

Thrombocytopenia Absent Radius (TAR)-Syndrome: From Current Genetics to Patient Self-Empowerment

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Abstract

Keywords

- ▶ thrombocytopenia absent radius syndrome
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- ▶ self-empowerment

Thrombocytopenia absent radius (TAR) syndrome is a rare form of hereditary thrombocytopenia associated with a bilateral radial aplasia. TAR syndrome is genetically defined by the combination of a microdeletion on chromosome 1 which includes the gene *RBM8A*, and a single nucleotide polymorphism (SNP) in the second *RBM8A* allele. While most patients with TAR syndrome harbor a SNP in either the 5' UTR region or in intron 1 of *RBM8A*, further SNPs associated with TAR syndrome are still being identified. Here, we report on the current understanding of the genetic basis, diagnosis, and therapy of TAR syndrome and discuss patient self-empowerment by enabling networking and exchange between affected individuals and families.

Introduction

Thrombocytopenia absent radius (TAR) syndrome (OMIM # 27400) is a rare congenital disorder characterized by a bilateral radius aplasia associated with thrombocytopenia. In 1969, Judith Hall summarized several case reports^{1,2} and coined the term “TAR syndrome.”³ A first comprehensive collection of patients has been presented by Hall and later also by Hedberg and Lipton.^{4,5} Patients can have many additional features including skeletal, urogenital, and heart defects (▶ Fig. 1).^{5–7} Although the clinical features seem to be pathognomonic, there is a variability in the skeletal anomalies that overlap with a small set of differential diagnoses (please see later). A recent summary of all relevant features can be found on <https://www.ncbi.nlm.nih.gov/books/NBK23758>.

Epidemiology

The estimated prevalence is 1:100,000 live births worldwide. There seems to be an excess of females over males, which differs slightly in distinct cohorts of Hall et al (1.85:1),³ Greenhalgh et al (3.8:1),⁶ Klopocki et al (1.7:1; *n* = 30),⁸ Albers et al (1.67:1),⁹ and Manukjan et al (1.53:1).¹⁰

Etiology

The inheritance of TAR syndrome resembles an autosomal-recessive pattern, but it has been deciphered to follow a more complex pattern.⁸ The relevant gene is *RBM8A*, which is localized on the long arm of chromosome 1 (1q21.1).^{8,9} The vast majority of patients carry a heterozygous

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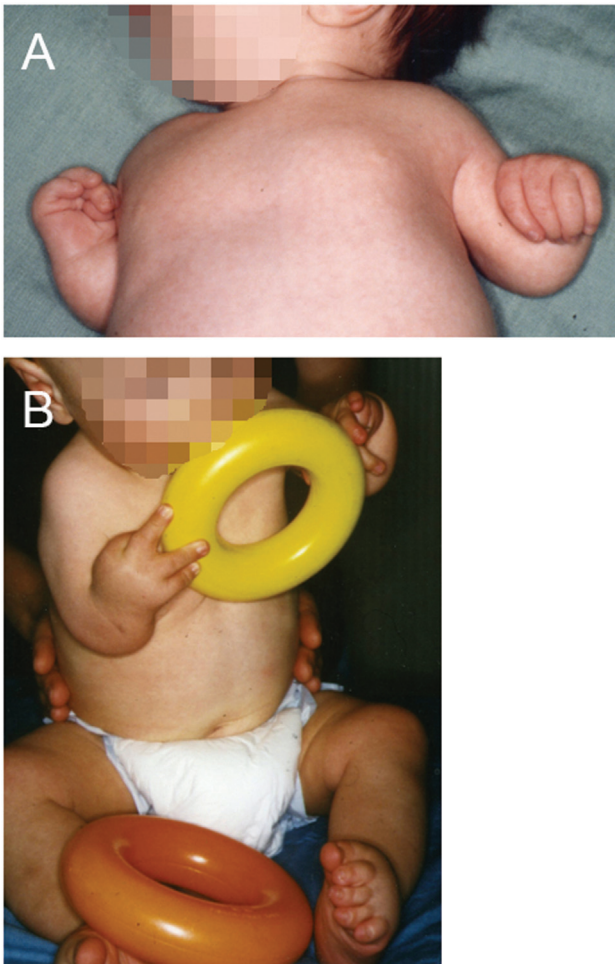


Fig. 1 A male patient with TAR syndrome with the characteristically shortened lower arm. (A) Patient at 6 weeks of age and (B) at 9 months.

microdeletion (approximately 120–200 kb, comprising about 8–12 genes including *RBM8A*) on one chromosome. The second allele harbors one single nucleotide polymorphism (SNP) in a noncoding region of *RBM8A*, resulting in compound heterozygosity. While most patients have a variant in the 5' UTR of *RBM8A* (rs139428292), a minor fraction has a variant in the first intron (rs201779890). Additionally, several other SNPs have been reported.^{11–13} In 75% of TAR cases, the microdeletion is inherited from one parent, whereas in about 25% of cases the microdeletion occurs *de novo*. In case that the carrier status of both parents is known, there is a recurrence risk of 25% in every pregnancy for a child with TAR syndrome as in autosomal recessive disorders. When the microdeletion occurred *de novo*, the risk will rather be 1:100,000. Of note, some rare null mutations of *RBM8A* have been reported in patients without a microdeletion^{9,11–13} (→Fig. 2), expanding the list of variant combinations underlying this disorder (→Table 1). Although the genetic basis of TAR has been identified, the underlying pathomechanisms leading to thrombocytopenia, the bilateral radius aplasia, or the other clinical features remain elusive.

Pathogenesis

The thrombocytopenia in patients with TAR syndrome has been attributed to a paucity of megakaryocytes (MKs) in the bone marrow, but this finding is based on overall few studies many decades ago, as nowadays a bone marrow biopsy is not indicated (and not necessary) to clearly diagnose TAR syndrome. Consequently, there are no reports on the bone marrow of older patients with TAR syndrome, especially when the peripheral platelet count has recovered.

The absence or deficiency of MKs in bone marrow was attributed by de Alarcon and colleagues to a lineage-specific

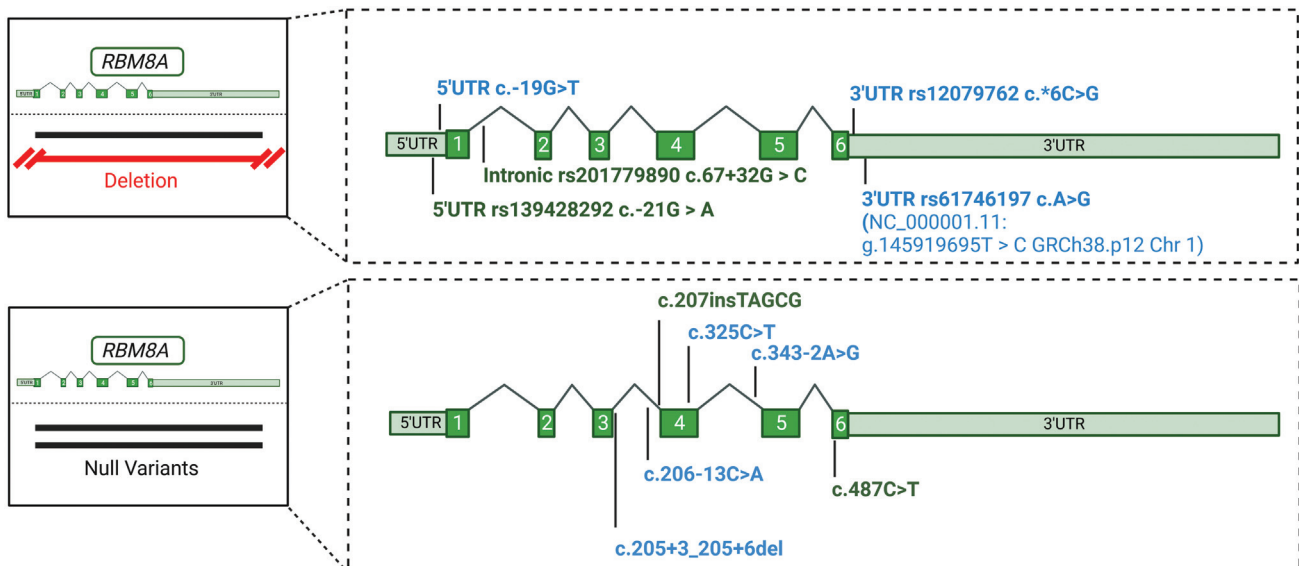


Fig. 2 Reported variants in *RBM8A* causing TAR syndrome summarized from Albers et al, Brodie et al, and Monteiro et al.^{9,12,13} The vast majority of patients carry the microdeletion on chromosome 1q21 on one allele in addition to either the 5' UTR SNP or the intronic SNP (green variants in upper panel). Three further noncoding variants (blue color) have been reported in case reports. In very few cases, loss of one functional *RBM8A* allele is not mediated by the microdeletion (red color, top panel), but by null variants (lower panel). In addition to the two initially reported mutations (green color), four additional null variants (blue color) have been described. *RBM8A* transcript ID NM_005105.5. (Figure was created with BioRender) [rerif].

Table 1 Summary of *RBM8A* genotypes of TAR syndrome patients

Allele 1	Allele 2	Cases reported	References
Del1q21.1	5' UTR c.-21G > T	86	Albers et al ⁹
Del1q21.1	Intron 1 c.67 + 32C > G	29	Albers et al ⁹
5' UTR c.-21G > T	c.207insTAGCG	1	Albers et al ⁹
5' UTR c.-21G > T	c.487C > T	1	Albers et al ⁹
Del1q21.1	3' UTR c.A > G	2	Brodie et al ¹²
Del1q21.1	3' UTR c.*6C > G	17	Monteiro et al ¹³
c.206-13C > A	5' UTR c.-19G > T	1	Monteiro et al ¹³
c.205 + 3_305 + 6delGAGT	5' UTR c.-21G > T	1	Monteiro et al ¹³
c.343-2A > G	5' UTR c.-21G > T	1	Monteiro et al ¹³

growth defect at a time before thrombopoietin (TPO) and its receptor c-Mpl have been discovered.¹⁴ With the understanding of TPO/c-Mpl biology, it became clear that on platelets of patients with TAR syndrome the thrombopoietin receptor c-Mpl is normally expressed or slightly reduced.^{15,16} Although mutations in c-Mpl have not been found, thrombopoietin fails to trigger differentiation of hematopoietic progenitor cells to MKs; thus, the c-Mpl downstream signaling cascade, including the key kinase Jak2, is not induced.^{17,18} Nevertheless, the presence of subthreshold levels of platelets and the increase of platelets over time imply that the TPO/c-Mpl axis is only partially impaired in contrast to congenital amegakaryocytic thrombocytopenia (OMIM # 604498), which is caused by mutations in *MPL* and abrogating TPO signaling.¹⁹

RBM8A is overall widely expressed, and it has remained at least partly enigmatic why two specific cell lineages, osteoblasts and MKs, are selectively affected. Haploinsufficiency of *RBM8A* does not cause TAR syndrome, as carriers of the microdeletion alone are overall unaffected.⁸ It is assumed that the 5' UTR SNP introduces a binding site for the transcription factor Evi1 that would act as a transcriptional repressor and further reduce the expression of *RBM8A*, finally leading to a critically reduced protein level in the compound heterozygous state.⁹ The specific binding of transcription factors expressed only in the osteoblastic and megakaryocytic lineage might thus provide an explanation. Homozygosity for this SNP does also not lead to TAR syndrome or affect platelet counts.⁹ Of note, the role of the intronic SNP has remained yet unsolved, which is also true for the newly identified SNPs.

RBM8A encodes for Y14, a key protein of the exon junction complex that plays a pivotal role in correct splicing and nonsense-mediated decay (NMD).²⁰ It is thus feasible that a differentially spliced transcriptome is causative for TAR syndrome. Mutations in the splice factors U2AF1 and SF3B1 have been identified in hematological deficiencies, which are now considered as spliceopathies.^{21–23}

Microdeletions on chromosome 1q21.1 are not only found in patients with TAR syndrome but are also associated with macro- or microcephaly and additional abnormalities. There, the deleted region is often larger than the 120 to 200 kb

microdeletion identified in TAR syndrome, additionally affecting the distal 1q21.1 region.²⁴ Incomplete penetrance and variable expressivity are reported. The breakpoint region is syntenic with the mouse genome and encompasses regions of segmental duplication suggesting that this region on chromosome 1q21 is somewhat prone to breakage, which would also explain the relatively high number of patients with TAR syndrome, in which the microdeletion has occurred de novo.^{8,25}

There are case reports in which patients do not carry the microdeletion, but missense mutations in *RBM8A* on one allele.⁹ This finding does support the notion that *RBM8A*/Y14 is the relevant gene/gene product that causes TAR syndrome. However, this does not fully exclude the possibility that haploinsufficiency of other genes within the deleted region may contribute to the severity of the phenotype. One candidate gene is *PIAS3*, a negative regulator of STAT3, a transcription factor that becomes activated in response to TPO binding to its receptor c-Mpl.^{26–29} *PIAS3* also affects osteoclast differentiation and might thus bridge thrombopoiesis and the skeletal defects.³⁰

The underlying mechanism of *RBM8A* insufficiency and the skeletal anomalies remains overall enigmatic. The 5' UTR variant is also effective in the osteoblastic cell line MC3T3,⁹ suggesting that a similar phenotype might be affective, while further evidence is yet missing. A recent review suggests FGF4 and TBX5 might be involved.³¹ A study by Bonsi et al suggests that a common hematopoietic and osteogenic mesenchymal progenitor cell might be responsible for the features underlying TAR syndrome, eventually on the level of CD105/TGFβ.³²

Animal models that reflect TAR syndrome are also missing. Several *Hox* genes have been considered as putative candidates due to their concomitant involvement in hematopoiesis and bone formation: Mice lacking both *HoxA11* and *HoxD11* lack the complete zeugopod (radius and ulna), which is found only in some TAR patients.³³ *HoxA11* knock-out alone does not have severe effects on bone development in mice, but variants have been reported to cause radio-ulnar synostosis (RUS) in patients.³⁴ *Rbm8a*-null mouse models have been generated. While the full knock-out is embryonically lethal, heterozygous mice had microcephaly and

neurological defects.³⁵ Recently, an MK-specific *Rbm8a*-null mouse has been generated and characterized that phenocopies some, albeit not all features of thrombocytopenia.³⁶ The most striking feature is the sex difference, which is not seen in humans.⁶ The amino acid sequence between humans and mice is fully conserved, but the 5' UTR and intron 1 sequences are less conserved, including the SNPs reported to be associated with TAR syndrome. This explains why there is yet no suitable mouse model. There are limited available data from zebrafish, further corroborating that lack of *rbm8a*/Y14 (by a CRISPR-Cas9-mediated approach) results in a defect in NMD.³⁷

Clinical Presentation

Patients from our German cohorts have been summarized by Klopocki et al and Manukjan et al.^{8,10} Descriptions of clinical features from other cohorts comprise the studies of Greenhalgh et al, Boussion et al, or an international cohort in Albers et al.^{6,9,11} Other reports describe single cases as indicated.

Hematopoiesis

Patients are typically born with very low platelet counts (often below 30/nL) and might already harbor petechiae. Usually, they receive platelet transfusions during the first years of life,⁵ often dependent on the treating physician or the experience of the hospital with rare bleeding disorders. Based on the authors' experience, only in case of severe bleeding and additional septicemia or virus infection, platelet transfusions should be given, as platelets often recover already in the first week of life. Hematopoietic stem and progenitor cells as well as platelets from young patients with TAR syndrome exhibit impaired responsiveness toward

TPO.^{14–16} Recently, we have demonstrated that this ameliorates in older patients and that this change occurs typically at the end of the second decade but cannot be predicted on an individual basis.³⁸ When platelet counts were correlated with the underlying noncoding SNPs, we could demonstrate that platelet counts were significantly lower in patients with 5' UTR SNP with platelet counts at birth below 80/nL (–Fig. 3; empty blue symbols, –Fig. 4). Patients with the intronic SNP also reported such low platelet counts during their first 2 months of life; however, they quickly reached almost normal levels (–Fig. 3; filled red symbols, –Fig. 4).¹⁰ In most patients, platelet counts remain low during the first 2 years and then increase up to 100/nL, although still not reaching the lower reference value (–Fig. 3).^{3,5,10,38} The mechanism underlying this increase in platelet count has remained enigmatic.

Additionally, certain white blood cell parameters might be altered. Especially after birth, leukocytosis and eosinophilia are quite frequently observed, but seem to return to normal values during the first weeks or months.^{3,5,10} The anemia in the first year of life, which is more frequent in patients harboring the 5' UTR SNP, cannot fully be attributed to an increased incidence of bleedings. Occasionally, patients need to be transfused with packed red cells.

In our cohort of patients^{10,15,38} we did not find any case of progression into leukemia, but there are case reports documented in the literature: three pediatric cases of acute myeloid leukemia (AML)^{39–41} and one adult case (42-year-old patient),⁴² as well as one pediatric case of acute lymphoblastic leukemia.⁴³ Among the AML cases, there was one 42-year-old patient. Of note, in most patients, the diagnosis of TAR syndrome has been solely raised on the clinical appearance and misdiagnoses cannot be ruled out in these cases.

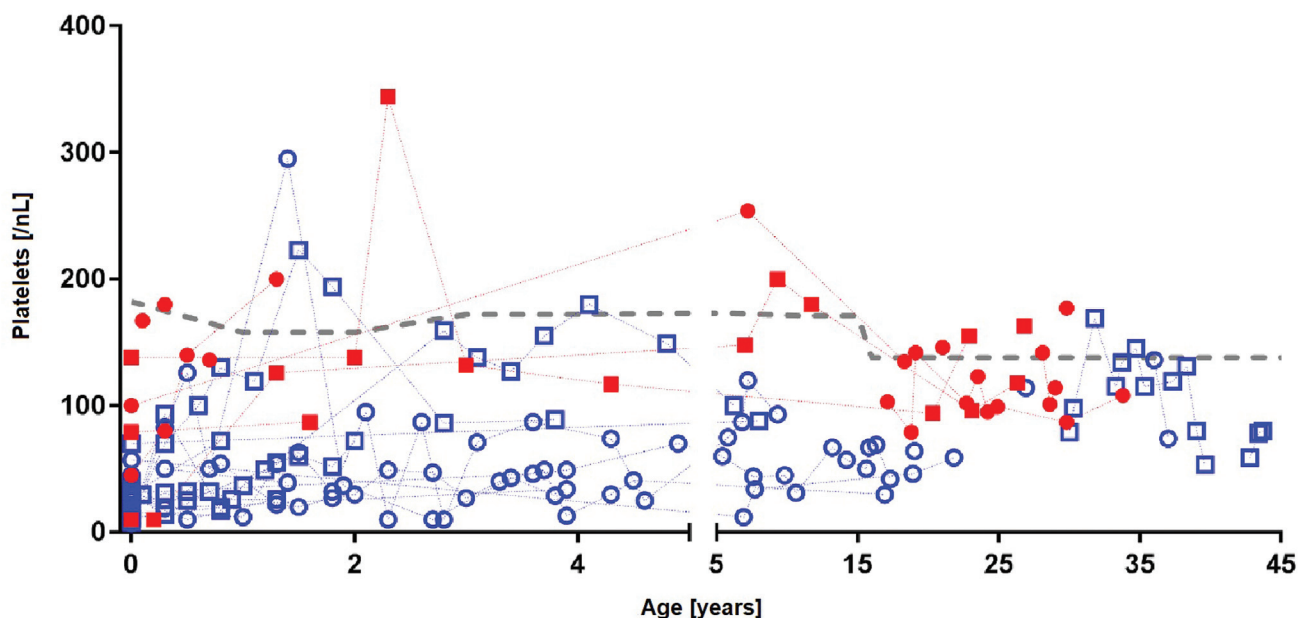


Fig. 3 Platelet counts over time. The dashed line represents the lower reference value for platelets. Squares represent males; circles represent female patients. Empty (blue) symbols represent 5' UTR patients; filled (red) symbols are used for patients with intronic SNP. (Figure based on data from Bösing.⁶⁴)

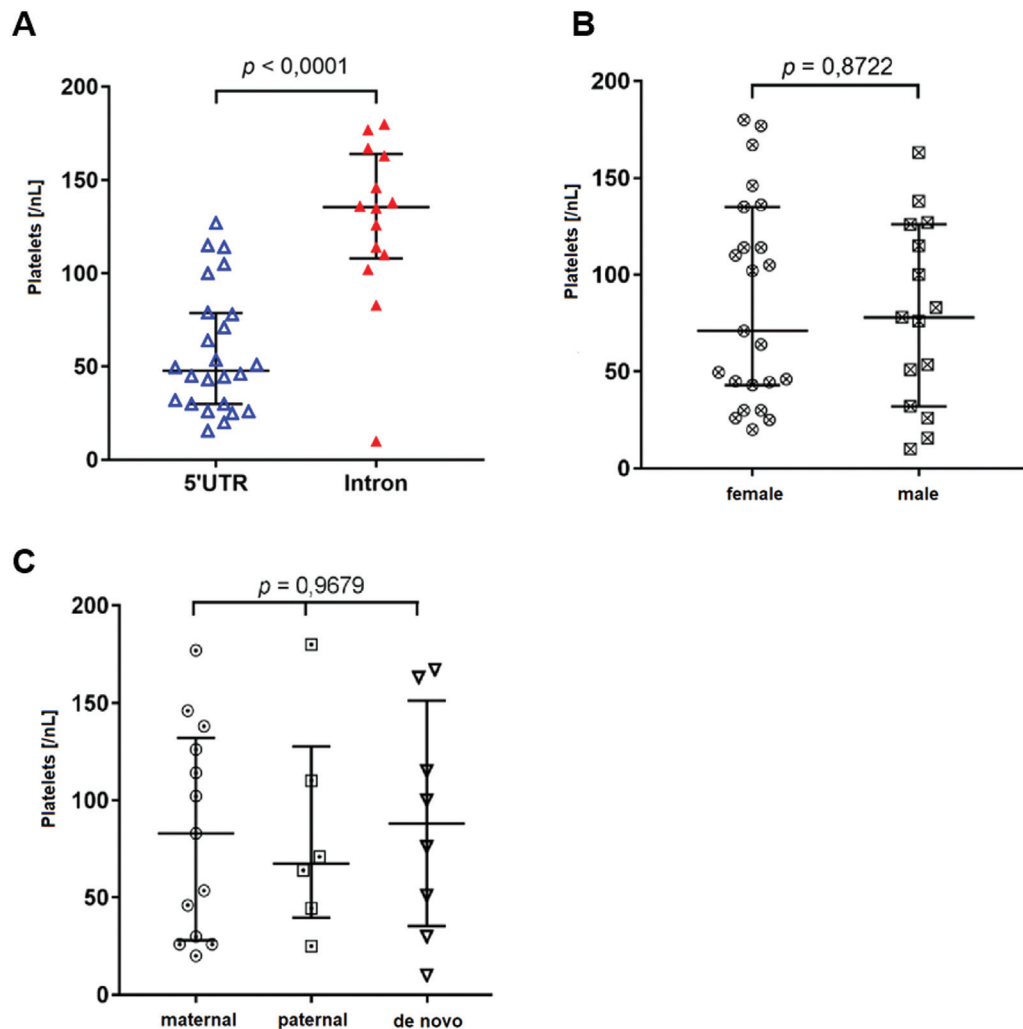


Fig. 4 Median platelet counts correlate only with the SNP (5' UTR in blue symbols, intronic SNP in red) (A) but not with gender of patients (B) or their trait of inheritance (C, with respect to the microdeletion). (A, B) Significance determined by nonparametric Mann–Whitney test. (C) Significance was evaluated using the nonparametric Kruskal–Wallis test. The central line indicates the median, whereas the outer lines confine the interquartiles. (Figure based on data from Bösing.⁶⁴)

Skeletal Features

The combined features of thrombocytopenia and skeletal malformation (shortened forearms and club hands) are readily associated with the diagnosis of TAR syndrome. Due to the fact that TAR syndrome is a rare disorder that many clinicians usually do not come in contact with, it could be misdiagnosed, especially with Fanconi anemia (FA), which is another hematological disorder that is also accompanied by skeletal anomalies. The presence of the thumbs is a hallmark feature of TAR syndrome, while thumb hypoplasia or aplasia is found in FA. For the diagnosis of TAR syndrome, FA should thus be excluded by standard chromosomal breakage analysis.^{44,45} Typically, all patients exhibit the bilateral absence of the radius, and some present with additional hypoplastic fingers but always with the thumbs. An additional hypoplasia of the shoulder girdle often leads to problems with constant back pain in later adulthood. To our knowledge, most patients with TAR syndrome benefit from reconstructive hand surgery. Thus, it is helpful for all patients to consult an experienced hand surgeon at the age of 10 to

12 months. It has to be evaluated which hand and hand function could benefit most due to surgery. Lengthening severely shortened upper limbs can also help improve quality of life for patients with TAR syndrome. Lower limb anomalies are seen in about 50% of patients. These include hip/patellar dislocation, knee dysplasia, lower limb phocomelia, as well as varus and valgus foot anomalies. The management of children with TAR syndrome has been described earlier, mostly with a focus on skeletal anomalies.^{46,47} Skeletal features like hip dysplasia should be discussed with orthopaedics after birth and primarily treated conservatively. In older children also, varus knees may become problematic. Skeletal malformations vary substantially among patients with TAR syndrome and do not correlate with the disease severity or with the presence of a certain SNP.⁹ Short stature is present in many patients and may prompt some to undergo surgical procedures during puberty to prolong limb growth.⁶ Treatment with growth hormones has been considered in individual cases (personal communication, Gabriele Strauss, MD, XX to G.S.).

Additional Malformations

Cardiac anomalies, often minor defects like small atrial septal defect or ventricular septal defects, which disappear without any treatment, are reported in 22 to 33% of patients with TAR syndrome. Furthermore, tetralogy of Fallot has been reported.⁴⁸ Association of TAR syndrome with different congenital anomalies, such as micrognathia, cleft palate, intracranial vascular malformation, and facial capillary hemangioma in the glabellar region, epilepsy, or scoliosis is rare.⁴⁹

Cow's milk intolerance is reported in older literature with a frequency around 60%.⁶ However, in the German cohorts, we have seen this only in single cases. The recommendation is, if possible, to avoid cow milk.³⁸ Urogenital anomalies like horseshoe kidneys are seen in 6 to 23% of TAR cases without secondary morbidity. In very rare cases, a missing uterus may be the cause in women who have primary amenorrhea.⁵⁰

Fertility

The issue of fertility is especially important for female patients. To our knowledge, there are several cases of women with TAR syndrome who have delivered healthy babies via caesarean section, but also through spontaneous induction of birth (personal communication, Gabriele Strauss, MD, XX to G.S.).⁵¹ During pregnancy, female TAR patients had lower platelet counts than before. Attempts to elevate the platelet count with corticosteroids were not successful.⁵²

Differential Diagnoses

Although the combination of the two main clinical features, thrombocytopenia and absent radii, seems to be quite pathognomonic, several differential diagnoses should be considered and excluded. Thrombocytopenia and absent radii might also be present in patients with FA. FA is caused by a large group of genes (complementation groups) that play key roles in DNA damage recognition and repair. FA is diagnosed by a standard chromosome breakage test, although tests by flow cytometry or mutational screening are also used. The pivotal feature to differentiate between FA and TAR syndrome is the presence of both thumbs in TAR syndrome, while they are absent or hypoplastic in FA. Similar phenotypes might occur in *Roberts syndrome* (OMIM #268300) associated with *ESCO2* mutations or in *Holt-Oram syndrome* (HOS; OMIM #142900), which is caused by mutations in the *TBX5* gene. Thrombocytopenia due to low MK numbers in the bone marrow is found in patients with RUS (a skeletal feature where the two zeugopod long bones are linked). Patients have been described with mutations in *HOXA11* (OMIM # 605432)³⁴ or in the *MECOM* gene (RUSAT2; OMIM # 616738), which encodes for the oncogenic transcription factor Evi1.⁵³

Diagnostic Aspects

Diagnostic genetic testing for TAR syndrome became possible in 2012 when the full molecular mechanism was deciphered.⁹ Before that time, only clinical diagnostics was

possible with an increased risk of wrong differential diagnoses.

The most accurate method for detecting TAR syndrome to date is the molecular genetic test of the *RBM8A* gene, typically by a combination of (1) Sanger sequencing to detect the causative SNPs and (2) a method to detect the microdeletion (i.e., by quantitative PCR using genomic DNA). To identify the exact size of the microdeletion on chromosome 1q21.1 which usually extends beyond the *RBM8A* gene, molecular karyotyping or other genome wide methods able to detect copy number variants are useful. In case next-generation sequencing-based methods are used, one should be aware to adjust filter settings to reliably detect the non-coding SNPs. To estimate recurrence risk in the family, testing of additional family members, typically the parents, should be offered. If both parents are confirmed carriers, prenatal testing is possible.

Therapy Options

The TAR syndrome treatment regarding thrombocytopenia or bleeding complications is symptomatic and supportive. The use of second-generation TPO mimetics, such as eltrombopag or romiplostim, for patients with excessive bleeding problems might be an option. TPO mimetics are approved for adult patients with refractory chronic immune thrombocytopenia (ITP) and pilot studies for pediatric patients are ongoing to assess efficacy and safety. Of note, the risk of bone marrow fibrosis in children is a common adverse effect of these drugs which should be monitored carefully. Romiplostim and Oprelvekin (Neumega) have been applied in a case report of TAR syndrome.⁵⁴ Another recent case report describes the management of end-stage heart failure in TAR syndrome.⁵⁵

In case of severe bleeding, platelet concentrates should be given cautiously to monitor and prevent bleedings rather than reaching a certain platelet count. However, to our knowledge, there are only very few individuals with TAR syndrome who suffered from severe blood loss in response to pronounced thrombocytopenia.

Platelet function is somewhat impaired as described by us and others,^{38,56,57} suggesting that drugs that additionally affect platelets, including nonsteroidal anti-inflammatory drugs, should be avoided or patients monitored carefully.

Genetic Counseling Aspects

When TAR syndrome has been **prenatally diagnosed** by examination of amniotic fluid, chorionic villi, ultrasound analysis, or abortion, parents usually wonder how life could be with TAR syndrome and approach genetic specialist to inquire if there is a recurrence risk in further children.^{58–62} Genetic counseling and addressing the parents' concerns in terms of family planning is simplified when molecular genetic testing for *RBM8A* gene has been performed and confirmed the TAR syndrome diagnosis. To estimate the recurrence risk, it is mandatory to genetically test both parents. If both parents are confirmed carriers, the

recurrence risk is 25% and prenatal testing can be offered to the couple in coming pregnancies.

It has become easier to find and approach scientists and specialists who treat patients with TAR syndrome thanks to publicly available online research databases. Prior to finding a medical doctor, parents (and patients) are nowadays able to get in touch with other affected families or adults via the internet (<http://www.tarsyndrom.de>) to connect with a closed national and international Facebook groups and patient support groups, where they can directly address their questions.

If the **diagnosis** was made unexpectedly **at birth**, it is difficult for gynecologists and neonatologist to estimate which major medical problems may occur. Before the underlying cause of TAR syndrome was discovered, **adults** with absent radii got in contact with the scientific working group from our labs to confirm their diagnosis. Most of them have never received a proper diagnosis and perceived the final confirmation of TAR syndrome as a relief, even when this did not result in a therapeutic option. Some patients are reluctant to exchange data, while others are eager to share their experience. We have been co-initiators of a self-empowerment group for patients with TAR syndrome, their parents, and family members. Many patients were happy to find others with the same condition, in the beginning by direct patient-to-patient contacts carefully connected by us, later by social media platforms like Facebook. The knowledge of the diagnosis helps a lot in understanding the disorder and finding a way to cope with orthopaedic, hematologic, and social challenges of TAR syndrome.

Conclusion

The information presented here results from personal experience as practicing physician responsible for more than 25 years, having treated more than 50 patients with TAR syndrome, parents and siblings of all age groups, and moreover from a review of the literature and personal communication within the working group THROMKIDplus during the pädGTH meeting held in September 2022 in Innsbruck (Austria).

In particular, for patients with TAR syndrome and their families, it now seems easier to obtain an early diagnosis, often during pregnancy before birth. It is known that patients with chronic disorders who have more information about the underlying disorder cope better.⁶³ In our experience, it is very helpful if families can connect with others affected by the disorder to see how life can be managed with short forearms or low platelets. In addition, it is possible for patients and relatives as well as physicians to clarify all open questions as competently as possible in the knowledge of the diagnosis. This step into self-determination is supported by the possibility of internet research and the search for specialists. Families having children with TAR syndrome can get in touch with medical doctors and specialists and vice versa. Genetic counseling has become easier when molecular genetic testing for the *RBM8A* gene has already been performed to answer parents' questions about family planning.

Authors' Contributions

G.S. treated patients and wrote the manuscript. K.M. and H.S. performed TAR diagnostics and wrote the manuscript. E.K. performed genetic diagnostics of TAR syndrome and wrote the manuscript.

Competing Interests

The authors declare no competing interests.

Conflict of Interest

The authors declare that they have no conflict of interest.

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