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LETTER TO THE EDITOR

Sperm Biology

Commentary on "morphological characteristics and initial genetic study of multiple morphological anomalies of the flagella in China"

Charles Coutton[1,2,3], Christophe Arnoult[1,2], Pierre F Ray[1,2,4]

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Dear Editor,

We have read with a great interest, the excellent article by Yang *et al.*[1] which, for the first time, fully describes the structural and ultrastructural defects of spermatozoa with multiple morphological anomalies of the flagella (MMAF) in Chinese patients. This study revealed in these patient's spermatozoa, a completely disorganized axoneme and, in particular, the displacement or absence of the central pair (CP) in most of the cross sections were analyzed.

It is interesting to note that the lack of the CPs leading to an abnormal "9+0" configuration of the axoneme is the main defect observed in most of the cases associated with MMAF[1] and that this defect was also predominantly observed in our patients with *DNAH1* mutations.[2] These observations further support the hypothesis that CP disorganization could be the key molecular factor leading to the MMAF phenotype.[3] In the AJA manuscript, Yang *et al.*[1] confirm that the onset of the axonemal defect occurs during the late stages of spermiogenesis due to a defective assembly of cytoskeletal components of the sperm tail.[4] This clearly demonstrates that CP plays a major role in maintaining the global flagellum organization throughout spermiogenesis. Overall, these data strongly suggest that the genetic abnormalities responsible for MMAF syndrome likely concern the genes involved directly or indirectly with the CP formation or assembly.

In human, only *DNAH1* mutations have been formally described to cause MMAF and were identified in 5 out of 18 unrelated affected subjects.[2] The authors sequenced the whole coding sequence of the *AKAP3* and *AKAP4* genes and only 4 exons (out of the 79) of the *DNAH1* gene and did not find any pathological variations. We can regret that they only sequenced a small portion of the *DNAH1* gene as this partial analysis does not permit to draw any conclusion regarding the implication of *DNAH1* in Chinese MMAF patients. We, thus, would like to encourage the authors to sequence the remaining 75 exons of *DNAH1*. Using next generation sequencing, we have identified five new pathogenic mutations in *DNAH1* in a small cohort of patients with MMAF phenotype, confirming the high prevalence of *DNAH1* gene alterations in this phenotype and the fact that mutations can be expected in any of the 79 *DNAH1* exons (unpublished data). Moreover, and as proposed by the authors, others genes and, in particular, those involved in the intra-flagellar transport (IFT) or intramanchette transport may be linked to MMAF phenotype.[1] Beyond the role of *DNAH1* in the motor function and the structure of the axoneme, its unexpected strong cytoplasmic expression suggests a possible involvement of this inner arm dynein to the flagellum assembly throughout the IFT.[2] We still believe that the molecular diagnosis of MMAF patients should first focus on *DNAH1* and then, as proposed by the authors, on genes involved in intra-flagellar transport (IFT) or intramanchette transport. As *DNAH1* alone is encoded by 79 exons, we believe that the best diagnosis strategy for MMAF diagnosis is the realization of exome sequencing. This will eventually permit to identify all the genes involved in this heterogeneous phenotype and perhaps confirm the above-mentioned hypothesis.

COMPETING INTERESTS

The authors declare no competing interests.

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[1]Université Grenoble Alpes, Grenoble, F-38000, France; [2]Equipe "Genetics Epigenetics and Therapies of Infertility" Institut Albert Bonniot, INSERM U823, La Tronche, F-38706, France; [3]Département de Génétique et Procréation, Hôpital Couple Enfant, CHU Grenoble, Grenoble, F-38000, France; [4]Laboratoire de Biochimie Génétique et Moléculaire, CHU Grenoble, Grenoble, F-38000, France.
Correspondence: Dr. C Coutton (ccoutton@chu-grenoble.fr)
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