A new case of TAR syndrome confirms the importance of noncoding variants in the etiopathogenesis of the disease.

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ABSTRACT

TAR syndrome is a rare congenital disorder whose genetic bases have remained unclear for many years. It has now been understood that the disease is caused by the compound inheritance of a rare null allele (usually the 1q21.1 deletion) and a low-frequency hypomorphic noncoding single nucleotide polymorphism (SNP) in *RBM8A* gene. Nevertheless, only a limited set of variants has been identified so far.

A recent report of Boussion et al. described four novel *RBM8A* noncoding SNPs (i.e., 1) c.205 + 3_205 + 6del, 2) c.206 − 13C>A, 3) c. − 19G>T, and 4) c.*6C>G) increasing the mutational spectrum of TAR syndrome.

Here, based on the recently published manuscript by Boussion et al., we report data regarding an additional African TAR patient carrying the 1q21.1q21.2 deletion in trans with the 3'UTR (c.*6C>G) variant.

Present data further confirm the pathogenic role of this hypomorphic SNP and highlights its relevance in the African population, leading to advice geneticists to directly search for the c.*6C>G

variant in African patients affected by TAR syndrome and carrying the 1q21.1 deletion, shortening the diagnostic time window.

INTRODUCTION

Thrombocytopenia absent radii (TAR) syndrome is a rare congenital disorder, with an incidence of about 2–10 per million, characterised by absent radii with the presence of thumbs and congenital or early-onset thrombocytopenia that tends to resolve in childhood (Toriello, 2011). The genetic bases of this rare autosomal recessive syndrome have remained unclear for many years. Still, it has now been understood that TAR is caused by the compound inheritance of a rare null allele and a low-frequency hypomorphic noncoding Single Nucleotide Polymorphism (SNP) in *RBM8A*, a gene encoding the exon-junction complex subunit member Y14 (Albers et al., 2013). In particular, according to literature data, the null allele is usually represented by a rare proximal microdeletion of 1q21.1 that could be *de novo* (25% of cases) or inherited from the parents (Manukjan et al., 2017). At the same time, the most frequent noncoding SNPs locate in the 5'UTR (i.e. rs139428292, NM_005105.4:c. − 21G>A) or within the first intron (i.e. rs201779890, NM_005105.4:c.67 + 32G>C) (Nicchia et al., 2016). A recent report from Boussion et al. (Boussion et al., 2020) described for the first time four novel noncoding variants detected in patients affected by TAR syndrome, increasing the mutational spectrum of such disease. In particular, the authors described and functionally characterised two intronic variants (c.205 + 3_205 + 6del and c.206 − 13C>A), one located in the 5′−UTR (c. − 19G>T), and the last one located in the 3′−UTR (c.*6C>G).

Here, we describe, the case of a patient affected by TAR syndrome and carrying the 1q21.1q21.2 deletion in trans with the 3′−UTR (c.*6C>G) allele, further confirming the pathogenic role of this variant.

CASE REPORT

A 31 years old male was referred to the genetics department with his consanguineous wife, for a prenatal couple counselling regarding their reproductive risks and prenatal diagnosis possibility. His wife was pregnant at 15 gestational weeks. The male patient presented with short stature (142 cm), bilateral radius aplasia, and an anamnestic history without haematological problems. Son of first cousins, both of them characterised by short stature (mother height: 142 cm, father height: 165 cm), he is one of six brothers and sisters, all of them characterised by short stature (except for one brother) and he is the only one showing radius aplasia and transient thrombocytopenia.

Informed consent for both genetic counselling and molecular genetic testing was collected for the analysis. We processed the proband's DNA for a series of genetic analyses, which included: 1) diepoxybutane (DEB) test, 2) Combined SNP-CGH (Comparative Genomic Hybridization) array probe, and finally, 3) Whole Exome Sequencing (WES).

The first one, DEB test, was performed to exclude a Fanconi Anemia disease and did not show increased chromosomal breakages or rearrangement in response to the alkylating agent.

The SNP-CGH arrays were carried out to identify copy number variants and homozygous areas (because of consanguinity history). It led to the identification of a heterozygous deletion of about 5 Mb on chromosome 1, spanning through 1q21.1q21.2, and including the *RBM8A* gene (Figure 1B). The presence of this deletion has been further confirmed through Fluorescent in Situ Hybridization (FISH) (Figure 1C). At this point, the deletion could have explained the short stature segregating within the family, but it was not the reason for the radial aplasia. In this light, we applied WES sequencing for searching for a hypomorphic allele on the *RBM8A* gene. Data analysis led to the identification of the 3'−UTR (c.*6C>G) (rs12079762) variant at the hemizygous state. No other pathogenic or likely pathogenic variants were detected as potentially correlated to the phenotype.

DISCUSSION

The genetic of TAR syndrome has been elucidated only during the last few years, with a series of papers suggesting a peculiar mechanism of inheritance, due to the compound (bi-allelic) inheritance

of one hypomorphic noncoding SNP and a rare null allele in *RBM8A* gene (Albers et al., 2012). Before the work of Boussion et al., only two noncoding SNPs were described (i.e. rs139428292 and rs201779890), that however could not explain the totality of TAR cases. The identification of novel alleles and the confirmation of their role in independent patients are extremely valuable to increase the mutations spectrum of *RBM8A* shading light on the molecular mechanism of TAR syndrome. All this information results in relevant clinical outcomes since it has been demonstrated that specific clinical features of patients are related to the specific SNP carried by them. As an example, the presence of the 5'UTR SNP (rs139428292) seems associated with lower platelet counts, even in older patients, and with red blood cell production defect during their first years of life that normalises afterwards. In contrast, patients with the intronic SNP (rs201779890) display higher platelet counts, even during the early months of life, and do not have red blood cell anomalies (Manukjan et al., 2017).

In this light, the identification of additional patients carrying novel variants could help in defining correct genotype-phenotype correlations that could ultimately impact on the management of the patients. Moreover, in agreement with data reported by Bouisson et al., the patient here described is a man of African origin, and in fact, the detected allele (rs12079762) seems to be significantly enriched in the African population with a Minor Allele Frequency (MAF) of 14.8%, (gnomAD database). In this light, the direct screening of the rs12079762 variant in African patients carrying the 1q21.1 deletion could powerfully shorten the time required for reaching a correct molecular diagnosis, providing valuable information about disease severity and therapy decision and thus reducing the healthcare costs. Moreover, no less important, a correct molecular diagnosis allows clinicians to inform couples about their reproductive risk correctly. Furthermore, our findings support also the hypothesis that TAR syndrome might have an increased incidence in the African population.

CONCLUSION

Here we describe a patient from West Africa affected by TAR and carrying a 1q21.1q21.1 deletion together with a 3′UTR (c.*6C>G) variant in the *RBM8A* gene. These findings further support the recent discovery of Bouissan et al. and should encourage other colleagues in performing direct Sanger sequencing of rs12079762 recurrent mutation in African patients with a suspected TAR disease.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the author(s).

FIGURES

Figure 1. Clinical and genetic features of the patient. A) Picture of the patient highlighting the bilateral agenesia of the radio. B) Schematic representation of Chromosome 1 and the deleted region. C) FISH results confirming the deletion identified by SNP-CGH arrays. The white arrow indicates the deleted chromosome 1. D) Schematic representation of the RBM8A gene and DNA sequence chromatograms of the RBM8A nucleotide variant identified in the patient. The red arrow indicates the 3'UTR c.*6C>G variant. Grey boxes represent UTRs; black boxes represent coding exons.

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