

**Table 3. Mutations of the *EDNRB* gene characterized in Waardenburg syndrome.**

Exon	cDNA*	Protein	In original paper	Conservation <sup>#</sup>	Inheritance	Phenotype	Remarks	Origin	Reference
Exon 2	<b>c.509G&gt;A</b>	<b>p.Gly170Glu</b>		+ / +	?	<b>WS4 in homozygotes</b>	<b>Consanguineous family?</b>	<b>Brazil</b>	<b>This paper</b>
	<b>c.509G&gt;A</b>	<b>p.Gly170Glu</b>		+ / +	?	<b>WS4 in heterozygotes or compound heterozygote</b>	<b>Patient also carries a p.Phe393Leu variation; it is unknown whether they are on the same or different alleles.</b>		<b>This paper</b>
	c.548C>G	p.Ala183Gly	A183G	± / -	familial	WS4 in homozygotes	Consanguineous family	Tunisia	[Attie et al., 1995]
	c.556G>A	p.Gly186Arg		+ / +	sporadic	WS4 in homozygotes	No known consanguinity; parents not tested.	Somalia	[Boardman et al., 2001]
	c.587G>A	p.Ser196Asn		+ / +	sporadic	WS4 in homozygotes	No known consanguinity	Thailand	[Sangkhatat et al., 2005]
	<b>c.587G&gt;C</b>	<b>p.Ser196Thr</b>		+ / +	<b>sporadic</b>	<b>WS4 in heterozygotes or compound heterozygote</b>	<b>Patient also carries a p.Val185Met variation (possibly polymorphic); it is unknown whether they are on the same or different alleles.</b>		<b>This paper</b>
Exon 3	c.601C>T	p.Arg201X	R201X		familial	WS4 / ABCD in homozygotes	Consanguineous family	Turkey	[Verheij et al., 2002]
	<b>c.601C&gt;T</b>	<b>p.Arg201X</b>			<b>sporadic</b>	<b>WS4 in homozygotes</b>	<b>Consanguineous family</b>	<b>Pakistan</b>	<b>This paper</b>
	<b>c.605C&gt;A</b>	<b>p.Ala202Asp</b>		+ / +	<b>familial</b>	<b>WS4 without deafness in heterozygotes</b>		<b>Italy</b>	<b>This paper</b>
	c.757C>T	p.Arg253X	Arg253→Stop		familial	WS4 in heterozygotes		Caribbean	[Syrris et al., 1999]
	<b>c.778G&gt;T<sup>§</sup></b>	<b>p.Val260Phe<sup>§</sup></b>		- / -	<b>familial</b>	<b>WS4 in heterozygotes or compound heterozygote; depigmentation in father</b>	<b>Patient also carries a p.Glu359X mutation; it is unknown whether they are on the same or different alleles.</b>		<b>This paper</b>
Exon 4	<b>c.809delA</b>	<b>p.Lys270ArgfsX26</b>			<b>familial</b>	<b>WS4 in heterozygotes</b>		<b>Italy</b>	<b>This paper</b>
	c.828G>T	p.Trp276Cys	W276C	+ / +	familial	WS4 in homozygotes; ±HD in heterozygotes	Very large inbred family over several generations; penetrance is incomplete even in homozygotes	American (Mennonite)	[Puffenberger et al., 1994]
	c.874T>C	p.Phe292Leu	F292L	+ / +	familial	WS4 in heterozygotes			[Pingault et al., 2002]
	<b>c.890C&gt;A</b>	<b>p.Thr297Asn</b>		± / +	<b>sporadic</b>	<b>WS4 in homozygotes</b>	<b>Consanguineous family</b>		<b>This paper</b>
Exon 5	<b>c.1008G&gt;A</b>	<b>p.Trp336X</b>			<b>sporadic</b>	<b>WS4 in compound heterozygote</b>	<b>Patient carries a full gene deletion on the second allele</b>		<b>This paper</b>
	<b>c.1025G&gt;T</b>	<b>p.Ser342Ile</b>		+ / +	<b>sporadic</b>	<b>WS4 in homozygotes</b>	<b>Consanguineous family</b>	<b>Lebanon</b>	<b>This paper</b>
	<b>c.1047_1050del TTAT</b>	<b>p.Tyr350IlefsX11</b>			<b>familial</b>	<b>WS4 in homozygotes; ±isolated depigmentations in relatives</b>		<b>Lebanon</b>	<b>This paper</b>
	<b>c.1075G&gt;T</b>	<b>p.Glu359X</b>			<b>familial</b>	<b>WS4 in heterozygotes or compound heterozygote</b>	<b>Patient also carries a p.Val260Phe<sup>§</sup> variation; it is unknown whether they are on the same or different alleles.</b>		<b>This paper</b>
Exon 6	<b>c.1163delT</b>	<b>p.Leu388TrpfsX2</b>			<b>familial</b>	<b>WS2 in heterozygotes</b>			<b>This paper</b>
	<b>c.1177T&gt;C</b>	<b>p.Phe393Leu</b>		+ / +	?	<b>WS4 in heterozygotes or compound heterozygote</b>	<b>Patient also carries a p.Gly170Glu variation; it is unknown whether they are on the same or different alleles.</b>		<b>This paper</b>

Non synonymous polymorphisms as reported in literature and in dbSNP (when confirmed in at least one control population):

Exon 1	c.13C>A	p.Pro5Thr	- / -				rs12720160 in dbSNP frequency 0.00 to 0.006		
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	c.20T>A	p.Leu7Gln		- /	rs5345 in dbSNP frequency 0.00 to 0.05		
	c.49C>T	p.Leu17Phe		- /	rs5346 in dbSNP frequency 0.00 to 0.05		
	c.169G>A	p.Gly57Ser	G57S	- /	rs1801710 in dbSNP frequency 0.00 to 0.08		[Hofstra et al., 1996]
	c.178G>A	p.Ala60Thr	178G/A	- /	Found in 3 HD patients and 1 control	South Africa	[Zaahl et al., 2003]
	c.227G>T	p.Arg76Met		- /	rs2228271 in dbSNP frequency 0.00 to 0.06		
	c.334T>G	p.Phe112Val		+ / +	rs5347 in dbSNP frequency 0.00 to 0.05		
Exon 2	c.553G>A	p.Val185Met	V185M	+ / +	found in several HD patients and 1 control	China	[Garcia-Barcelo et al., 2004]
Exon 3	c.731C>T	Thr244Met		± / -	rs5350 in dbSNP frequency 0.00 to 0.05		
Exon 4	c.914G>A	p.Ser305Asn	S305N	- / -	rs5352 in dbSNP frequency 0.00 to 0.06		[Auricchio et al., 1996]

\*cDNA nucleotide numbering with +1 as the A of the initiation codon in the reference sequence NM\_000115.2.

#Conservation refers to: amino-acid conservation among species / amino-acid conservation between human ETB and ETA (note that the N-terminal extracellular domain, encoded by exon 1, is not aligned between ETB and ETA). It is indicated only for missense variations.

\*The p.Val260Phe variation has been found in a patient and not characterized so far in controls to our knowledge. However the Val260 is not conserved and is replaced by a Phe in several species, making its pathogenicity especially unclear.

ABCD = Albinism, black lock, cell migration disorder of the neurocytes of the gut, deafness; HD = Hirschsprung disease.