765

Thrombocytopenia-Absent Radius Syndrome 1q21.1 Deletions in the Prenatal and Postnatal Setting: Analysis of Inheritance and Ascertainment in a Large Cohort

A. Arreola[1], I. Gadi[1], P. Papenhausen[1], K. Phillips[1], V.R. Potluri[1], H. Risheg[2], M.K. Rudd[1], J. Schleede[1], J.H. Tepperberg[1], J. Wiley[1], S. Schwartz[1]
[1]Laboratory Corporation of America® Holdings, Center for Molecular Biology and Pathology, Department of Cytogenetics, Research Triangle Park, NC
[2]Laboratory Corporation of America® Holdings/Dynacare, Seattle, Washington

Integrated GENETICS
LabCorp Specialty Testing Group

I. Introduction

The thrombocytopenia-absent radius (TAR) syndrome is a rare autosomal recessive disorder seen in less than 1 in 100,000 individuals. TAR syndrome is characterized by bilateral absence of the radii with both thumbs present and may include other anomalies of the skeleton (upper and lower limbs, ribs, and vertebrae), with varying degrees of severity. Thrombocytopenia (<50 platelets/nL) in patients can present at birth or have an early-onset. While the thrombocytopenia is usually transient, it can also be exacerbated by cow's milk. Congenital heart defects are observed in approximately half of cases, and genitourinary system abnormalities have also been reported.[1-4]

The TAR syndrome phenotype is associated with proximal 1q21.1 microdeletions and in trans pathogenic mutations involving the critical gene, *RBM8A*. This gene encodes for a conserved RNA binding protein that functions as a component of the exon junction complex which is important for mRNA splicing, export, and non-sense mediated decay. It has been proposed that the severity of TAR syndrome phenotype in affected individuals with a compound heterozygous deletion and *RBM8A* mutation, may be determined by the position of the *RBM8A* mutation along the gene (i.e. coding vs non-coding region).[3,4]

Distal 1q21.1q21.2 microdeletions and microduplications, which may be seen in conjunction with TAR microdeletions, are inherited in an autosomal dominant manner. Similar to other microdeletion and microduplications, there is reduced penetrance and variable expressivity, with some carriers being apparently unaffected. Because of the variable expressivity for these copy number changes, the phenotypic features associated with either genomic imbalance are highly variable and have not been fully elucidated. In general, features of the distal 1q21.1q21.2 microdeletions can include autism susceptibility, mild intellectual disability, schizophrenia, mild craniofacial dysmorphisms, microcephaly, developmental delays, congenital heart defects and other congenital anomalies. The reciprocal microduplications have been associated with macrocephaly, mild dysmorphic features, developmental delay, intellectual disability, and autism spectrum disorders.[2,5-7]

II. Materials & Methods

The chromosome segments surrounding and including band 1q21 are marked by numerous segmental duplications, which mediate recurrent microdeletions and microduplications at proposed breakpoint regions (see **Fig.1**). The 1q21.1 microdeletion results from abnormal crossing over mediated by low-copy repeat regions in the 1q21 region, and has been increasingly identified by chromosome microarray analysis. Although the deletion is facilitated by low-copy repeats, it has been seen in our population less frequently than other deletions caused by this mechanism. TAR is a variable syndrome where postnatal patients are more often ascertained as larger 1q21.1 deletion carriers containing the adjacent 1q21.1q21.2 autism susceptibility region (ASR), or as a secondary finding to an unrelated chromosomal disorder.

Our cohort was derived from an analysis of the SNP Microarray of over 150,000 postnatal patients over a ~2 year period and 32,000 prenatal patients over a ~6 year period. We focused on prenatal and postnatal cases with 1q21.1 microdeletions that span the TAR region, or 1q21.1q21.2 deletions that included the ASR in addition to the TAR region. Inheritance patterns were assessed in cases where familial testing was available. Where possible, the results were correlated with the phenotypic/clinical information provided.

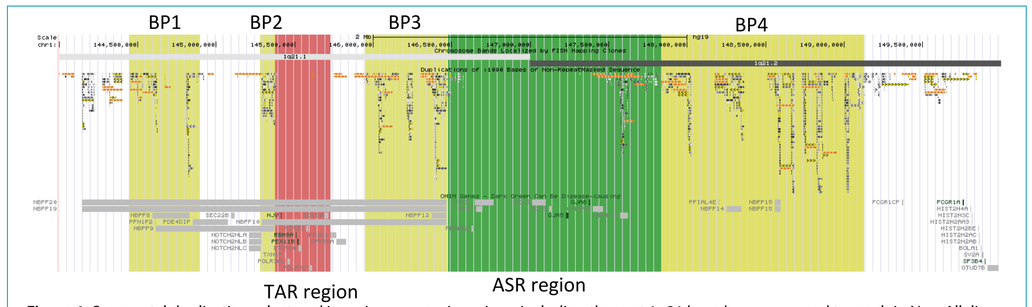

Figure 1. Segmental duplications clustered in various genomic regions, including those at 1q21 have been proposed to result in Non-Allelic Homologous Recombination at the cluster breakpoint regions (yellow). It has been proposed that BP2-BP3 rearrangements result in the TAR region microdeletions (red) and BP3-BP4 rearrangements give rise to the distal 1q21.1q21.2 ASR microdeletions and microduplications (green). (Adapted from [6,7,10])

III. Results

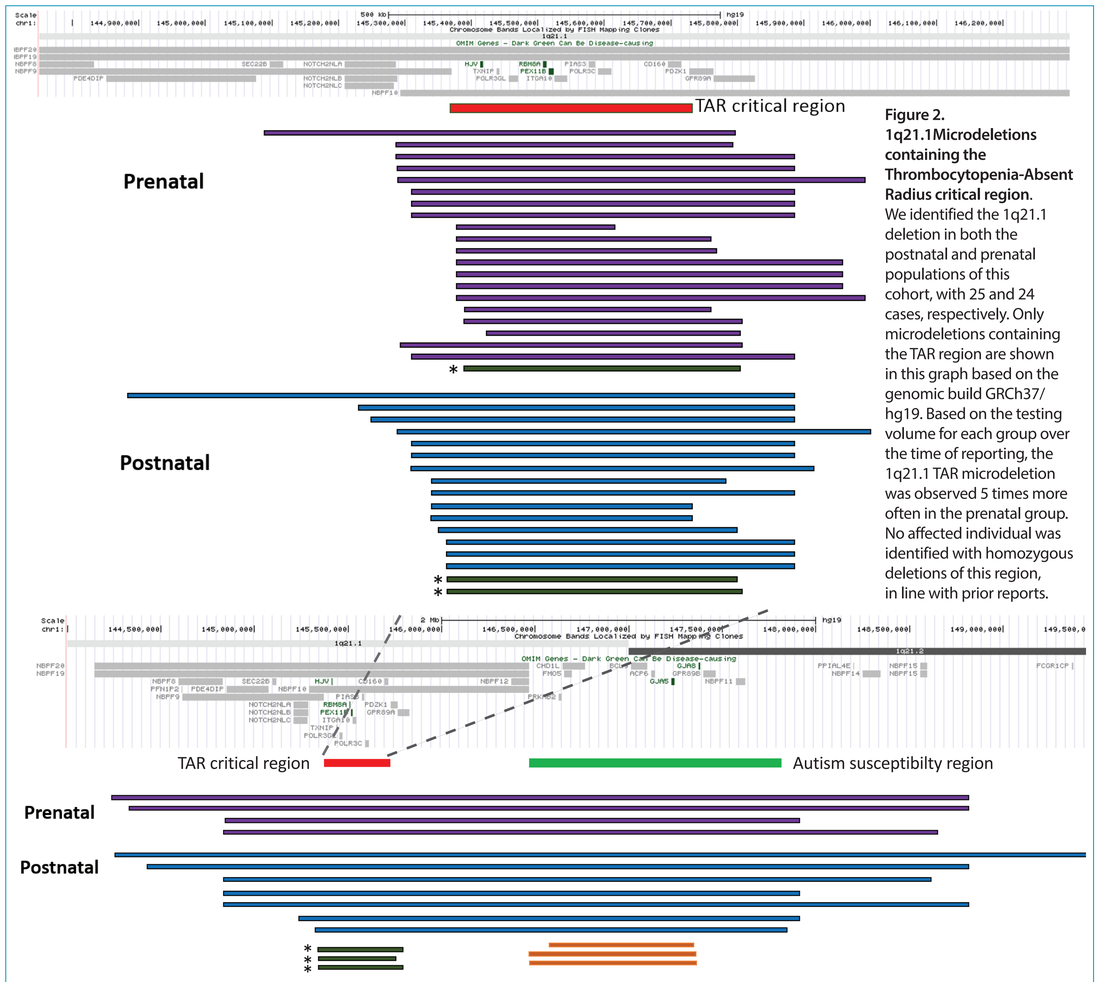

Figure 2. 1q21.1Microdeletions containing the Thrombocytopenia-Absent Radius critical region. We identified the 1q21.1 deletion in both the postnatal and prenatal populations of this cohort, with 25 and 24 cases, respectively. Only microdeletions containing the TAR region are shown in this graph based on the genomic build GRCh37/hg19. Based on the testing volume for each group over the time of reporting, the 1q21.1 TAR microdeletion was observed 5 times more often in the prenatal group. No affected individual was identified with homozygous deletions of this region, in line with prior reports.

Figure 3. 1q21.1q21.2 Microdeletions containing the Thrombocytopenia and Absent Radius critical region and the Autism susceptibility region. We identified the 1q21.1 TAR microdeletion in both the postnatal and prenatal populations of this cohort, with 25 and 24 cases, respectively. The larger deletions that encompass both regions are shown for each cohort (Prenatal in purple, Postnatal in blue). One prenatal and 2 postnatal cases with a TAR region microdeletion and ASR microduplication are shown (*).

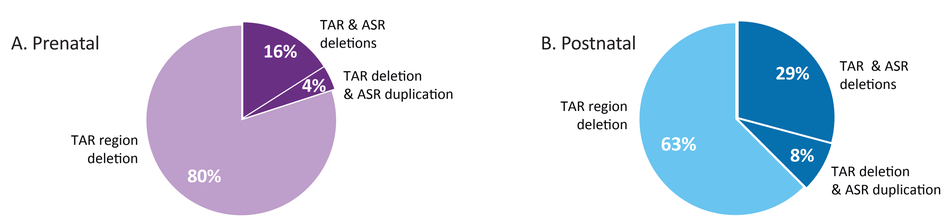

Figure 4: Microdeletion distribution in the prenatal cohort (A) and postnatal cohort (B). The 1q21.1 TAR microdeletion was present as an isolated finding in 80% of the prenatal cohort vs 63% in the postnatal group. The majority of the remaining larger microdeletions observed contained both the proximal 1q21.1 TAR region and the distal 1q21.1q21.2 autism susceptibility region (ASR), (16% prenatally vs 29% postnatally). Interestingly, in about 4% of the prenatal and 8% of the postnatal patients there was an unusual pairing of a 1q21.1 TAR region microdeletion and 1q21.1q21.2 ASR microduplication (*shown in **Figure 3**).

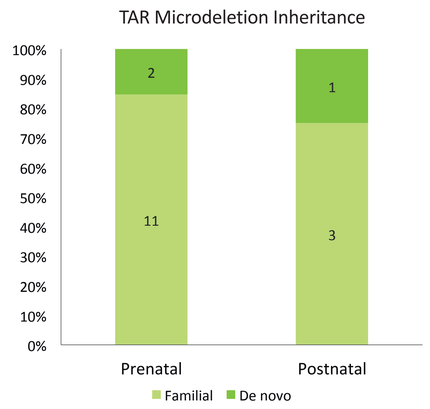

Figure 5: Inheritance of TAR and ASR microdeletions. From the 49 cases in both cohorts, 21 pursued follow-up parental testing. Approximately 82% (14/17) of the isolated 1q21.1 TAR region microdeletions were inherited. Of the 4 additional cases that underwent parental testing, 3 with the larger microdeletion containing TAR and ASR (2 prenatal and 1 postnatal), and 1 prenatal case with TAR microdeletion and ASR microduplication, all 4 were found to be familial copy number changes (data not shown).

Tables 1 and 2. The ultrasound findings and clinical indications for testing are listed for each individual, including the segments involved and the size of the copy number change identified.

- Cases with skeletal abnormalities are denoted by (*). Of note, we are aware of one prenatal case (^) in which *RBM8A* mutation testing was performed and identified an unspecified familial point mutation.
- Two postnatal cases (*) contained skeletal abnormalities, one of which was ascertained in the prenatal setting.
- Out of close to 19,000 prenatal cases with ultrasound findings, 390 of them reported the presence of skeletal abnormalities. The prenatal cases in our analysis, with TAR region deletions and skeletal abnormalities made up 3.6% (14/390) of all the prenatal cases with skeletal defects identified by ultrasound.

Table 1. Prenatal Cohort Clinical Indications

Case#	Microdeletion	Size (Mb)	U/S Findings and Clinical Indications
1*	TAR	0.739	Radial hypoplasia; triphalangeal thumb
2*	TAR	0.502	Hypertelorism; tetralogy of fallot; bilateral absence of radius; Hereditary disease in family possibly affecting fetus, affecting management of mother, antepartum condition or complication
3*	TAR	0.601	Bilateral radial aplasia; abnormal MSS for T21
4*	TAR	0.6	Bilateral absent radii and short ulnar. Normal brain, humerus and femur. Suspected TAR syndrome.
5*	TAR	0.698	Arthrogryposis; previous pregnancy with TAR syndrome
6	TAR	0.577	Unilateral renal agenesis; cleft lip
7*	TAR	0.577	Phocomelia; short humerus; short femur; clubfeet
8	TAR	0.577	Cleft lip
9	TAR	0.238	Clinical features of DiGeorge syndrome
10*	TAR	0.389	Limb reduction deformity: skeletal dysplasia; bent femur. Prev child (w/ other partner) with possible TAR syndrome.
11*	TAR	0.395	Severe skeletal dysplasia
12*	TAR	0.583	Shortened long bones; absent radius bilaterally; possible TAR syndrome
13*	TAR	0.583	Multiple congenital anomalies; echogenic intracardiac focus; clubfoot; pelviectasis
14	TAR	0.583	Not given; incompetent cervix
15*	TAR	0.611	Absent radius, ulna, humerus bilaterally; short bowed lower extremities; small chest; micrognathia
16	TAR	0.383	Abnormal CNS
17	TAR	0.427	Multiple anomalies
18	TAR	0.406	Increased NT (3.8)
19	TAR	0.521	Not given; AMA
20*^	TAR	0.578	Bilateral radial agenesis; shortened right humerus; abnl hands; rocker bottom feet; increased nuchal fold; *RBM8A* point mutation identified
21*	TAR del & ASR dup	0.422 / 0.889	Bilateral radial ray aplasia
22	TAR & ASR	4.55	Not given: AMA
23	TAR & ASR	4.46	Ventriculomegaly; 2 vessel cord
24*	TAR & ASR	3.04	Abnl upper/lower extremities; AMA; Prev pregnancy with skeletal dysplasia
25	TAR & ASR	3.78	Positive MSS for XXY

Table 2. Postnatal Cohort Clinical Indications

Case#	Microdeletion	Size (Mb)	Clinical Findings and Indications
1*	TAR	1.01	Unspecified reduction defect of upper limb, bilateral; Endocarditis, valve unspecified; short stature; shortened forearms; systolic heart murmur
2	TAR	0.661	Not given
3	TAR	0.65	Webbing of neck
4	TAR	0.724	Autism
5	TAR	0.578	Not given
6	TAR	0.577	Not given
7	TAR	0.616	Unspecified intellectual disabilities
8	TAR	0.417	Not given
9	TAR	0.52	Unspecified delay in development
10	TAR	0.358	Developmental disorder of speech and language, unspecified; Unspecified lack of coordination
11	TAR	0.358	Tetralogy of fallot
12	TAR	0.431	Genitourinary, ambiguous genitalia; 46,XY karyotype
13	TAR	0.507	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy; Unspecified delay in development
14	TAR	0.507	Not given
15	TAR	0.55	Myopathy with acute rhabdomyolysis
16	TAR del & ASR dup	0.41 / 0.896	Unspecified rider injured in nontraffic accident; bilateral hearing loss; ADD; speech/developmental delays.
17	TAR del & ASR dup	0.422 / 0.905	Not given
18*	TAR & ASR	5.47	Fetal anomalies: 2 vessel cord; proximal radioulnar synostosis
19	TAR & ASR	4.36	Bilateral sensorineural hearing loss; Unspecified lack of expected normal physiological development in childhood
20	TAR & ASR	3.81	Not given
21	TAR & ASR	3.05	Unspecified encephalopathy
22	TAR & ASR	3.95	Not given
23	TAR & ASR	2.6	Other specified congenital anomalies
24	TAR & ASR	2.5	Generalized convulsive epilepsy, with intractable epilepsy

IV. Summary

- We identified an estimated 5 times more prenatal cases with a 1q21.1 TAR region microdeletion than postnatal cases, suggesting the prevalence for this syndrome may be greater than previously suggested.
- However, our rate of detection may also be inflated due to ascertainment bias from a larger number of cases with skeletal abnormalities pursuing prenatal microarray testing.
- No homozygous 1q21.1 TAR region deletions were identified, consistent with previous reports.
- From the 21 cases that underwent parental follow-up testing, 85.7% were found to be inherited.
- Based on the considerable likelihood for inheritance of the TAR region microdeletions, identifying an affected individual has important counseling implications for future pregnancies.

V. References

1. Toriello HV. Thrombocytopenia Absent Radius Syndrome. 2009 Dec 8 [Updated 2014 May 29]. *GeneReviews®* [Internet]. PMID:20301781
2. Busè, Martina et al. *Italian J Peds* (2017) PMID: 28724436
3. Albers et al. *Nat Genet* (2012) PMID:22366785
4. Albers et al. *Current Op. Gen& Dev* 2013 PMID: 23602329
5. Haldeman-Englert et al. (2011) CR, Jewett T. 1q21.1 Recurrent Microdeletion. 2011 Feb 24 [Updated 2015 Nov 12]. *GeneReviews®* [Internet] PMID: 21348049
6. Rosenfeld et al. *EJHG* (2012) PMID:22317977
7. Wang et al. *J Gene Med* (2017) PMID: 28220983
8. Bernier et al. *Genet Med* (2016) PMID:26066539
9. Watson et al. *An Rev Genom & Hum Genet* (2014) PMID:24773319
10. Mefford et al. *NEJM* (2008) PMID: 18784092

Integrated Genetics is a brand used by Esoterix Genetic Laboratories, LLC, a wholly owned subsidiary of Laboratory Corporation of America® Holdings
Poster presented at the *ACMG Annual Clinical Genetics Meeting*; 2019 April 3-5; Seattle, WA.