Germline *NLRP7* mutations: genomic imprinting and hydatidiform mole

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Hydatidiform moles are abnormal gestations with trophoblastic proliferation and villous hydrops and are generally classified into complete and partial moles [1]. At the genetic level, the presence of excessive paternal genome plays a key role in the development of the disease, likely through altered genomic imprinting. Identification of specific gene mutations of *NLRP7* and *KHDC3L* in recent decades in a subset of familial biparental complete moles (FBCHM) has provided insight to our understanding of pathogenesis of both sporadic moles and FBCHMs. In this issue of *Virchows Archives*, Allias and co-authors describe a 24-year-old woman who carried a novel germline *NLRP7* truncating mutation and developed four consecutive gestations with abnormal chorionic villous phenotypes ranging from complete to partial mole-like changes [2]. The paper provides new evidence of interest.

The mammalian placenta is enriched with imprinted genes, many of which are functionally related to cellular proliferation and almost all imprinted genes that are specific to the placenta are paternally imprinted and functionally expressed only from the maternal alleles [3]. Based on the “parental conflict hypothesis” [4], the intent of the paternal genome is to maximize resources for the father’s own progeny but the interest of the maternal genome is to distribute resources equally among her offspring, implying that growth-promoting genes are mainly expressed from the paternally inherited genome and are suppressed in the maternally inherited counterparts. Paternal-only or excess paternal genomic composition is the key genetic event underlying the development of sporadic moles. Sporadic complete moles inherit a diploid, androgenic-only nuclear genome of either homozygosity (up to 90%) or heterozygosity (10%). Partial moles have a triploid diandric-monogynic genome, harboring two heterozygous sperm haploid genomes in over 95% of the cases. Such excessive

paternal genomic representation in sporadic moles likely disrupts the normal imprinting control leading to abnormal placental trophoblast proliferation [5]. Systemic evaluation of imprinting defects revealed that there was total paternalization of all ubiquitous and placenta-specific DMRs (differentially methylated regions) in sporadic androgenetic moles. Consistent with the “parental conflict interest” theory, the molar phenotypes are likely due to defective placenta-specific imprinting and abnormal overexpression of paternally imprinted gene transcripts.

FBCHM is an exceptional condition of recurrent complete moles in multiple pregnancies [6]. *NLRP7* is a human maternal effect gene that is expressed in the oocyte to support embryonic development until the activation of embryonic genome occurs. Around 50 mutations of *NLRP7* gene are responsible for majority of FBCHM as a causal event. *KHDC3L* is the second maternal effect gene identified in 10–14% of FBCHM cases. Mutations in *NLRP7* and *KHDC3L* could confer a complete molar phenotype on digynic triploid conceptions [7] and that normal egg donation enables FBCHM patients to achieve normal term pregnancy firmly establish a pivotal role of *NLRP7* and *KHDC3L* in the pathogenesis of FBCHM [8].

NLRP7 plays an essential role in controlling the timing of oocyte growth or in transducing signals for the initiation of imprint establishment and works in a stage-dependent fashion during human preimplantation development. *KHDC3L* protein displays a juxta perinuclear signal and colocalizes with *NLRP7* in human oocytes and preimplantation embryo. Although the genome of FBCHM is contributed by both parents, gene expression patterns are found similar to those seen in sporadic androgenetic complete moles [9]. Molar tissue of FBCHM of patients with either *NLRP7* or *KHDC3L* mutations demonstrated imprinting gene defects with silencing of maternally imprinted genes and expression of paternally imprinted counterparts. It is plausible that *NLRP7* or *KHDC3L* mutations result in defective placental-specific imprinting mechanism shutting down or reducing expression of maternally imprinted genes and overexpression of paternally derived transcripts.

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While *NLRP7* mutations are primarily described in FBCHM, depending on the severity of *NLRP7* mutations, a subset of FBCHMs expressed variable levels of p57(KIP2) expression and showed histological features simulating diandric triploid partial moles and were closely associated with missense mutations. In contrast, cases of FBCHMs with abnormal p57(KIP2) expression and histological changes of complete mole were significantly associated with protein-truncating mutations [10]. This is further complicated by the observation in the current paper by Allias et al. that even an identical *NLRP7* truncating mutation in the same patient presented with gestations of variable histological phenotypes and p57 staining patterns, ranging from complete to partial mole. P57 gene is a paternally imprinted gene encoding a cyclin-dependent kinase inhibitor and is located within the imprinting gene clusters on the short arm of chromosome 11 (11p15.4). In a closely related scenario, uniparental isodisomy is an abnormal genetic condition in which both homologous chromosomes or part of the chromosome are inherited from one parent and the other parent's homologous chromosome is lost. We recently described three cases of gestations with paternal uniparental isodisomy at tyrosine hydroxylase or *TH01* (another paternally imprinted gene) locus on chromosome 11p15.4. The three cases demonstrated a spectrum of morphological changes and/or p57 immunohistochemical features simulating either partial or complete mole. One of the three patients even developed clinical complications simulating persistent gestational trophoblastic disease/neoplasia that required multiagent chemotherapy [11]. It is striking that, similar to FBCHM, paternal uniparental isodisomy at the *TH01* locus (colocalizing with p57 at chromosome 11p15.4) results in abnormal gestations simulating hydatidiform moles both histologically and clinically and the degree to which it simulates a hydatidiform mole appears to depend on the extent of altered expression of paternally imprinted genes on chromosome 11p15.

Taken together, it can be hypothesized that the global imprinting alteration at a critical time point in a preimplantation embryo is acquired by either the de novo absence of the maternal haploid genome in sporadic androgenetic complete moles or mutations of *NLRP7* or *KDC3L* leading to the suppression of the entire maternal imprinting gene expression in FBCHM. The findings in Allias's paper further emphasize a close and complex interplay between *NLRP7* mutations, DNA methylation regulation, and imprinting gene expression, such as p57 in the oocytes that likely drives villous trophoblasts to acquire molar phenotypes in FBCHM. Future investigations into the role of *NLRP7* mutations in FBCHM may ultimately

elucidate the converging biological event that underscores the development of hydatidiform moles of both sporadic and familial biparental nature.

Compliance with ethical standards Dr. Pei Hui is the sole author of the work.

Conflict of interest The author declares no conflict of interest.

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