

Hematologically Important Mutations: Spectrin Variants in Hereditary Elliptocytosis and Hereditary Pyropoikilocytosis

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Erythrocyte spectrin maintains the cellular shape, regulates the lateral mobility of integral membrane proteins and provides structural support for the lipid bilayer (1,2). Spectrin is composed of two subunits, α and β spectrin, that, despite some similarities, are structurally distinct and are encoded by separate genes (3,4). As visualized on SDS-PAGE with Coomassie blue staining, α and β spectrin are the most abundant proteins of the erythrocyte membrane skeleton.

α and β spectrin chains intertwine in an antiparallel manner to form heterodimers, which in turn self-associate in a head-to-head manner to form tetramers and to a lesser extent, higher order oligomers. Disruption of spectrin self-association leads to disorders characterized by abnormally shaped erythrocytes, specifically hereditary elliptocytosis and hereditary pyropoikilocytosis (1,2,5). Study of spectrin mutants has shown that defects

of either the NH₂-terminal end of the α -spectrin chain or the COOH-terminal end of the β -spectrin chain may lead to impaired spectrin self-association. Detailed characterization of the spectrin self-association site and its abnormalities can be found in recent reviews (5-7).

A variety of mutations in α spectrin and β spectrin have been reported. These are listed in Tables 1 and 2. The nucleotide numbers shown in the table are based on the cDNA sequences listed in the GenBank/EMBL Data Banks, the accession numbers of which are: J05244 (α spectrin cDNA) (8) and J05500 (β spectrin cDNA) (9). In accordance with recommendations for the use of systematic names in nomenclature for mutations, the nucleotide numbers of the cDNA coding sequences (c) presented here begin with +1, which refers to the A in the ATG initiation codon (10). This numbering is different from that used in GenBank/EMBL Data Bank files.

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Table 1. α Spectrin Mutations in HE/HPP

Variant Name	Tryptic Phenotype	Systematic Name	Mutation	Amino Acid Variation	Reference
Lograno	α I/74	c71G	Missense	24 Ile→Ser	11
Corbeil	α I/74	c83T	Missense	28 Arg→His	12
Unnamed	α I/74	c83T	Missense	28 Arg→Leu	13,14
Unnamed	α I/74	c82A	Missense	28 Arg→Ser	13,14
Unnamed	α I/74	c82T	Missense	28 Arg→Cys	13
Marseille	α I/74	c92C	Missense	31 Val→Ala	15
Genova	α I/74	c100T	Missense	34 Arg→Trp	16
Tunis	α I/78	c121T	Missense	41 Arg→Trp	17
Clichy	α I/78	c134T	Missense	45 Arg→Ser	18
Anastasia	α I/78	c133C	Missense	45 Arg→Thr	19
Culoz	α I/74	c137T	Missense	46 Gly→Val	20
Unnamed	α I/74	c142G	Missense	48 Lys→Arg	14
Lyon	α I/74	c145T	Missense	49 Leu→Phe	20
Ponte de Sôr	α I/65	c452A	Missense	151 Gly→Asp	21
Unnamed	α I/65	c464TTG465ins	Insertion	154 +Leu	22
Dayton	α I/50-46	insertion in intron 4 ¹	Splicing	178-226 deleted	23
Saint-Louis	α I/50-46	c620C	Missense	207 Leu→Pro	24
Nigerian	α I/50-46	c779C	Missense	260 Leu→Pro	25
Unnamed	α I/50-46	c781C	Missense	261 Ser→Pro	25
Sfax	α I/36	c1086G ²	Splicing	362-371 deleted	26
Alexandria	α I/50b	c1405-1407del	Missense	469 His→Del	27
Barcelona	α I/50b	c1406C	Missense	469 His→Pro	28
Unnamed	α I/50b	c1412C	Missense	471 Gln→Pro	25
Jendouba	α II/31	c2473A	Missense	791 Asp→Glu	29
Oran	α II/21	IVS17-1A ³	Splicing	822-863 deleted	44

¹ skipping of exon 5.² in-frame deletion due to alternative splicing of the 3' end of exon 8.³ -1 refers to the last nucleotide of IVS 17; results in skipping of exon 18.

Table 2. β Spectrin Mutations in HE/HPP

Variant Name	Tryptic Phenotype	Nucleotide Change	Mutation	Amino Acid Variation	Reference
Cagliari	α I/74	c6052C	missense	2018 Ala→Gly	30
Providence	α I/74	c6055C	missense	2019 Ser→Pro	31
Paris	α I/74	c6068T	missense	2023 Ala→Val	32
Linguere	α I/74	c6070A	missense	2024 Trp→Arg	32
Buffalo	α I/74	c6074G	missense	2025 Leu→Arg	33
Tandil	α I/74	c6124-6130del	deletion	2041 ³ →frameshift	34
Nice	α I/74	c6136GA6137ins	insertion	2046 ³ →frameshift	35
Kayes	α I/74	c6157	missense	2053 Ala→Pro	36
Napoli	α I/74	c6160-6167del	deletion	2053 ³ →frameshift	37
Tokyo	α I/74	c6177del	deletion	2059 ³ →frameshift	38
Cotonou	α I/74	c6181A	missense	2061 Trp→Arg	39
Nagoya	α I/74	c6205T	missense	2069 Glu→Stop	40
Göttingen	α I/74	IVS 31+2A ¹	splicing	2007 ³ →frameshift	41
Le Puy	α I/74	IVS 31+4G ¹	splicing	2007 ³ →frameshift	42
Rouen	α I/74	IVS 32+3T ²	splicing	2073 ³ →frameshift	43

¹ skipping of exon 30.

² skipping of exon 31.

³ frameshift generating novel amino acid sequence followed by premature chain termination.

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