Untangling the Phenotypic Heterogeneity of Diamond Blackfan Anemia

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Diamond Blackfan anemia (DBA) is a lineage-selective inherited bone marrow failure syndrome characterized primarily by anemia and physical malformations. Recent advances in identifying the genetic abnormalities underlying DBA have demonstrated involvement of genes encoding both large (RPL) and small (RPS) ribosomal subunit proteins, including mutations of *RPL5*, *RPL11*, *RPL35A, RPS7, RPS10*, *RPS17, RPS19, RPS24,* and *RPS26* in 50% to 60% of affected patients. Despite significant progress, identification of gene abnormalities in the remaining patients remains an important question since present data suggest that mutations in other members of the ribosomal protein gene complement do not explain those cases without an identified genetic lesion in these genes. Genetic studies have also raised new questions with the recognition of substantial variability in the manifestations of DBA, ranging from ribosomal protein mutations in otherwise asymptomatic individuals to those with classic severe red blood cell aplasia with characteristic malformations, at times within the same kindred. In this review, we summarize the genetic basis of DBA and discuss mechanisms by which the phenotype of DBA might be modified.
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Understanding of the genetic basis of Diamond Blackfan anemia (DBA) has evolved rapidly in the past decade, with the pace of identification of new DBA-related genes markedly accelerating in the past several years. Aside from the difficulties of keeping current with and assimilating a burgeoning lexicon of affected small and large ribosomal protein genes, there have been significant developments in understanding what constitutes DBA, based in part on these genetic studies. However, the rapid pace of recent gene discoveries belies a tenuous understanding of the fundamental connections between these specific genetic events and the many clinical features of DBA. Genetic discovery in DBA has progressed in a process comparable to pulling the end of a line to unroll a ball of twine: work so far has exposed a good length of twine; however, a large ball still remains, and in places there are tangled knots where none were initially obvious. In this article, we review the current literature regarding the genetics of DBA, explore current information of how genotype may influence phenotype in DBA, and review some mechanisms by which allelic and nonallelic factors may modify the phenotype in DBA.

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TUGGING THE STRING: GENE DISCOVERY IN DBA

The first significant breakthrough in defining the genetic basis for DBA developed from the identification of a child with a t(X;19) balanced reciprocal translocation.[1] This finding was followed by polymorphic marker linkage studies localizing a critical region in 29 multiplex families (ie, families with multiple affected members) to 19q13 and defining a critical region based on three probands with microdeletions involving 19q13.2.[2,3] A ribosomal protein (r-protein) gene, *RPS19,* was subsequently implicated as the causative gene by positional cloning of the 19q13 breakpoint from the t(X;19) index patient and confirmed by the finding of *RPS19* mutations in 10 of 40 additional patients, including six multiplex families in whom *RPS19* mutations segregated with a clinical DBA phenotype.[4] Since this initial report, the proportion of patients in whom DBA is attributable to coding sequence mutations in *RPS19* has been consistently estimated at around 25% in numerous studies from case series as

Table 1. Ribosomal Protein Gene Involvement in DBA

Ribosomal Subunit	Gene	% Mutation (mutations/screened)*	95% CI	Mutation Types	Origin Country(ies)/Group	Reference
Small	*RPS19*	25% (10/40)	14–38%	Genomic Del/rearrangement, frame shifting In/Del, premature stop, splice disruption, initiator codon disruption, a.a. substitution	Europe and North Africa	4
		17% (4/24)	6–36%		Northern Europe	5
		24% (42/172)	18–31%		Europe and North Africa	6
		21% (10/48)	15–42%		SHIP Working Group DBA (France)	10
		25% (5/20)	10–47%		Czech DBA Registry	7
		25% (24/97)	17–34%		AIEOP (Italy)	11
		15% (16/104)	10–24%		UK DBA Registry	13
		24% (19/81)	15–34%		USA and Europe	12
		11% (5/45)	4–24%		Japan	15
	RPS24	<2% (3/215)	0–4%	Premature stop, splice disruption, a.a. substitution, a.a. Del, initiator codon disruption	USA and Europe	22
		~2% (2/92)	0–8%		Italy	31
		NR (0/45)	0–9%		Japan	15
		Patient report	—		Sweden	24
		Patient report	—		European	25
	RPS17	<2% (1/24)	0–22%	Initiator codon disruption, frame shifting In/Del	Czech DBA Registry	26
		<1% (1/193)	0–3%		USA and Europe	27
		~2% (1/45)	0–13%		Japan	15
	RPS26	10% (12/117)	6–17%	Frame shifting In/Del, initiator disruption, a.a. substitution, splice disruption	USA and Europe	32
	RPS10	4% (5/117)	2–10%	Frame shifting In/Del, premature stop, initiator disruption	USA and Europe	32
	RPS7	<1% (1/159)	0–4%	Splice disruption	USA and Europe	27
Large	*RPL35A*	~3% (5/148)	1–8%	Genomic Del, splice disruption, a.a. substitution	USA and Europe	29
		NR (0/92)	0–5%		Italian	31
		NR (0/45)	0–9%		Japan	15
	RPL5	9% (18/196)	6–14%	Frame shifting In/Del, premature stop, a.a. substitution, initiator codon disruption, splice disruption	USA and Europe	27
		21% (6/28)	10–40%		Czech DBA Registry	30
		13% (12/92)	7–22%		Italy	31
		9% (4/45)	3–21%		Japan	15
	RPL11	7% (13/196)	4–11%	Frame shifting In/Del, premature stop, a.a. deletion, splice disruption	USA and Europe	27
		7% (2/28)	0–24%		Czech DBA Registry	30
		13% (12/92)	7–22%		Italy	31
		~4% (2/45)	0–16%		Japan	15

Abbreviations: NR, none reported; a.a., amino acid; In, insertion; Del, deletion.

*Frequency data are not included for single patient and small series reports. 95% CI indicates 95th percentile confidence interval by modified Wald method.

well as national DBA registries (Table 1).[4–15] Interestingly, a lower frequency of *RPS19* mutations was recently reported in a Japanese cohort of DBA patients (5/45 probands, 11%),[15] suggesting the possibility of racial or ethnic differences in the frequency of DBA mutations, an area that has not yet been well explored.

At the time of writing, more than 120 unique *RPS19* alterations have been cataloged, ranging from genomic deletions, single base substitutions resulting in both nonsense and missense mutations, splicing consensus changes, and small insertions or deletions causing predominantly nonsense changes (www.dbagenes.unito.it, accessed January 2011).[16] It was unclear how mutations or deletions of a structural constituent of a ubiquitous cellular component, the ribosome, could lead to such a distinct and fairly limited phenotype of erythroid insufficiency and physical developmental abnormalities. Since extra-ribosomal functions have been demonstrated for a number of ribosomal proteins, one hypothesis was that an unidentified erythroid-sensitive extra-ribosomal function of RPS19 might underlie the disorder. With the functional studies that would ultimately demonstrate deleterious effects on ribosomal assembly in *RPS19*-mutated DBA samples just underway,[17–21] it was additional genetic data that suggested the ribosome was indeed the center of attention in DBA.

Another small subunit r-protein gene, *RPS24*, was identified as a DBA gene by sequencing of candidate r-protein genes contained in a region of chromosome 10 that was one of three regions identified by microarray-based linkage study of a single large multiplex family.[22] As with *RPS19*, the informative finding from this family was confirmed by identifying additional heterozygous *RPS24* mutations in unrelated probands as well as by segregation of the mutant alleles with the DBA phenotype in the index and in an unrelated family. Loss of *RPS24* has since been shown to disrupt 18S ribosomal RNA (rRNA) processing in model systems and in DBA patient specimens.[23] All of the mutations identified in

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