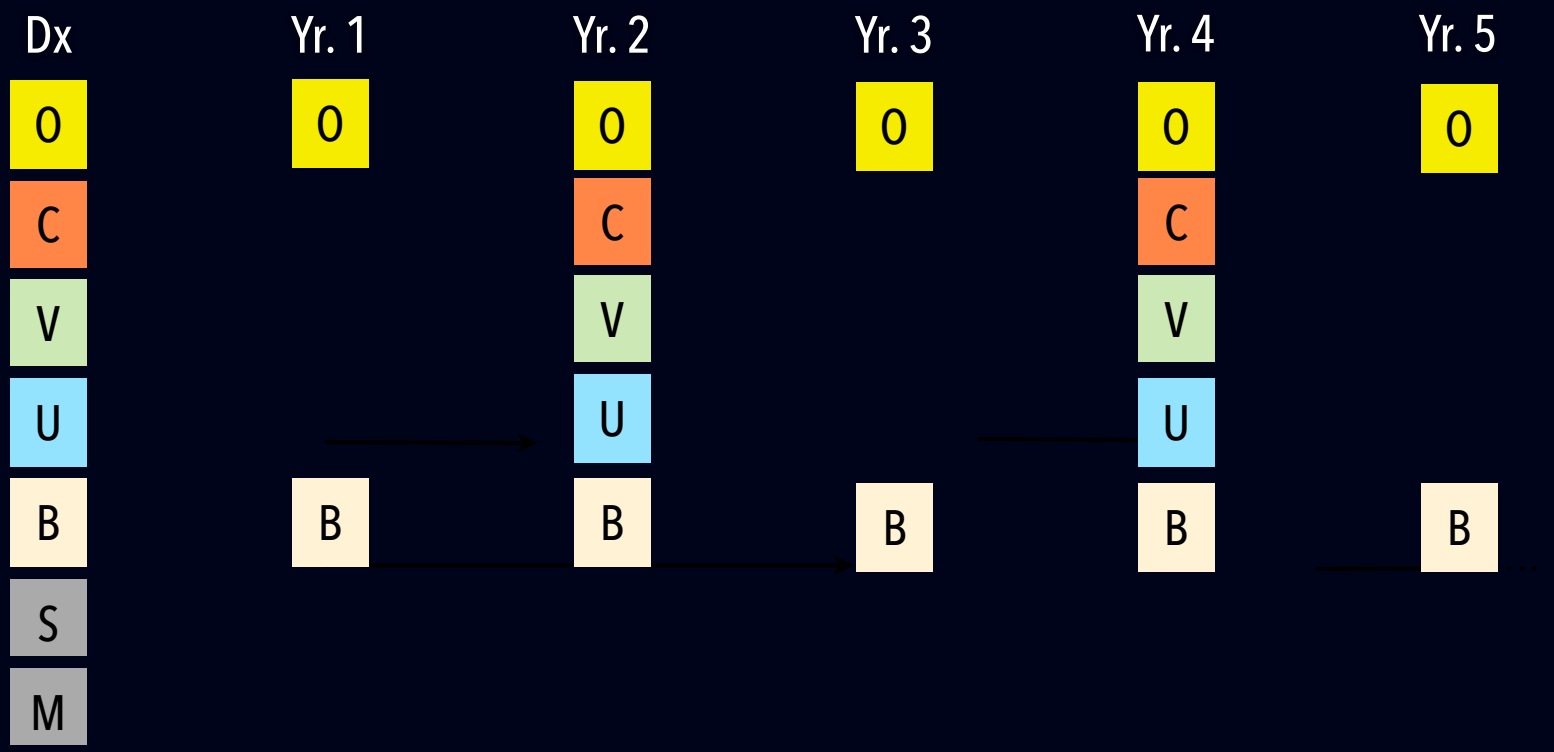


MULTIDISCIPLINARY

Clinical & molecular genetics

Dermatology	Ophthalmology	Cardiology	Vascular surgery
Psychology	Neurology	Plastic surgery	Radiology
Non-invasive vascular surgery	Internal Medicine	Paediatrics	Cardiosurgery

PXE



Focus on prevention and early detection

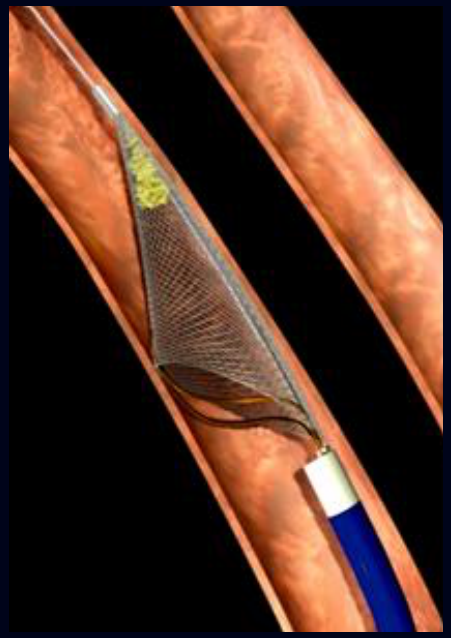
ECTOPIC MINERALIZATION | PREVENTION

- No contact sports
- Avoid ball sports
- No deep sea diving / mountain climbing
- No longterm NSAIDs
- Avoid anti-coagulants

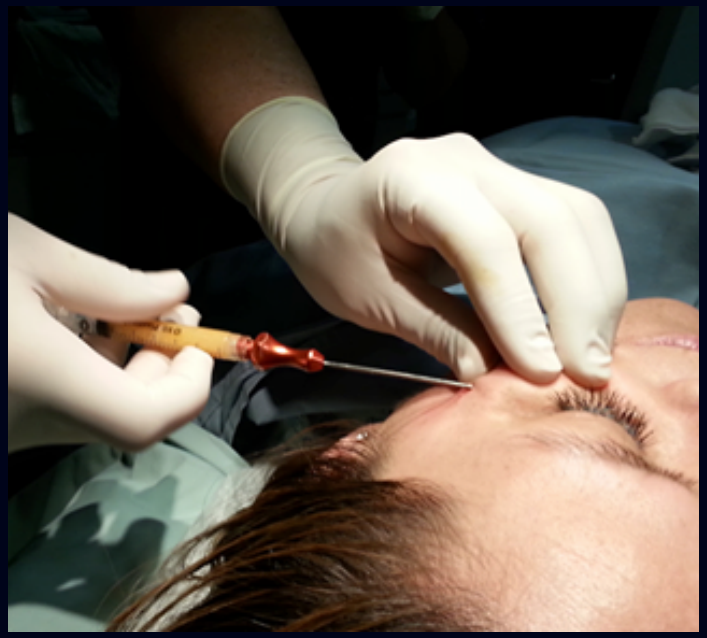
ECTOPIC MINERALIZATION | SYMPTOMATIC TREATMENT

Anti-VEGF antibodies

Vascular stenting



Subcutaneous lipofilling



Early treatment of the complications

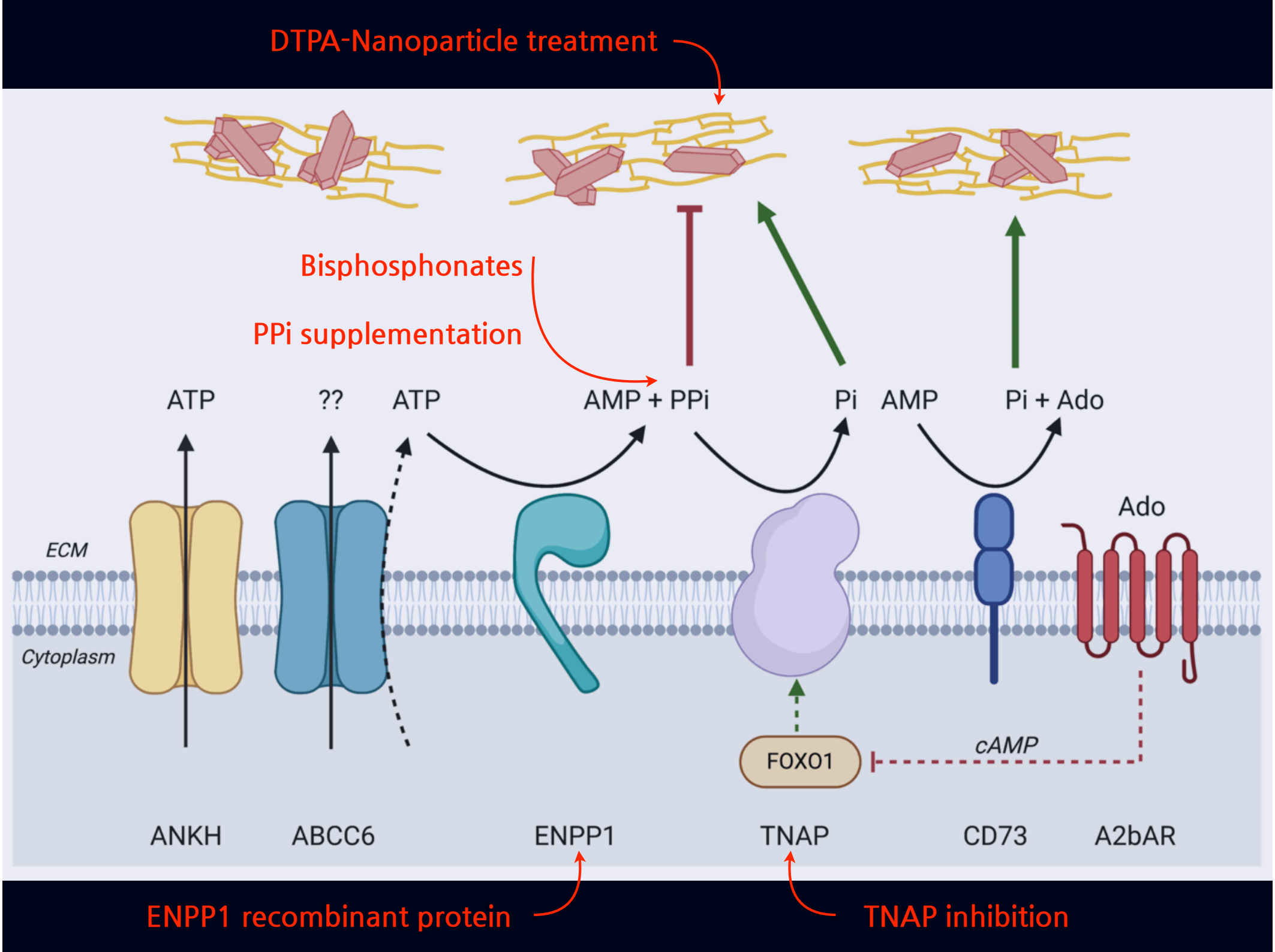
ECTOPIC MINERALIZATION | TREATMENT

DISEASE-SPECIFIC TREATMENT

- Gene therapy
- Allele-specific therapy
- Stem cell treatment

CALCIFICATION-DIRECTED TREATMENT

- Stop progression
- Reverse ectopic calcification
- Reverse matrix damage


DTPA-Nanoparticle treatment
Bisphosphonates
PPi supplementation
ATP
??
ATP
AMP + PPi
Pi
AMP
Pi + Ado
ECM
Cytoplasm
Ado
FOXO1
cAMP
ANKH
ABCC6
ENPP1
TNAP
CD73
A2bAR
ENPP1 recombinant protein
TNAP inhibition

TREATMENT | NANOPARTICLE TREATMENT

Nanoparticle

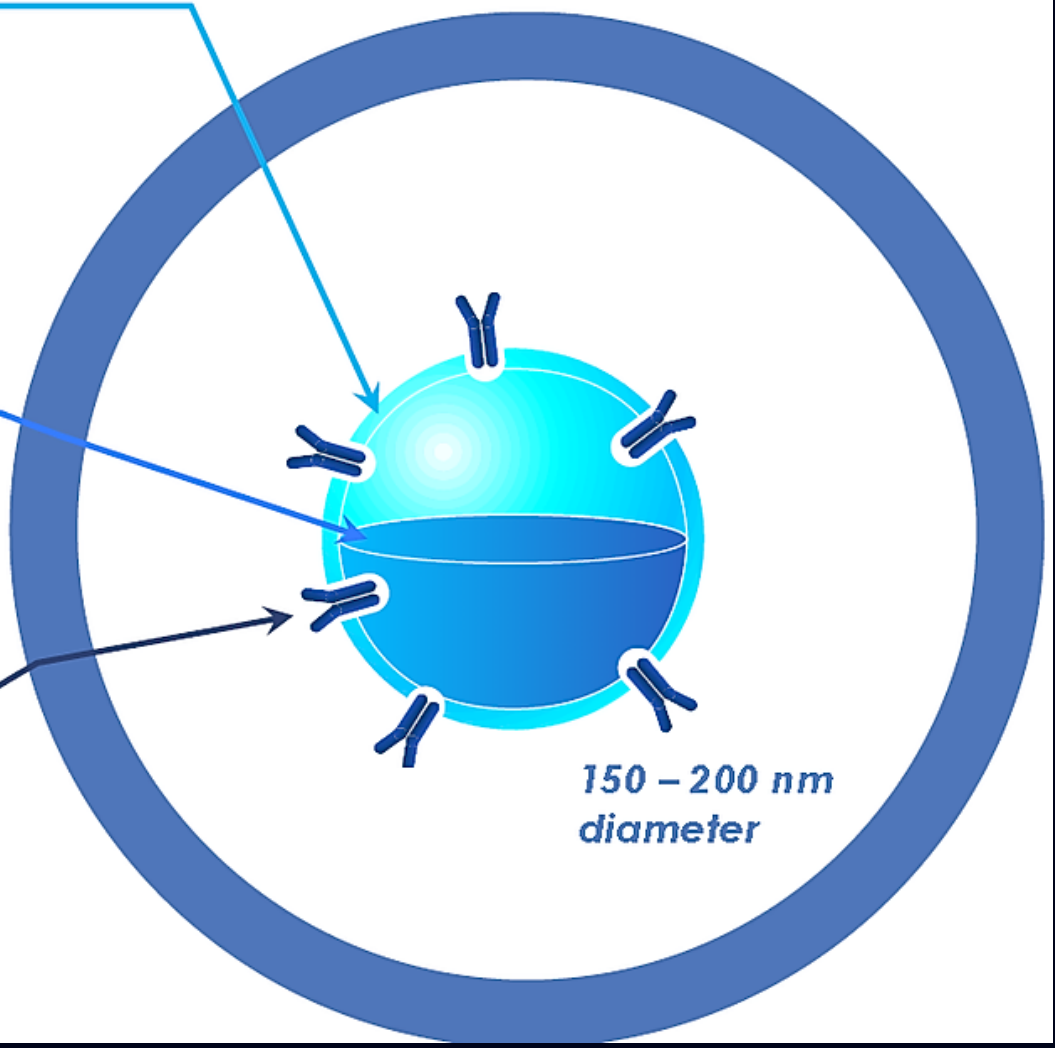
Albumin nanoparticle with charge & size optimized for targeting the extracellular matrix

Drug

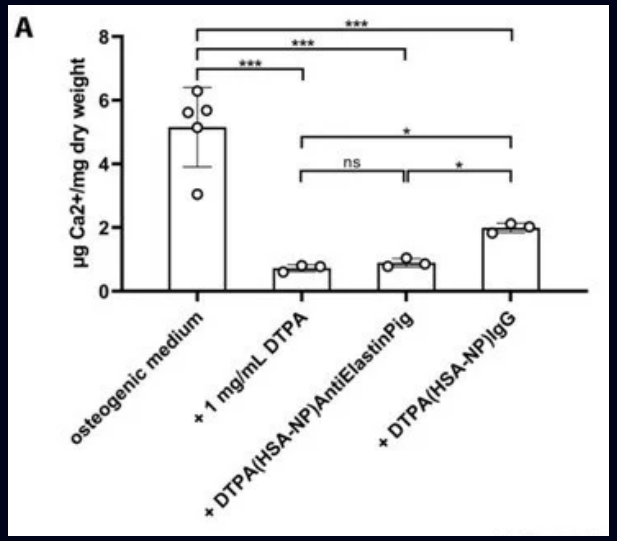
Drug loaded into nanoparticle. Various drugs have been used successfully

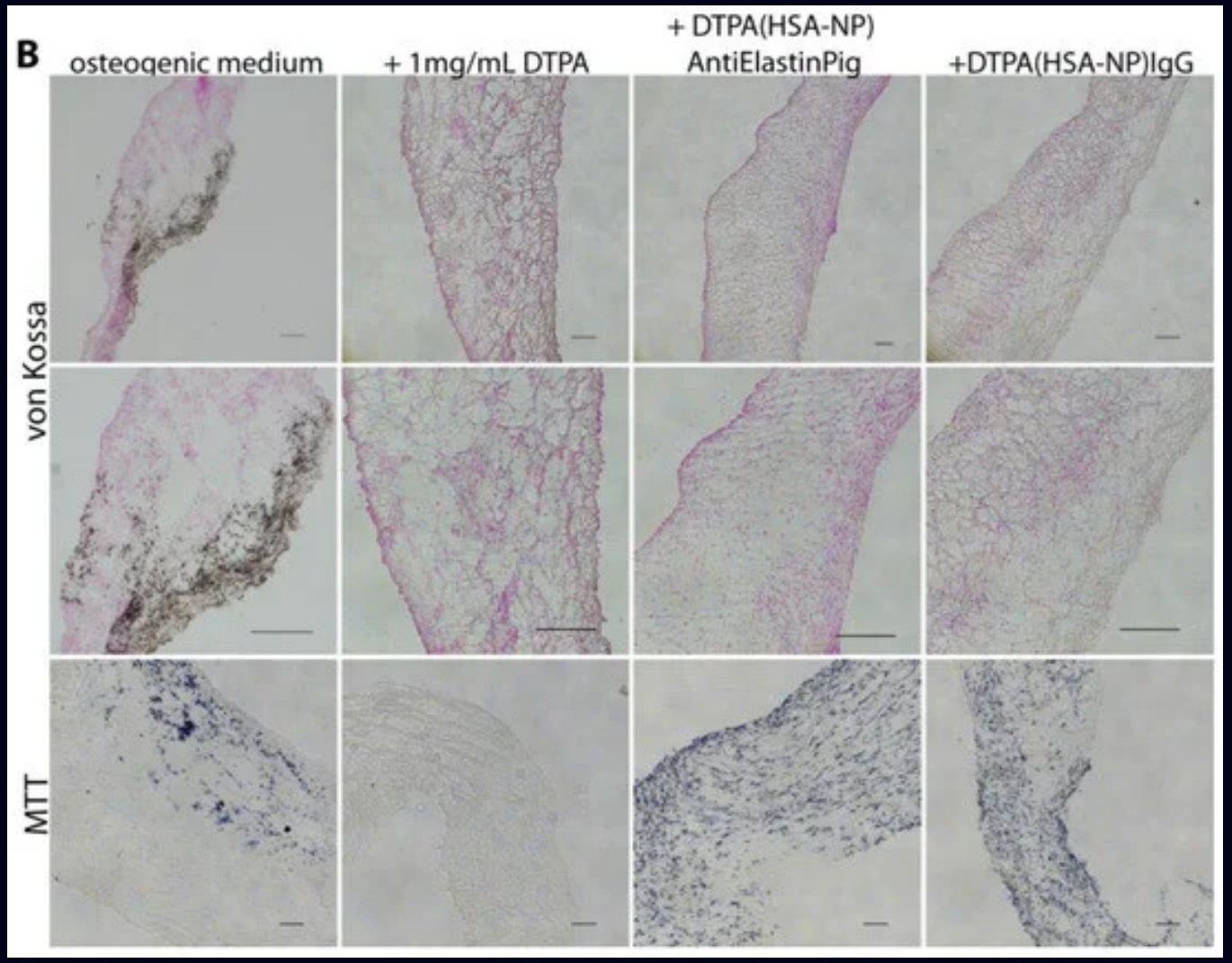
Anti-elastin Antibody Flexibzumab

Uniquely recognizing damaged elastin



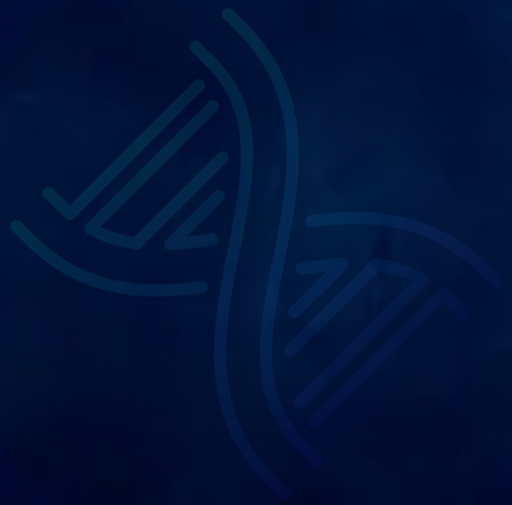
TREATMENT | NANOPARTICLE TREATMENT



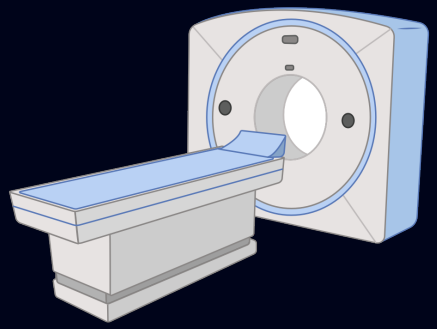


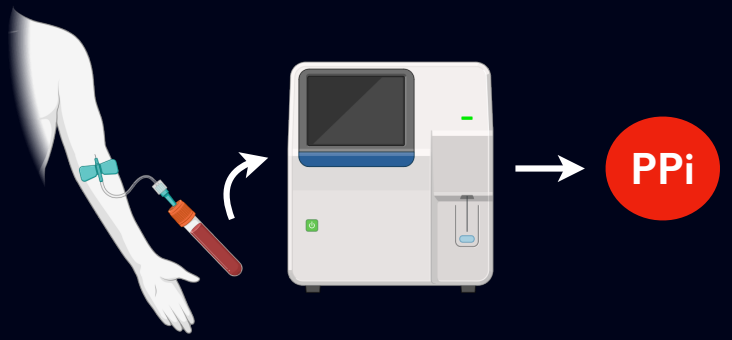
Feldmann et al, *IJMS*, 2023

ECTOPIC CALCIFICATION | MONITORING



MINERALIZATION | DIAGNOSIS AND MONITORING





CENTRAL ILLUSTRATION: Proposed Decision-Making Approach to Selective Use of Coronary Artery Calcium Measurement for Risk Prediction

Using 10-year ASCVD risk estimate plus coronary artery calcium (CAC) score to guide statin therapy				
Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate:	<5%	5-7.5%	>7.5-20%	>20%
Consulting ASCVD risk estimate alone	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Consulting ASCVD risk estimate + CAC				
If CAC score =0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend statin
If CAC score >0	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan?	✗ CAC not effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	✗ CAC not effective for this population

Greenland, P. et al. J Am Coll Cardiol. 2018;72(4):434-47.

Article

Inorganic Pyrophosphate Plasma Levels Are Decreased in Pseudoxanthoma Elasticum Patients and Heterozygous Carriers but Do Not Correlate with the Genotype or Phenotype

Matthias Van Gils [1,2,3], Justin Depauw [3], Paul J. Coucke [1,2,3], Shari Aerts [1,2,3], Shana Verschuere [1,2,3], Lukas Nollet [1,2,3] and Olivier M. Vanakker [1,2,3,*]

Article

Plasma Level of Pyrophosphate Is Low in Pseudoxanthoma Elasticum Owing to Mutations in the ABCC6 Gene, but It Does Not Correlate with ABCC6 Genotype

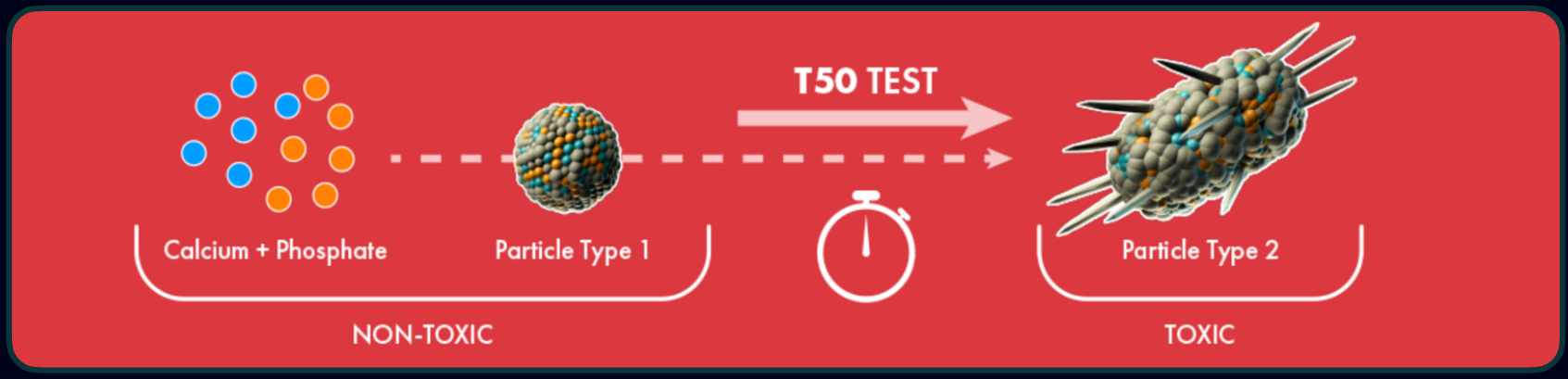
Eszter Kozák [1,†], Jonas W. Bartstra [2,†], Pim A. de Jong [2], Willem P. T. M. Mali [2], Krisztina Fülöp [1], Natália Tőkési [1], Viola Pomozi [1], Sara Risseeuw [3], Jeannette Ossewaarde-van Norel [3], Redmer van Leeuwen [3], András Váradi [1,‡] and Wilko Spiering [4,*,‡]

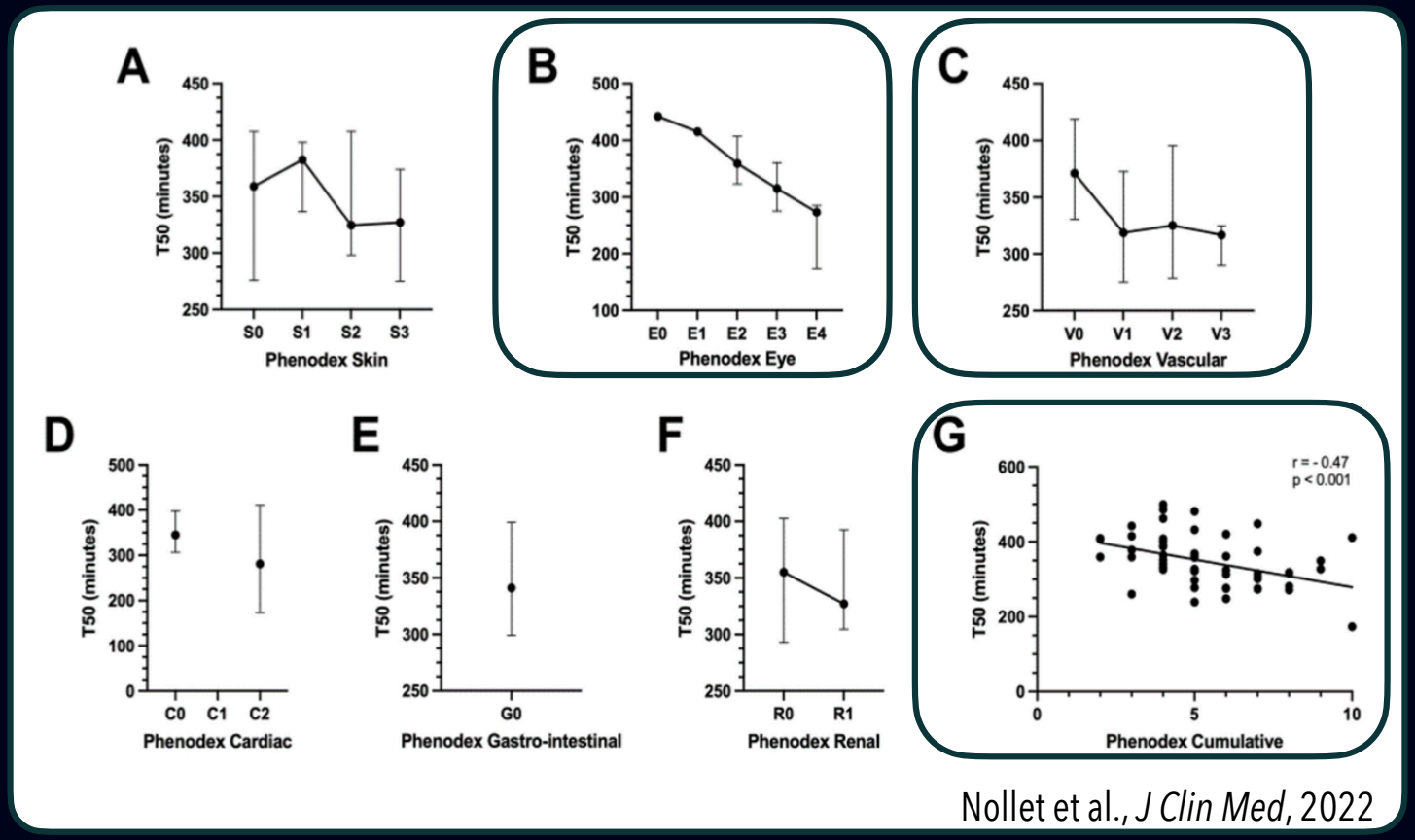
Article

Relationships between Plasma Pyrophosphate, Vascular Calcification and Clinical Severity in Patients Affected by Pseudoxanthoma Elasticum

Georges Leftheriotis [1,2,*], Nastassia Navasiolava [3], Laetitia Clotaire [2], Christophe Duranton [2], Olivier Le Saux [4], Saïd Bendahhou [2], Audrey Laurain [2], Isabelle Rubera [2] and Ludovic Martin [3]

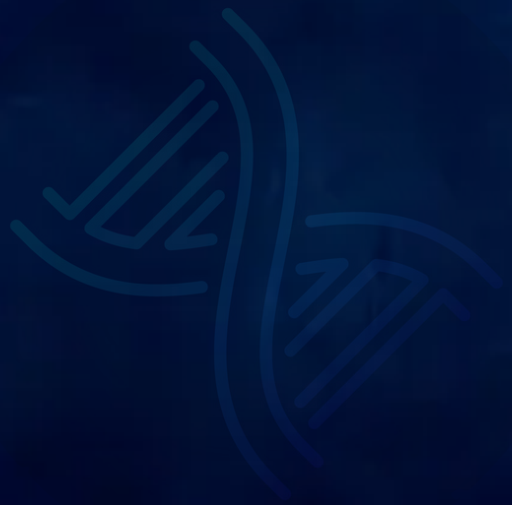
MONITORING | T50 CALCIFICATION PROPENSITY





Nollet et al., *J Clin Med*, 2022

ECTOPIC MINERALIZATION | INTEGRATIVE APPROACH



SOFT TISSUE MINERALIZATION

SHOULD BE CONSIDERED

A DISEASE

RATHER THAN AN (INNOCENT)

EPIPHENOMENON

EMR GHENT

Ectopic Mineralization Research Ghent

Instagram: @ectopicmineralizationresearch

EMR GHENT

Ectopic Mineralization Research Group Ghent

- Ghent PXE & EC Reference Center — PATIENTS, CARRIERS
- RESEARCH — Clinical, Genetic, Epigenetic

ectopicmineralizationresearch


INTEC
International Network on Ectopic Calcification

INTEC

International Network on Ectopic Calcification

GHENT UNIVERSITY PARTNERS

Coordinator
- Olivier VANAKKER

Project manager
- Karolien AELBRECHT

Members
- Paul COUCKE
- Tine DE BACKER
- Bart LEROY
- Filip VAN NIEUWERBURGH
- Eckhard WITTEN
- Julie DE ZAEYTIJD
- Dimitri HEMELSOET
- Ann HUYSSEUNE

AFFILIATED PARTNERS

VIB
SANIFIT
Genetic Alliance
Elastrin – Restoring the Elastic of Life
inozyme pharma
Haltex Therapeutics
WWU Münster
KAROLINSKA University Hospital
mta ttk
RVC Royal Veterinary College University of London
QUEEN'S UNIVERSITY BELFAST
THE UNIVERSITY OF EDINBURGH
UKM Universitätsklinikum Münster
Karolinska Institutet
OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG
UZ GENT
GHENT UNIVERSITY
Centre Hospitalier Universitaire de Nice
UNIVERSITÉ CÔTE D'AZUR
CHU ANGERS CENTRE HOSPITALIER UNIVERSITAIRE
cnrs
UNIVERSITÉ DE LORRAINE
UAlg UNIVERSIDADE DO ALGARVE
UNIVERSIDAD DE MÁLAGA
UNIMORE UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA
Tel-Aviv Sourasky Medical Center
GUANGZHOU MEDICAL UNIVERSITY 1958

INTERNATIONAL PARTNERS

- Semmelweis University, Hungary — Prof. Tamas ARANYI — P1
- Karolinska Institute & Karolinska University Hospital, Sweden — Prof. Dr. Magnus BACK — P2
- University of Magdeburg, Germany — Prof. Jessica BERTRAND — P3
- University of Algarve, Portugal — Prof. Leonor M. CANCELA — P4
- Shahjalal University of Science and Technology, Bangladesh — Prof. Mohammad Jakir HOSEN — P5
- CNRS & Université de Lorraine, France — Dr. Hervé KEMPF — P6
- University of Edinburgh, UK — Prof. Vicky MACRAE — P7
- Angers University Hospital, France — Prof. Dr. Ludovic MARTIN — P8
- University & University Hospital of Münster, Germany — Prof. Dr. Frank RUTSCH, Dr. Yvonne NITSCHKE — P9, P11
- University of Modena and Reggio Emilia, Italy — Prof. Dr. Daniela QUAGLINO — P10
- Čakovec Hospital, Croatia — Dr. Dijana SONTACCHI — P12
- Tel Aviv Medical Center, Israel — Prof. Dr. Eli SPRECHER — P13
- Research Centre for Natural Sciences, Hungary — Prof. Flora SZERI — P14
- University of Malaga, Spain — Prof. Dr. Pedro VALDIVIELSO — P15
- Royal Veterinary College, UK — Prof. Isabel ORRISS — P16
- Research Centre for Natural Sciences, Hungary — Prof. Andras VARADI — P17
- University of Belfast, Ireland — Prof. Imre LENGYEL — P18
- Guangzhou Medical University, China — Prof. Dongxing ZHU — P19
- Nice University, France — Prof. Dr. Georges Lefthériotis — P20

28 | 16 | 12 | 18

www.itnintec.com

ECTOPIC MINERALIZATION | TAKE HOME MESSAGES

- **MULTIFACETTED** PATHOPHYSIOLOGY
- **HEREDITARY** & **COMMON** DISORDERS AS WELL AS **AGING**
- DIRECT RELATION TO **MORBIDITY** AND **MORTALITY**
- HIGHLY **VARIABLE** PHENOTYPES
- DIAGNOSIS BASED ON **COMBINED** CLINICAL, MOLECULAR & BIOCHEMICAL EVALUATION
- SHOULD BE CONSIDERED A SEPARATE AND UNIQUE **DISEASE ENTITY**
- OPTIMAL CARE REQUIRES AN **INTEGRATIVE MANAGEMENT** APPROACH

EMRg | GHENT ECTOPIC MINERALIZATION RESEARCH GROUP

UZ GENT

200 JAAR UNIVERSITEIT GENT

EMR GHENT

@ectopicmineralizationresearch

INTEC | INTERNATIONAL NETWORK ON ECTOPIC CALCIFICATION

INTEC
International Network on Ectopic Calcification

www.itnintec.com

ISSEC | INTERNATIONAL SCIENTIFIC SOCIETY OF ECTOPIC CALCIFICATION

ISSEC
International Scientific Society of Ectopic Calcification

www.issec.org