

Title: Diamond-Blackfan Anemia *GeneReview* – Less Common Genetic Causes

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Note: The following information has been updated by the authors and has not been reviewed by *GeneReviews* staff.

[GATA1](#)

[RPL15](#)

[RPL26](#)

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[RPL31](#)

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[TSR2](#)

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[RPS27A](#)

For a detailed summary of gene and protein information for the genes below, see [Table A, Gene](#).

### **GATA1**

**Gene structure.** *GATA1* contains six exons with the start codon in exon 2 ([NM\\_002049.3](#)).

**Pathogenic allelic variants.** Four pathogenic variants have been identified in six individuals with DBA in four families [Sankaran et al 2012, Klar et al 2014, Ludwig et al 2014, Parrella et al 2014]. The pathogenic variants include a small deletion IVS2+1delG and a transversion 220G>C (p.Leu74Val).

**Normal gene product.** GATA1 comprises 413 amino acids. GATA1 is a transcription factor necessary for erythroid differentiation.

**Abnormal gene product.** Reported variants result in impaired production of the full-length form of the GATA1 protein.

### **RPL15**

**Gene structure.** *RPL15* has five isoforms 1 (transcripts variants 1-5) and one isoform 2 (transcript variant 6). Four isoforms 1, [NM\\_002948.3](#), [NM\\_001253379.1](#),

[NM\\_001253382.1](#) and [NM\\_001253383.1](#), comprise four exons each with the translation start codon in exon 2, while one isoform 1, [NM\\_001253380.1](#), comprises three exons with translational start codon in exon 1. Isoform 2, [NM\\_001253384.1](#), comprises five exons with the translational start codon in exon 2.

**Pathogenic variants.** One pathogenic deletion of exon 4 has been identified in one individual with DBA [Landowski et al 2013].

**Normal gene product.** *RPL15* has two isoforms, 1 and 2, which comprise 204 and 145 amino acids, respectively. *RPL15* encodes a ribosomal protein that is a component of the 60S ribosomal subunit.

**Abnormal gene product.** Deletion of exon 4 (which encodes 102 amino acids of the RPL15 protein) most likely causes premature degradation of *RPL15* mutated transcript.

## ***RPL26***

**Gene structure.** *RPL26* contains four exons with the start codon in exon 2 ([NM\\_000987.3](#)).

**Pathogenic allelic variants.** One pathogenic variant has been identified in one individual with DBA [Gazda et al 2012]. The pathogenic variant is a *de novo* frameshift variant.

**Normal gene product.** RPL26 comprises 145 amino acids. RPL26 is a component of the large ribosomal subunit.

**Abnormal gene product.** The reported variant results in abnormal truncated protein and in one individual (c.120\_121delGA) causing a frameshift at codon 41 and premature termination codon (p.Lys41ValfsTer12).

## ***RPL27***

**Gene structure.** *RPL27* contains five exons with start codon in exon 2 (NM\_000988.3).

**Pathogenic allelic variants.** One pathogenic variant has been reported in one individual with DBA [Wang et al 2015]. The pathogenic variant is a *de novo* splicing variant.

**Normal gene product.** RPL27 comprises 136 amino acids. RPL27 is a component of the large ribosomal subunit.

**Abnormal gene product.** The reported variant is predicted to result in abnormal truncated protein in one individual.

## ***RPL31***

**Gene structure.** *RPL31* has three isoforms: 1, 2, and 3. The translation start codon in all isoforms is in exon 2. Isoforms 1 ([NM\\_000993.4](#)) and 2 (NM\_0019857.2) comprise five exons, while isoform 3 ([NM\\_001099693.1](#)) comprises four exons.

**Pathogenic allelic variants.** Deletion of one allele has been identified in one individual with DBA [Farrar et al 2014].

**Normal gene product.** The three isoforms (1, 2, and 3) comprise 125, 128, and 121 amino acids, respectively. *RPL31* encodes a ribosomal protein that is a component of the 60S ribosomal subunit.

**Abnormal gene product.** Deletion of one allele causes haploinsufficiency of RPL31.

## ***RPS7***

**Gene structure.** *RPS7* has seven exons with the translation start codon in exon 2 ([NM\\_001011.3](#)).

**Pathogenic allelic variants.** One pathogenic variant has been described [Gazda et al 2008].

**Table 5. Selected *RPS7* Pathogenic Variants**

DNA Nucleotide Change (Alias <sup>1</sup> )	Protein Amino Acid Change	Reference Sequences
c.148+1G>A (IVS3+1G>A)	--	<a href="#">NM_001011.3</a> <a href="#">NP_001002.1</a>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([www.hgvs.org](http://www.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

**Normal gene product.** *RPS7* comprises 194 amino acids. *RPS7* is a component of the small ribosomal subunit.

**Abnormal gene product.** See [Molecular Genetic Pathogenesis](#).

## ***RPS27***

**Gene structure.** *RPS27* contains four exons with start codon in exon 1 (NM 001030.4).

**Pathogenic allelic variants.** One pathogenic frameshift variant has been reported in one individual with DBA [Wang et al 2015].

**Normal gene product.** *RPS27* comprises 84 amino acids. *RPS27* is a component of the small ribosomal subunit.

**Abnormal gene product.** The reported variant is predicted to result in abnormal truncated protein in one individual.

## ***RPS28***

**Gene structure.** *RPS28* contains four exons with start codon in exon 1 ([NM\\_001031.4](#)).

**Pathogenic allelic variants.** One pathogenic variant c.A1G affecting AUG translation initiation codon of *RPL28* has been reported in two families with DBA with mandibulofacial dystostosis [Gripp et al 2014].

**Normal gene product.** RPS28 comprises 69 amino acids. RPS28 is a component of the small ribosomal subunit.

**Abnormal gene product.** The reported variant is predicted to result in severe inhibition of protein translation leading to haploinsufficiency [Gripp et al 2014].

## ***RPS29***

**Gene structure.** *RPS29* has two isoforms, 1 and 2. The translation start codon in both isoforms is in exon 1. Isoform 1, [NM\\_001032](#), and isoform 2, [NM\\_001030001](#), comprise three exons.

**Pathogenic variants.** Two pathogenic missense variants of *RPS29* have been described [Mirabello et al 2014].

**Normal gene product.** The two isoforms, 1 and 2, comprise 56 and 67 amino acids, respectively. These isoforms are produced by alternative splicing. *RPS29* encodes a ribosomal protein S29 that is a component of the 40S ribosomal subunit.

**Abnormal gene product.** The two reported pathogenic variants result in substitution p.Ile31Phe and Ile50Thr [Mirabello et al 2014].

## ***TSR2***

**Gene structure.** *TSR2* contains five exons with start codon in exon 1 (NM 058163.1).

**Pathogenic allelic variants.** One pathogenic variant has been reported in one family with DBA with mandibulofacial dystostosis [Gripp et al 2014].

**Normal gene product.** *TSR2* comprises 191 amino acids. It is involved in rRNA processing [Gripp et al 2014].

**Abnormal gene product.** The reported pathogenic variant results in substitution p.Glu64Gly [Gripp et al 2014].

## ***RPL36***

**Gene structure.** *RPL36* has two isoforms; one isoform comprises four exons with the translation start codon in exon 2 ([NM\\_033643.2](#)) and the other isoform comprises three exons with the translation start codon in exon 1 ([NM\\_015414.3](#)).

**Pathogenic allelic variants.** A deletion of *RPL36* (250\_251delGA, [NM\\_015414.3](#)) in one individual has been described. This variant was classified as a rare variant of unknown significance and a possible pathogenic variant [Gazda et al 2008].

**Normal gene product.** Both isoforms of *RPL36* contain 105 amino acids. *RPL36* is a component of the large ribosomal subunit.

**Abnormal gene product.** The possible pathogenic variant 250\_251delGA is predicted to give rise to a gene product nine amino acid longer than wild type gene product [Gazda et al 2008].

## ***RPS15***

**Gene structure.** *RPS15* has four exons with the translation start codon in exon 1.

**Pathogenic allelic variants.** One possible pathogenic variant of *RPS15* has been described: a missense variant (c.208A>G) in one individual. This variant was classified as a rare variant of unknown significance and a possible pathogenic variant [Gazda et al 2008].

**Table 6. Selected *RPS15* Allelic Variants**

<b>Class of Variant Allele</b>	<b>DNA Nucleotide Change</b>	<b>Protein Amino Acid Change</b>	<b>Reference Sequences</b>
Uncertain	c.208A>G	p.Met70Val	<a href="#">NM_001018.3</a> <a href="#">NP_001009.1</a>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([www.hgvs.org](http://www.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

**Normal gene product.** *RPS15* comprises 145 amino acids. *RPS15* is a component of the small ribosomal subunit.

**Abnormal gene product.** The possible pathogenic missense variant c.208A>G is predicted to give rise to a gene product with substitution p.Met70Val [Gazda et al 2008].

## ***RPS27A***

**Gene structure.** *RPS27A* has six exons with the translation start codon in exon 2 (reference sequence [NM\\_002954.4](#)).

**Pathogenic allelic variants.** One possible pathogenic variant of *RPS27A* has been described: a missense variant (c.169T>C) in one family. This variant was classified as a rare variant of unknown significance and a possible pathogenic variant [Gazda et al 2008].

**Table 7. Selected *RPS27A* Allelic Variants**

<b>Class of Variant Allele</b>	<b>DNA Nucleotide Change</b>	<b>Protein Amino Acid Change</b>	<b>Reference Sequences</b>
Uncertain	c.169T>C	p.Ser57Pro	<a href="#">NM_002954.4</a> <a href="#">NP_002945.1</a>

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([www.hgvs.org](http://www.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

RPS27A is expressed as a fusion protein with ubiquitin at its N-terminal part. After translation, the ubiquitin part is processed to free ubiquitin monomer and RPS27A. Since the identified variant localizes to the ubiquitin part of the fusion protein and not to the RPS27A part, it is possible that this sequence change does not cause DBA.

**Normal gene product.** RPS27A comprises 156 amino acids. RPS27A is a component of the small ribosomal subunit.

**Abnormal gene product.** The possible pathogenic missense variant c.169T>C is predicted to give rise to a gene product with substitution p.Ser57Pro [Gazda et al 2008].

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