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Letter to the editor

Genetic causes of macrozoospermia and proposal for an optimized genetic diagnosis strategy based on sperm parameters

Introduction

Macrozoospermia, characterized by the presence of large-headed spermatozoa usually carrying several flagella, is one of the most severe phenotypes of male infertility phenotypes, as in most cases, the gametes are chromosomally abnormal and cannot be used for assisted reproductive technologies (ART) (Ray et al., 2017). In 2007, subjects from consanguineous families were shown to carry the same homozygous deleterious *AURKC* variant (NM_001015878.2: c.144delC, later renamed c.145delC, p.Leu49TrpfsTer23), establishing *AURKC* as the first and main gene associated with macrozoospermia (Dieterich et al., 2007). Using flow cytometry, all spermatozoa from patients homozygous for the c.145delC variant were shown to be tetraploid, highlighting a cytokinesis blockage of the first meiotic divisions thus confirming that ART cannot be successful for these patients (Dieterich et al., 2009). Since then, the predominance of the c.145delC variant (present in approximately 85% of all *AURKC* deleterious alleles) was confirmed and several other deleterious variants were identified including a second frequent allele c.744C>G, p.Tyr248ter accounting for 13% of the *AURKC* alleles (Ben Khelifa et al., 2012). A few ultra-rare mutations were then reported (Bai et al., 2020; Kobesiy et al., 2020). *AURKC* is highly expressed in the testis, particularly in dividing spermatocytes but also in oocytes. In the mouse, the absence of AURKC seems to be partially compensated by AURKB as male knock out are not completely sterile but present some sperm anomalies (heterogenous chromatin condensation, loose acrosomes, and blunted heads) (Kimmins et al., 2007). AURKB and AURKC ensure the coordination of chromosome restructuring events during the G2/MI transition and maintain an ordered progression through meiosis I and II that is critical for accurate chromosome segregation (Wellard et al., 2020). Since the identification of *AURKC*, several other genes have been described to cause macrozoospermia such as *ZMYND15* (Kherraf et al., 2021) and *NUP210L* (Arafah et al., 2021) but deleterious variants have only been identified in few subjects.

Here, we present the exhaustive genetic analysis of 156 patients described to present large-headed spermatozoa in their ejaculate and sent to Grenoble by clinicians from various centers between 2007 and 2021 for the genetic diagnosis of their sperm defect. Partial results from some of these patients were published previously (Dieterich et al., 2009; Ben Khelifa et al., 2012; Arafah et al., 2021; Kherraf et al., 2021) but a reanalysis of all patients, including 70 unreported subjects was never done. We note that the percentage of large-headed spermatozoa varied from 2% to 100% with an average of 64.9% of macrozoospermia and the percentage of multiple flagella varied from 0 to 75% with an average of 30.2%. Targeted analysis of *AURKC* was first carried out before performing whole exome sequencing (WES) on the undiagnosed patients, allowing the identification of candidate variants in five additional genes, including three new candidate genes. In addition, we performed a genotype-phenotype correlation to establish an algorithm to optimize the genetic diagnosis of subjects with macrozoospermia.

Analysis of AURKC (NM_001015878.2) Sanger sequencing data from 156 subjects

Sequencing of *AURKC* exons 3 and 6 was first carried out in 156 patients. Eighty-seven (56%) carried mutations in these two exons. Seventy subjects were homozygous for the c.145delC, p.Leu49TrpfsTer23 variant, eleven were homozygous for the c.744C>G, p.Tyr248* variant, five were compound heterozygous carrying the variants c.145delC and c.744C>G, and the last patient was compound heterozygous carrying the c.145delC and the c.686G>A, p.Cys229Tyr (exon 6) variants (Fig. 1A). Sanger sequencing of the remaining *AURKC* exons (exons 1, 2, 4, 5, and 7) was then performed for patients who did not carry bi-allelic variants in exons 3 and 6. Three additional mutations were identified: two brothers were compound heterozygous for the c.145delC and the c.436-2A>G (intron 4), the other patient was homozygous for the c.539T>A; p.Val180Glu (exon 5). Interestingly, bi-allelic variants in *AURKC* exons 3 and 6 were found in 87/90 (97%) of *AURKC*-positive individuals and only one subject did not have at least one variant in these exons. For future diagnosis purposes, we propose to only sequence these two exons, to perform targeted sequencing of the other exons only for the heterozygotes, and to proceed to WES for all negative subjects. As previously reported, the c.145delC variant was mainly found in subjects originating from North Africa (Ben Khelifa et al., 2012). Overall, a causal alteration of the *AURKC* gene was found in 90 patients (57.7%).

Analysis of whole exome sequencing data from 29 subjects

Among the 66 patients without causal anomaly in *AURKC*, whole exome sequencing was performed for 29. Unfortunately, DNAs from many of the early patients ($n = 37$) did not pass the quality tests and could not be used for WES. We aimed to search for variants in novel candidate genes responsible for macrozoospermia. We only retained the homozygous variants predicted to introduce a premature stop codon present in genes described to be highly expressed in the testis or previously associated with an infertility phenotype. Two patients from the cohort were already published individually and carried variants in *ZMYND15* (Kherraf et al., 2021) and *NUP210L* (Arafah et al.,

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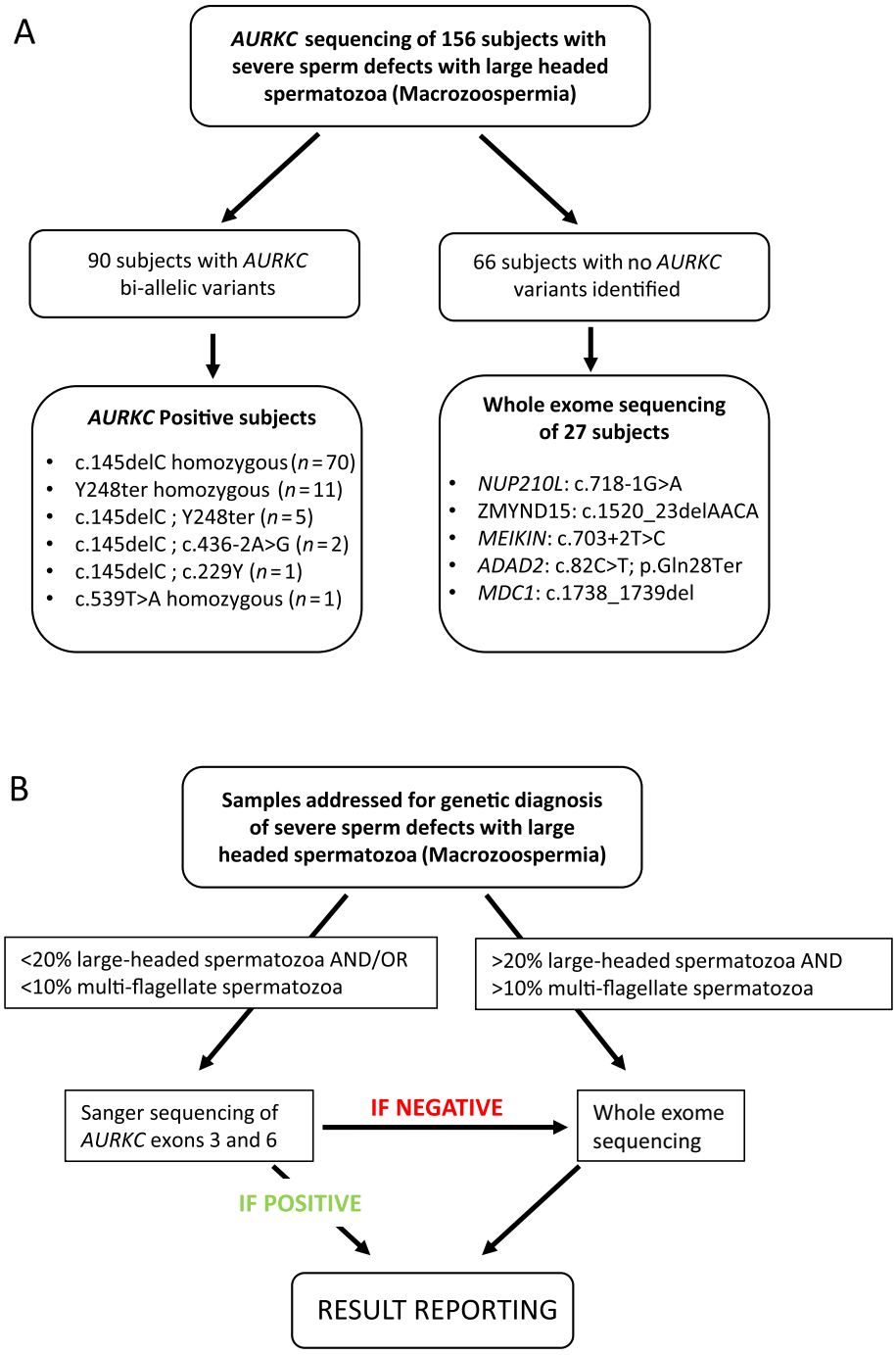

Fig. 1. A: Schematic representation of the molecular diagnostic investigations carried out on 156 patients with large-headed spermatozoa. Sequencing of *AURKC* exons 3 and 6 was performed for 156 patients. In case of negative results, the other exons were sequenced. In total, *AURKC* sequencing allowed to diagnose 90 patients with mutation. Whole exome sequencing (WES) was performed for 27 subjects. WES could not be performed for 39 patients because of poor DNA quality. A total of five candidate variant/genes were identified. **B**: Logigram for the genetic analysis of patients with large-headed spermatozoa.

2021) and three patients carried a homozygous deleterious variant in new candidate genes. All identified variants were confirmed by Sanger sequencing.

Patient 1 had a homozygous splice donor variant in *MEIKIN*: NM_001303622: c.703+2T>C. *MEIKIN* is a meiosis-specific factor localizing to the kinetochores in meiosis I (Kim et al., 2015). This variant located in intron 8 of 12 is predicted to have an impact on splicing with a SpliceAI score of 0.24 and a CADD score of 24.4. The allele frequency in the general population is low (0.0003748 GnomAD v2.1.1). The patient had oligoasthenoteratozoospermia with a total sperm count of 0.25 $\times$ 10^6/mL progressive mobility of 5% and 100% of atypical spermatozoa with 68% of macrocephalic spermatozoa but a limited number of multiple flagella (4%) (Table S1). To our knowledge, this gene has not been reported in human pathology. Both knockout (KO) male and female mice are reported to be infertile (Kim et al., 2015). In males especially, an apparently normal meiotic prophase progression has been observed, however, the round spermatids produced after meiosis became enlarged resulting

from an apparent absence of meiosis II. Moreover, examination of the testis revealed a decreased number of mature sperms. *MEIKIN* shows a specific expression in germ cells (Kim et al., 2015). *MEIKIN* encodes for a meiosis-I-specific kinetochore protein whose localization is mediated by its interaction with the centromere protein C (CENP-C). It plays a role in the mono-orientation of sister kinetochores and in the protection of centromeric cohesion (Kim et al., 2015; Miyazaki et al., 2017; Galander et al., 2019; Galander and Marston, 2020).

Patient 2 had a homozygous truncating variant in *ADAD2*: NM_001145200.2: c.82C>T; p.Gln28Ter. This alteration in the first exon results in a premature stop codon in position 28, which induces the production of a truncated protein losing its functional domains. This variant was absent from GnomAD (v2.1.1). A homozygous variant in *ADAD2* was previously reported in an infertile man with azoospermia (Krausz et al., 2021). To our knowledge, no other patient carrying variants in *ADAD2* was reported. Patient 2 presented a total sperm count of 0.45×10^6/mL. No motile sperm was observed, in agreement with a vitality test showing only dead spermatozoa. He had 70% of atypical spermatozoa with less than 10% of macrocephalic spermatozoa. The deletion of *Adad2* in mice resulted in male sterility. Only few germ cells from KO animals would progress beyond the round spermatid stage (Snyder et al., 2020). Elongating spermatids showed clear defects with reduced numbers and large multinucleated cells. *Adad2* is expressed predominantly in the testis and exclusively in mid and late pachytene spermatocytes, suggesting a role in meiosis regulation affecting post-meiotic events (Snyder et al., 2020). More specifically, the loss of ADAD2 leads to abnormal meiotic and post-meiotic heterochromatin and this outcome is driven by a reduced translation of *MDC1*, which is required for the intra-S phase DNA damage checkpoint (Chukrallah et al., 2022).

Patient 3 had a homozygous frameshift variant in *MDC1*: NM_01461.3: c.1738_1739del; p.Asp580CysfsTer36. This alteration in exon 5 results in a premature stop codon in position 580 which induces the production of a truncated protein losing the FHA domain and the BRCT domain, a regulator of the Ty1 transposition protein. Patient 3 had oligoasthenoteratozoospermia with a total sperm count of 7×10^6/mL and a null progressive mobility. The vitality was 21%. All spermatozoa examined were atypical with 20% of macrocephalic spermatozoa. *MDC1* is required for the intra-S-phase DNA damage checkpoint during meiosis I (Lou et al., 2006; Choi et al., 2022) and was previously reported in an infertile man with sperm motility defect (Oud et al., 2021). KO mice models showed a phenotype including growth retardation, male infertility, immune defects, chromosome instability, and DNA repair defects (Lou et al., 2006). *MDC1* encodes a protein required for the DNA damage checkpoint described to act as a mediator of the DNA damage checkpoint by facilitating the amplification and the transduction of DNA damage signals (Choi et al., 2022).

Comparison of sperm parameter and proposal of an optimized diagnostic strategy

Two groups of patients were constituted according to their *AURKC* genotype to enable the comparison of sperm parameters between positive and negative subjects. The five patients with variants in candidate genes were excluded from the calculation of the second group and sperm parameters for the three unpublished patients were presented separately (Table S1). The *AURKC* positive group had a statistically higher percentage of macrocephalic spermatozoa and multiple flagella than the undiagnosed group (85.6% vs. 32.32% with P value < 0.0001 and 38.8% vs. 13.2% with P value < 0.0001, respectively). Patients 1−3, with variants in newly identified genes, had an oligozoospermia with a sperm count clearly inferior to the mean of the *AURKC* negative group.

We then analyzed the correlations between several sperm parameters and the results of the genetic analyses. Our purpose was to assess if the sperm parameters could help to decide between two strategies of genetic investigation: perform an initially targeted sequencing of *AURKC* or directly perform WES either in all patients or in a subpopulation of patients with an atypical macrocephalic phenotype and low chances of harboring *AURKC* mutations. The aim is to propose simple guidelines to optimize the genetic diagnosis in infertile men with reported macrozoospermia. This would permit to obtain of a diagnosis for many patients using the cheap Sanger sequencing while limiting the number of patients for whom WES will be used in first intention and those for whom both Sanger and WES would be used. It would also reduce the overall length of the analysis, as fewer patients would have two successive analyses. Macrozoospermia is defined by the presence of macrocephalic spermatozoa with multiple flagella. We assessed the diagnostic performances for these two criteria taken individually and combined (Table S2). For this purpose, we analyzed these criteria with different thresholds to evaluate the diagnostic efficiency of *AURKC* sequencing in the first intention, followed, in case of a negative result, by whole exome sequencing. We also calculated the average cost per patient based on an estimation of the cost of an exome at 1000 euros and the sequencing of exons 3 and 6 at 200 euros.

In our series, 90 out of 156 patients were *AURKC* positive after Sanger sequencing of exons 3 and 6 (57.7%) and WES should then be applied to the 66 negative patients. In the absence of a threshold, Sanger sequencing would be carried out for all subjects and WES to the 66 negative patients. The average cost per patient would be $(156 \times 200 + 66 \times 1000)/156 = 623.10$ € (Table S2). On the other hand, if WES was performed directly on all patients, the cost for each patient would logically be 1000 €. We then applied different thresholds but data for all sperm parameters was not available for all patients. For example, the percentage of macrocephalic spermatozoa was available for only 112 subjects, and information regarding both the rate of large-headed spermatozoa and of multiple flagella was available only for 66 subjects. With this limited dataset, we observe that the cheapest strategy would be to carry out *AURKC* sequencing only on patients with >20% macrocephalic spermatozoa and >10% multiple flagella (Fig. 1B). According to our data, the average cost per patient would then be $(46 \times 200 + 23 \times 1000)/66 = 487.9$ € (Table S2).

In conclusion, we demonstrated the interest of whole exome sequencing of patients with severe teratozoospermia with macrozoospermia by identifying variants of interest in five patients, including three novel candidate genes. In each case, only one patient was identified and additional patients should be recruited and studied and functional work should be done in vitro and in vivo on animal models to confirm the role of these genes in spermatogenesis and macrozoospermia. In addition, this work was permitted to propose an optimized strategy for the routine genetic investigation of macrozoospermic patients according to the percentage of large headed spermatozoa. Sanger sequencing of exons 3 and 6 of *AURKC* should be performed for the patients with more than 20% of macrocephalic and more than 10% of multi-flagellate spermatozoa, followed by a whole exome sequencing in case of a negative result (Fig. 1B). For patients below these thresholds, whole exome sequencing should be performed first.

Ethics statement

Informed consent was obtained from all the individuals participating in the study according to local protocols and the principles of the Declaration of Helsinki. The study was approved by local ethics committees, and samples were then stored in the Fertithèque collection declared to the French Ministry of health (DC-2015-2580) and the French Data Protection Authority (DR-2016-392).

Conflict of interest

The authors declare no conflict of interest.

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Supplementary data

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