GENETICS OF HYDATIDIFORM MOLES

Madhulatha Pantrangi, PhD, FACMG

Assistant Professor of Clinical Pathology and Laboratory Medicine

Associate Director of Cytogenetics Laboratory

NewYork-Presbyterian
Weill Cornell Medical Center

E-mail: map9501@med.cornell.edu

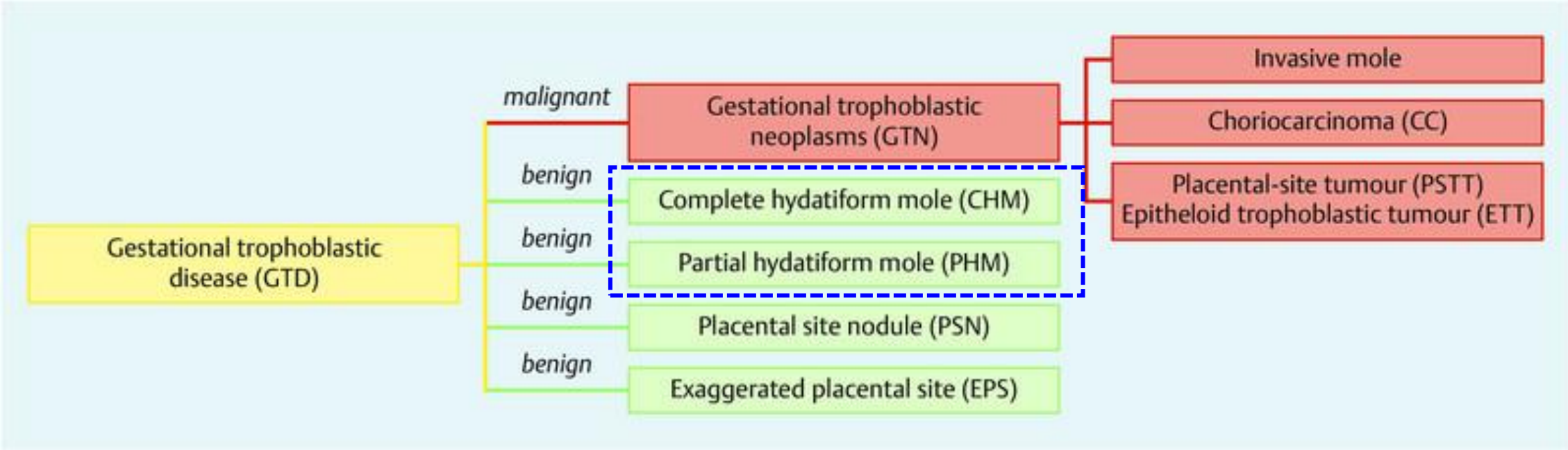
AMAZING THINGS ARE HAPPENING HERE

Outline

- Hydatidiform moles Classification, morphology, follow up
- Genetic Origin
- Screening methods
- Cases and diagnosis
- Genomic Imprinting role

Classification of GTD

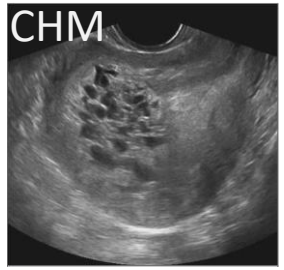
- GTD encompasses a heterogeneous family of diseases with abnormal proliferation of placental trophoblastic tissue
- HM is the most common form of GTD, with an incidence of 1 to 3 out of every 1000 pregnancies.

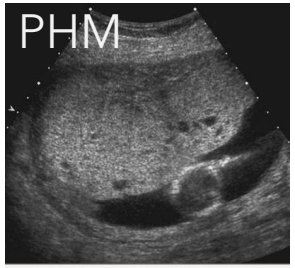


PMID: 22469506

Hydatidiform mole (HM)

- **CHM** : Rapidly progressing affecting the whole placenta, with widespread and gross trophoblastic hyperplasia in the absence of an embryo and its covering amnion.
- **PHM**: A slow change that affects only some of the villi in the placenta.

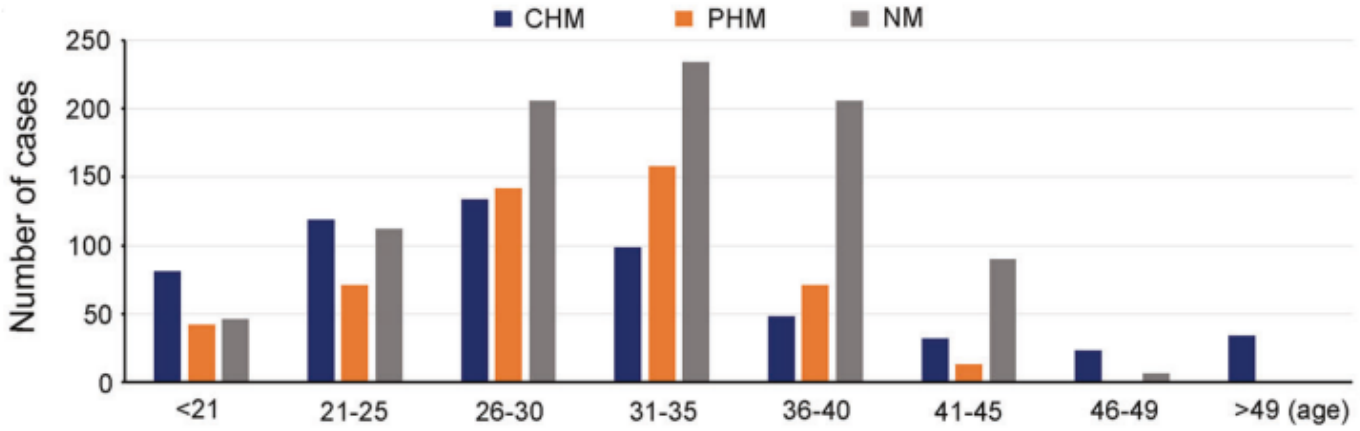




Characteristic	Complete Mole	Partial Mole
Karyotype	Diploid; 46,XX (usually), 46,XY	Triploid
Results on immunostaining of maternally expressed gene products (*p57, PHLDA2*)	Negative	Positive
Fetal or embryonic tissue	Absent	Present
Hydropic swelling of villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Trophoblast at implantation site	Marked atypia	Mild atypia

•PMID: 19369669

Age distribution of patients with CHM, PHM, and NM



CHMs dominated in patients aged < 21 and >45 years and were the only kind of molar conception found in the latter group.

PMIDs: 33024305; 36936581

Hydatidiform mole and Follow-up

CHM (Diploid and androgenetic origin)

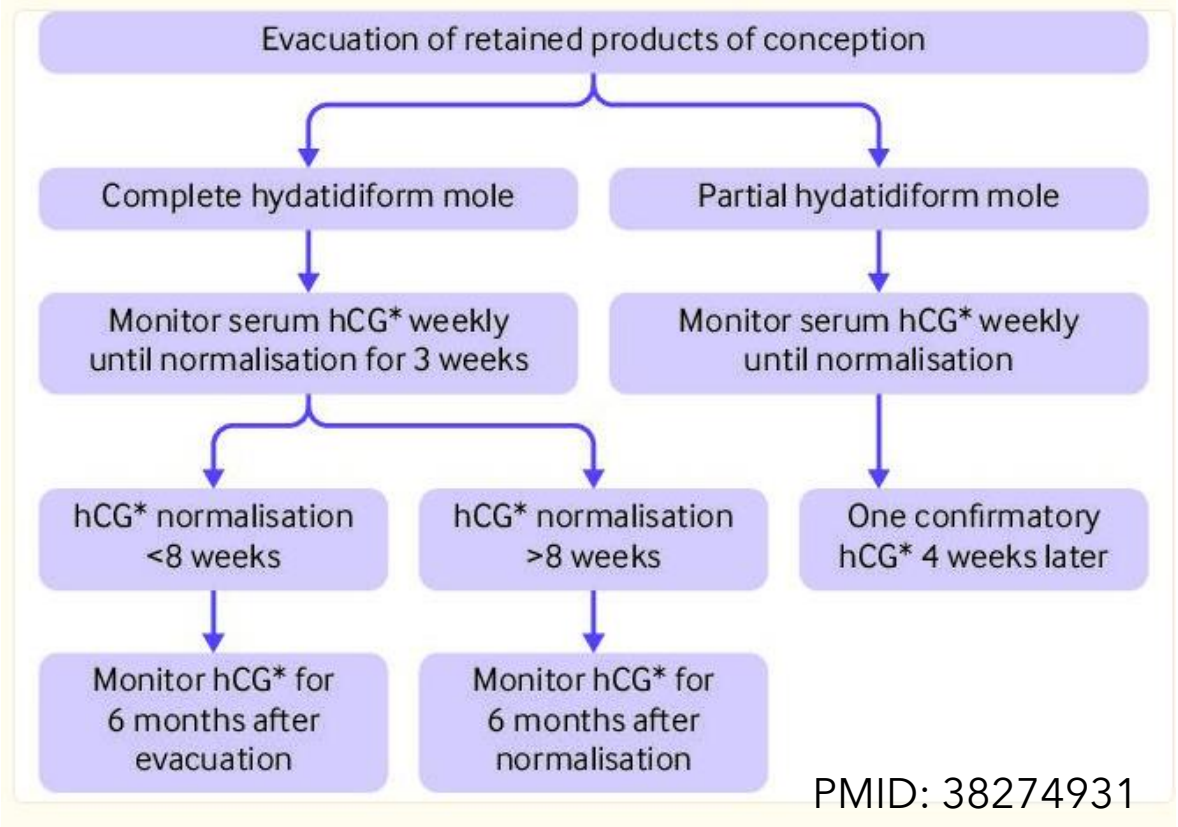
- Risk of GTD 15-20%
- Risk of choriocarcinoma 3-5%

PHM (Diandric triploid)

- GTD risk <5%
- Risk of choriocarcinoma is low

Non-molar conceptuses (Digynic triploid)

- No risk
- No β-hCG monitoring

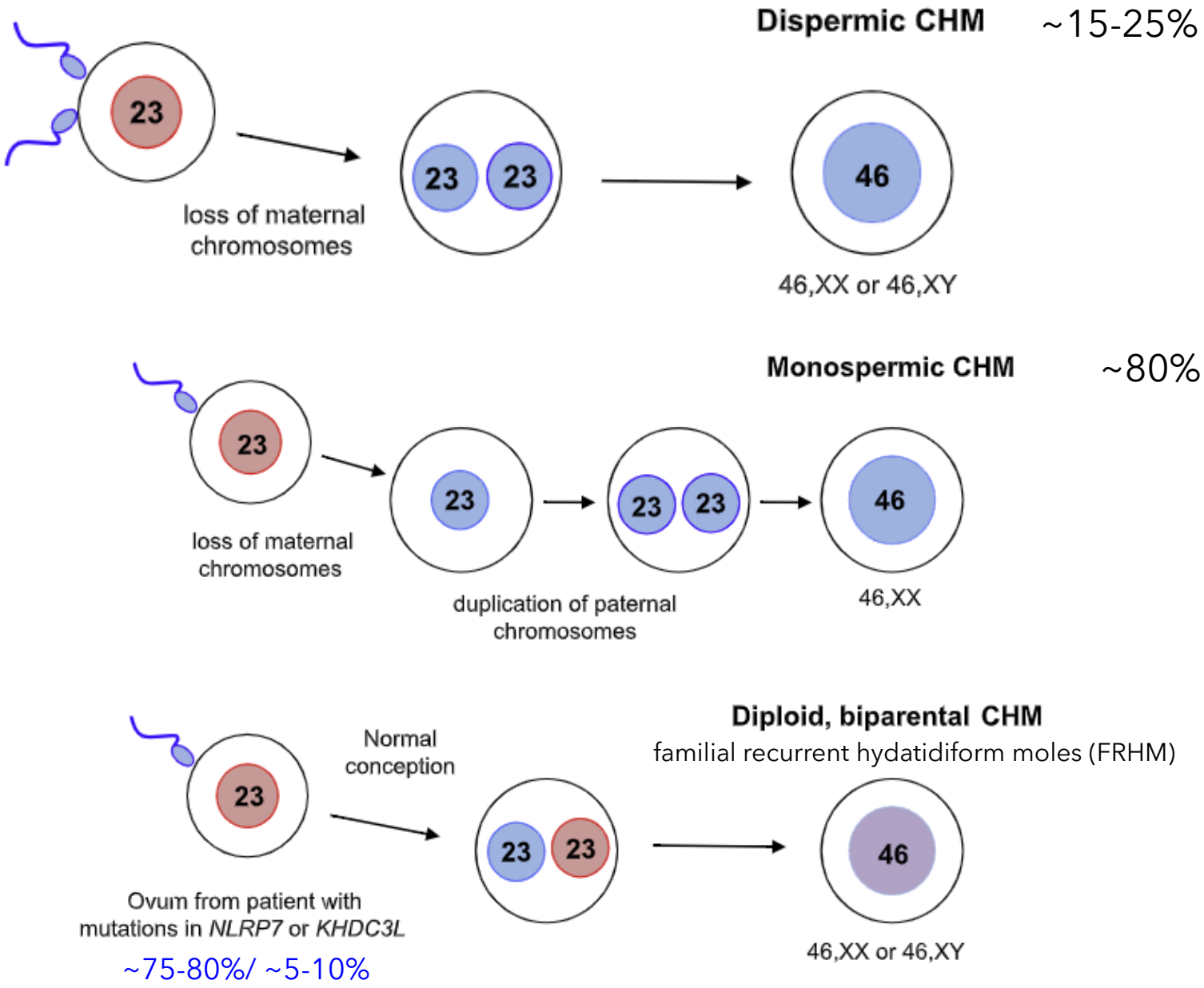


PMID: 38274931

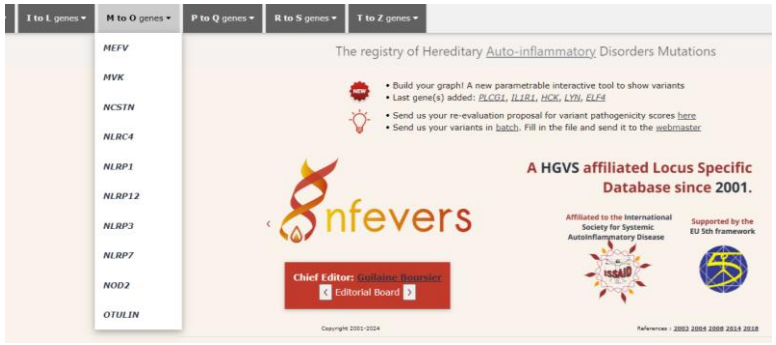
ACOG Bulletin : PMID: 15196847
NCCN guidelines: https://doi.org/10.6004/jnccn.2019.0053

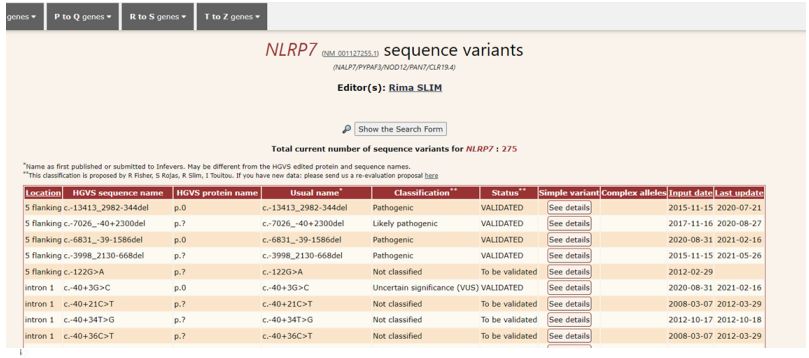
Genetic origins of CHM

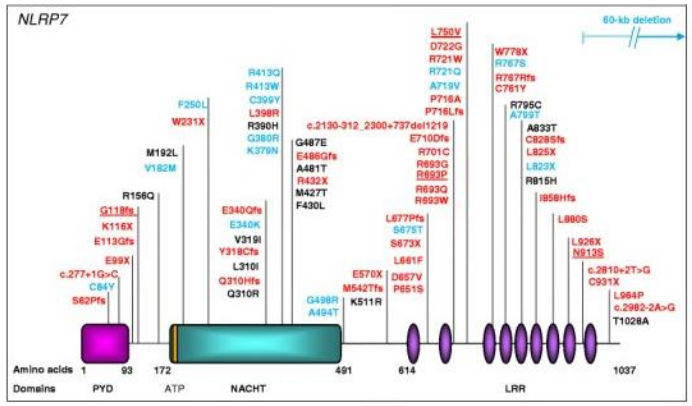
- Mitochondrial DNA is maternally derived
- NLRP7 and KHDC3L are required for correct imprinting.
- All imprinted genes known to be specific to the placenta are paternally imprinted



Infevers database







Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19q13.42	Hydatidiform mole, recurrent, 1	231090	AR	3	NLRP7	609661

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

INHERITANCE
- Autosomal recessive

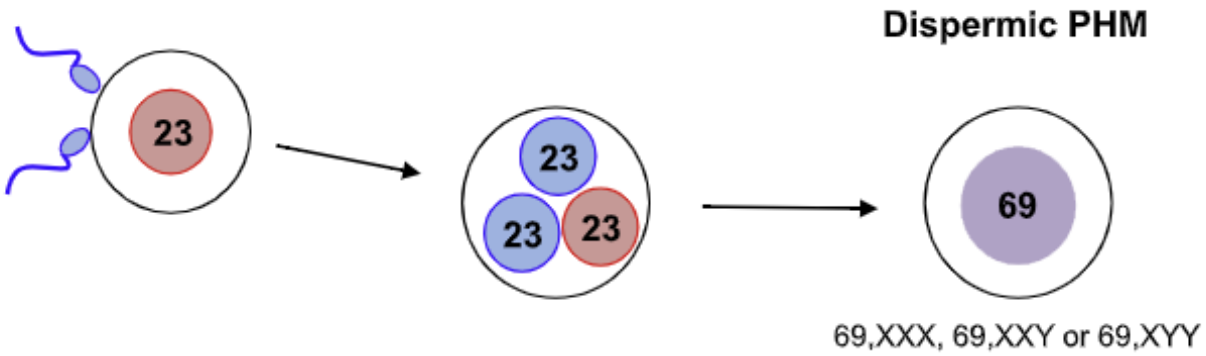
PRENATAL MANIFESTATIONS
Placenta & Umbilical Cord
- Gestational trophoblastic disease
- Hydatidiform mole

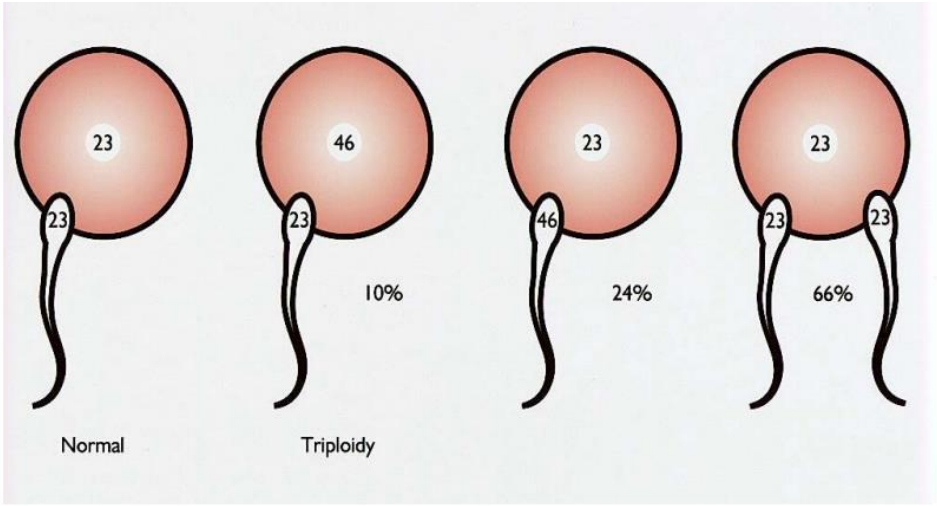
MOLECULAR BASIS
- Caused by mutation in the NLR family pyrin-domain containing 7 gene (NALP7, 609661.0001)

https://www.omim.org/entry/231090

- NLRP7 codes for a NOD-like receptor pyrin containing protein
- Inflammatory response,
- Trophoblastic tissue differentiation and proliferation,
- Protein is part of the oocyte cortical cytoskeleton
- The role of different NLRP7 variants in reproductive wastage.
- It appears that the LoF variants in NALP7 are more severe than the missense variants.

Genetic origins of triploidy





Diandric/Paternal triploidy (type I)

Digynic/Maternal triploidy or type II

Triploidy

Diandric/Paternal triploidy (type I)

- normal intrauterine growth
- Microcephaly /normal-sized head
- Large cystic placenta
- Hydropic changes in chorionic villi.
- predominate among "typical" spontaneous abortions

Digynic/Maternal triploidy or type II

- severe asymmetrical IUGR
- Relative macrocephaly
- Noncystic small placenta
- No evidence of trophoblastic hyperplasia
- early or with late embryonic demise involving a well-formed fetus.

Diandric
(Partial Hydatidiform mole)

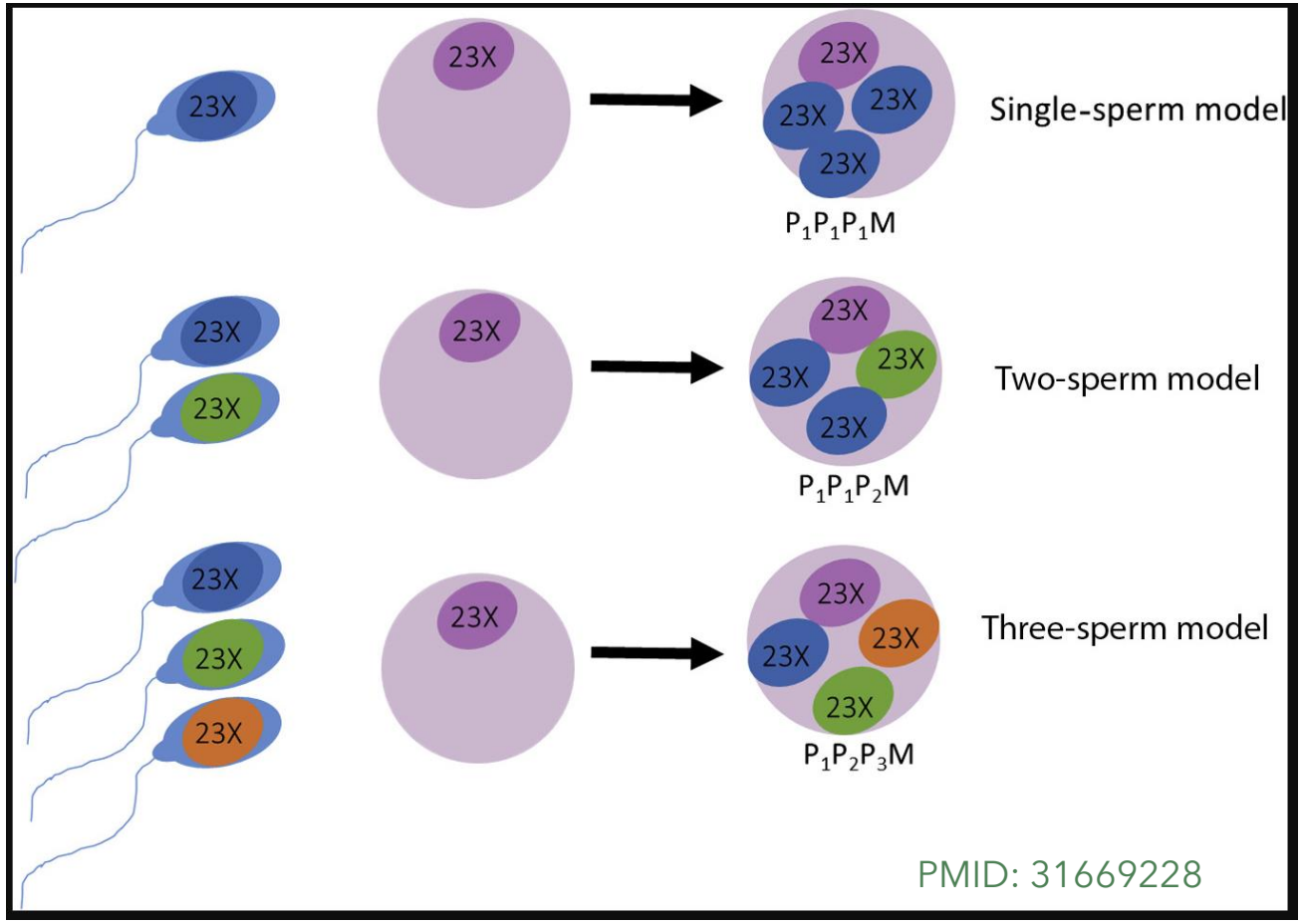
Digynic
(Non molar)

The AGT Cytogenetics Laboratory Manual, 4th Edition

Common features : Syndactyly of 3rd and 4th finger; Incomplete skull ossification

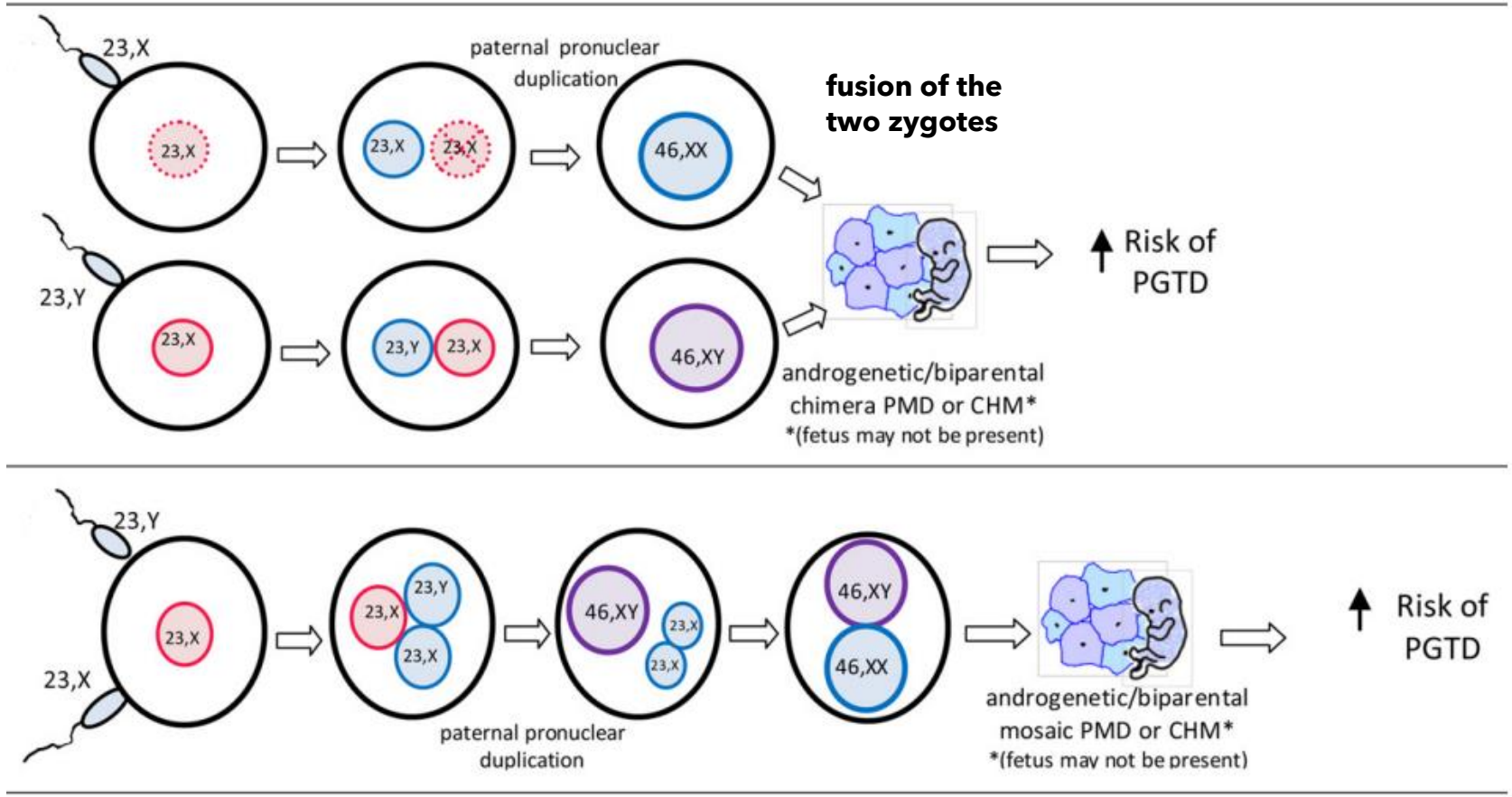
Genetic origins of Teraploidy

- tetraploidy
- 92,XXXX/92,XXXY/92,XXYY/92,XYYY
- Frequency of zygotic tetraploidy among conceptus with the molar phenotype seems to be ‘less than 1%.
- Most tetraploid cells appear to have developed by somatic endoreduplication of diploid cells,
- Minority originated from tetraploid zygotes.



Modes of fertilization in HMs with tetraploid cells.

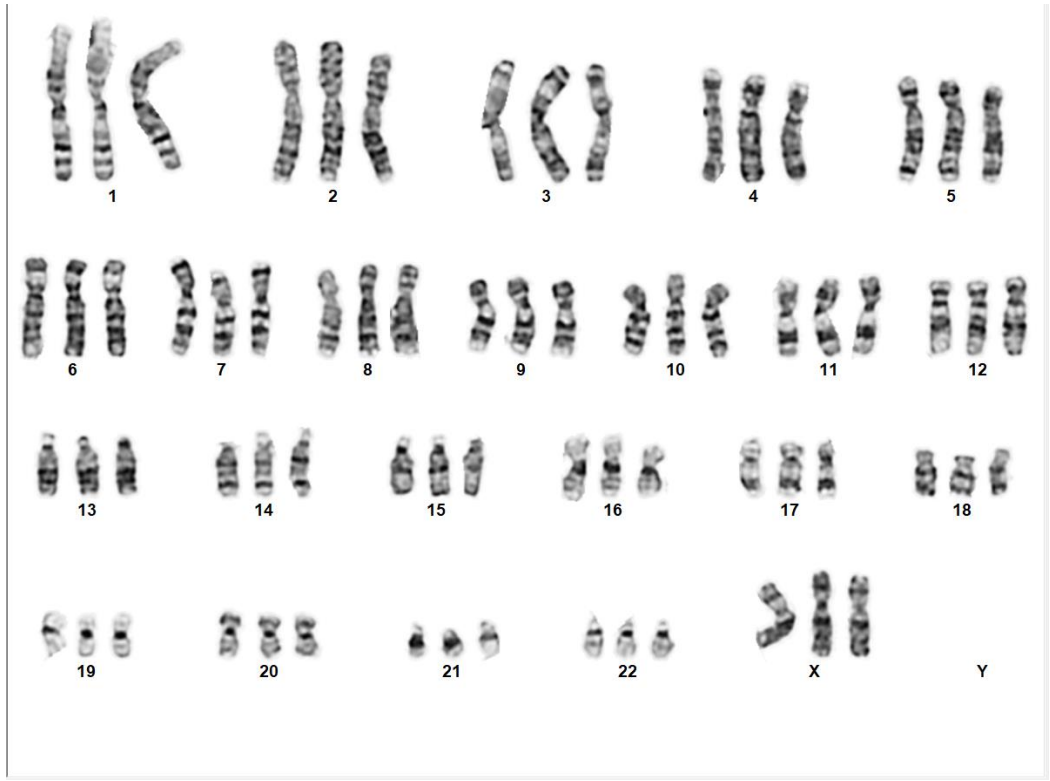
Androgenetic/biparental chimeric & mosaic conception



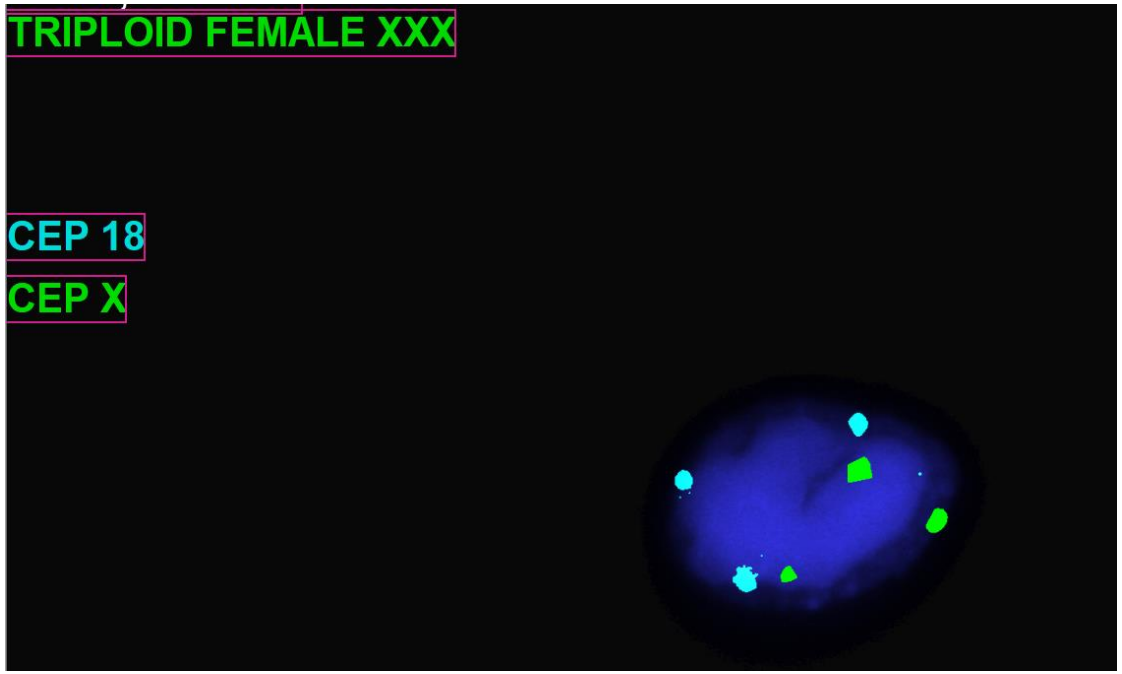
Case 1

Clinical information: Missed Abortion

Specimen: Products of conception

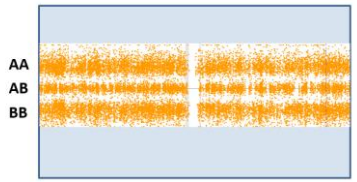


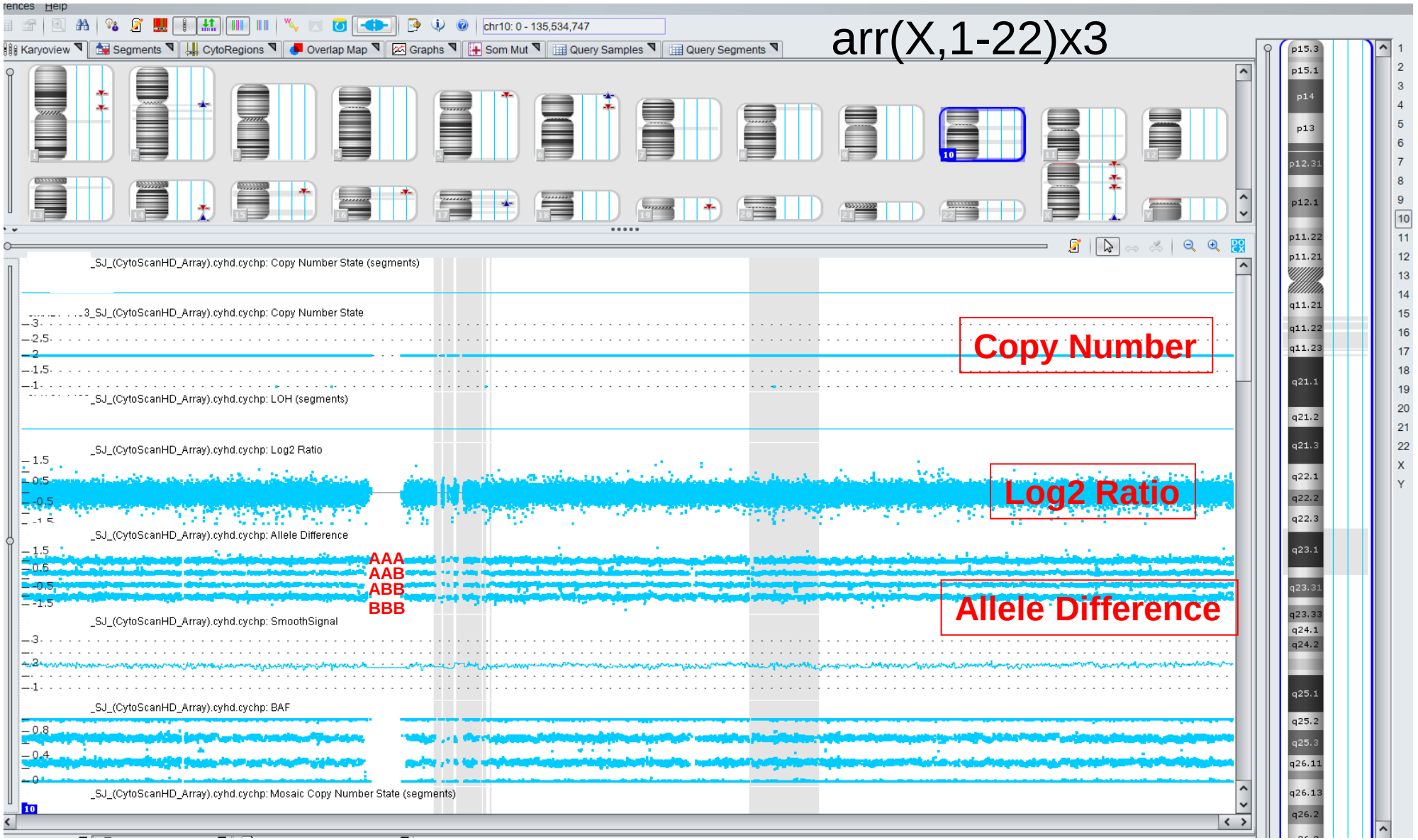
Abnormal Female Karyotype - Triploidy (69,XXX)



FISH (Fluorescent In Situ Hybridization)

Chromosomal Microarray





T22-XXX

DIAGNOSIS(ES):
A. Products of conception, spontaneous/missed:
Decidua

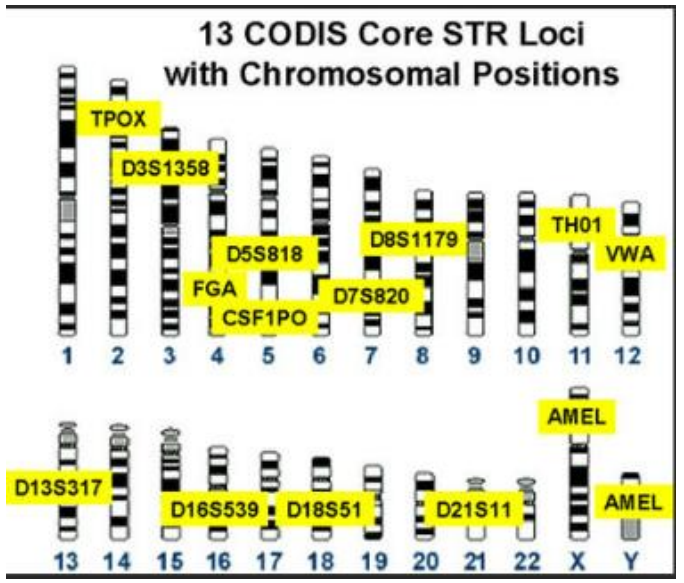
B. Products of conception, spontaneous/missed:
Portions of immature placenta
Decidua

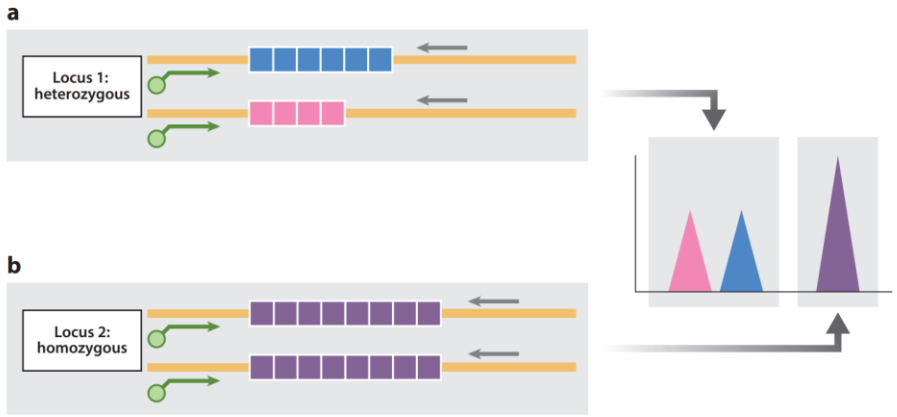
INTERPRETATION

Paraffin embedded slides were received from Pathology containing sections of immature placenta. FISH with chromosome-specific probes showed three signals for chromosome 15, 16, 18 and XXY, indicating the presence of triploid cells in ~80% of the 100 cells analyzed. The remaining 20% were XX, normal and most likely represent maternal cells. Triploidy accounts for approximately 11% of abnormal karyotypes observed in miscarriage specimens and typically presents as a partial molar pregnancy when the third haploid genome is paternally derived.

Microsatellite Marker Genotyping

- Microsatellites, or Short Tandem Repeats (STR) 1–6 bp, usually show high levels of polymorphism.
- Capillary electrophoresis- separate by size and by fluorophore
- Identity, forensics, ancestry, bone marrow engraftment monitoring, maternal cell contamination

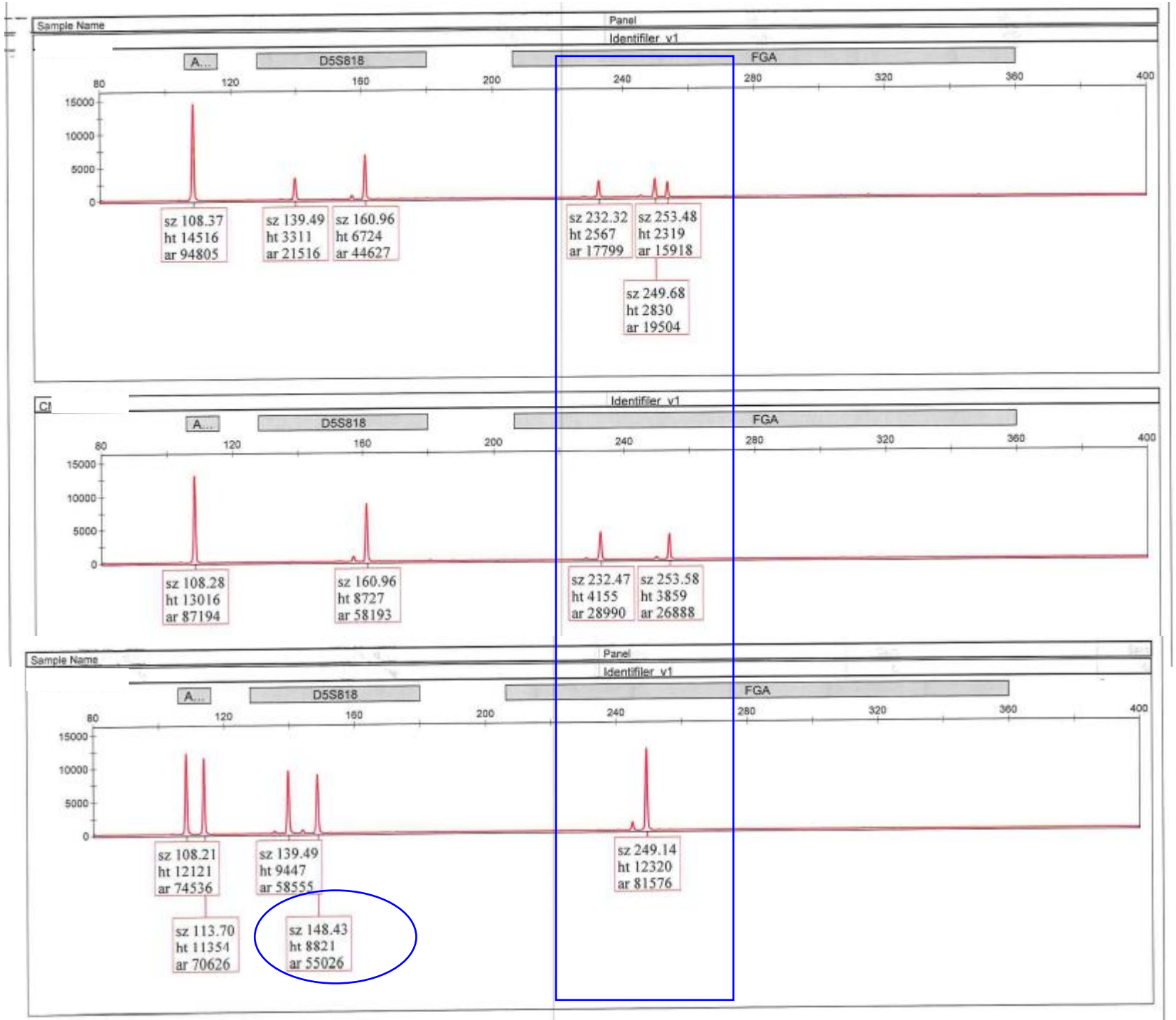




Fetus

Mother

Father



The comparison of the fetal and parental STR patterns showed maternal origin of the extra haploid chromosome set (Digynic).

Case 2

CLINICAL INFORMATION: Missed abortion, Clinical suspicion for a hydatidiform mole has been noted

SPECIMEN: Products of conception

RESULTS

91,XXXY,-22

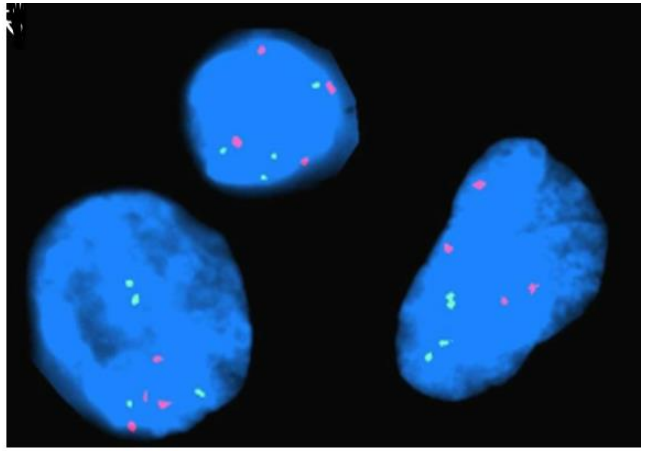
INTERPRETATION

Conventional karyotyping analysis of this product of conception specimen revealed an extra two sets of chromosomes and a loss of chromosome 22, resulting in tetraploidy karyotype (91,XXXY,-22) in all 20 metaphase cells analyzed. Tetraploidy is incompatible with life and often associated with pregnancy losses. Genetic counseling is recommended.

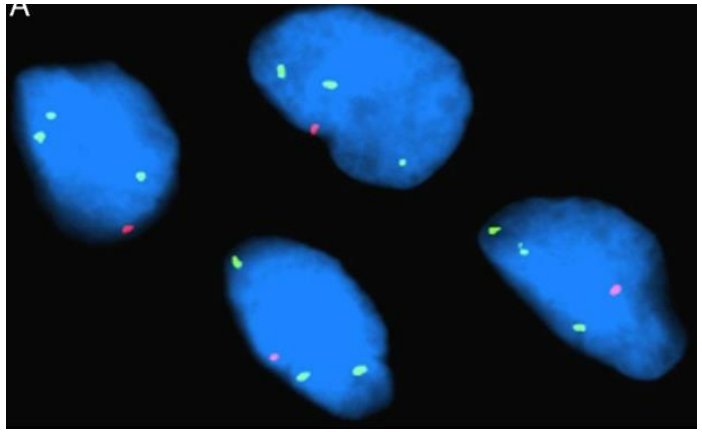
Of note, triandric tetraploid partial hydatidiform moles are uncommon, and their pathogenesis is unknown (PMIDs: 31669228; 23633551).

Tetraploid PHM

FISH

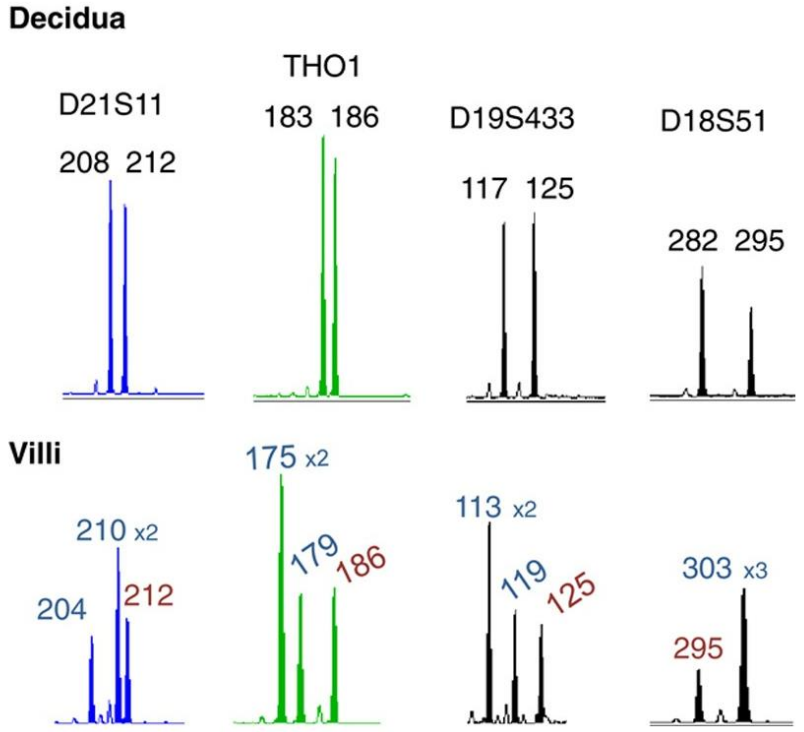


FISH probe set for the pericentromeric regions of chromosome 15 (D15Z4, FITC) and the heterochromatic region of chromosome 9 (D9Z3, Texas Red)



FISH probe set for the pericentromeric regions of X (DXZ1, Spectrum Green) and Y (DYZ3, Spectrum Orange)

STRP assay

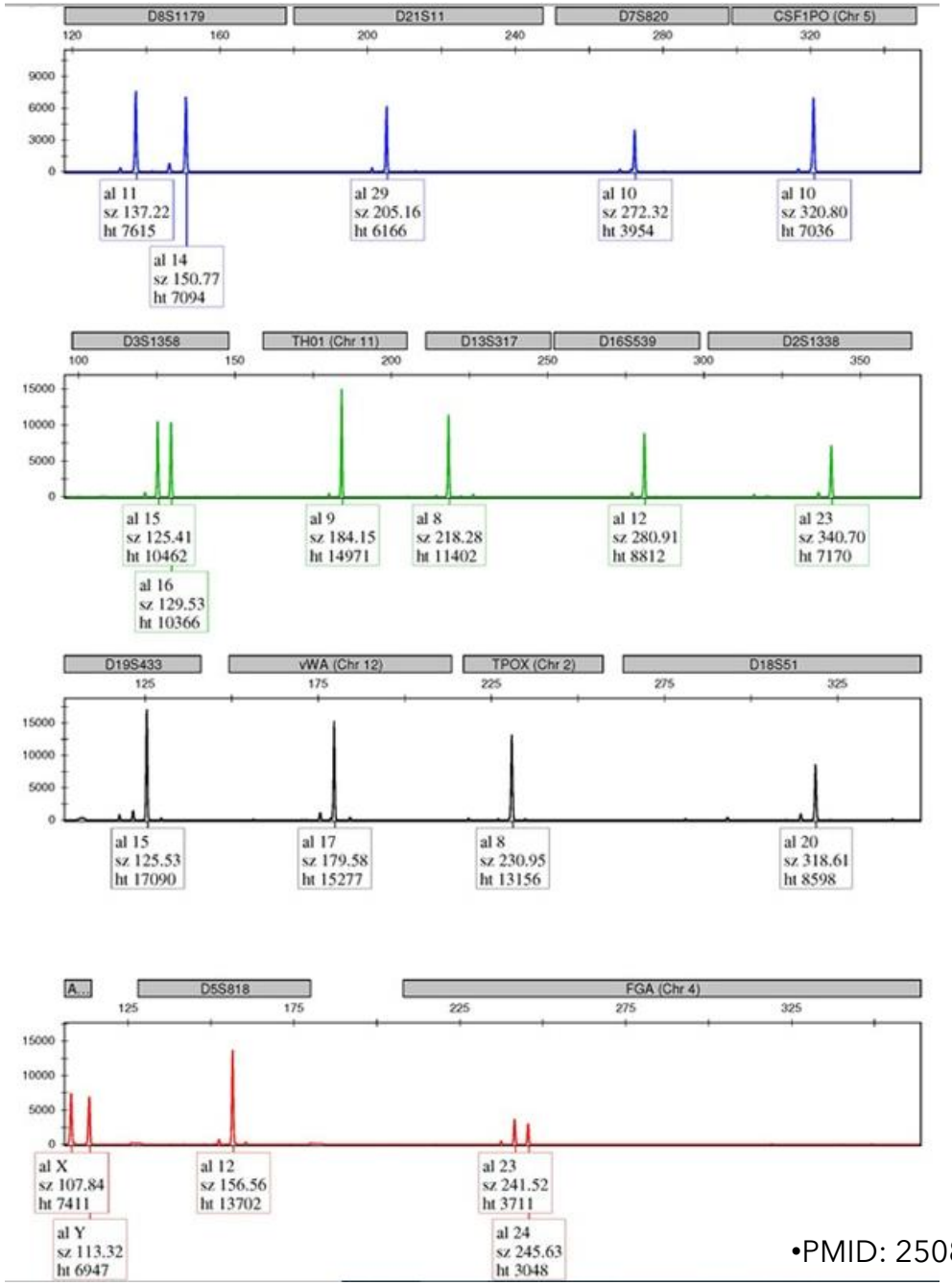


PMID: 22123726

Tetraploid PHM

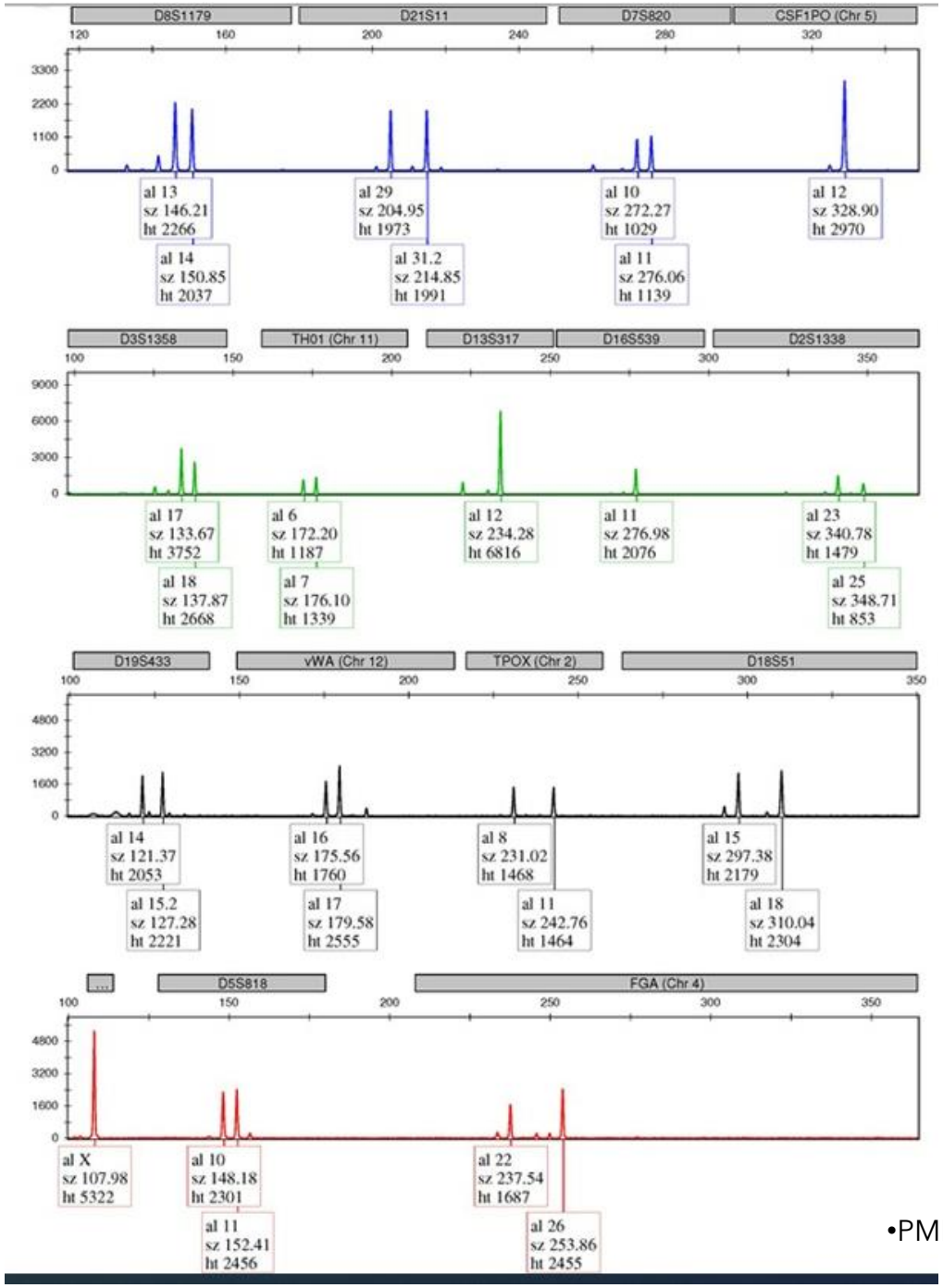
Genotype results (chorionic villi only)

monospermic CHM, showing alleles at all 15 loci tested are homozygous.



•PMID: 25083967

Egg donor pregnancy misinterpreted as CHM



•PMID: 25083967

Comparison of Allele Zygosity Patterns in Genotypes of CHM versus Donor Egg Pregnancy

Diagnosis	No. Heterozygous Loci	No. Homozygous Loci	Heterozygous Loci:Homozygous Loci (%)	Ratio of Heterozygous:Homozygous Loci
Monospermic CHM (n = 31)	0	15 ± 0	0:100	0:1
Dispermic CHM (n = 5)	4 ± 1.6	11 ± 2.2	27:73	1:3
Donor egg POC (n = 11)	12.3 ± 1.4	2.6 ± 1.5	82:18	4:1
*P**	<0.0001	<0.0001		

CHM indicates complete hydatidiform mole; POC, products of conception.
**P*-value between dispermic CHM and donor egg nonmolar POC.

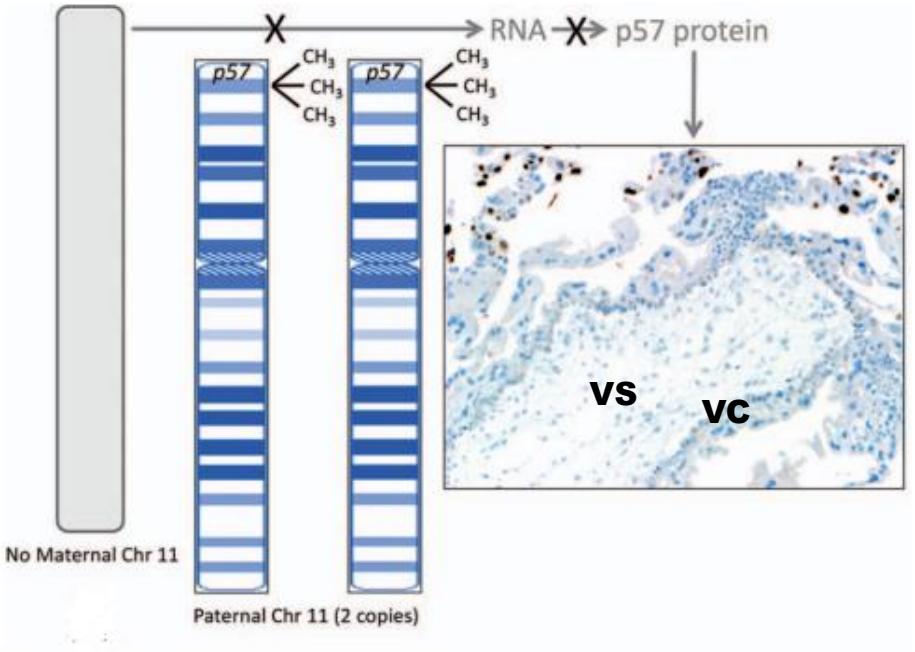
•PMID: 25083967

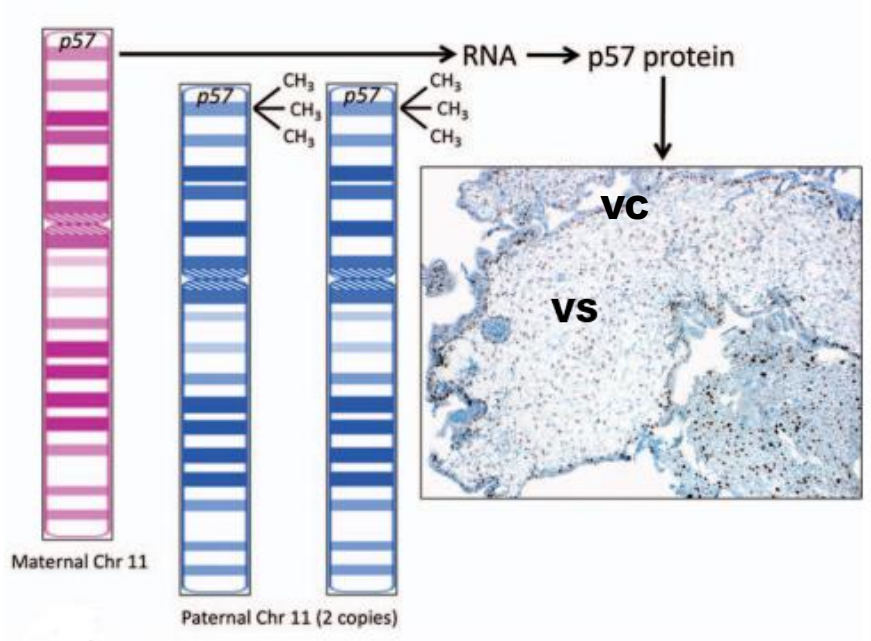
Donor egg POC – How to mitigate the risk of misinterpretation

- ❑ Communication from the clinician regarding the use of a donor egg, provide complete clinical information when submitting specimen for pathologic evaluation
- ❑Attention to the allele zygosity ratio in the evaluation of genotype results
- ❑Secondary confirmation of a genotype-based diagnosis of dispermic CHM by p57 immunohistochemistry and correlation with histologic findings

•PMID: 25083967

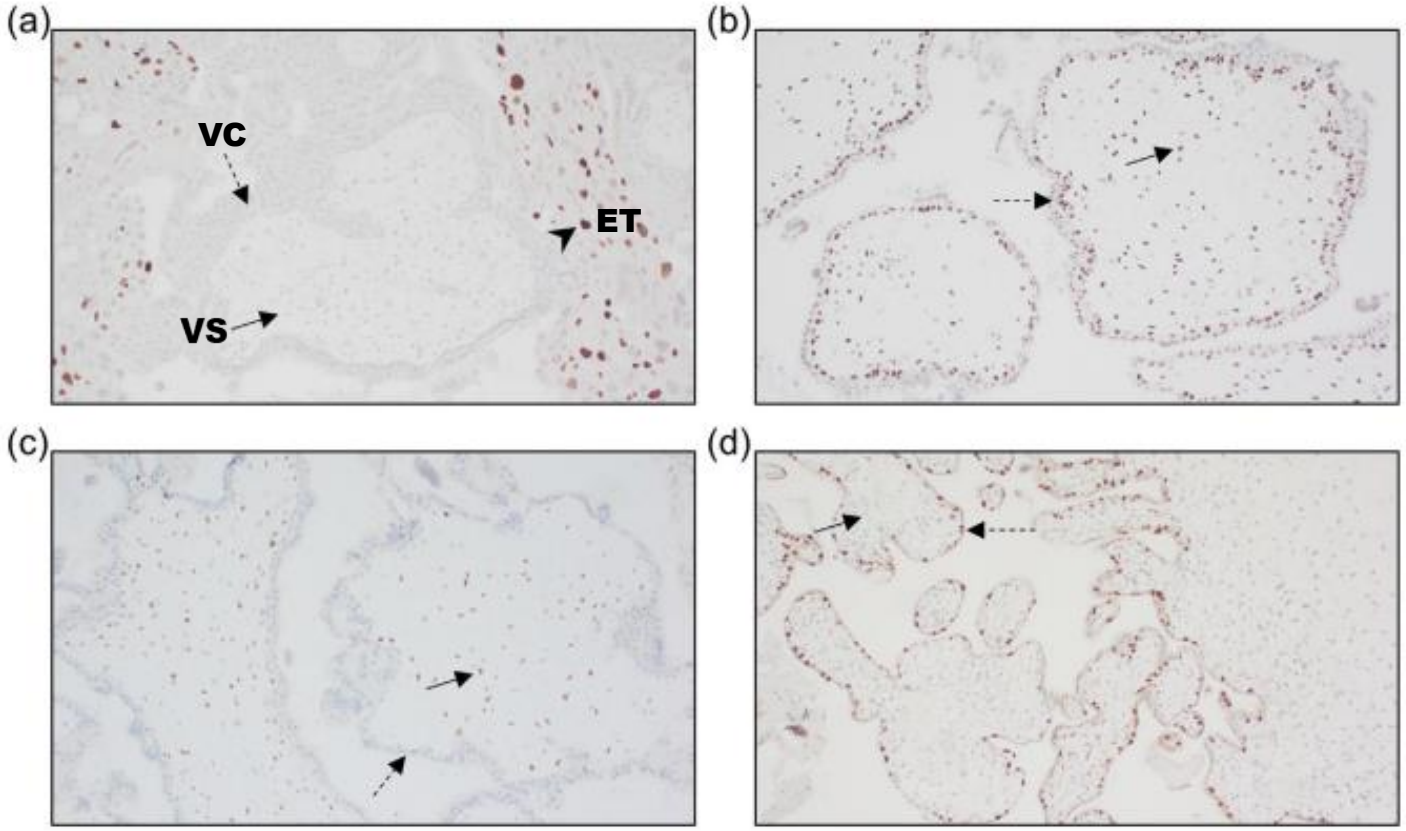
Mechanism of p57 expression in HM



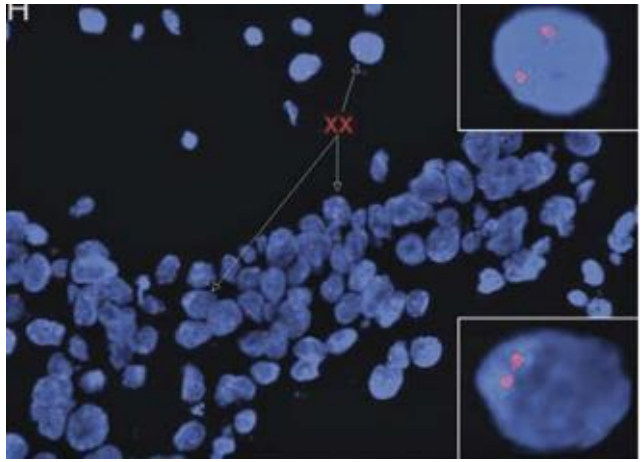


Villous stroma (**VS**)
Villous Cytotrophoblast (**VC**)

Immunostaining of p57 in different types of conceptions

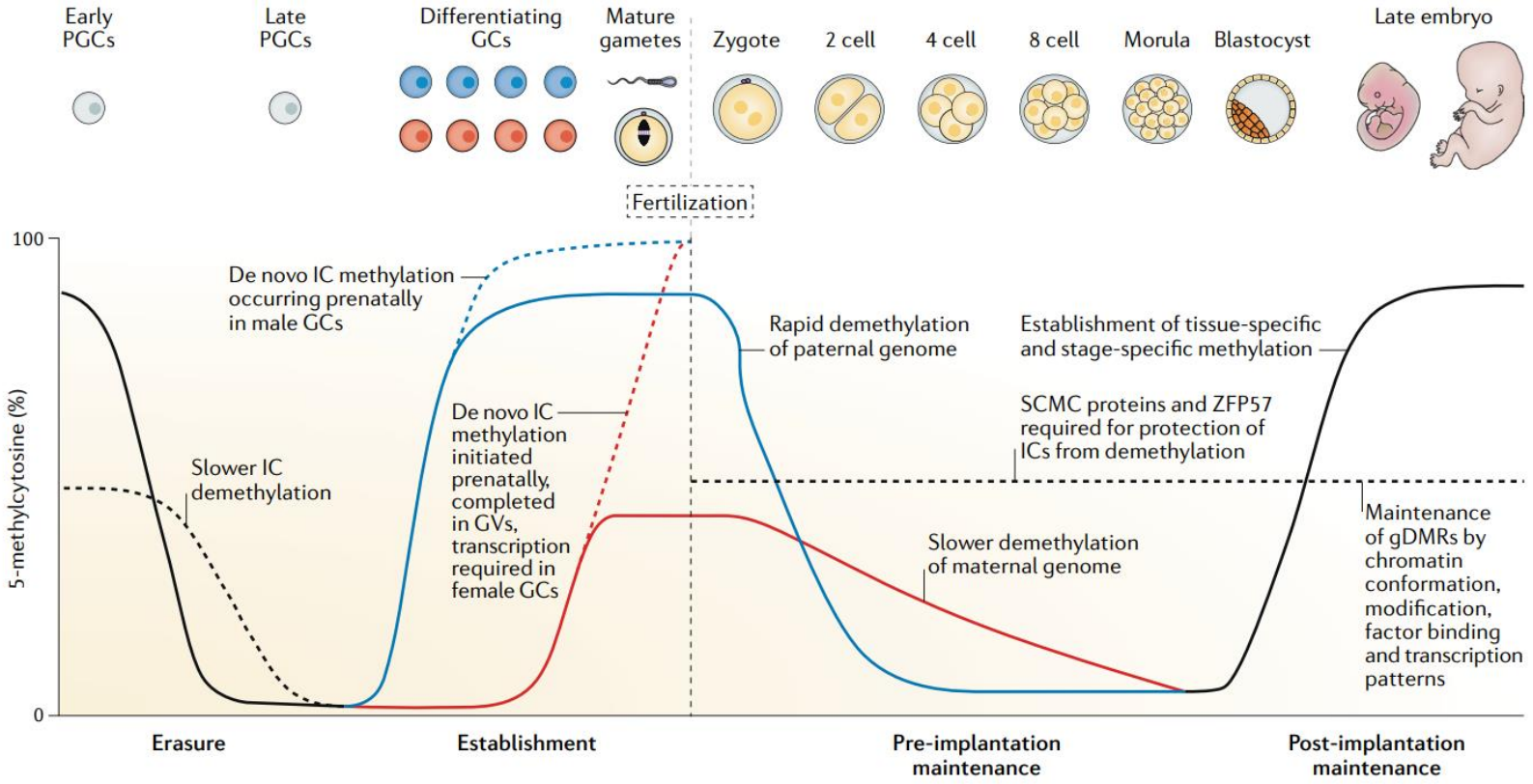


Villous stroma (**VS**)
Villous Cytotrophoblast (**VC**)
Extravillous trophoblast (**ET**)



p57 IHC, STR genotyping, and FISH to analyze specimens and correlates the findings with morphology and risk of PGTD

Genomic Imprinting



DNA methylation reprogramming during human development.
Factors and events involved in each stage, 5-methylcytosine level and approximate timing of imprint erasure, establishment and pre-implantation and post-implantation maintenance are indicated.

PMID: 30647469

Genomic imprinting role in the malignant potential of CHMs

- Genomic imprinting seems to have an important relationship to the characteristic pathological features shared by CHM and PHM, namely, trophoblastic proliferation and abnormal or absent embryonic development.

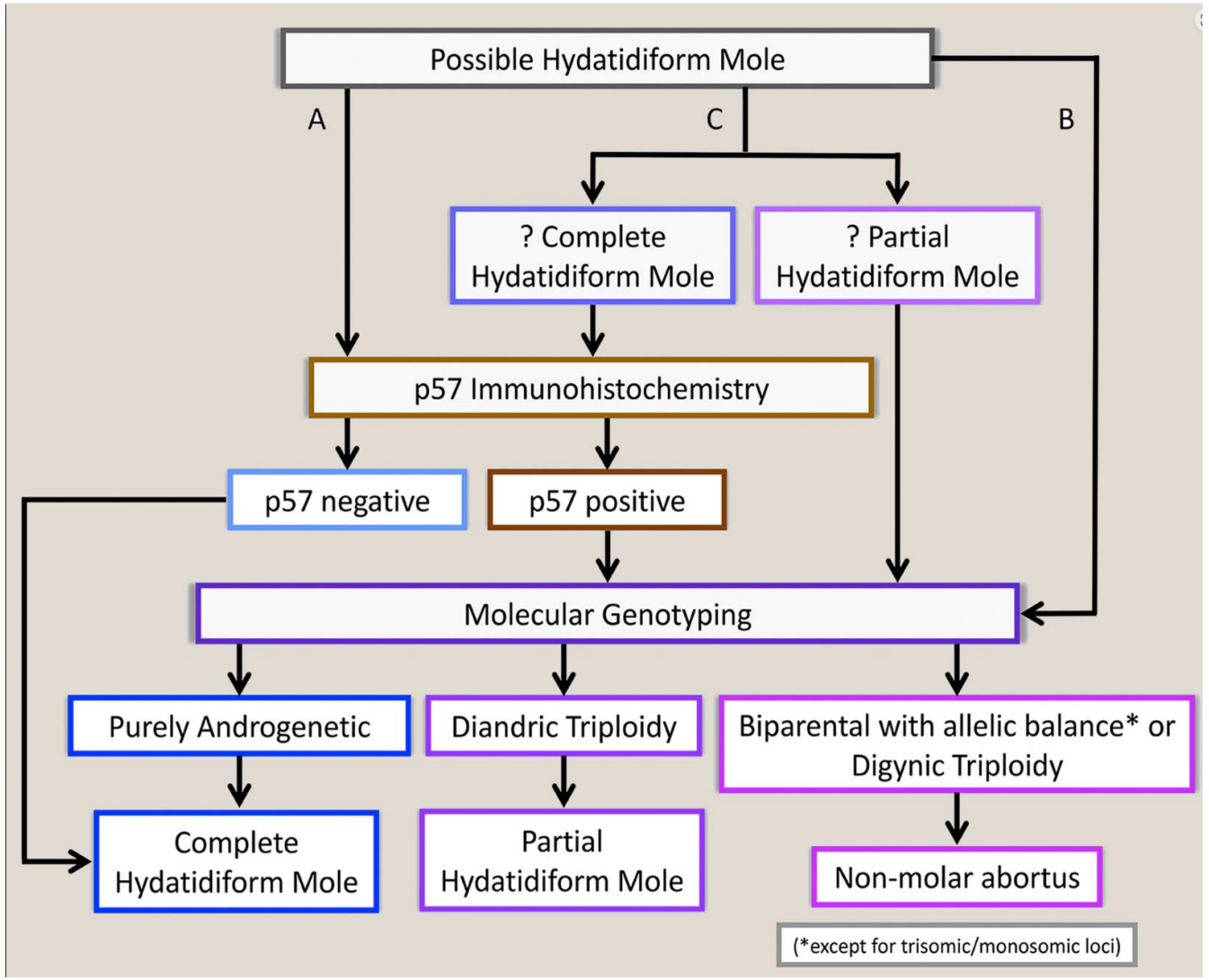
- AnCHMs fail to express imprinted genes. Dysregulation of the normal methylation patterns of imprinted genes likely to play a role in molar development.

- Diploid biparental CHMs display the same aberrant patterns of expression and methylation status for imprinted genes as AnCHMs and seem to carry the same risk of PGTD.

- This indicates that it is not the double dosage of a recessive mutation in the paternal genome but unbalanced expression of imprinted genes that predisposes to malignant transformation.

- The inherent growth-promoting role of paternal genes, in the absence of growth-inhibiting maternal genes, may contribute to the malignant potential of CHMs

Algorithmic approach in the diagnostic workup of hydatidiform moles



PMID: 30500280

Summary

- Identification of molar pregnancy is critical for appropriate management
- Morphological assessment of HM continues to be negatively impacted by interobserver diagnostic variability
- HMs should require integration of ancillary techniques, particularly p57 immunohistochemistry and STR genotyping
- Goal is to provide refined diagnosis, accurate assessment of the risk of persistent GTD

Acknowledgements

- Hannah Rennert, PhD
- Wing Kay Fok, MD, MS
- Vimla Aggarwal, MBBS, FACMG

THANK YOU