Supplementary table. *PROKR2* and *PROK2* mutations in Kallmann syndrome

Exon	Nucleotide change	Aminoacid change	Protein domain	References
PROKR2				
1	58del	Frameshift	N-terminal region	Dodé et al., 2006
-	151G>A	A51T	-	C. Dodé, unpublished
	190A>G	M64V	1st transmembrane domain	Sykiotis et al., 2010
-	238C>T	R80C	1st intracellular loop	Abreu et al., 2008
-	253C>T	R85C	-	Cole et al., 2008; Monnier et al., 2009; Sarfati et al., 2010
-	253C>G	R85G	-	Sarfati et al., 2010
-	254G>T	R85L	-	Sarfati et al., 2010
-	254G>A	R85H	-	Dodé et al., 2006; Monnier et al., 2009
-	332T>G	M111R	1st extracellular loop	Sykiotis et al., 2010
-	337T>C	Y113H	-	Cole et al., 2008
-	343G>A	V115M	-	Cole et al., 2008
	349C>T	R117W	-	C. Dodé, unpublished
-	420C>G	Y140X	3rd transmembrane domain	Abreu et al., 2008
2	491G>A	R164Q	2nd intracellular loop	Dodé et al., 2006; Cole et al., 2008; Monnier et al., 2009
-	518T>G	L173R	4th transmembrane domain	Dodé et al., 2006; Abreu et al., 2008; Cole et al., 2008; Monnier et al., 2009; Avbelj Stefanija et al., 2012
-	533G>C	W178S	-	Dodé et al., 2006; Cole et al., 2008; Monnier et al., 2009
-	563C>T	S188L	-	Cole et al., 2008
-	604A>G	S202G	2nd extracellular loop	Chan et al., 2009
-	629A>G	Q210R	-	Dodé et al., 2006; Monnier et al., 2009; Sykiotis et al., 2010
-	701G>A	G234D	5th transmembrane domain	Tommiska et al., 2013; C. Dodé, unpublished
-	743G>A	R248Q	3rd intracellular loop	Cole et al., 2008
-	752G>T	W251L	-	Sarfati et al., 2010
-	779C>T	T260M	-	Sykiotis et al., 2010
-	802C>T†	R268C	-	Dodé et al., 2006; Abreu et al., 2008; Monnier et al., 2009; Sarfati et al., 2010; Tommiska et al., 2013
-	808C>T	R270C	-	Sykiotis et al., 2010
-	T820>A	V274D	6th transmembrane domain	Sinisi et al., 2008
-	868C>T	P290S	-	Dodé et al., 2006; Monnier et al., 2009
-	969G>A	M323I	7th transmembrane domain	Dodé et al., 2006; Monnier et al., 2009
-	989del	Frameshift	-	Sarfati et al., 2010
-	991G>A	V331M	-	Dodé et al., 2006; Cole et al., 2008; Monnier et al., 2009; Sarfati et al., 2010
-	c.1000G>A	V334M	-	C. Dodé, unpublished
-	1069C>T	R357W	C-terminal region	Cole et al., 2008

PROK2				
1	-4C>A		Translation initiation site	Dodé et al., 2006
-	1A>C	M1L	Translation initiation codon	C. Dodé, unpublished
-	70G>C	A24P	Signal peptide	Cole et al., 2008
-	94G>C	G32R	AVITGA motif	Dodé et al., 2006
2	101G>A	C34Y	Cysteine-rich region	Cole et al., 2008
-	137G>A	C46Y	-	C. Dodé, unpublished
-	150C>G	I50M	-	Cole et al., 2008
-	161G>A	S54N	-	Sarfati et al., 2010
-	163del	Frameshift	-	Pitteloud et al., 2007; Leroy et al., 2008
-	217C>T	R73C	-	Dodé et al., 2006; Leroy et al., 2008; Cole et al., 2008
4	292T[7]	Frameshift	-	Dodé et al., 2006; Abreu et al, 2008
-	301C>T	R101W	-	C. Dodé, unpublished
-	302G>A	R101Q	-	C. Dodé, unpublished
-	310C>T	H104Y	-	Sarfati et al., 2010
-	364C>T	R122X	-	C. Dodé, unpublished

Most mutations of *PROKR2* and *PROK2* are missense mutations. The mutations are found in the heterozygous state in most patients. The R85C, R85H, R164Q, L173R, G234D, and P290S *PROKR2* mutations, and the R73C, c.163del, and c.297_298insT *PROK2* mutations have, however, been found in both the heterozygous and homozygous (or compound heterozygous) states, suggesting that patients heterozygous for *PROKR2* or *PROK2* mutations carry additional mutations, presumably in other, as yet unidentified Kallmann syndrome genes in most cases. Two such patients have the L173R mutation of *PROKR2* together with S396L or R423X mutations of *KAL1* (Dodé et al., 2006; Sarfati et al., 2010), another patient has the V115M mutation of *PROKR2* together with the A24P mutation of *PROK2* (Cole et al., 2008), and yet another patient has the R85L mutation of *PROKR2* together with a A604T mutation of *FGFR1* (Sarfati et al., 2010). In addition, the patient with the S202G mutation of *PROKR2* also has I239T and R31C monoallelic mutations of *FGFR1* and *GNRH1*, respectively (Chan et al., 2009). Finally, two patients carrying the R268C and V331M mutations of *PROKR2* also carry A189T and R240Q monoallelic mutations of *KISS1R* and *GNRHR*, respectively (Sarfati et al., 2010).

[†] This mutation (p.R268C) has also been found in the heterozygous state in 174 of 2203 (7.9%) individuals from the African-American general population, and in the homozygous state in six individuals from the same population (0.3%) (see Exome Variant Server website URL: http://evs.gs.washington.edu/EVS/). No clear deleterious effect of the R268C mutation on PROKR2 signaling via Gq protein activation could be detected in transfected HEK-293 cells, calling into question the pathogenic effect of this missense variant.

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