The Use of Variant Maps to Explore Domain-Specific Mutations of *FGFR1*

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Appendix

Appendix Table 1. Published cases of Hartsfield syndrome to date.

Diagnosis	Causal Gene	Nucleotide Change	Amino Acid Change	Protein Domain	Sex	Reference
Hartsfield	*FGFR1*	494T>C	L165S	IgII	M	Vilian et al., 2009 "Patient 3"; Simonis et al., 2013
Hartsfield	*FGFR1*	572T>C	L191S	IgII	M	Simonis et al., 2013
Hartsfield	*FGFR1*	758A>C	H253P	AB	M	Takagi et al., 2016
Kallmann	*FGFR1*	1286T>A**	V429E**	TM	M	Villanueva et al., 2014
Hartsfield	*FGFR1*	1454G>T	G485V	TK	Not Reported	Dubourg et al., 2016
Hartsfield	*FGFR1*	1459G>T	G487C	TK	M	Lansdon et al.
Hartsfield	*FGFR1*	1460G>A	G487D	TK	M	Hong et al., 2016
Hartsfield	*FGFR1*	1468G>C	G490R	TK	M	Vilian et al., 2009 "Patient 5"; Simonis et al., 2013
Hartsfield	*FGFR1*	1468G>C	G490R	TK	Not Reported	Dubourg et al., 2016
Hartsfield	*FGFR1*	1867G>T	D623Y	TK	F	Simonis et al., 2013
Hartsfield	*FGFR1*	1869C>G(A)	D623E	TK	Not Reported	Hong et al., 2016
Hartsfield	*FGFR1*	1880G>C	R627T	TK	M	Keaton et al., 2010 "Patient 13"; Dhamija et al., 2014 "Older brother"
Hartsfield	*FGFR1*	1880G>C	R627T	TK	M	Dhamija et al., 2014 "Younger brother"
Hartsfield	*FGFR1*	1880G>C	R627T	TK	M	Oliver et al., 2017 “Oldest son”
Hartsfield	*FGFR1*	1880G>C	R627T	TK	M	Oliver et al., 2017 “Middle son”
Hartsfield	*FGFR1*	1880G>C	R627T	TK	M	Oliver et al., 2017 “Youngest son”
Hartsfield	*FGFR1*	1883A>G	N628S	TK	M	Prasad et al., 2016
Ectrodactyly-	*FGFR1*	1884T>G	N628K	TK	M	Van Maldergem et al., 1992;

Ectodermal Dysplasia-Clefting Syndrome						Vilian et al., 2009 "Patient 2"; Simonis et al., 2013
Hartsfield	*FGFR1*	1921G>A	D641N	TK	F	Hong et al., 2016
Hartsfield	*FGFR1*	2174G>A	C725Y	TK	M	Vilian et al., 2009 "Patient 4"; Simonis et al., 2013
Same condition as reported in Hartsfield 1984	Balanced reciprocal translocation (46,XY,t(2:4)(q14.2,q35))	N/A	N/A		M	Corona-Rivera et al., 2000
Hartsfield	Unknown	No change detected	No change detected		F	Simonis et al., 2013
Hartsfield	Unknown	Not tested	Not tested		M	Hartsfield 1984
Same condition as reported in Hartsfield 1984	Unknown	Not tested	Not tested		M	Young et al., 1992
Same condition as reported in Hartsfield 1984	Unknown	Not tested	Not tested		M	Imaizumi et al., 1998
Same condition as reported in Hartsfield 1984	Unknown	Not tested	Not tested		M	Abdel-Meguid and Ashour 2001
Unknown	Unknown	Not tested	Not tested		M	Koing et al., 2003
Hartsfield	Unknown	Not tested	Not tested		M	Vilian et al., 2009 "Patient 1"
Hartsfield	Unknown	Not tested	Not tested		M	Zechi-Ceide et al., 2009
Hartsfield	Unknown	Not tested	Not tested		M	Metwalley Kalil et al., 2012
Hartsfield	Unknown	Not tested	Not tested		F	Keaton et al., 2010
Hartsfield	Unknown	Not tested	Not tested		F	Keaton et al., 2010

**indicates biallelic variants (IgII – immunoglobulin-like 2 domain; AB – acidic box; TK – tyrosine kinase domain)

Appendix Table 2. Detailed phenotypic description of all individuals with Hartsfield Syndrome and detected variants in *FGFR1*.

Reference	Sex	Nucleotide Change	Amino Acid Change	Protein Domain	HS	CHH/KS	CL/P	Malformed Ears	Hearing Loss	Limb Defects	ID/DD	CCA	HPE
Vilian et al., 2009 "Patient 3"; Simonis et al., 2013	M	494T>C	L165S	IgII	x	x	x			ECC (H/F)	x	x	x
Simonis et al., 2013	M	572T>C	L191S	IgII	x					S; ECC(H/F)	x	x	x
Takagi et al., 2016	M	758A>C	H253P	AB	x	x	x			ECC (H)	mild		x
Villanueva et al., 2014	M	1286T>A**	V429E**	TM	x	x				ECC (H/F)		hypoplastic	
Dubourg et al., 2016	?	1454G>T	G485V	TK	x[1]								
Lansdon et al.	M	1459G>T	G487C	TK	x	x	x	x	x	ECC (H/F)	x	x	x
Hong et al., 2016	M	1460G>A	G487D	TK	x	x	x			ECC (F)	x	x	x
Vilian et al., 2009 "Patient 5"; Simonis et al., 2013	M	1468G>C	G490R	TK	x	x	x			ECC (H/F)	x		x
Dubourg et al., 2016	?	1468G>C	G490R	TK	x[1]								
Simonis et al., 2013	F	1867G>T	D623Y	TK	x	x				ECC (H)	mild	x	x
Hong et al., 2016	?	1869C>G(A)	D623E	TK	x	x				ECC (H/F)			x
Keaton et al., 2010 "Patient 13"; Dhamija et al., 2014 "Older brother"	M	1880G>C	R627T	TK	x	x	x	x		ECC			x
Dhamija et al., 2014 "Younger brother"	M	1880G>C	R627T	TK	x	x	x			ECC			x
Oliver et al., 2017 "Oldest son"	M	1880G>C	R627T	TK	x		x	microtia	x	ECC (H/F)	x		x
Oliver et al., 2017 "Middle son"	M	1880G>C	R627T	TK	x		x	x	x	ECC (H/F)			x
Oliver et al., 2017 "Youngest son"	M	1880G>C	R627T	TK	x		x	x		ECC (H/F)			x
Prasad et al., 2016	M	1883A>G	N628S	TK	x		x	x		C; ECC (H/F)			x
Van Maldergem et al., 1992; Vilian et al., 2009 "Patient 2"; Simonis et al., 2013	M	1884T>G	N628K	TK	x		x			ECC (H/F)	x	x	x
Hong et al., 2016	F	1921G>A	D641N	TK	x		x	x		S (H); O (F)	x		x
Vilian et al., 2009 "Patient 4"; Simonis et al., 2013	M	2174G>A	C725Y	TK	x					ECC (H/F)	mild	x	x

(HS – Hartsfield syndrome; CHH/KS – nomosomic congenital hypogonadotropic hypogonadism/Kallmann syndrome; CL/P – cleft lip and/or palate; ID/DD – intellectual disability/developmental delay; HPE – holoprosencephaly; ECC – ectrodactyly; S – syndactyly; O – oligodactyly; H/F – indicates hands (H) or feet (F) affected; [1]additional phenotypes not reported; ? – not reported; ** – biallelic; IgII – immunoglobulin-like 2 domain; AB – acidic box; TK – tyrosine kinase domain)

Appendix Table 3. Published PubMed variants of *FGFR1* and corresponding diseases.

Nucleotide Change	Amino Acid (Domain)	Benign or VUS	CADD Phred[3]	HS	PS/ OGD	ECCL	SOD	CHH/ KS	DA	CL/P	ME	HL	LD	CS	ID/ DD	CCA	HPE	CR	CR + LD	Reference
-1G>A	?							x												(Marcos, Sarfati et al. 2014)
6G>A	W2* (SP)		42					x												(Akkus, Kotan et al. 2017)
11G>A 12G>A	W4* (SP)		43					x x												(Laitinen, Vaaralahti et al. 2011) C. Dodé, unpublished
12G>T	W4C (SP)	dbSNP	16.14					x												(Goncalves, Bastos et al. 2015)
27delC	Frameshift (SP)							x												(Qin, Gong et al. 2014)
47C>G	A16G (SP)		18.06					x												C. Dodé, unpublished
64C>A	R22S (SP)	dbSNP, EVS, 1KG, ExAC	14.85					x												(Nair, Jadhav et al. 2016)
92-1G>C	Splice site (SP)							x												(Akkus, Kotan et al. 2017)

95dupA	Frameshift (SP)							x											(Goncalves, Bastos et al. 2015)
142G>A 165_171del 201_215dup15	G48S (IgI) Frameshift[1,] (IgI) R68_Q72dup (IgI)		36					x x x x											(Trarbach, Costa et al. 2006) (Laitinen, Vaaralahti et al. 2011, Hero, Laitinen et al. 2015) (Shaw, Seminara et al. 2011) (Costa-Barbosa, Balasubramanian et al. 2013)
208G>C	G70R (IgI)	dbSNP, EVS, ExAC	18.33					x											(Marcos, Sarfati et al. 2014)
214C>T	Q72*[1] (IgI)							x											(Quaynor, Bosley et al. 2016)
231C>G	N77K (IgI)		17.15					x											(Dode, Fouveaut et al. 2007)
232C>G	R78C (IgI)		32					x x x											(Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al.

																			2013)
246_247delAG	Frameshift (IgI)							x x x	x										(Laitinen, Vaaralahti et al. 2011, Hero, Laitinen et al. 2015) (Entrala-Bernal, Montes-Castillo et al. 2014) (Marcos, Sarfati et al. 2014)
286T>C	S96P (IgI)		22.8					x											(Vizeneux, Hilfiger et al. 2013)
287C>G	S96C (IgI)		22.4					x											(Goncalves, Bastos et al. 2015)
289G>A	G97S (IgI) [1]		35					x x x	x	 x		x	 EC (H)						(Jarzabek, Wolczynski et al. 2012) (Tommiska, Kansakoski et al. 2014) (Ohtaka, Fujisawa et al. 2017)
290G>A	G97D (IgI)		32					x											(Dode, Levilliers et al. 2003)
296A>G	Y99C (IgI)		22.1					x x											(Dode, Levilliers et al. 2003) (Raivio, Sidis et al. 2009, Raivio, Avbelj et al. 2012)

								x x x												(Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
301T>G	C101G (IgI)		21.2					x												(Quaynor, Kim et al. 2011, Quaynor, Bosley et al. 2016)
302G>T	C101F (IgI)		21.2					x												(Dode, Fouveaut et al. 2007)
303C>A	C101* (IgI)		19.2					x												C. Dodé, unpublished
303-304insCC	Frameshift (IgI)							x												(Dode, Levilliers et al. 2003)
304G>A	V102I (IgI)	dbSNP, EVS, 1KG, ExAC dbSNP, EVS, 1KG, ExAC dbSNP, EVS, 1KG, ExAC dbSNP, EVS, 1KG,						x x x x												(Albuisson, Pecheux et al. 2005) (Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Fukami, Iso et al. 2013)

		ExAC																	
		dbSNP, EVS, 1KG, ExAC						x											(Izumi, Suzuki et al. 2014)
		dbSNP, EVS, 1KG, ExAC						x											(Costa-Barbosa, Balasubramanian et al. 2013)
		dbSNP, EVS, 1KG, ExAC								x									(Hong, Hu et al. 2016)
319T>A	S107T (IgI)		8.975					x											(Izumi, Suzuki et al. 2014)
320C>A	S107* (IgI)		17.82					x											(Sato, Katsumata et al. 2004, Sato, Hasegawa et al. 2005)
320C>T	S107L (IgI)	dbSNP, EVS, 1KG, ExAC						x											(Sykiotis, Plummer et al. 2010)
		dbSNP, EVS, 1KG, ExAC						x											(Fukami, Iso et al. 2013)
		dbSNP, EVS, 1KG, ExAC						x											(Ayers, Bouty et al. 2017)
		dbSNP, EVS, 1KG, ExAC						x											(Correa, Trarbach et al. 2015)
		dbSNP, EVS, 1KG,						x											(Costa-Barbosa, Balasubramanian et al.

		ExAC																		2013)
326dupG	Frameshift (Ig I)							x												C. Dodé, unpublished
327del	Frameshift (Ig I)							x												C. Dodé, unpublished
336C>T	Splice site (AB)	dbSNP, EVS, 1KG, ExAC					x									x				(Raivio, Falardeau et al. 2007)
346G>A	V116I (AB)		13.92					x												(Marcos, Sarfati et al. 2014)
347T>G	V116G (AB)		22.1					x												C. Dodé, unpublished
350A>G	N117S (AB) [1]		13.32					x x												(Raivio, Avbelj et al. 2012) (Shaw, Seminara et al. 2011)
358C>T	R120C (AB)		32					x	x	x										(Xu, Niu et al. 2015)
386A>C	D129A (AB)		29.8					x												(Albuisson, Pecheux et al. 2005)
407C>A	S136* (AB)		42					x												C. Dodé, unpublished

412G>T	E138* (AB)		42					x											C. Dodé, unpublished
416A>G	K139R (AB)		15.03					x											C. Dodé, unpublished
418G>T	E140* (AB)		42					x											C. Dodé, unpublished
422C>G	T141R (AB)		14.69					x											(Costa-Barbosa, Balasubramanian et al. 2013)
424_427del	Frameshift (AB)							x x											(Sarfati, Fouveaut et al. 2013) C. Dodé, unpublished
443G>A	R148H (AB)		22.4					x											(Nair, Jadhav et al. 2016)
454G>A	A152T[1] (AB)								x	x						x			(Hong, Hu et al. 2016)
482T>C	M161T (IgII)		17.05					x											(Jarzabek, Wolczynski et al. 2012)
494T>C	L165S (IgII)		24	x						x			EC (H/F)		x	x	x		(Simonis, Migeotte et al. 2013)
499G>T	A167S**		27.6					x		x		x	S			x			(Dode, Levilliers et al. 2003)

	(IgII)							x x		x	x		S			x			(Thurman, Kathir et al. 2012) (Jarzabek, Wolczynski et al. 2012)
506C>T	P169L** (IgII)		29.2					x											(Costa-Barbosa, Balasubramanian et al. 2013)
521T>C	V174A (IgII)		25.1					x											(Marcos, Sarfati et al. 2014)
535G>C	C178S (IgII)		33					x	x	x	x	x							(Zenaty, Bretones et al. 2006)
565C>T	R189C (IgII)		22.6					x											C. Dodé, unpublished
570G>A	W190* (IgII)		42					x											(Costa-Barbosa, Balasubramanian et al. 2013)
572T>C	L191S (IgII)		21.2	x									S; EC (H/F)		x	x	x		(Simonis, Migeotte et al. 2013)
591C>A	F197L (IgII)		17.02					x											(Sykiotis, Plummer et al. 2010)
625C>T	R209C (IgII)		32					x											(Tommiska, Kansakoski et al. 2014)

								x x x											(Xu, Niu et al. 2015) (Akkus, Kotan et al. 2017) C. Dodé, unpublished
626G>A	R209H (IgII)		34					x											(Laitinen, Tommiska et al. 2010)
646A>G	I216V (IgII)	dbSNP, ExAC	13.43					x											(Nair, Jadhav et al. 2016)
650T>C	M217T (IgII)		22.3					x											C. Dodé, unpublished
670G>C	D224H (IgII)		34					x x											(Pitteloud, Meysing et al. 2006) (Costa-Barbosa, Balasubramanian et al. 2013)
672C>G	D224E (IgII)		34					x											C. Dodé, unpublished
682T>G	Y228D (IgII) [1]		31					x x											(Raivio, Sidis et al. 2009) (Shaw, Seminara et al. 2011)
709G>A	G237S (IgII)		32					x											(Pitteloud, Acierno et al. 2006)

								x x											(Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
710G>A	G237D (IgII)		33					x											(Pitteloud, Meysing et al. 2006)
716T>C	I239T[1] (IgII) [1]							x x x											(Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010) (Shaw, Seminara et al. 2011)
730_732insG	Frameshift (IgII)													x					(Ye, Guilmatre et al. 2016)
734T>C	L245P (IgII)		19.37					x		x									(Trarbach, Costa et al. 2006)
748C>T	R250W (IgII-IgIII)		25.3					x x x		 x					x				(Trarbach, Costa et al. 2006) (Dode, Fouveaut et al. 2007) (Gu, Li et al. 2016)
749G>A	R250Q (IgII-IgIII)		37					x											(Falardeau, Chung et al. 2008)

	[1]							x x x x x												(Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010) (Marcos, Sarfati et al. 2014) (Choi, Balasubramanian et al. 2015) (Costa-Barbosa, Balasubramanian et al. 2013)
749G>C	R250P (IgII-IgIII)		34				x			x						x	x			(Dubourg, Carre et al. 2016)
755C>G	P252R (IgII-IgIII)		32		x x x x x x								S S	x x x x x x		x				(Chokdeemboon, Mahatumarat et al. 2013) Ma et al., 1998 (Roscioli, Flanagan et al. 2000) (Bessenyei, Tihanyi et al. 2014, Bessenyei, Nagy et al. 2015) (Lajeunie, Heuertz et al. 2006) (Muenke, Schell et al. 1994) (Bellus, Gaudenz et al. 1996)

					x x x x x x x								C; S C; S S	x x x x x x x x x						(Meyers, Orlow et al. 1995) (Gaudenz, Roessler et al. 1998) (Passos-Bueno, Sertie et al. 1998) (Nieuwenhuyzen-De Boer, Hoogeboom et al. 2014) (Roscioli, Elakis et al. 2013) (Rossi, Jones et al. 2003) (Barik, Bajpai et al. 2015) (Cerrato, Nuzzi et al. 2014) (Hackett and Rowe 2006) (Pandey, Bajpai et al. 2013) (Schell, Hehr et al. 1995)
758A>C	H253P (IgII-IgIII)		28.7	x				x		x			EC (H)		x		x			(Takagi, Miyoshi et al. 2016)
760C>T	R254W (IgII-IgIII)		24.2					x x	 x			x	 S							(Koika, Varnavas et al. 2013) (Sarfati, Bouvattier et al. 2015)
761G>A	R254Q (IgII-IgIII)		31					x												(Pitteloud, Meysing et al. 2006) (Koika, Varnavas et al. 2013)

								x x											(Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
776G>A	G259E (IgIII)		35					x		x									(Xu, Niu et al. 2015)
779G>A	G260E (IgIII)																		(Caronia, Martin et al. 2011)
790A>C	N264H (IgIII)		32					x					C						(Nair, Jadhav et al. 2016)
809G>A	G270D (IgIII)		36					x x											(Dode, Fouveaut et al. 2007) (Jarzabek, Wolczynski et al. 2012)
817G>A	V273M (IgIII)		35					x x x x		x									(Albuisson, Pecheux et al. 2005) (Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)

821A>G	E274G (IgIII)		28.1					x x x x		x									(Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
830G>A	C277Y (IgIII)		34					x											(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007)
837_838del	Frameshift (IgIII)							x											(Marcos, Sarfati et al. 2014)
841A>G	S281G (IgIII)		32					x											(Costa-Barbosa, Balasubramanian et al. 2013)
841_846del	S281-D282del (IgIII)							x	x										(Bailleul-Forestier, Gros et al. 2010)
848C>G	P283R (IgIII)		22.1					x x	x										(Dode, Fouveaut et al. 2007) (Costa-Barbosa, Balasubramanian et al. 2013)
854C>G	P285R		20.3					x											(Sykiotis, Plummer et al.

	(IgIII)[1]							x x												2010) (Shaw, Seminara et al. 2011) (Costa-Barbosa, Balasubramanian et al. 2013)
858_866del	Frameshift (IgIII)							x												C. Dodé, unpublished
867G>A	W289* (IgIII)		44					x												(Luo, Zheng et al. 2017)
880G>A	E294K[1] (IgIII)	dbSNP, 1KG, ExAC													x		x			(Hong, Hu et al. 2016)
887A>T	N296I (IgIII)		32					x												(Costa-Barbosa, Balasubramanian et al. 2013)
891del	Frameshift (IgIII)							x												C. Dodé, unpublished
899T>C	I300T (IgIII)		15.48																	(Roscioli, Elakis et al. 2013)
925C>T	Q309* (IgIII)		43					x												(Costa-Barbosa, Balasubramanian et al. 2013)
936G>A	Splice site							x	x											(Dode, Fouveaut et al. 2007)

	(IgIII)																		
937C>T	H313Y (IgIII)		19.13					x											(Costa-Barbosa, Balasubramanian et al. 2013)
1054G>A	A352T (IgIII)		19.55					x											(Goncalves, Bastos et al. 2015)
1070C>T	T357I (IgIII)		33					x x											(Miura, Miura et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
961_962delAA	Frameshift (IgIII)							x x											(Laitinen, Vaaralahti et al. 2011, Hero, Laitinen et al. 2015) C. Dodé, unpublished
961_964del	Frameshift (IgIII)							x											C. Dodé, unpublished
962_963delAA	Frameshift (IgIII)							x											(Vizeneux, Hilfiger et al. 2013)
967G>T	E324* (IgIII)		34					x		x									(Dode, Fouveaut et al. 2007)
989T>A	N330I (IgIII)		28.1		x									x					(White, Cabral et al. 2005)

					x								EC	x						(Farrow, Davis et al. 2006)
995C>G	S332C (IgIII)		22.8					x												(Dode, Fouveaut et al. 2007)
1004A>T	D335V (IgIII)		23					x												C. Dodé, unpublished
1016A>G	Y339C (IgIII)		24.4					x x x												(Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
1018A>G	T340A (IgIII)		19.3					x												C. Dodé, unpublished
1019C>T	T340M (IgIII)		27.4					x x												(Sarfati, Fouveaut et al. 2013) C. Dodé, unpublished
1023C>G	C341W (IgIII)		24.2					x	x											(Bailleul-Forestier, Gros et al. 2010)
1025T>C	L342S[1] (IgIII)							x x					C							(Pitteloud, Quinton et al. 2007) (Sykiotis, Plummer et al.

																				2010)
1028C>T	A343V (IgIII)		19.55					x												(Trarbach, Costa et al. 2006)
1037C>G	S346C (IgIII)		32					x												(Pitteloud, Meysing et al. 2006)
1037_1038del	Frameshift (IgIII)							x												(Costa-Barbosa, Balasubramanian et al. 2013)
1038dupT	Frameshift (IgIII)							x												(Sykiotis, Plummer et al. 2010)
1038T[3]	Frameshift (IgIII)							x												C. Dodé, unpublished
1037delCT	Frameshift (IgIII)							x x												(Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
1039insT	Frameshift (IgIII)							x x												(Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
1040dupT	Frameshift (IgIII)							x												(Costa-Barbosa, Balasubramanian et al. 2013)

1042G>A	G348R (IgIII)		32					x x x x	x	x x			EC (F)						(Bailleul-Forestier, Gros et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013) (Marcos, Sarfati et al. 2014) (Villanueva, Jacobson-Dickman et al. 2015)
1043G>A	G348E (IgIII)		33					x											(Xu, Niu et al. 2015)
1057G>A	S353T (IgIII)		17.23					x											(Goncalves, Bastos et al. 2015)
1063T>C	W355R (IgIII)		25.5					x											(Costa-Barbosa, Balasubramanian et al. 2013)
1081G>C	A361P (JM)		16.32					x											(Dode, Fouveaut et al. 2007)
1088_1089insAG	Frameshift (JM)							x											C. Dodé, unpublished
1093_1094delAG	Frameshift (JM)							x	x										(Albuisson, Pecheux et al. 2005)
1097C>T	P366L (JM)		16.29					x											(Trarbach, Costa et al. 2006)

								x x												(Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
1107G>T(C,A)	M369I (JM)		15.06							x										(Riley, Mansilla et al. 2007)
1115G>A	Y372C (JM)		26.1		x									x						(White, Cabral et al. 2005)
1122C>A	Y374* (JM)		44					x												C. Dodé, unpublished
1135T>C	C379R (JM)		26.4		x									x						(White, Cabral et al. 2005)
1141T>C	C381R (JM)		26.4		x x				x				S	x						(Farrow, Davis et al. 2006) (Sow, Ramli et al. 2010)
1151C>A	A384D (TM)		19.58					x												C. Dodé, unpublished
1279G>T	V427L (TM)		25.2					x												(Sykiotis, Plummer et al. 2010)
1285-2A>G	Splice site (TM)							x												(Costa-Barbosa, Balasubramanian et al. 2013)

1286T>A	V429E (TM) **		24.2	x				x x					EC (H/F)			x				(Sykiotis, Plummer et al. 2010) (Villanueva, Jacobson-Dickman et al. 2015) (Costa-Barbosa, Balasubramanian et al. 2013)
1305_1306dupAT	Frameshift (TM)							x												(Laitinen, Vaaralahti et al. 2011) (Hero, Laitinen et al. 2015)
1307C>G	S436C (ID)	dbSNP, ExAC						x												(Vaaralahti, Wehkalampi et al. 2011)
1317_1318delTG	Frameshift (ID)							x x	x	 x		 x								(Sato, Ohyama et al. 2006) (Dode, Fouveaut et al. 2007)
1342C>T	R448W (ID)		18.78					x												(Correa, Trarbach et al. 2015)
1349C>T	S450F (ID)		32				x		x							x				(Raivio, Avbelj et al. 2012)
1368G>T	M456I (ID)		21.1					x x												(Sykiotis, Plummer et al. 2010) C. Dodé, unpublished
1377_1378insA	Frameshift							x												(Novo, Guerra et al. 2012)

	(ID)																		
1383T[3]	Frameshift (ID)							x											C. Dodé, unpublished
1399G>A	E467K (ID)		16.01							x									(Riley, Mansilla et al. 2007)
1409G>T	R470L (ID) [1] [1] [1]		16.58					x x x x											(Pitteloud, Quinton et al. 2007) (Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010) (Shaw, Seminara et al. 2011) (Abel, Shaw et al. 2013)
1423C>T	R475W (ID)		19.96					x											C. Dodé, unpublished
1424G>A	R475Q (ID)		36					x											C. Dodé, unpublished
1428C>G	D476E (ID)		15.32					x		x		x							(Wang, Wang et al. 2014)
1447C>A	P483T (TK)		27.2					x											(Costa-Barbosa, Balasubramanian et al. 2013)

1447C>T	P483S (TK)		29.8				x			x										(Raivio, Avbelj et al. 2012)
1453G>A	G485R (TK)		36					x	x	x			EC (F)							(Villanueva, Jacobson-Dickman et al. 2015)
1454G>T	G485V (TK)		34	x																(Dubourg, Carre et al. 2016)
1459G>T	G487C (TK)		35	x				x	x	x	x	x	EC (H/F)		x	x	x			Lansdon et al.
1460G>A	G487D (TK)		36	x				x		x			EC (F)		x	x	x			(Hong, Hu et al. 2016) (Nair, Jadhav et al. 2016)
1468G>C	G490R (TK)		36	x x						x			EC (H/F)		x		x			(Simonis, Migeotte et al. 2013) (Dubourg, Carre et al. 2016)
1474G>A	V492M (TK)		18.33					x												(Costa-Barbosa, Balasubramanian et al. 2013)
1535C>T	A512V (TK) [1]		36					x x		x										(Tommiska, Kansakoski et al. 2014) (Shaw, Seminara et al. 2011)
1553-2A>G	[1]							x												(Sykiotis, Plummer et al.

																				2010)
1561G>A	A520T (TK)		36					x												(Albuisson, Pecheux et al. 2005)
1604T>A	M535K (TK)		33						x	x					x					(Hong, Hu et al. 2016)
1609A>G	M537V (TK)	dbSNP, ExAC	17.65					x												(Sykiotis, Plummer et al. 2010)
1612A>G	I538V (TK)		19.69					x x												(Pitteloud, Meysing et al. 2006) (Costa-Barbosa, Balasubramanian et al. 2013)
1614C>T	Splice site (TK)							x												(Tommiska, Kansakoski et al. 2014)
1638C>A	N546K (TK)		23.4			x														(Bennett, Tan et al. 2016)
1663+1G>T	Splice site (TK)							x					P; EC (H)							(Ohtaka, Fujisawa et al. 2017)
1664-2A>G	Splice site (TK)							x x												(Sarfati, Fouveaut et al. 2013) (Marcos, Sarfati et al. 2014)

1708C>T	R570W (TK)		24.6					x											(Izumi, Suzuki et al. 2014)
1755T>A	Y585* (TK)		44					x x											(Pitteloud, Acierno et al. 2006) (Sykiotis, Plummer et al. 2010)
1780C>T	Q594* (TK)		45					x					EC (H/F)						(Villanueva, Jacobson-Dickman et al. 2015)
1810G>A	A604T (TK)		26.6					x											(Sarfati, Fouveaut et al. 2013, Sarfati, Bouvattier et al. 2015)
1819G>A	V607M (TK)		34					x											(Dode, Fouveaut et al. 2007) (Dode, Levilliers et al. 2003)
1825C>T	R609* (TK)		45					x		x									(Riley, Mansilla et al. 2007)
								x	x	x									(Laitinen, Vaaralahti et al. 2011, Hero, Laitinen et al. 2015)
								x											(Marcos, Sarfati et al. 2014)
1835A>G	E612G (TK)		27.2					x											(Costa-Barbosa, Balasubramanian et al. 2013)
1836_1837insT	Frameshift							x											(Albuisson, Pecheux et al. 2005)

	(TK)																		
1852_1853delAA	Frameshift (TK)							x											(Trarbach, Costa et al. 2006)
1854G>T	K618N (TK) [1]		33					x x											(Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010)
1862A>G	H621R (TK)		30					x		x			P			x			(Dode, Fouveaut et al. 2007)
1864C>T	R622* (TK) [1]		44					x x x x x		x									(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007) (Pitteloud, Acierno et al. 2005) (Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Xu, Niu et al. 2015) (Costa-Barbosa, Balasubramanian et al. 2013) (Zhu, Choa et al. 2015)
1864C>G	R622G (TK)		21.1					x	x		x		S						(Zenaty, Bretones et al. 2006)

								x	x		x		S						(Bailleul-Forestier, Gros et al. 2010)
1865G>A	R622Q (TK)		37					x x	 x	x x									(Zenaty, Bretones et al. 2006) (Bailleul-Forestier, Gros et al. 2010)
1867G>T	D623Y (TK)		33	x									EC (H)		x	x	x		(Simonis, Migeotte et al. 2013)
1869C>G(A)	D623E (TK)		23.2	x									EC (H/F)				x		(Hong, Hu et al. 2016)
1880G>C	R627T (TK)		35	x x				x x		x x x	x x x	 x	EC (H) EC (H/F) EC (H/F)			x	x x		(Keaton, Solomon et al. 2010) (Dhamija, Kirmani et al. 2014) (Hong, Hu et al. 2016) (Oliver, Menapace et al. 2017)
1883A>G	N628S (TK)		33	x						x	x		C; EC (H/F)				x		(Prasad, Brewer et al. 2016)
1884T>G	N628K (TK)		33	x						x			EC (H/F)		x	x	x		(Simonis, Migeotte et al. 2013)
1889T>C	L630P (TK)		29.8					x											Abel et al., 2012

								x x												(Costa-Barbosa, Balasubramanian et al. 2013) (Xu, Niu et al. 2015)
1907_1908del	Frameshift (TK)							x x												Sarfati et al., 2013 (Marcos, Sarfati et al. 2014)
1916T>C	I639T (TK)		28.6					x												(Zhu, Choa et al. 2015)
1921G>A	D641N (TK)		36	x						x	x		S (H); O (F)		x		x			(Hong, Hu et al. 2016)
1928G>A	G643D (TK)		35						x						x		x			(Dubourg, Carre et al. 2016)
1936C>T	R646W (TK)		22					x	x	x										(Tommiska, Kansakoski et al. 2014)
1961dupA	Y654* (TK)		43					x												(Goncalves, Bastos et al. 2015)
1966A>G	K656E[2] (TK)		27.3			x														(Bennett, Tan et al. 2016)
1970_1971delCA	Frameshift (TK)							x												(Dode, Fouveaut et al. 2007)

1977+1G>A	Splice site (TK) [1]							x x x									x			(Sarfati, Fouveaut et al. 2013) (Dallago, Abech et al. 2008) (Dode, Fouveaut et al. 2007) (Dubourg, Carre et al. 2016)
1981C>T	R661* (TK)		44					x												(Dode, Fouveaut et al. 2007)
1987C>T	P663S (TK)		34					x												C. Dodé, unpublished
1996T>A	W666R (TK)		27.5					x												(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007)
2008G>A	E670K (TK)		36					x												(Costa-Barbosa, Balasubramanian et al. 2013)
2009A>C	E670A (TK)		32					x x		x x			EC (F)							(Laitinen, Vaaralahti et al. 2011) (Villanueva, Jacobson-Dickman et al. 2015)
2011G>C	A671P (TK)		36					x x												(Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010)

								x											(Costa-Barbosa, Balasubramanian et al. 2013)
2038C>T	Q680* (TK)		45					x x x x	x	x									(Pitteloud, Acierno et al. 2006) (Raivio, Sidis et al. 2009) (Sykiotis, Plummer et al. 2010) (Zhu, Choa et al. 2015)
2048+1G>A	(TK)							x											(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007)
2049-1G>C	Frameshift (TK)							x											(Laitinen, Tommiska et al. 2010)
2049-2A>G	(TK)							x											C. Dodé, unpublished
2049-1G>A	(TK)							x											(Marcos, Sarfati et al. 2014)
2054C>T	S685F (TK)		25.8					x x		x x									(Dode, Fouveaut et al. 2007) (Jarzabek, Wolczynski et al. 2012)
2059G>A	G687R (TK)		27.5					x x											(Sato, Hasegawa et al. 2005) (Sykiotis, Plummer et al. 2010)

								x x x x x											(Quaynor, Kim et al. 2011) (Quaynor, Bosley et al. 2016) C. Dodé, unpublished (Zhu, Choa et al. 2015) (Choi, Balasubramanian et al. 2015) (Costa-Barbosa, Balasubramanian et al. 2013)
2062G>T	V688L (TK)		24.3					x		x			EC (F)						(Villanueva, Jacobson-Dickman et al. 2015)
2069T>G	L690P (TK)		23.1					x	x										(Bailleul-Forestier, Gros et al. 2010)
2074G>A	E692K (TK)		35					x		x							x		(Dubourg, Carre et al. 2016) C. Dodé, unpublished
2075A>G	E692G (TK)		27.2					x											(Costa-Barbosa, Balasubramanian et al. 2013)
2077A>T	I693F (TK)		28					x											(Dode, Fouveaut et al. 2007)
2084C>T	T695I		28					x	x										(Nair, Jadhav et al. 2016)

	(TK)																		
2099C>T	P700L (TK)		26					x											(Sykiotis, Plummer et al. 2010)
2107G>C	G703R (TK)		23.7					x x x											(Pitteloud, Meysing et al. 2006) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
2107G>A	G703S (TK)		17.39					x											(Pitteloud, Meysing et al. 2006)
2135T>C	L712P (TK)							x					EC (F)						(Villanueva, Jacobson-Dickman et al. 2015)
2146G>T	G716C (TK)		27.1					x											(Costa-Barbosa, Balasubramanian et al. 2013)
2152C>T	R718C (TK)		21					x											(Costa-Barbosa, Balasubramanian et al. 2013)
2155A>G	M719V (TK)		21.6					x											(Goncalves, Bastos et al. 2015)
2156T>G	M719R		21.6					x											(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007)

	(TK)																		
2164C>T	P722S (TK) [1] [1]		29.1					x x	 x	x x					x x				(Trarbach, Costa et al. 2006) (Dode, Levilliers et al. 2003) (Hong, Hu et al. 2016) (Hong, Hu et al. 2016)
[2165C>A; 2172C>G]	[P722H; N724K] (TK)							x	x										(Pitteloud, Acierno et al. 2006)
2174G>A	C725Y (TK)		23.9	x									EC (H/F)		x	x	x		(Simonis, Migeotte et al. 2013)
2180+3insT	(TK)							x											(Quaynor, Bosley et al. 2016)
2188-5C>A	Splice site (TK)							x											(Sykiotis, Plummer et al. 2010)
2190C>G	Y730* (TK)		45					x											(Albuisson, Pecheux et al. 2005)
2203del	Frameshift (TK)							x											C. Dodé, unpublished
2209T>C	W737R (TK)		22.1					x											(Costa-Barbosa, Balasubramanian et al. 2013)

								x											(Zhu, Choa et al. 2015)
2231G>C	R744T (TK)		23.6					x					EC (H/F)						(Ohtaka, Fujisawa et al. 2017)
2233C>T	P745S (TK) [1]		25.5					x x x											(Sato, Katsumata et al. 2004, Sato, Hasegawa et al. 2005) (Sykiotis, Plummer et al. 2010) (Costa-Barbosa, Balasubramanian et al. 2013)
2241C>A	F747L (TK)		19.91					x											(Sykiotis, Plummer et al. 2010)
2254delG	Frameshift[1] (TK)							x											(Quaynor, Bosley et al. 2016)
2267G>A	R756H (TK)																		(Caronia, Martin et al. 2011)
2292+3A>G	Splice site (TK)							x											(Costa-Barbosa, Balasubramanian et al. 2013)
2292G>T	Q764H[1] (TK)							x											(Sykiotis, Plummer et al. 2010)
2302G>C	D768H[1] (TK)							x											(Sykiotis, Plummer et al. 2010)

								x											(Quaynor et al., 2011)
2302G>T	D768Y[1] (TK)		23.5					x											(Sykiotis, Plummer et al. 2010)
2314C>T	P772S (CT)	dbSNP, EVS, 1KG, ExAC	16.89					x											(Dode, Levilliers et al. 2003, Dode, Fouveaut et al. 2007)
		dbSNP, EVS, 1KG, ExAC						x											(Sykiotis, Plummer et al. 2010)
		dbSNP, EVS, 1KG, ExAC							x	x					x		x		(Hong, Hu et al. 2016)
		dbSNP, EVS, 1KG, ExAC						x											(Correa, Trarbach et al. 2015)
2383G>A	V795I (CT)		23.7					x											(Trarbach, Costa et al. 2006)
2399C>T	P800L (CT)		22.3					x											Sarfati et al., 2013
								x											C. Dodé, unpublished
2464C>T	R822C (CT)		22.6					x											(Dode, Fouveaut et al. 2007)
[2292G>T (+) 2302G>T]	[Q764H (+) D768Y]							x											(Falardeau, Chung et al. 2008)

	(CT)																		

X’s indicate the published syndromes and phenotypes for the individual. (**biallelic; [1]variant identified in second gene; [2]mosaic; [3]CADD Phred scores are annotated for exonic, non-benign/VUS variants when no variants in additional genes were reported for the individual. The variants with CADD Phred scores appear in protein model figures and were used in the statistical analysis; SP – signal peptide, IgI – immunoglobulin-like 1 domain, AB – acidic box, IgII – immunoglobulin-like 2 domain, IgII-IgIII – IgII/IgIII linker, IgIII – immunoglobulin-like 3 domain, JM – juxtamembrane domain, TM – transmembrane domain, ID – intramembrane domain, TK – tyrosine kinase domain, CT – C terminus; HS – Hartsfield syndrome, PS/OGD – Pfeiffer syndrome/osteoglophonic dysplasia, ECCL – encephalocraniocutaneous lipomatosis, SOD – septo-optic dysplasia, CHH/KS – normosomic congenital hypogonadotropic hypogonadism/Kallmann syndrome, DA – dental agenesis, CL/P – cleft lip and/or palate, ME – malformed ears, HL – hearing loss, LD – limb defects, CS – craniosynostosis, ID/DD – intellectual disability/developmental delay, CCA – corpus callosum agenesis, HPE – holoprosencephaly, CR – craniofacial defects, CR + LD – craniofacial defects and limb defects).

Appendix Table 4. Benign, likely benign and variants of unknown significance of *FGFR1* identified in control databases.

Protein Domain	Nucleotide Change	Amino Acid Change	Reference	CADD Phred	Pathogenicity
SP	8G>A	S3N	dbSNP, ExAC	16.85	Unknown significance
SP	12G>C	W4C	dbSNP	15.92	Unknown significance
SP	15C>T	T5T	dbSNP, ExAC	Moderate	Unknown significance
SP	16C>T	R6W	dbSNP, ExAC	6.675	Likely benign
SP	16C>G	R6G	dbSNP, ExAC	0.007	Likely benign
SP	17G>C	R6P	dbSNP, ExAC	0.755	Likely benign
SP	17G>A	R6Q	dbSNP, ExAC	1.652	Likely benign
SP	20T>G	L7R	dbSNP, 1K Genomes, ExAC	16.9	Unknown significance
SP	24C>T	F8F	dbSNP, ExAC	Moderate	Unknown significance
SP	24C>A	L8L	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
SP	25T>A	F9I	dbSNP, ExAC	16.67	Unknown significance
SP	25G>A	G9S	dbSNP, ExAC	0.202	Likely benign
SP	27G>A	R9R	dbSNP, ExAC	Moderate	Unknown significance
SP	29G>A	R10K	dbSNP, ExAC	5.667	Likely benign
SP	31G>A	A11T	dbSNP, ExAC	20.2	Unknown significance
SP	32C>T	A11V	dbSNP, ExAC	9.842	Unknown significance
SP	33T>C	A11A	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
SP	34G>A	E12K	dbSNP, 1K Genomes, ExAC	6.525	Likely benign
SP	38T>C	L13P	dbSNP, ExAC	1.342	Unknown significance
SP	39G>A	L13L	dbSNP, ExAC	Moderate	Unknown significance
SP	47G>T	G16V	dbSNP, ExAC	0.091	Likely benign
SP	47C>T	A16V	dbSNP, ExAC	19.68	Unknown significance
SP	48G>A	E16E	dbSNP, ExAC	Moderate	Unknown significance
SP	49C>T	R17W	dbSNP, ExAC	3.941	Unknown significance
SP	51T>C	Y17Y	dbSNP, ExAC	Moderate	Unknown significance
SP	52C>T	L18F	dbSNP, ExAC	17.45	Unknown significance

SP	54C>T	V18V	dbSNP, ExAC	Moderate	Unknown significance
SP	56G>C	C19S	dbSNP, ExAC	7.798	Unknown significance
SP	60C>T	T20T	dbSNP, ExAC	Moderate	Unknown significance
SP	62C>G	A21G	dbSNP, ExAC	17.22	Likely benign
SP	63C>T	A21A	dbSNP, ExAC	Moderate	Unknown significance
SP	63C>G	A21A	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
SP	64G>A	G22R	dbSNP, 1K Genomes, ExAC	12.26	Likely benign
SP	64A>G	R22G	dbSNP, EVS, ExAC	15.1	Unknown significance
SP	66G>C	R22S	dbSNP, EVS, 1K Genomes, ExAC	14.85	Benign
SP	68C>T	P23L	dbSNP, EVS, ExAC	16.88	Unknown significance
SP	69G>A	P23P	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Benign
SP	74C>T	S25L	dbSNP, ExAC	8.274	Unknown significance
SP	75G>A	P25P	dbSNP, EVS, ExAC	Moderate	Unknown significance
SP	75A>C	S25S	dbSNP, ExAC	Moderate	Unknown significance
SP	77C>T	P26L	dbSNP, ExAC	10.36	Likely benign
SP	79A>T	T27S	dbSNP, 1K Genomes, ExAC	10.9	Benign
SP	79A>G	T27A	dbSNP, 1K Genomes, ExAC	12.5	Benign
SP	83C>T	P28L	dbSNP, EVS, ExAC	12.41	Unknown significance
SP	85A>G	N29D	dbSNP, EVS	13.11	Unknown significance
SP	86A>G	E29G	dbSNP, ExAC	15.12	Unknown significance
SP	90C>T	C30C	dbSNP, ExAC	Moderate	Unknown significance
SP	93C>T	A31A	dbSNP, ExAC	Moderate	Unknown significance
SP	103G>A	G35R	dbSNP, ExAC	12.05	Likely benign
SP	108C>T	A36A	dbSNP	Moderate	Unknown significance
SP	112G>A	V38M	dbSNP, EVS, ExAC	13.54	Likely benign
IgI	130C>T	L44L	dbSNP, ExAC	Moderate	Unknown significance
IgI	132G>A	L44L	dbSNP, ExAC	Moderate	Unknown significance
IgI	136C>T	H46Y	dbSNP, ExAC	8.721	Unknown significance
IgI	140C>T	P47L	dbSNP, ExAC	14.82	Unknown significance
IgI	141C>T	P47P	dbSNP, ExAC	Moderate	Unknown significance

IgI	141C>G	P47P	dbSNP, ExAC	Moderate	Unknown significance
IgI	153G>A	L51L	dbSNP, ExAC	Moderate	Unknown significance
IgI	160C>T	R54C	dbSNP, ExAC	20.3	Unknown significance
IgI	161G>A	R54H	dbSNP, 1K Genomes, ExAC	20.6	Unknown significance
IgI	162C>G	R54R	dbSNP, ExAC	Moderate	Unknown significance
IgI	167G>A	R56Q	dbSNP, ExAC	13.78	Unknown significance
IgI	168G>T	R56R	dbSNP, ExAC	Moderate	Unknown significance
IgI	168G>A	R56R	dbSNP, EVS, ExAC	Moderate	Unknown significance
IgI	173G>A	R58Q	dbSNP, 1K Genomes, ExAC	17.75	Unknown significance
IgI	174G>A	R58R	dbSNP	Moderate	Unknown significance
IgI	174C>T	N58N	dbSNP, ExAC	Moderate	Unknown significance
IgI	175C>T	R59C	dbSNP, ExAC	Moderate	Unknown significance
IgI	176A>T	D59V	dbSNP, 1K Genomes, ExAC	26.5	Unknown significance
IgI	176A>G	D59G	dbSNP, ExAC	21.6	Unknown significance
IgI	177C>T	D59D	dbSNP, EVS, ExAC	Moderate	Unknown significance
IgI	181G>A	V61M	dbSNP, ExAC	18.72	Unknown significance
IgI	182T>C	V61A	dbSNP, ExAC	8.293	Unknown significance
IgI	193A>C	N65H	dbSNP, ExAC	14.4	Unknown significance
IgI	194A>G	N65S	dbSNP, EVS, ExAC	4.235	Unknown significance
IgI	202C>T	R68W	dbSNP, ExAC	25.9	Unknown significance
IgI	207C>T	D69D	dbSNP, EVS, ExAC	Moderate	Unknown significance
IgI	208G>A	G70R	dbSNP, EVS, ExAC	18.91	Unknown significance
IgI	211G>T	V71L	dbSNP, 1K Genomes, ExAC	18.32	Unknown significance
IgI	221C>T	A74V	dbSNP, EVS, ExAC	10.27	Likely benign
IgI	222G>C	A74A	dbSNP, ExAC	Moderate	Unknown significance
IgI	226A>G	S76G	dbSNP, ExAC	9.352	Unknown significance
IgI	227G>C	S76T	dbSNP, ExAC	12.76	Unknown significance
IgI	230A>G	N77S	dbSNP, ExAC	20.6	Unknown significance
IgI	233G>A	R78H	dbSNP, ExAC	17.2	Unknown significance
IgI	238C>T	R80C	dbSNP, ExAC	28.1	Unknown significance

IgI	239G>A	R80H	dbSNP, 1K Genomes, ExAC	18.22	Unknown significance
IgI	240C>T	R80R	dbSNP, ExAC	Moderate	Unknown significance
IgI	241A>G	I81V	dbSNP, EVS, ExAC	11.78	Unknown significance
IgI	243C>T	I81I	dbSNP, ExAC	Moderate	Unknown significance
IgI	245C>G	T82R	dbSNP, ExAC	13.59	Unknown significance
IgI	248G>A	G83E	dbSNP, ExAC	16.75	Unknown significance
IgI	262G>T	V88L	dbSNP, EVS, ExAC	6.666	Unknown significance
IgI	264G>T	V88V	dbSNP, ExAC	Moderate	Unknown significance
IgI	266A>G	Q89R	dbSNP, ExAC	8.945	Likely benign
IgI	268G>T	D90Y	dbSNP, ExAC	22.5	Unknown significance
IgI	273C>T	S91S	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
IgI	273C>A	S91S	dbSNP, ExAC	Moderate	Unknown significance
IgI	274G>A	V92M	dbSNP, ExAC	19.9	Unknown significance
IgI	277C>T	P93S	dbSNP, EVS, ExAC	13.55	Unknown significance
IgI	279C>T	P93P	dbSNP, ExAC	Moderate	Unknown significance
IgI	280G>T	A94S	dbSNP, ExAC	13.18	Likely benign
IgI	280G>A	A94T	dbSNP, ExAC	14.35	Likely benign
IgI	281C>A	A94E	dbSNP, EVS	1.97	Likely benign
IgI	282A>C	A94A	dbSNP, ExAC	Moderate	Unknown significance
IgI	288C>T	S96S	dbSNP, ExAC	Moderate	Unknown significance
IgI	297T>C	Y99Y	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
IgI	303C>T	C101C	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
IgI	304G>A	V102I	dbSNP, EVS, 1K Genomes, ExAC	10.95	Benign
IgI	311G>A	S104N	dbSNP, ExAC	6.568	Likely benign
IgI	320C>T	S107L	dbSNP, EVS, 1K Genomes, ExAC	4.294	Benign
IgI	321G>A	S107S	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
IgI	332C>T	T111I	dbSNP, ExAC	14.66	Unknown significance
IgI	333C>T	T111T	dbSNP, ExAC	Moderate	Unknown significance
IgI	336C>T	T112T	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Benign
IgI	342C>T	F114F	dbSNP, ExAC	Moderate	Unknown significance

IgI	345C>T	S115S	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Benign
AB	359A>G	D120G	dbSNP, ExAC	20.7	Unknown significance
AB	374C>T	S125L	dbSNP, ExAC	19.09	Unknown significance
AB	375G>A	S125S	dbSNP, 1K Genomes, ExAC	Moderate	Benign
AB	378G>T	E126D	dbSNP, ExAC	9.827	Unknown significance
AB	381T>G	D127E	dbSNP, ExAC	20.4	Unknown significance
AB	383A>C	D128A	dbSNP	22.5	Unknown significance
AB	388G>A	D130N	dbSNP, ExAC	21	Unknown significance
AB	394G>T	D132Y	dbSNP, ExAC	28	Unknown significance
AB	394G>C	D132H	dbSNP	28.9	Unknown significance
AB	394G>A	D132N	dbSNP, ExAC	32	Unknown significance
AB	401C>T	S134F	dbSNP, ExAC	27.1	Unknown significance
AB	403T>A	S135T	dbSNP, ExAC	22.9	Unknown significance
AB	404C>T	S135F	dbSNP, ExAC	26.4	Unknown significance
AB	405T>C	S135S	dbSNP, EVS, ExAC	Moderate	Unknown significance
AB	414G>A	E138E	dbSNP	Moderate	Unknown significance
AB	415A>G	K139E	dbSNP, ExAC	9.381	Unknown significance
AB	430A>G	T144A	dbSNP, ExAC	14.38	Unknown significance
AB	431C>A	T144N	dbSNP, ExAC	11.53	Unknown significance
AB	448C>T	R150C	dbSNP, ExAC	21.1	Unknown significance
AB	449C>A	A150D	dbSNP, ExAC	21.4	Unknown significance
AB	450C>T	A150A	dbSNP, ExAC	Moderate	Unknown significance
AB	451G>A	V151I	dbSNP, ExAC	12.68	Unknown significance
AB	456T>C	A152A	dbSNP, EVS, ExAC	Moderate	Unknown significance
AB	468A>T	T156T	dbSNP, ExAC	Moderate	Unknown significance
AB	471C>T	S157S	dbSNP, EVS	Moderate	Unknown significance
AB	473C>T	P158L	dbSNP, ExAC	34	Unknown significance
AB	476A>G	E159G	dbSNP, ExAC	20.3	Unknown significance
IgII	496C>T	H166Y	dbSNP, ExAC	16.51	Unknown significance
IgII	501A>G	A167A	dbSNP, ExAC	Moderate	Unknown significance

IgII	501A>C	A167A	dbSNP, ExAC	Moderate	Unknown significance
IgII	507G>A	P169P	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
IgII	540C>T	S180S	dbSNP, ExAC	Moderate	Unknown significance
IgII	566G>A	R189H	dbSNP, ExAC	23.8	Unknown significance
IgII	584A>G	K195R	dbSNP, ExAC	14.47	Unknown significance
IgII	600C>T	D200D	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Benign
IgII	613G>A	G205S	dbSNP	36	Unknown significance
IgII	615C>T	G205G	dbSNP, ExAC	Moderate	Unknown significance
IgII	636C>G	T212T	dbSNP, ExAC	Moderate	Unknown significance
IgII	637T>G	W213G	dbSNP	25.4	Unknown significance
IgII	645C>T	I215I	dbSNP	Moderate	Unknown significance
IgII	646A>G	I216V	dbSNP, ExAC	13.43	Unknown significance
IgII	648A>C	I216I	dbSNP, ExAC	Moderate	Unknown significance
IgII	660G>A	V220V	dbSNP, ExAC	Moderate	Unknown significance
IgII	663G>T	V221V	dbSNP, ExAC	Moderate	Unknown significance
IgII	678C>T	G226G	dbSNP	Moderate	Unknown significance
IgII	680A>G	N227S	dbSNP, ExAC	29.2	Unknown significance
IgII	684C>T	Y228Y	dbSNP, ExAC	Moderate	Unknown significance
IgII	694G>T	V232L	dbSNP, ExAC	36	Unknown significance
IgII	708C>T	Y236Y	dbSNP	Moderate	Unknown significance
IgII	713G>A	S238N	dbSNP, ExAC	16.99	Unknown significance
IgII	715A>G	I239V	dbSNP, ExAC	16.07	Unknown significance
IgII	719A>G	N240S	dbSNP, ExAC	20.2	Unknown significance
IgII	723C>T	H241H	dbSNP, ExAC	Moderate	Unknown significance
IgII	726A>G	T242T	dbSNP, ExAC	Moderate	Unknown significance
IgII	737A>G	D246G	dbSNP, ExAC	21.7	Unknown significance
IgII	741C>T	V247V	dbSNP, ExAC	Moderate	Unknown significance
IgII-IgIII	742G>A	V248M	dbSNP, EVS, 1K Genomes, ExAC	20.7	Unknown significance
IgII-IgIII	754C>A	P252T	dbSNP	32	Unknown significance
IgII-IgIII	762G>C	R254R	dbSNP	Moderate	Unknown significance

IgIII	783G>C	L261F	dbSNP	21.2	Unknown significance
IgIII	786C>T	P262P	dbSNP, ExAC	Moderate	Unknown significance
IgIII	787G>A	A263T	dbSNP, ExAC	36	Unknown significance
IgIII	789C>T	A263A	dbSNP, ExAC	Moderate	Unknown significance
IgIII	793A>C	K265Q	dbSNP, ExAC	11.37	Unknown significance
IgIII	798A>G	T266T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	819G>C	V273V	dbSNP, ExAC	Moderate	Unknown significance
IgIII	834G>A	K278K	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
IgIII	837G>A	V279V	dbSNP, ExAC	Moderate	Unknown significance
IgIII	840C>T	Y280Y	dbSNP, ExAC	Moderate	Unknown significance
IgIII	849G>A	P283P	dbSNP, EVS, ExAC	Moderate	Unknown significance
IgIII	854C>T	P285L	dbSNP	26.1	Unknown significance
IgIII	855G>A	P285P	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
IgIII	870A>G	L290L	dbSNP	Moderate	Unknown significance
IgIII	877A>G	I293V	dbSNP, ExAC	6.565	Unknown significance
IgIII	880G>A	E294K	dbSNP, 1K Genomes, ExAC	27.7	Unknown significance
IgIII	891G>A	G297G	dbSNP, ExAC	Moderate	Unknown significance
IgIII	902G>A	G301D	dbSNP, ExAC	31	Unknown significance
IgIII	912C>T	N304N	dbSNP, ExAC	Moderate	Unknown significance
IgIII	921T>C	Y307Y	dbSNP, EVS, ExAC	Moderate	Unknown significance
IgIII	923T>C	V308A	dbSNP	21.3	Unknown significance
IgIII	941C>T	A314V	dbSNP, ExAC	23.4	Unknown significance
IgIII	954C>T	T318T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	957C>T	T319T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	979C>T	H327Y	dbSNP, ExAC	14.87	Unknown significance
IgIII	1011G>A	G337G	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1020G>C	T340T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1020G>A	T340T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1044A>C	G348G	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1048T>A	S350T	dbSNP, ExAC	13.88	Unknown significance

IgIII	1059T>C	S353S	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
IgIII	1062A>G	A354A	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1068G>A	L356L	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1071C>T	T357T	dbSNP, ExAC	Moderate	Unknown significance
IgIII	1072G>A	V358I	dbSNP, ExAC	34	Unknown significance
JM	1077G>A	L359L	dbSNP, ExAC	Moderate	Unknown significance
JM	1082C>A	A361D	dbSNP, ExAC	16.21	Unknown significance
JM	1085T>C	L362P	dbSNP, ExAC	8.711	Unknown significance
JM	1089A>G	E363E	dbSNP, ExAC	Moderate	Unknown significance
JM	1092G>A	E364E	dbSNP, EVS, ExAC	Moderate	Unknown significance
JM	1096C>T	P366S	dbSNP, ExAC	17.41	Unknown significance
JM	1098G>A	P366P	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
JM	1099G>T	A367S	dbSNP, ExAC	10.09	Unknown significance
JM	1106T>C	M369T	dbSNP, ExAC	2.817	Unknown significance
JM	1110C>T	T370T	dbSNP, ExAC	Moderate	Unknown significance
JM	1113G>A	S371S	dbSNP, ExAC	Moderate	Unknown significance
JM	1114C>T	P372S	dbSNP, EVS, ExAC	16.54	Unknown significance
JM	1136T>C	I379T	dbSNP, EVS, ExAC	23.5	Unknown significance
JM	1137C>T	I379I	dbSNP, ExAC	Moderate	Unknown significance
JM	1139A>G	Y380C	dbSNP, ExAC	20.5	Unknown significance
JM	1143C>T	C381C	dbSNP, ExAC	Moderate	Unknown significance
TM	1156C>T	L386F	dbSNP, ExAC	14.83	Unknown significance
TM	1159A>G	I387V	dbSNP, ExAC	11.56	Unknown significance
TM	1163C>T	S388F	dbSNP, EVS, ExAC	10.69	Unknown significance
TM	1168A>G	M390V	dbSNP, EVS, ExAC	11.11	Unknown significance
TM	1171G>A	V391M	dbSNP	15.58	Unknown significance
TM	1172T>C	V391A	dbSNP, 1K Genomes, ExAC	15.33	Unknown significance
TM	1176G>A	G392G	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
TM	1178C>T	S393L	dbSNP, EVS, ExAC	5.28	Unknown significance
TM	1179G>A	S393S	dbSNP, EVS, ExAC	Moderate	Unknown significance

TM	1185C>T	I395I	dbSNP, ExAC	Moderate	Unknown significance
TM	1186G>A	V396I	dbSNP, ExAC	8.074	Likely benign
TM	1218T>C	S406S	dbSNP, ExAC	Moderate	Unknown significance
TM	1224C>G	F408L	dbSNP	21.8	Unknown significance
TM	1227C>G	H409Q	dbSNP, ExAC	10.36	Unknown significance
TM	1229G>A	S410N	dbSNP, ExAC	16.06	Unknown significance
TM	1234A>G	M412V	dbSNP, ExAC	3.843	Unknown significance
TM	1249C>T	L417L	dbSNP, ExAC	Moderate	Unknown significance
TM	1257G>A	K419K	dbSNP, ExAC	Moderate	Unknown significance
TM	1269G>A	L423L	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
TM	1270C>T	R424C	dbSNP, EVS, ExAC	22	Unknown significance
TM	1271G>A	R424H	dbSNP, 1K Genomes, ExAC	15.35	Unknown significance
TM	1274G>T	R425I	dbSNP, ExAC	28	Unknown significance
TM	1287G>A	V429V	dbSNP, ExAC	Moderate	Unknown significance
TM	1300A>G	S434G	dbSNP, EVS	15.81	Unknown significance
TM	1302T>G	S434R	dbSNP, ExAC	21.8	Unknown significance
ID	1304C>T	A435V	dbSNP, ExAC	21.9	Unknown significance
ID	1307C>G	S436C	dbSNP, ExAC	26.9	Unknown significance
ID	1308C>T	S436S	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
ID	1316C>G	S439C	dbSNP, ExAC	22.5	Unknown significance
ID	1319G>A	G440E	dbSNP, EVS, ExAC	18.35	Unknown significance
ID	1321G>A	V441I	dbSNP, ExAC	13.22	Unknown significance
ID	1323T>G	V441V	dbSNP, ExAC	Moderate	Unknown significance
ID	1324C>T	L442F	dbSNP, ExAC	13.3	Unknown significance
ID	1324C>G	L442V	dbSNP, ExAC	6.691	Unknown significance
ID	1328T>C	L443P	dbSNP, ExAC	21.7	Unknown significance
ID	1329G>A	L443L	dbSNP, ExAC	Moderate	Unknown significance
ID	1333C>T	R445W	dbSNP, ExAC	19.77	Unknown significance
ID	1334G>A	R445Q	dbSNP, EVS, ExAC	32	Unknown significance
ID	1336C>T	P446S	dbSNP, ExAC	11.09	Unknown significance

ID	1337C>T	P446L	dbSNP, ExAC	14.49	Unknown significance
ID	1341A>C	S447S	dbSNP, ExAC	Moderate	Unknown significance
ID	1343G>A	R448Q	dbSNP, ExAC	27.3	Unknown significance
ID	1352C>G	S451C	dbSNP, EVS	32	Unknown significance
ID	1359G>T	G453G	dbSNP, ExAC	Moderate	Unknown significance
ID	1363C>G	P455A	dbSNP, 1K Genomes, ExAC	23.1	Unknown significance
ID	1366A>G	M456V	dbSNP, ExAC	14.35	Unknown significance
ID	1378G>T	V460F	dbSNP, ExAC	22.7	Unknown significance
ID	1385A>G	E462G	dbSNP, EVS, ExAC	32	Unknown significance
ID	1386G>A	E462E	dbSNP, EVS, ExAC	Moderate	Unknown significance
ID	1388A>G	Y463C	dbSNP, ExAC	15.2	Unknown significance
ID	1398C>T	P466P	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
ID	1408C>T	R470C	dbSNP, ExAC	17.41	Unknown significance
ID	1409G>A	R470H	dbSNP, ExAC	24.9	Unknown significance
ID	1410C>T	R470R	dbSNP, ExAC	Moderate	Unknown significance
ID	1417C>G	L473V	dbSNP, ExAC	12.06	Unknown significance
ID	1420C>G	P474A	dbSNP, 1K Genomes, ExAC	16.86	Unknown significance
ID	1425G>A	R475R	dbSNP, EVS	Moderate	Unknown significance
ID	1441G>A	G481S	dbSNP, ExAC	36	Unknown significance
TK	1448C>G	P483R	dbSNP, ExAC	26.9	Unknown significance
TK	1449C>T	P483P	dbSNP, ExAC	Moderate	Unknown significance
TK	1449C>A	P483P	dbSNP, ExAC	Moderate	Unknown significance
TK	1477G>A	V493M	dbSNP, ExAC	18.33	Unknown significance
TK	1482G>A	L494L	dbSNP	Moderate	Unknown significance
TK	1492A>G	I498V	dbSNP, ExAC	2.903	Likely benign
TK	1495G>A	G499R	dbSNP, ExAC	34	Unknown significance
TK	1509C>T	D503D	dbSNP, ExAC	Moderate	Unknown significance
TK	1509C>G	D503E	dbSNP, EVS, ExAC	13.35	Unknown significance
TK	1517A>G	N506S	dbSNP, 1K Genomes, ExAC	12.72	Unknown significance
TK	1519C>A	R507S	dbSNP, ExAC	16.85	Unknown significance

TK	1520G>A	R507H	dbSNP, EVS, ExAC	21.5	Unknown significance
TK	1533G>C	V511V	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	1538T>G	V513G	dbSNP, ExAC	22.7	Unknown significance
TK	1538T>C	V513A	dbSNP, ExAC	25.7	Unknown significance
TK	1540A>G	K514E	dbSNP	33	Unknown significance
TK	1544T>C	M515T	dbSNP, ExAC	24.3	Unknown significance
TK	1548G>A	L516L	dbSNP, ExAC	Moderate	Unknown significance
TK	1551G>A	K517K	dbSNP, ExAC	Moderate	Unknown significance
TK	1553C>T	A518V	dbSNP, ExAC	36	Unknown significance
TK	1554G>A	A518A	dbSNP, ExAC	Moderate	Unknown significance
TK	1595T>C	M532T	dbSNP, ExAC	25.5	Unknown significance
TK	1600A>G	M534V	dbSNP, 1K Genomes	19.43	Unknown significance
TK	1609A>G	M537V	dbSNP, ExAC	17.65	Unknown significance
TK	1615G>A	G539R	dbSNP	36	Unknown significance
TK	1616G>A	G539E	dbSNP, ExAC	35	Unknown significance
TK	1621C>T	H541Y	dbSNP, 1K Genomes, ExAC	35	Unknown significance
TK	1626G>A	K542K	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
TK	1638C>T	N546N	dbSNP, ExAC	Moderate	Unknown significance
TK	1639C>G	L547V	dbSNP, ExAC	24.7	Unknown significance
TK	1642C>T	L548L	dbSNP, ExAC	Moderate	Unknown significance
TK	1652G>C	C551S	dbSNP, ExAC	33	Unknown significance
TK	1655C>T	T552M	dbSNP, ExAC	34	Unknown significance
TK	1656G>A	T552T	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
TK	1669T>C	L557L	dbSNP, ExAC	Moderate	Unknown significance
TK	1677C>A	V559V	dbSNP, ExAC	Moderate	Unknown significance
TK	1679T>C	I560T	dbSNP, ExAC	28.9	Unknown significance
TK	1686G>A	E562E	dbSNP, ExAC	Moderate	Unknown significance
TK	1694C>G	S565C	dbSNP, ExAC	25.6	Unknown significance
TK	1697A>G	K566R	dbSNP, 1K Genomes	34	Unknown significance
TK	1701C>T	G567G	dbSNP, ExAC	Moderate	Unknown significance

TK	1710G>T	R570R	dbSNP, ExAC	Moderate	Unknown significance
TK	1711G>A	E571K	dbSNP, ExAC	37	Unknown significance
TK	1752C>G	C584W	dbSNP, ExAC	14.7	Unknown significance
TK	1757A>T	N586I	dbSNP, ExAC	28.9	Unknown significance
TK	1757A>C	N586T	dbSNP, ExAC	19.74	Unknown significance
TK	1764C>T	S588S	dbSNP, ExAC	Moderate	Unknown significance
TK	1772C>T	P591L	dbSNP, ExAC	25.7	Unknown significance
TK	1774G>A	E592K	dbSNP, ExAC	20.5	Unknown significance
TK	1775A>G	E592G	dbSNP, ExAC	16.34	Unknown significance
TK	1809C>T	C603C	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	1812C>G	A604A	dbSNP, ExAC	Moderate	Unknown significance
TK	1815C>T	Y605Y	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	1826G>A	R609Q	dbSNP, ExAC	37	Unknown significance
TK	1836G>A	E612E	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	1843G>T	A615S	dbSNP, ExAC	23.9	Unknown significance
TK	1845C>T	A615A	dbSNP, ExAC	Moderate	Unknown significance
TK	1845C>A	A615A	dbSNP, ExAC	Moderate	Unknown significance
TK	1869C>T	D623D	dbSNP, ExAC	Moderate	Unknown significance
TK	1875A>G	A625A	dbSNP, ExAC	Moderate	Unknown significance
TK	1888C>T	L630L	dbSNP, ExAC	Moderate	Unknown significance
TK	1904A>T	N635I	dbSNP, 1K Genomes, ExAC	25.3	Unknown significance
TK	1904A>G	N635S	dbSNP, ExAC	17.22	Unknown significance
TK	1905T>C	N635N	dbSNP, ExAC	Moderate	Unknown significance
TK	1920A>G	A640A	dbSNP, ExAC	Moderate	Unknown significance
TK	1932C>T	L644L	dbSNP, ExAC	Moderate	Unknown significance
TK	1936C>A	R646R	dbSNP, ExAC	Moderate	Unknown significance
TK	1944T>C	I648I	dbSNP, ExAC	Moderate	Unknown significance
TK	1953C>T	I651I	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	1954G>A	D652N	dbSNP, ExAC	37	Unknown significance
TK	1956C>G	D652E	dbSNP	23.5	Unknown significance

TK	1958A>G	Y653C	dbSNP, 1K Genomes, ExAC	25.5	Unknown significance
TK	1981C>G	R661G	dbSNP, ExAC	23.4	Unknown significance
TK	2007C>T	P669P	dbSNP, ExAC	Moderate	Unknown significance
TK	2007C>G	P669P	dbSNP, ExAC	Moderate	Unknown significance
TK	2023C>T	R675W	dbSNP, EVS, ExAC	25.1	Unknown significance
TK	2024G>C	R675P	dbSNP, ExAC	35	Unknown significance
TK	2046T>C	D682D	dbSNP, ExAC	Moderate	Unknown significance
TK	2067C>T	L689L	dbSNP, ExAC	Moderate	Unknown significance
TK	2077A>G	I693V	dbSNP, ExAC	24.5	Unknown significance
TK	2091C>T	G697G	dbSNP, ExAC	Moderate	Unknown significance
TK	2094C>G	G698G	dbSNP, ExAC	Moderate	Unknown significance
TK	2097C>T	S699S	dbSNP, ExAC	Moderate	Unknown significance
TK	2106C>T	P702P	dbSNP, ExAC	Moderate	Unknown significance
TK	2121G>A	E707E	dbSNP, ExAC	Moderate	Unknown significance
TK	2127T>G	L709L	dbSNP, ExAC	Moderate	Unknown significance
TK	2130C>T	F710F	dbSNP, ExAC	Moderate	Unknown significance
TK	2141A>G	K714R	dbSNP, ExAC	13.72	Unknown significance
TK	2145G>T	E715D	dbSNP, ExAC	17.48	Unknown significance
TK	2160C>T	D720D	dbSNP, ExAC	Moderate	Unknown significance
TK	2161A>C	K721Q	dbSNP, ExAC	16.31	Unknown significance
TK	2163G>A	K721K	dbSNP, EVS, ExAC	Moderate	Unknown significance
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TK	2168G>A	S723N	dbSNP, ExAC	16.49	Unknown significance
TK	2172C>T	N724N	dbSNP, ExAC	Moderate	Unknown significance
TK	2181C>T	N727N	dbSNP, ExAC	Moderate	Unknown significance
TK	2182G>A	E728K	dbSNP, ExAC	27.3	Unknown significance
TK	2191A>G	M731V	dbSNP, 1K Genomes	15.3	Unknown significance
TK	2201G>A	R734Q	dbSNP, ExAC	21.2	Unknown significance
TK	2202G>T	R734R	dbSNP, ExAC	Moderate	Unknown significance
TK	2220G>A	V740V	dbSNP, ExAC	Moderate	Unknown significance

TK	2237C>A	T746N	dbSNP, ExAC	22.5	Unknown significance
TK	2238C>T	T746T	dbSNP, ExAC	Moderate	Unknown significance
TK	2259C>T	D753D	dbSNP, ExAC	Moderate	Unknown significance
TK	2262G>A	L754L	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Benign
TK	2271C>T	I757I	dbSNP, ExAC	Moderate	Unknown significance
TK	2272G>A	V758M	dbSNP, 1K Genomes, ExAC	18.9	Unknown significance
TK	2277C>G	A759A	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	2278T>C	L760L	dbSNP, EVS, ExAC	Moderate	Unknown significance
TK	2288A>G	N763S	dbSNP	14.91	Unknown significance
TK	2289C>G	N763K	dbSNP, ExAC	16.55	Unknown significance
CT	2298C>T	Y766Y	dbSNP, EVS, ExAC	Moderate	Unknown significance
CT	2300T>G	L767R	dbSNP	22.6	Unknown significance
CT	2305C>G	L769V	dbSNP	18.75	Unknown significance
CT	2309C>T	S770F	dbSNP, ExAC	27.2	Unknown significance
CT	2314C>T	P772S	dbSNP, EVS, 1K Genomes, ExAC	16.89	Benign
CT	2331C>G	S777S	dbSNP, ExAC	Moderate	Unknown significance
CT	2337C>T	S779S	dbSNP, ExAC	Moderate	Unknown significance
CT	2339T>C	F780S	dbSNP, ExAC	12.46	Unknown significance
CT	2343C>T	P781P	dbSNP, EVS, ExAC	Moderate	Unknown significance
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CT	2346C>T	D782D	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
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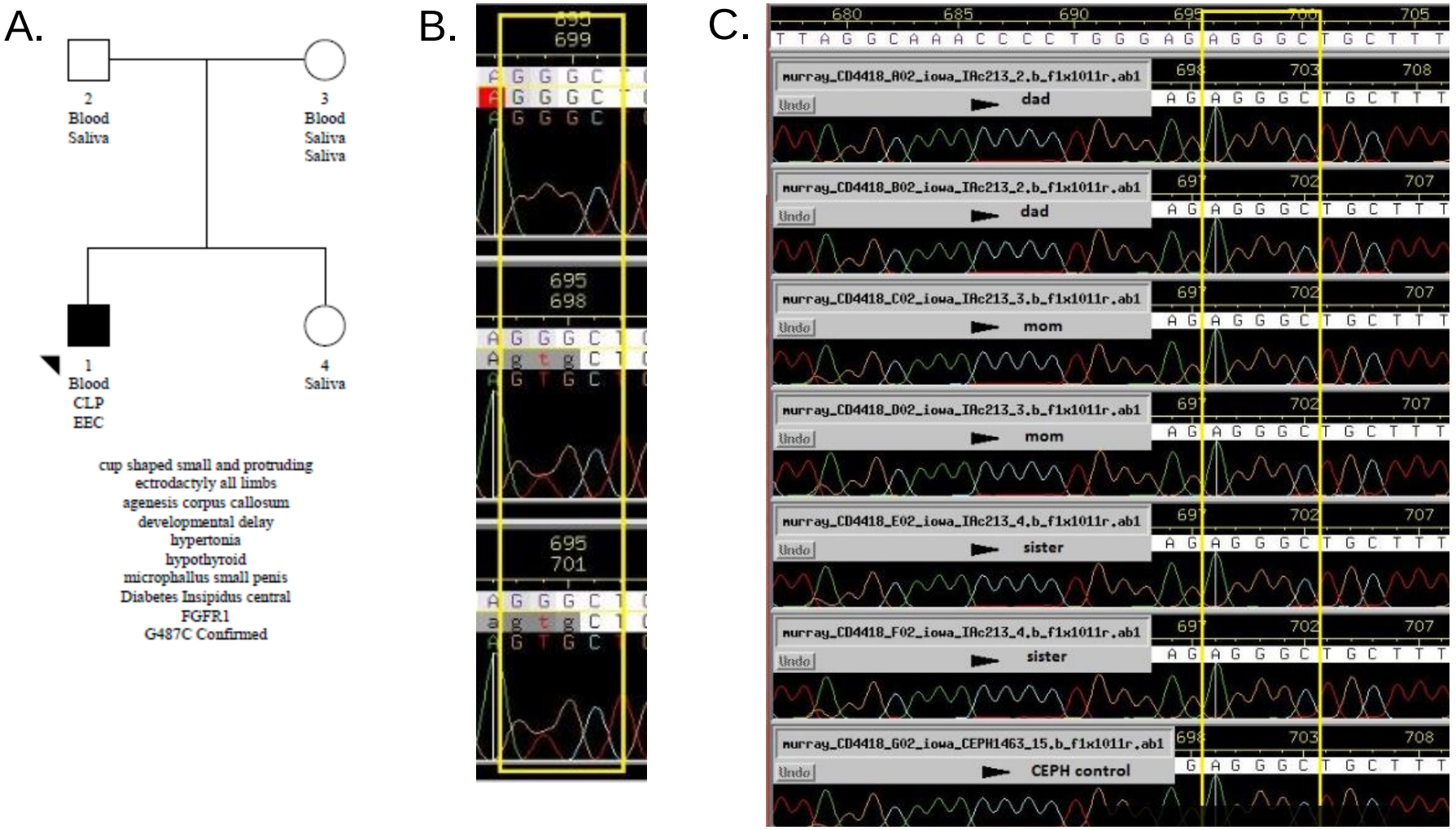
CT	2351G>A	R784Q	dbSNP, ExAC	23.1	Unknown significance
CT	2357C>G	S786C	dbSNP, ExAC	21.5	Unknown significance
CT	2358T>C	S786S	dbSNP, ExAC	Moderate	Unknown significance
CT	2360C>T	T787M	dbSNP, 1K Genomes, ExAC	23.5	Unknown significance
CT	2361G>A	T787T	dbSNP, EVS, ExAC	Moderate	Unknown significance
CT	2367C>T	S789S	dbSNP, ExAC	Moderate	Unknown significance
CT	2382C>T	S794S	dbSNP, EVS, 1K Genomes, ExAC	Moderate	Unknown significance
CT	2393A>G	H798R	dbSNP, ExAC	17.36	Unknown significance

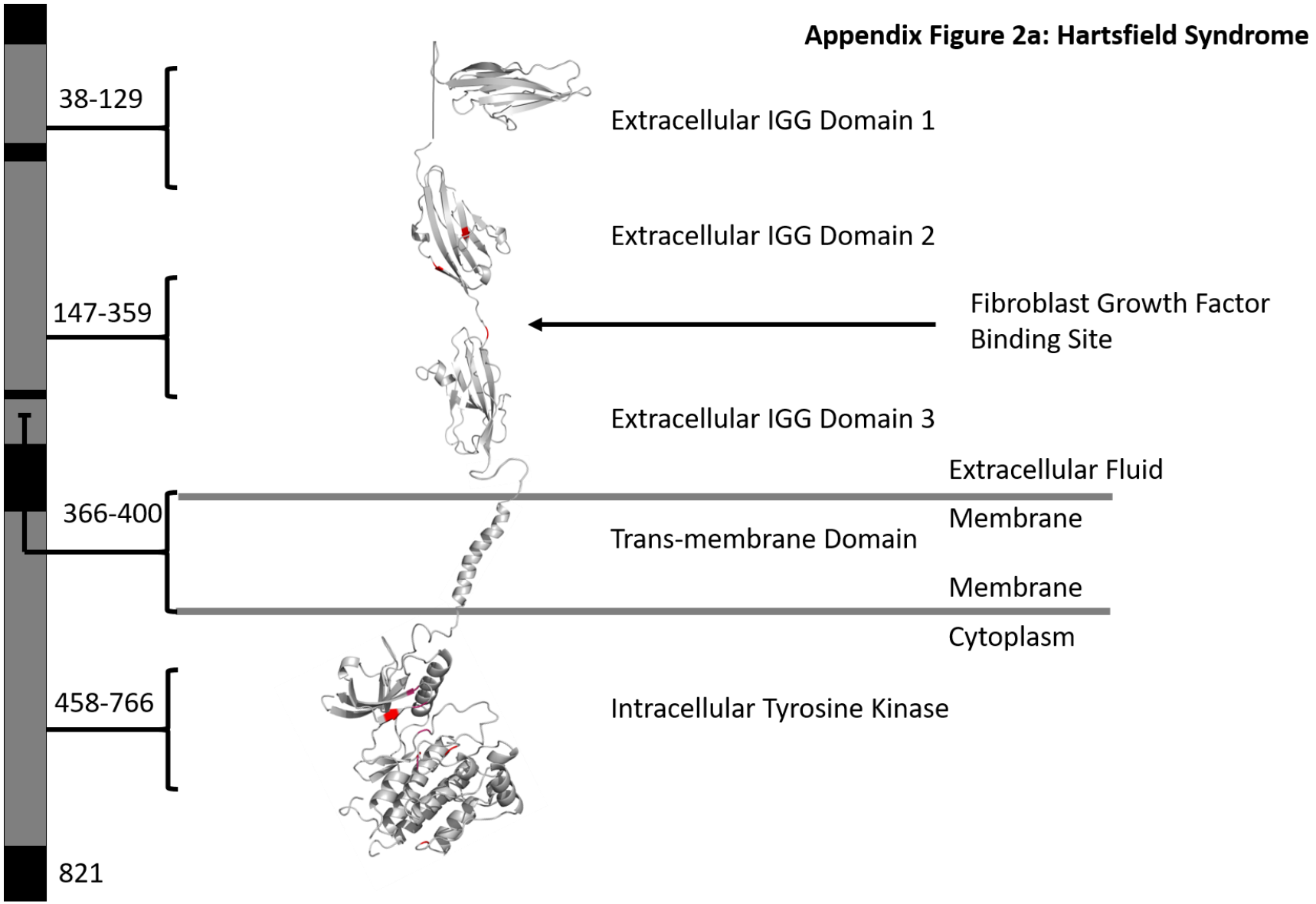
CT	2400G>A	P800P	dbSNP, ExAC	Moderate	Unknown significance
CT	2406C>T	P802P	dbSNP, ExAC	Moderate	Unknown significance
CT	2406C>A	P802P	dbSNP, 1K Genomes, ExAC	Moderate	Unknown significance
CT	2407G>T	E803*	dbSNP, ExAC	45	Unknown significance
CT	2415C>T	P805P	dbSNP, ExAC	Moderate	Unknown significance
CT	2417G>A	C806Y	dbSNP, ExAC	25.9	Unknown significance
CT	2418C>A	C806*	dbSNP, ExAC	44	Unknown significance
CT	2424C>G	P808P	dbSNP, EVS, ExAC	Moderate	Unknown significance
CT	2425C>T	R809*	dbSNP, ExAC	45	Unknown significance
CT	2426G>A	R809Q	dbSNP, ExAC	9.862	Unknown significance
CT	2428C>A	H810N	dbSNP, ExAC	14.66	Unknown significance
CT	2432C>G	P811R	dbSNP, ExAC	25.6	Unknown significance
CT	2433A>G	P811P	dbSNP, ExAC	Moderate	Unknown significance
CT	2439G>A	Q813Q	dbSNP, ExAC	Moderate	Unknown significance
CT	2452G>A	G818R	dbSNP	29.5	Unknown significance
CT	2457C>T	L819L	dbSNP, ExAC	Moderate	Unknown significance
CT	2461C>T	R821C	dbSNP, ExAC	19.82	Unknown significance
CT	2462G>A	R821H	dbSNP, ExAC	19.11	Unknown significance
CT	2465G>A	R822H	dbSNP, ExAC	23	Unknown significance

These variants were identified in the ExAC, dbSNP, 1000 Genomes (1K Genomes) and EVS databases and scored as non-pathogenic using the Deafness Variation Database strategy (see methods). These variants were used in the statistical analysis to compare locations of non-pathogenic variants to those identified in individuals with a disease phenotype. “Moderate” CADD Phred scores indicate synonymous changes. (IgI – immunoglobulin-like 1 domain, IgII – immunoglobulin-like 2 domain, IgIII – immunoglobulin-like 3 domain, TM – transmembrane domain, TK – tyrosine kinase domain)

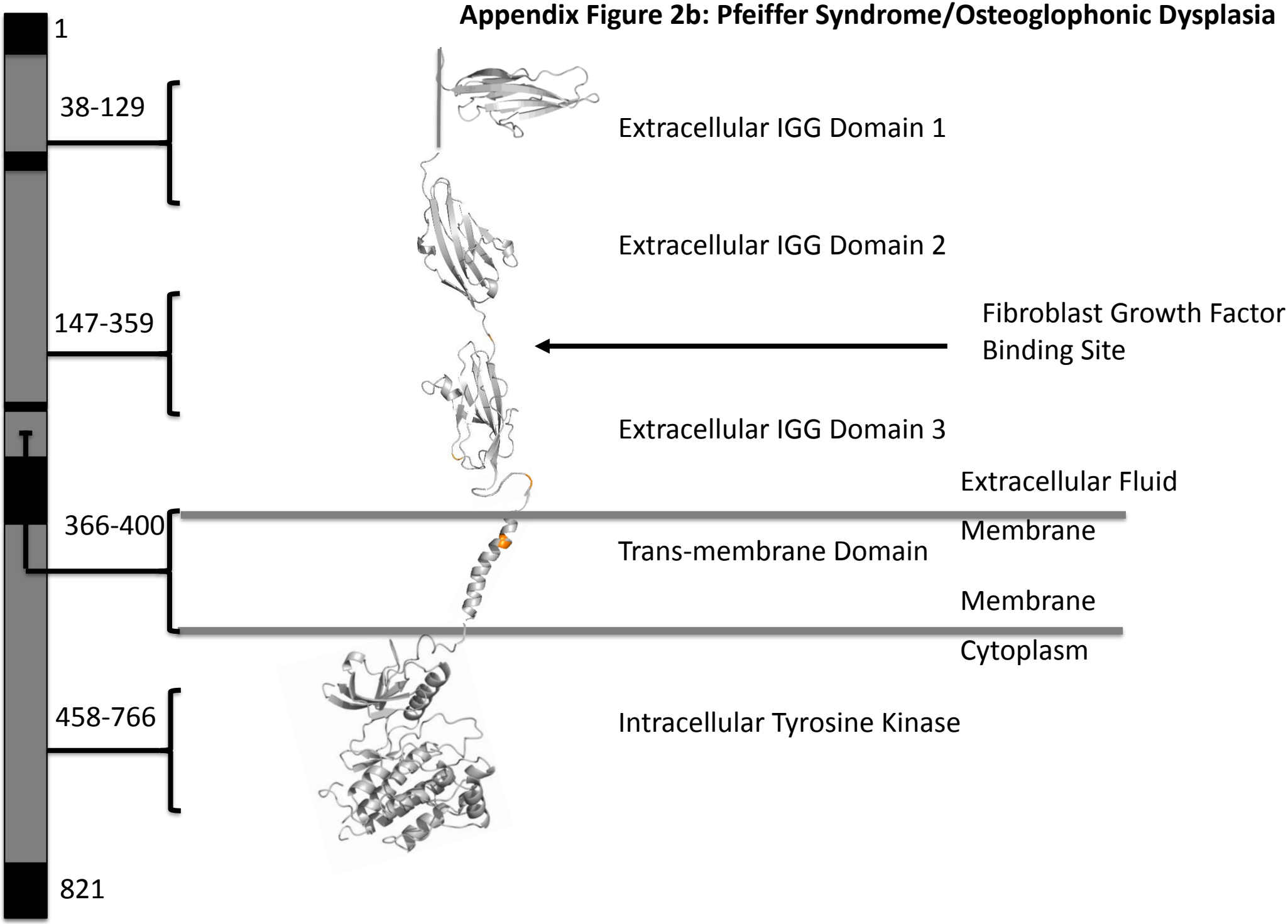


Appendix Figure 1. Pedigree and chromatograms of the proband with Hartsfield syndrome. A. Pedigree showing sample types and nuclear family of proband with a phenotypic summary. B. Chromatogram showing the control sequence (top sequence; GGG) followed by the detected 1459G>T (G487C) in two sequence reads of the proband's DNA. C. Chromatograms showing the presence of the consensus sequence in unaffected dad, mom and sister compared to a control sample (CEPH) all wildtype at nucleotide.

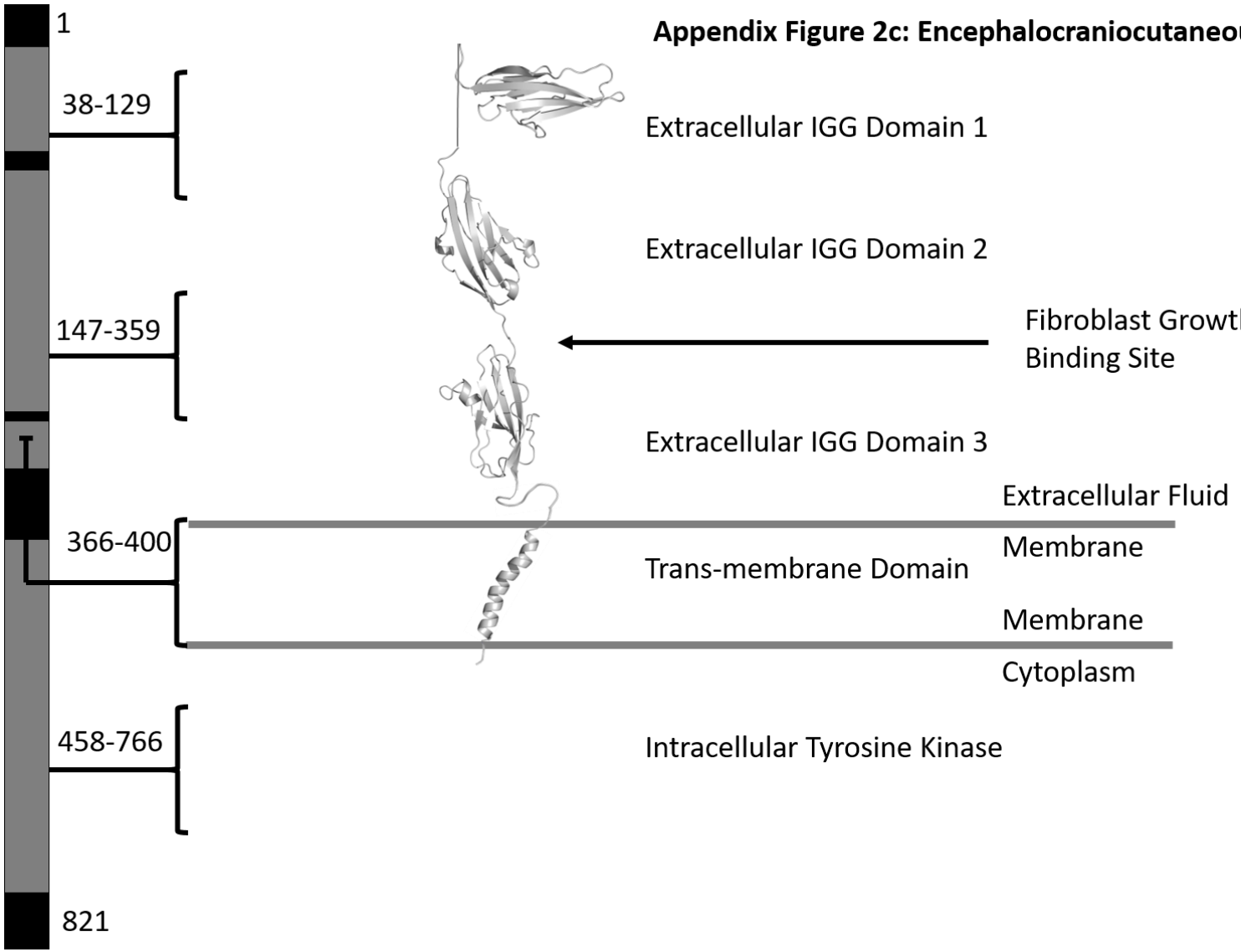
Appendix Figure 2a: Hartsfield Syndrome



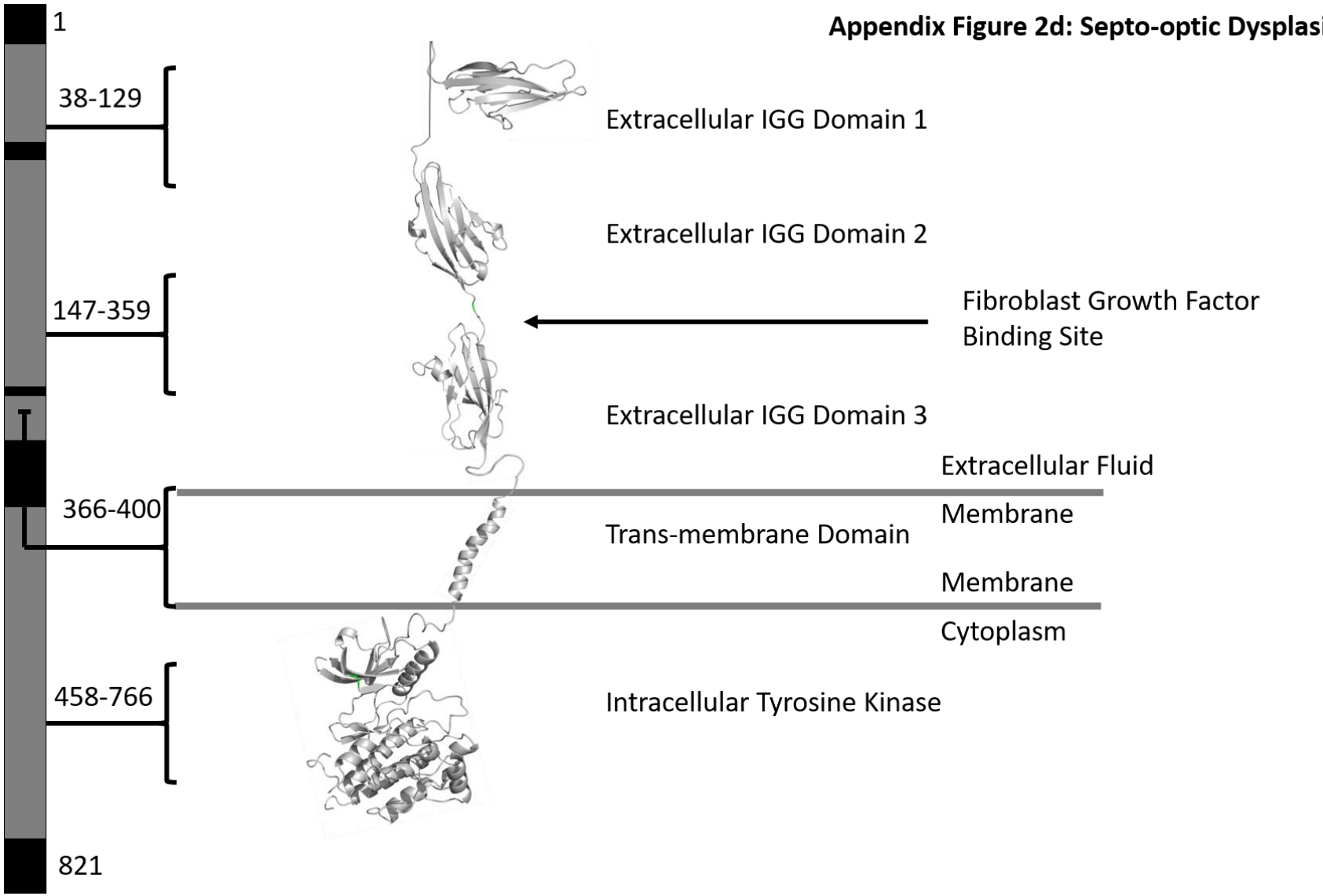
Appendix Figure 2b: Pfeiffer Syndrome/Osteoglophonic Dysplasia



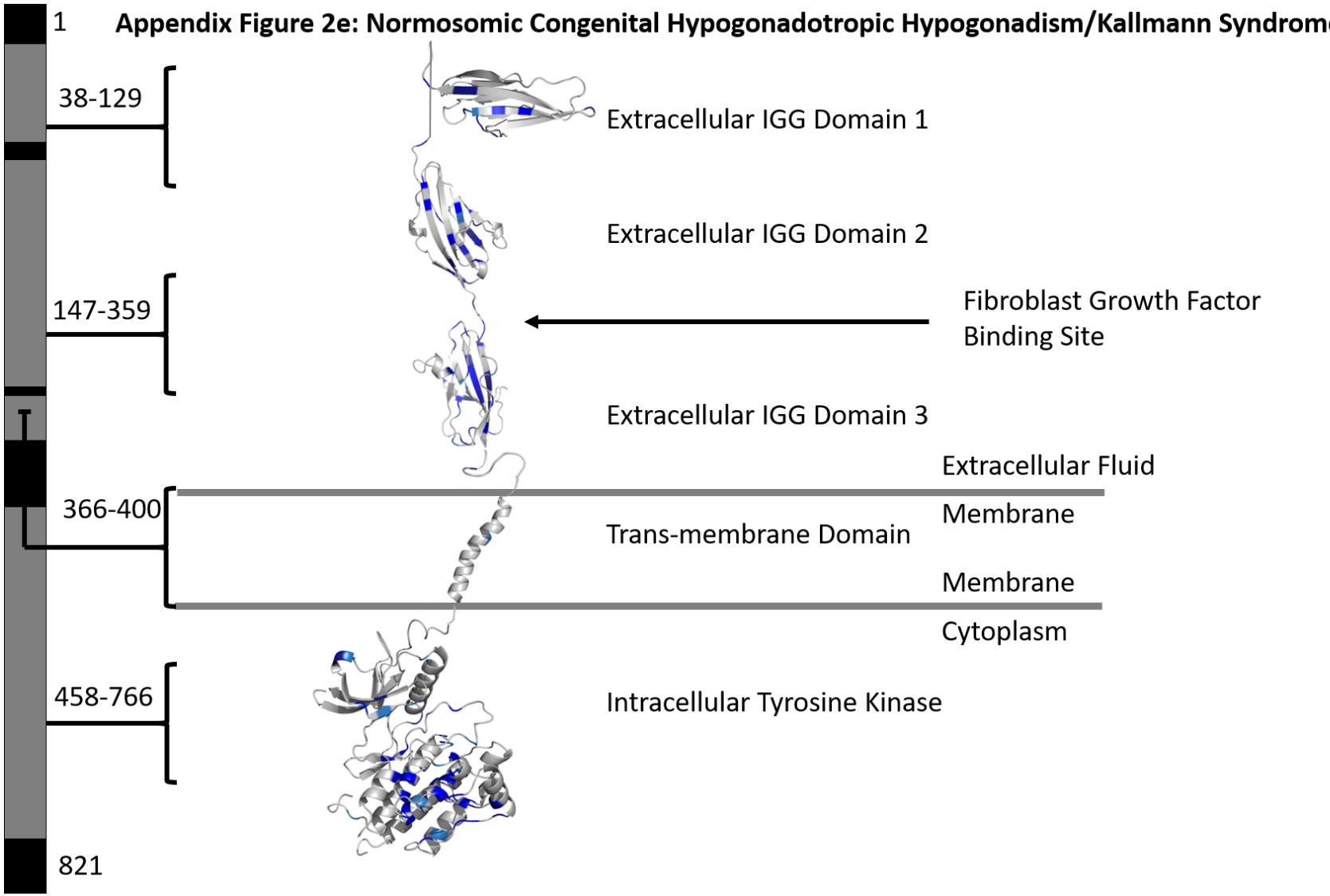
Appendix Figure 2c: Encephalocraniocutaneous Lipomatosis



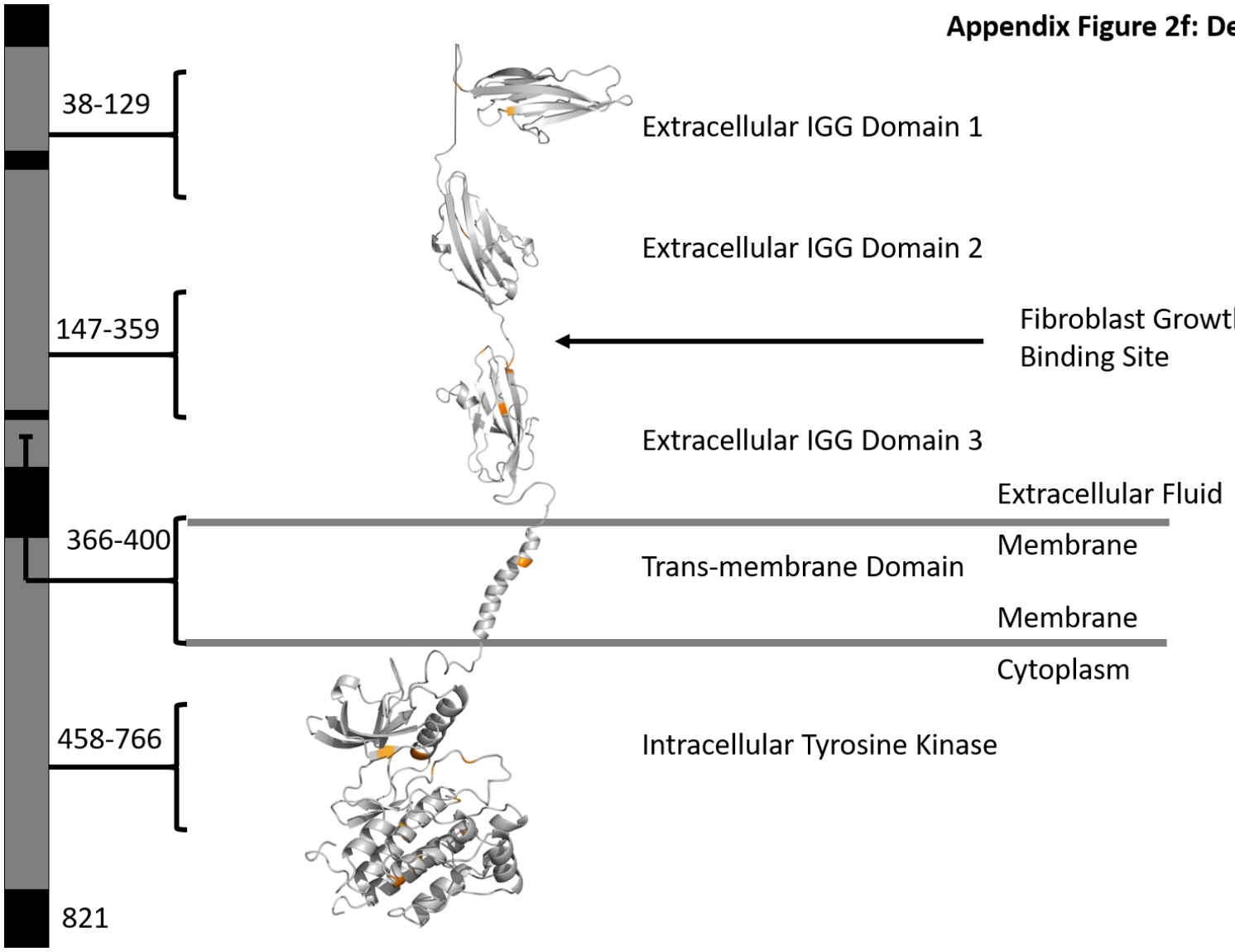
Appendix Figure 2d: Septo-optic Dysplasia



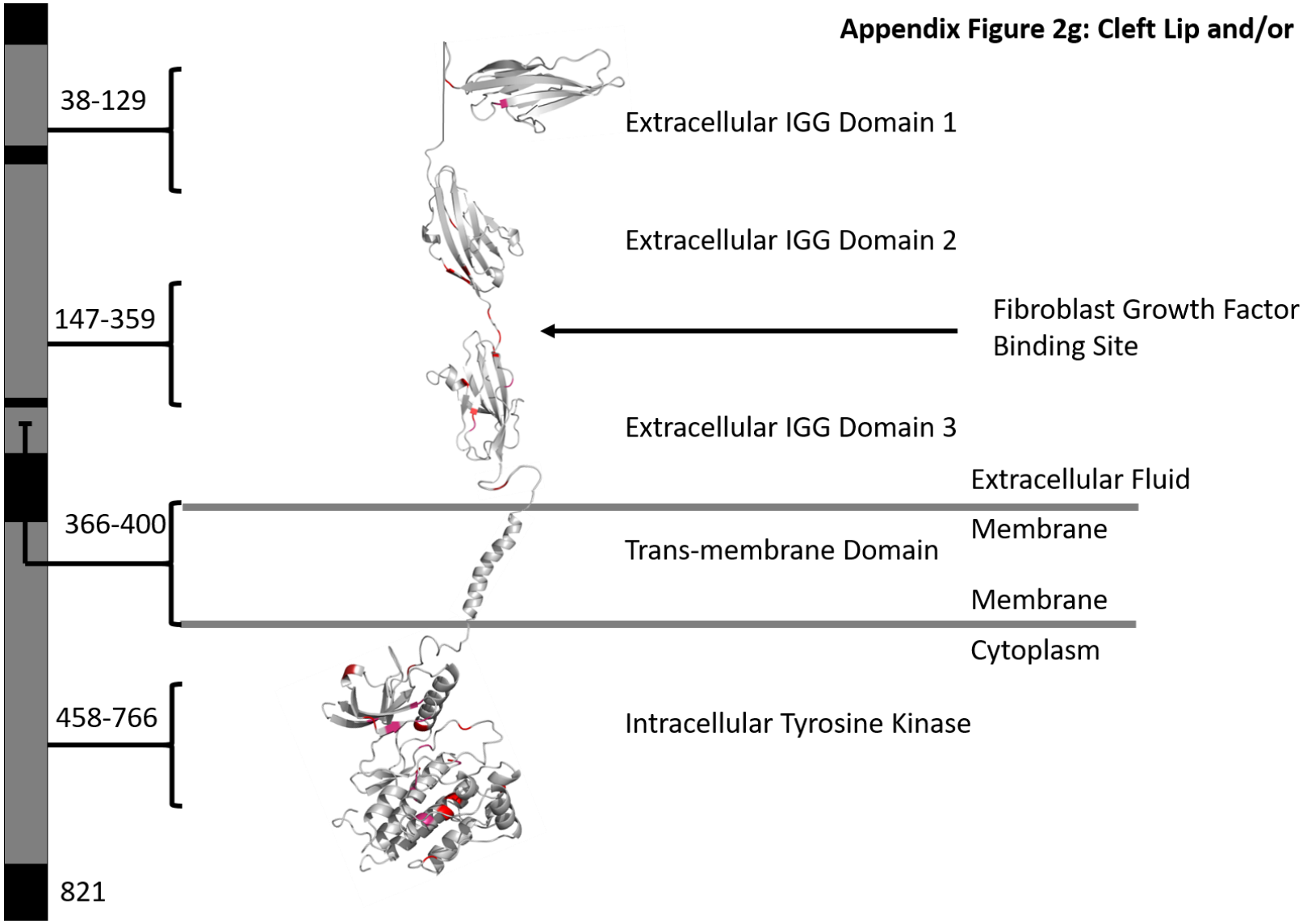
Appendix Figure 2e: Normosomic Congenital Hypogonadotropic Hypogonadism/Kallmann Syndrome



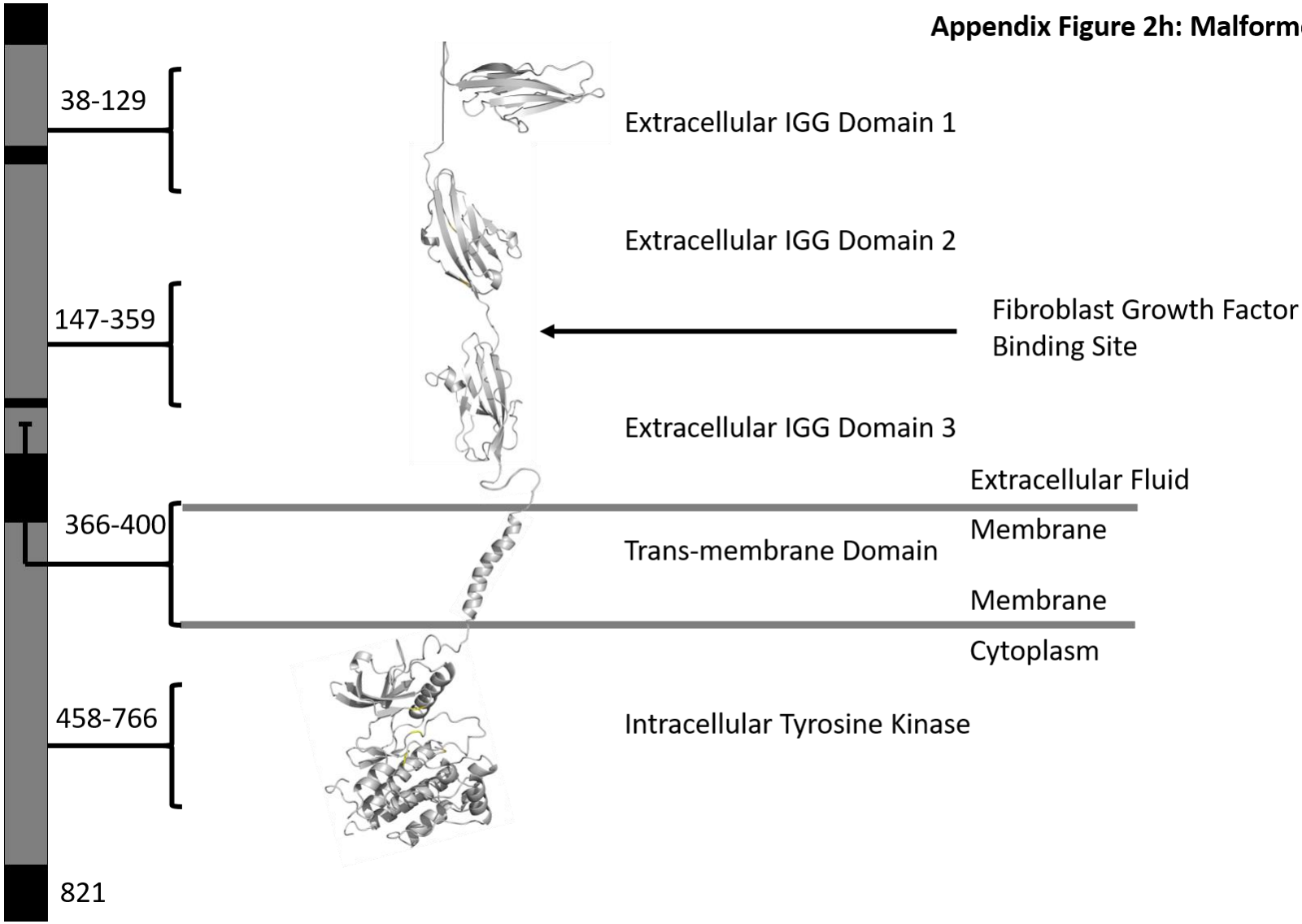
Appendix Figure 2f: Dental Agenesis



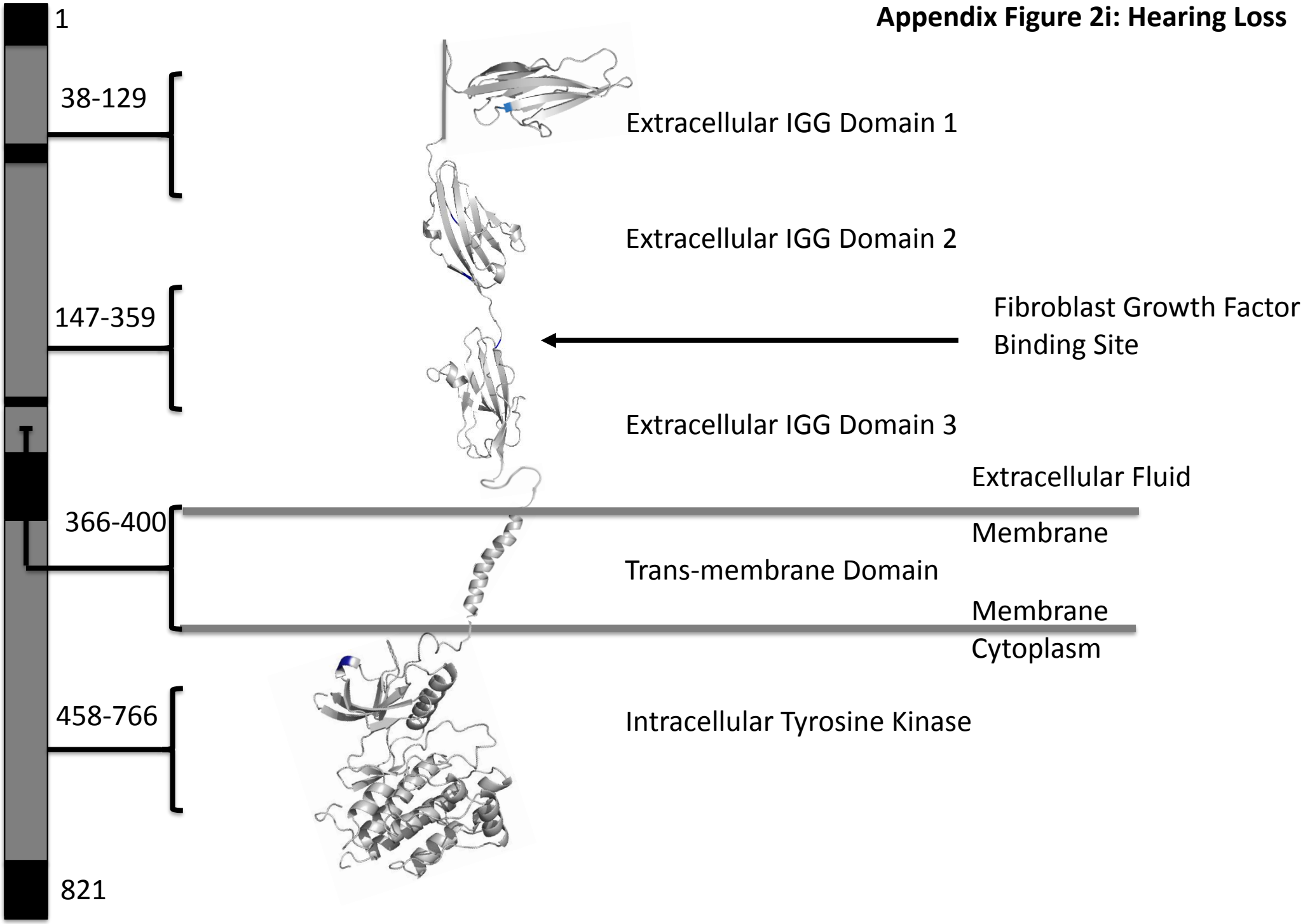
Appendix Figure 2g: Cleft Lip and/or Palate



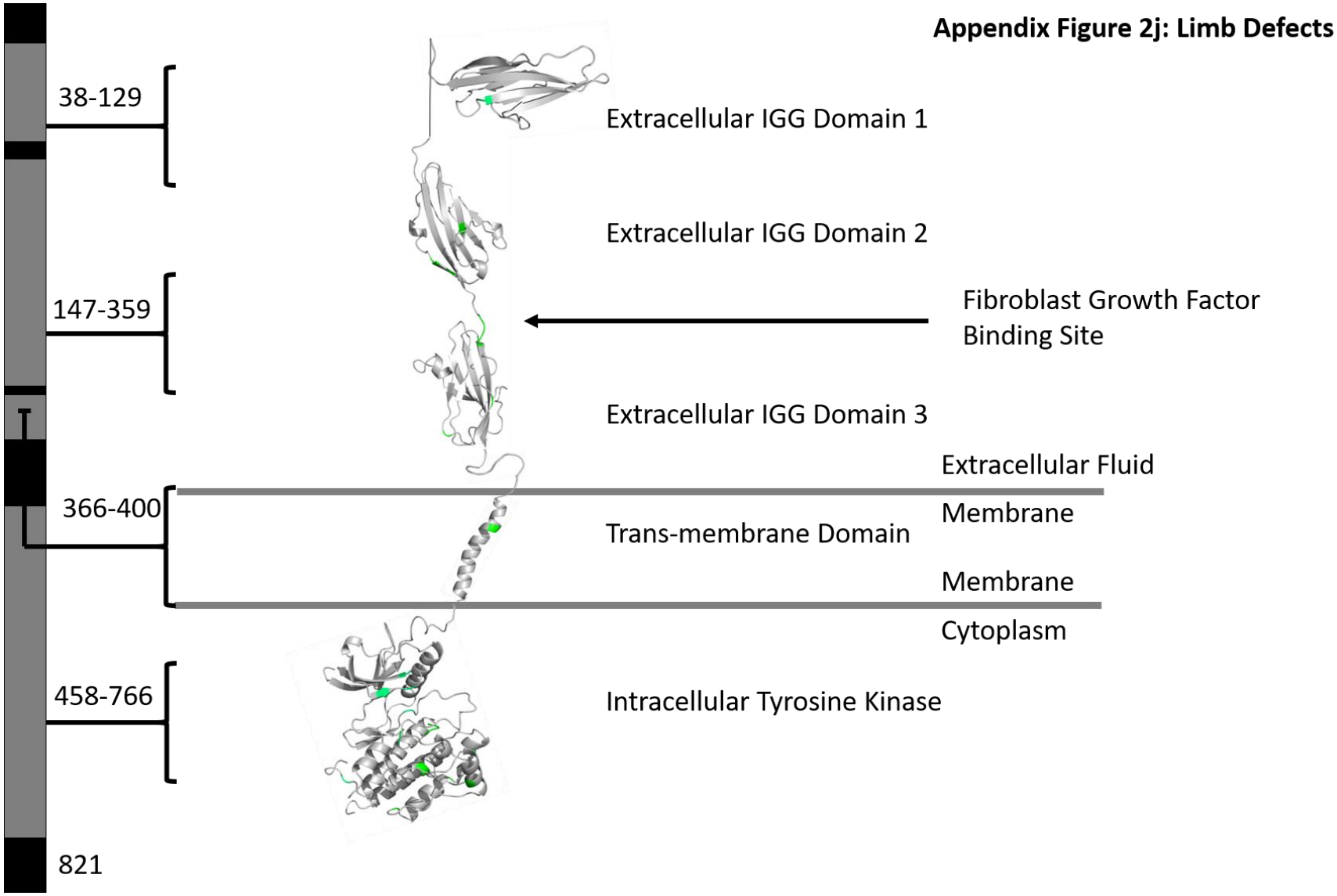
Appendix Figure 2h: Malformed Ears



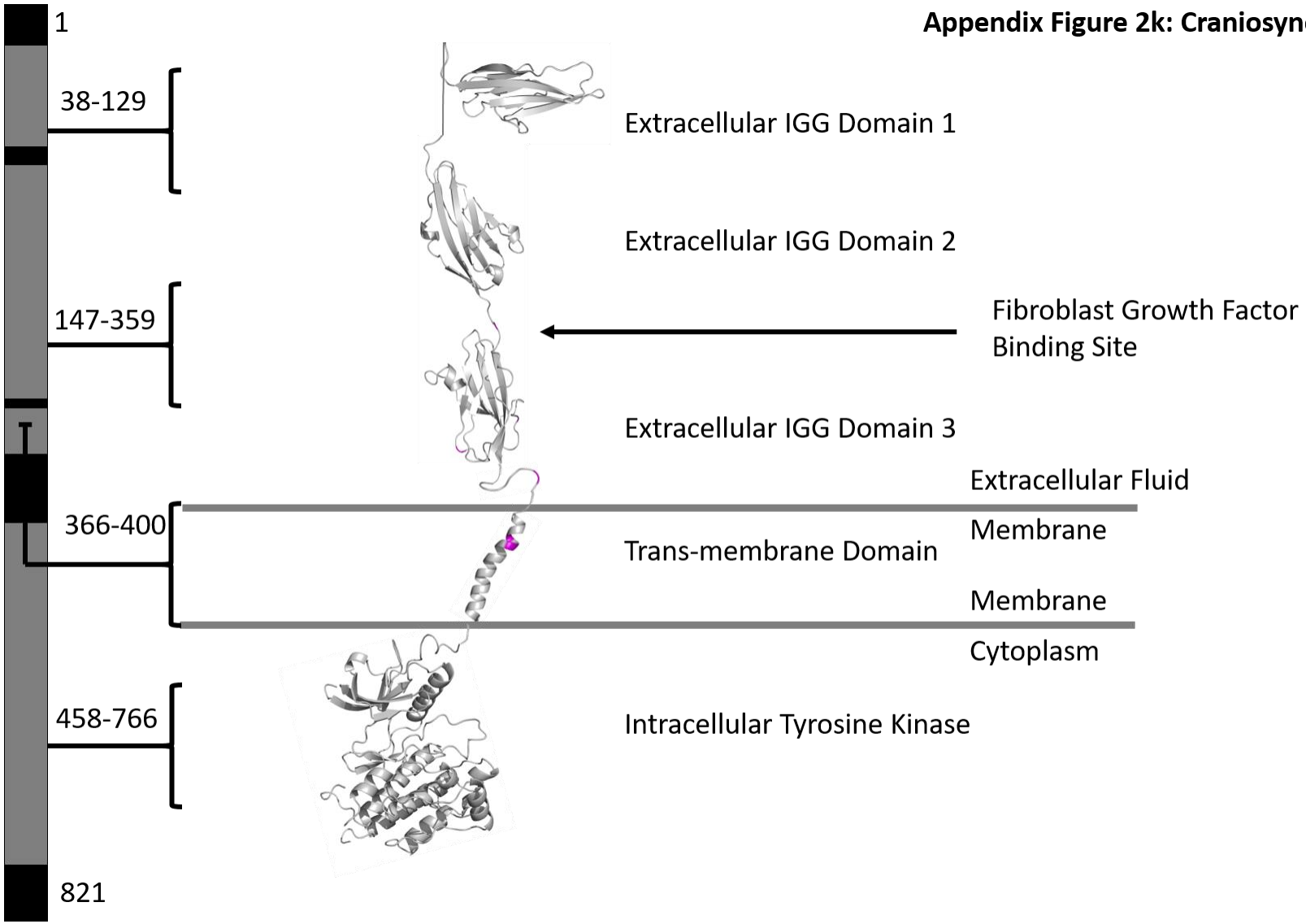
Appendix Figure 2i: Hearing Loss



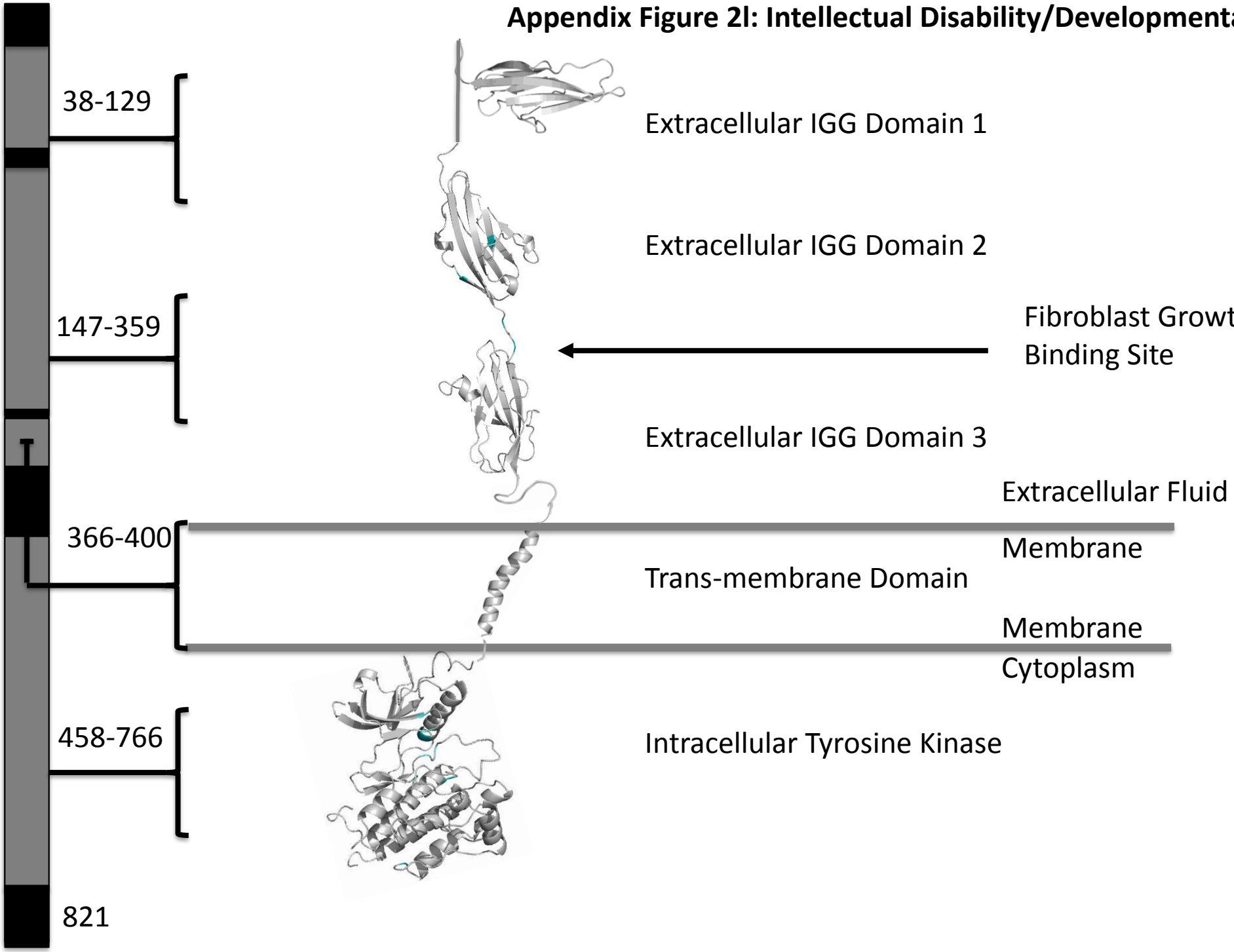
Appendix Figure 2j: Limb Defects



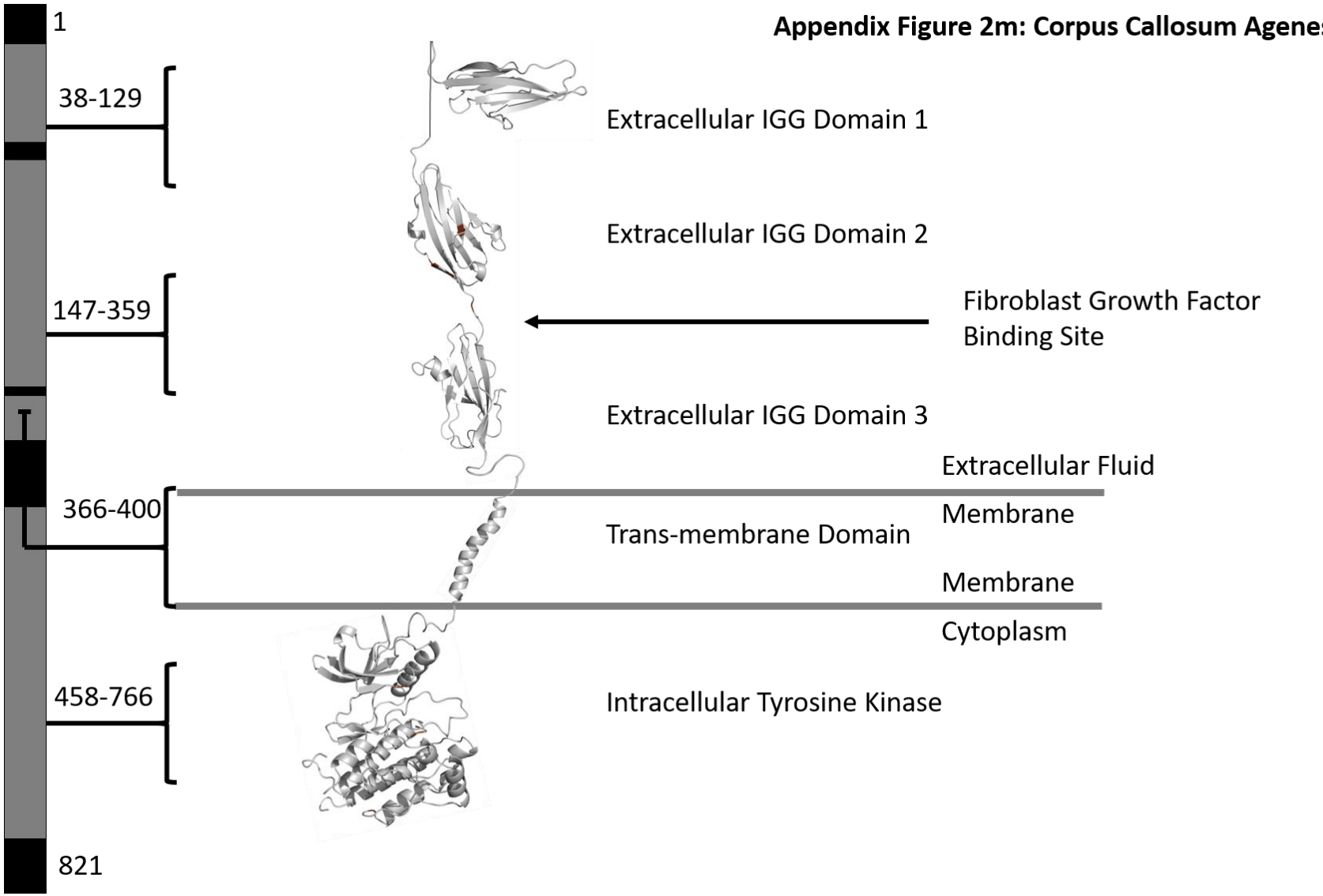
Appendix Figure 2k: Craniosynostosis



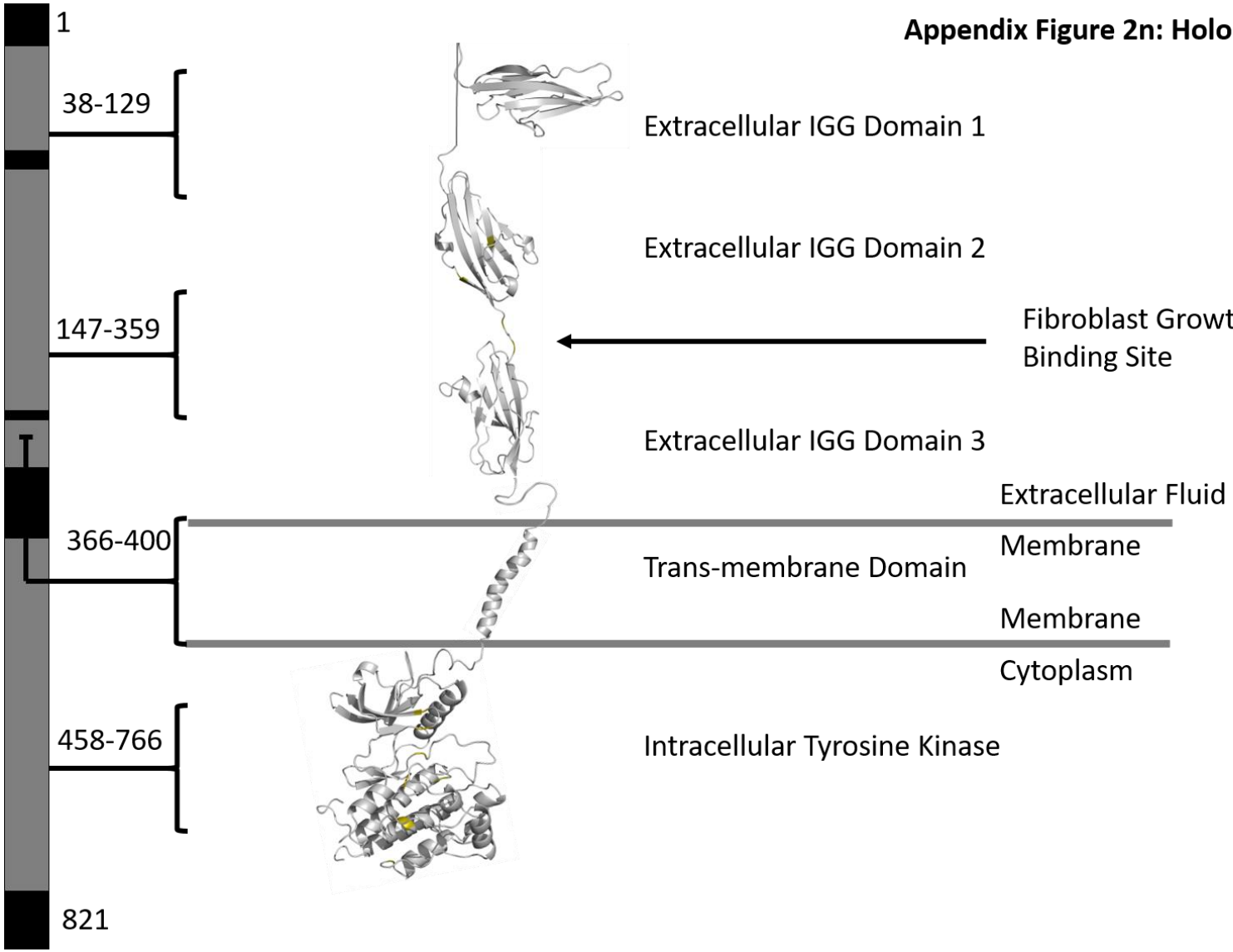
Appendix Figure 2l: Intellectual Disability/Developmental Delay



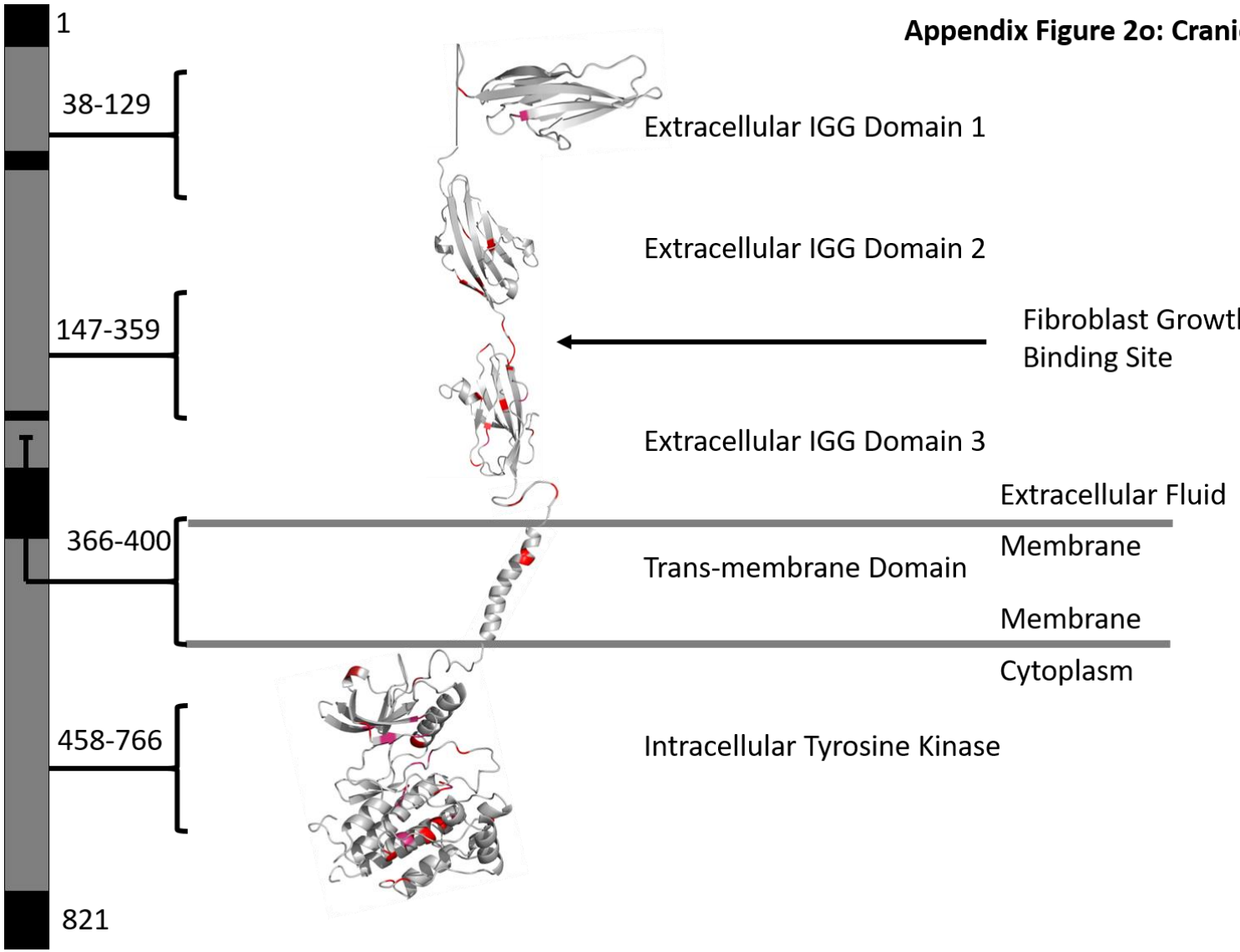
Appendix Figure 2m: Corpus Callosum Agenesis



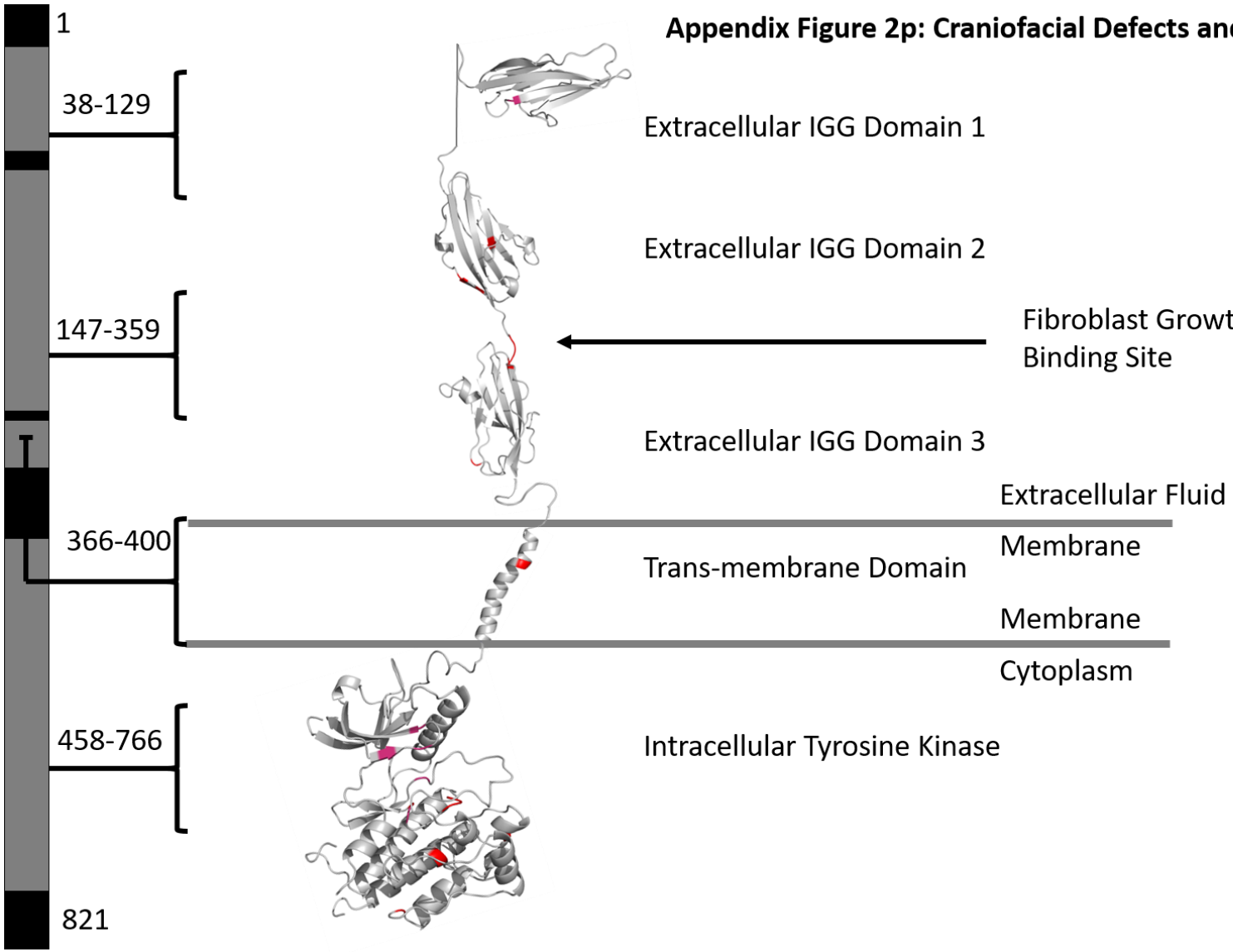
Appendix Figure 2n: Holoprosencephaly



Appendix Figure 2o: Craniofacial Defects



Appendix Figure 2p: Craniofacial Defects and Limb Defects



Appendix Figure 2a-p: Maps of *FGFR1* variants by clinical disease and phenotype

Variants of *FGFR1* reported in PubMed were recorded with published clinical phenotypes. A map of FGFR1 was generated for each disease and phenotype with the corresponding variants color coded by CADD phred score (more vibrant – more deleterious; less vibrant – less deleterious). Maps were generated for (a) Hartsfield syndrome, (b) Pfeiffer syndrome/osteoglophonic dysplasia, (c) encephalocraniocutaneous lipomatosis, (d) septo-optic dysplasia, (e) normosomic congenital hypogonadotropic hypogonadism/Kallmann syndrome, (f) dental agenesis, (g) cleft lip and/or palate, (h) malformed ears, (i) hearing loss, (j) limb defects (ectrodactyly, syndactyly polydactyly, oligodactyly or clinodactyly), (k) craniosynostosis, (l) intellectual disability/developmental delay, (m) corpus callosum agenesis, (n) holoprosencephaly, (o) craniofacial defects (dental agenesis, cleft lip and/or palate, malformed ears, and/or craniosynostosis), (p) craniofacial defects + limb defects (any variants modeled in o which are also associated with limb defects).

Protein Model Building and Testing

Model information for isoform 1 of *FGFR1* (ENST00000447712) was obtained using the Protein Data Bank (Berman, Westbrook et al. 2000) and Uniprot (UniProt 2015). Force Field X (Fenn and Schnieders 2011) was used to refine the structure using the polarizable AMOEBA force field (Shi, Xia et al. 2013). The refinement used a three-step procedure consisting of a local energy minimization, side-chain rotamer optimization using dead-end elimination (LuCore, Litman et al. 2015), and a final local energy minimization. Remaining unfavorable side-chain conformations were identified using MolProbity (Chen, Arendall et al. 2010), prompting further rounds of local minimization and rotamer optimization until no further improvements could be made.

Since the mutated amino acid residue is located within the tyrosine kinase (TK) domain, the Visual Molecular Dynamics (VMD (Humphrey, Dalke et al. 1996)) software was used to mimic a cellular environment and create the TK structure and topology files for simulation in the molecular dynamics program NAMD (Phillips, Braun et al. 2005). A tri-peptide surrogate for the unfolded state was created using Glycine residue 487 and its two surrounding residues (Glutamate and Cysteine)—a common approximation based on the premise that the unfolded state is largely unstructured. The NAMD software was used to compute thermodynamic stability changes using the CHARMM 27 force field (MacKerell, Banavali et al. 2000). The systems were equilibrated using local minimization followed by a 50 psec molecular dynamics simulation at 300 Kelvin. Production of alchemical-free energy simulations for the folded and unfolded states sampled an alchemical thermodynamic pathway between wildtype and variant end states ("alchemical" is the accepted term for a mathematically rigorous, but unphysical pathway between chemical states). The alchemical path was divided into ten windows, where each window defined an intermediate thermodynamic state along the pathway. Each window was sampled using molecular dynamics for 5 nsec based on a time step of 1 fsec and the NPT ensemble (constant number of particles, constant pressure of 1 atm and constant temperature of 300 K). The relative change in protein folding stability was then calculated as $\Delta\Delta G = \Delta G_{Folded} - \Delta G_{Unfolded}$.

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