

SUPPLEMENTAL MATERIALS

Supplemental Tables 1 - 4 and Figures 1 - 5

Supplemental Table 1. Control chromosomes screened for *GAB1* and *METTL13* variants

Variants	Pakistani	Indian	Coriell Human Diversity Panel	1000 Genome	NHLBI-EPS	ExAC	Total
<i>GAB1</i> c.347G>A (p.Gly116Glu)	0/380	0/192	-	0/2000	0/13,006	0/131,412	0/ 146,990
<i>METTL13</i> c.1631G>A (p.Arg544Gln)	0/380	0/192	0/172	0/2000	1/13,006	3/121,410	4/137,160

Supplemental Table 2: Novel changes found in the affected individuals of PK-2 family

Affected VII:5								
Gene ^A	Position ^B	Change	Genotype	Amino acid change	Transcript	PolyPhen-2	PROVEAN	SIFT
ANKS3	Chr16:4751002	T>C	homozygous	p.(Gln212Arg) p.(Gln418Arg)	ENST00000450067 ENST00000304283	Benign Deleterious	Neutral Neutral	Damaging Tolerated
ARHGEF16	Chr1:3394988	C>T	Homo	p.(Ala437Val)	ENST00000485984	No result	Neutral	Tolerated
CDCP2	Chr1:54606867	G>A	Homo	p.(Pro223Ser)	ENST00000371330	Deleterious	Deleterious	Damaging
FES	Chr15:91428302	C>T	Homo	p.(Pro38Ser)	ENST00000481665	No result	Neutral	Tolerated
GAB1	Chr4:144336904	G>A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging
GPR78	Chr4:8588919	C>T	Heterozygous	p.(His241Tyr)	ENST00000509216	No result	Neutral	Tolerated
GPR78	Chr4:8589000	C>T	Hetero	p.(Pro268Ser)	ENST00000509216	No result	Neutral	Tolerated
VWA8	Chr13:42295559	T>G	Hetero	p.(Ile875Leu)	ENST00000251030	Benign	Neutral	Tolerated
VWA8	Chr13:42295503	C>G	Hetero	p.(Gln892His)	ENST00000251030	Deleterious	Deleterious	Damaging
LRBA	Chr4:151729542	A>G	Homo	p.(Ser1772Pro)	ENST00000357115	Benign	Neutral	Tolerated
MUC16	Chr19:9075478	C>T	Hetero	p.(Ala3990Thr)	ENST00000397910	Benign	Neutral	Tolerated
MUC16	Chr19:8973588	A>G	Hetero	p.(Leu14234Pro)	ENST00000397910	Benign	Neutral	Tolerated
MUC16	Chr19:9062400	G>A	Hetero	p.(Thr8349Ile)	ENST00000397910	Deleterious	Neutral	Tolerated
PLA2G6	Chr22:38508070	C>T	Hetero	p.(Ala199Thr)	ENST00000463287	3' UTR	No result	No result
PLA2G6	Chr22:38541464	G>A	Hetero	p.(His136Tyr)	ENSP00000401242	Benign	Damaging	Damaging
PRDM16	Chr1:3347452	G>A	Homo	p.(Val1100Met)	ENST00000441472	Deleterious	Neutral	Tolerated
SLC7A11	Chr4:139106340	T>C	Homo	p.(Thr284Ala)	ENST00000280612	Benign	Neutral	Tolerated
SOX7	Chr8:10587750	A>C	Homo	p.(Val65Gly)	ENST00000304501	Deleterious	Neutral	Damaging
STARD9	Chr15:42976705	G>A	Hetero	p.(Ala977Thr)	ENST00000290607	No result	Neutral	Tolerated
STARD9	Chr15:42981314	A>C	Hetero	p.(Glu2513Ala)	ENST00000290607	No result	Neutral	Damaging
TTN	Chr2:179432791	A>G	Hetero	p.(Ile16956Thr)	ENST00000356127	Benign	Deleterious	Tolerated

<i>TTN</i>	Chr2:179606454	C>T	Hetero	p.(Val3473Met)	ENST00000356127	Intronic	Neutral	Tolerated
Affected VII:4								
<i>AKAP13</i>	Chr15:86064735	T/C	Hetero	p.(Leu36Ser)	ENST00000394516	Neutral	Neutral	Tolerated
<i>AKAP13</i>	Chr15:86198885	A/G	Hetero	p.(Met1537Val)	ENST00000394516	Deleterious	Neutral	Damaging
<i>DIP2B</i>	Chr12:51121533	C/T	Homo	p.(Pro1150Ser)	ENST00000301180	Neutral	Deleterious	Tolerated
<i>GAB1</i>	Chr4:144336904	G/A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging
<i>LRBA</i>	Chr4:151729542	A/G	Homo	p.(Ser1772Pro)	ENST00000357115	Neutral	Neutral	Tolerated
<i>PKHD1</i>	Chr6:51513969	C/T	Homo	p.(Ala3742Thr)	ENST00000371117	Neutral	Neutral	Tolerated
<i>PRDM16</i>	Chr1:3347452	G/A	Homo	p.(Val1100Met)	ENST00000441472	Deleterious	Neutral	Tolerated
<i>SLC7A11</i>	Chr4:139106340	T/C	Homo	p.(Thr284Ala)	ENST00000280612	Neutral	Neutral	Tolerated
<i>SP6</i>	Chr17:45924855	A/T	Homo	p.(Phe314Trp)	ENST00000342234	Deleterious	Deleterious	Tolerated
<i>TTN</i>	Chr2:179606454	C/T	Hetero	p.(Val3473Met)	ENST00000342992	No result	Neutral	Tolerated
<i>TTN</i>	Chr2:179423176	C/T	Hetero	p.(G19936Ser)	ENST00000356127	Neutral	Deleterious	Tolerated
Affected VII:14								
<i>ABCA7</i>	Chr19:1045149	C/T	Homo	p.(Pro455Leu)	ENST00000263094	Neutral	Neutral	Tolerated
<i>ADCY1</i>	Chr7:45743331	G/A	Homo	p.(Ala902Thr)	ENST00000297323	Deleterious	Deleterious	Damaging
<i>AKAP13</i>	Chr15:86064735	T/C	Hetero	p.(Leu36Ser)	ENST00000394516	Neutral	Neutral	Tolerated
<i>AKAP13</i>	Chr15:86198885	A/G	Hetero	p.(Met1537Val)	ENST00000394516	Deleterious	Neutral	Damaging
<i>ATP8B3</i>	Chr19:1800301	G/A	Homo	p.(Leu381Phe)	ENST00000532824	Deleterious	Deleterious	Tolerated
<i>BTC</i>	Chr4:75695294	C/G	Homo	p.(Cys46Ser)	ENST00000395743	Deleterious	Neutral	Tolerated
<i>C2orf69</i>	Chr2:200776268	G/C	Homo	p.(Gly36Ala)	ENST00000319974	Neutral	Neutral	Damaging
<i>CCDC137</i>	Chr17:79639582	C/T	Hetero	p.(Pro240Ser)	ENST00000329214	Neutral	Neutral	Tolerated
<i>CCDC137</i>	Chr17:79639603	C/T	Hetero	p.(Arg247Cys)	ENST00000329214	Deleterious	Deleterious	Damaging
<i>CDH23</i>	Chr10:73270973	G/A	Homo	p.(Gly145Arg)	ENST00000224721	No result	Neutral	Damaging
<i>CKAP4</i>	Chr12:106641268	G/A	Homo	p.(Ala121Val)	ENST00000553039	Neutral	Neutral	Damaging

<i>DCHS1</i>	Chr11:6653567	G/T	Homo	p.(Ala1059Glu)	ENST00000299441	Neutral	Neutral	Tolerated
<i>DNHD1</i>	Chr11:6588288	A/G	Homo	p.(Tyr118Cys)	ENST00000525883	Deleterious	Deleterious	Damaging
<i>GAB1</i>	Chr4:144336904	G/A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging
<i>HDAC5</i>	Chr17:42155937	C/T	Hetero	p.(Ser1002Asn)	ENST00000336057	Neutral	Neutral	Tolerated
<i>HDAC5</i>	Chr17:42168769	C/T	Hetero	p.(Ser420Asn)	ENST00000225983	Neutral	Neutral	Tolerated
<i>IGSF9</i>	Chr1:159897181	G/T	Hetero	p.(Ala1149Asp)	ENST00000361509	Neutral	Neutral	Damaging
<i>IGSF9</i>	Chr1:159912788	C/T	Hetero	p.(Gly71Asp)	ENST00000198587	Deleterious	Neutral	Tolerated
<i>KIAA0564</i>	Chr13:42264348	A/C	Hetero	p.(Tyr1214*)	ENST00000251030	No result	NA	NA
<i>KIAA0564</i>	Chr13:42265469	T/C	Hetero	p.(Ser1189Gly)	ENST00000251030	Neutral	Neutral	Tolerated
<i>LRBA</i>	Chr4:151729542	A/G	Homo	p.(Ser1772Pro)	ENST00000357115	Neutral	Neutral	Tolerated
<i>MAP3K15</i>	ChrX:19482479	A/C	Hetero	p.(Cys191Gly)	ENST00000338883	No result	Neutral	Tolerated
<i>MAP3K15</i>	ChrX:19482477	G/C	Hetero	p.(Cys191Trp)	ENST00000338883	No result	Deleterious	Tolerated
<i>MLL</i>	Chr11:118376712	A/G	Homo	p.(Asn2276Asp)	ENST00000359313	Neutral	Neutral	Damaging
<i>NLRC3</i>	Chr16:3611771	G/T	Hetero	p.(Phe649Leu)	ENST00000301749	Neutral	Neutral	Tolerated
<i>NLRC3</i>	Chr16:3611710	T/C	Hetero	p.(Lys670Glu)	ENST00000301749	Neutral	Neutral	Tolerated
<i>PGAP1</i>	Chr2:197706020	A/G	Homo	p.(Tyr140His)	ENST00000422444	Deleterious	Deleterious	Damaging
<i>RBMXL2</i>	Chr11:7110371	C/T	Homo	p.(Pro7Leu)	ENST00000306904	Deleterious	Deleterious	Damaging
<i>SLC3A2</i>	Chr11:62623793	C/T	Homo	p.(Gln18*)	ENST00000377889	No result	NA	NA
<i>SLC7A11</i>	Chr4:139106340	T/C	Homo	p.(Thr284Ala)	ENST00000280612	Neutral	Neutral	Tolerated
<i>SPECC1L</i>	Chr22:24718797	G/C	Homo	p.(Glu617Gln)	ENST00000314328	Deleterious	Neutral	Tolerated
<i>TTN</i>	Chr2:179423176	C/T	Hetero	p.(Gly19936Ser)	ENST00000356127	No result	Deleterious	Tolerated
<i>TTN</i>	Chr2:179432791	A/G	Hetero	p.(Ile16956Thr)	ENST00000356127	No result	Deleterious	Tolerated
<i>UBASH3A</i>	Chr21:43829569	C/G	Homo	p.(Pro69Arg)	ENST00000291535	Deleterious	Neutral	Tolerated
<i>VSIG10</i>	Chr12:118511557	C/T	Homo	p.(Arg389Gln)	ENST00000359236	Deleterious	Neutral	Tolerated
<i>ZNF7</i>	Chr8:146066983	C/G	Homo	p.(Thr164Ser)	ENST00000325241	Neutral	Neutral	Tolerated

Affected VI:2								
<i>DNAH10</i>	Chr12:124358220	G/A	Hetero	p.(Arg2516His)	ENST00000409039	Deleterious	Deleterious	Damaging
<i>DNAH10</i>	Chr12:124417990	G/A	Hetero	p.(Arg4352His)	ENST00000409039	Neutral	Deleterious	Tolerated
<i>GAB1</i>	Chr4:144336904	G/A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging
<i>HSPG2</i>	Chr1:22178407	G/A	Hetero	p.(Arg2295Cys)	ENST00000374695	Deleterious	Deleterious	Tolerated
<i>HSPG2</i>	Chr1:22211313	C/T	Hetero	p.(Arg485Gln)	ENST00000374695	Deleterious	Neutral	Tolerated
<i>RPTOR</i>	Chr17:78899204	A/G	Hetero	p.(Lys790Arg)	ENST00000544334	Neutral	Neutral	Tolerated
<i>RPTOR</i>	Chr17:78831665	G/A	Hetero	p.(Val307Ile)	ENST00000537330	Deleterious	Neutral	Tolerated
<i>SDK1</i>	Chr7:4006954	C/G	Hetero	p.(Ile478Met)	ENST00000389531	Neutral	Neutral	Tolerated
<i>SDK1</i>	Chr7:3678709	C/T	Hetero	p.(Leu178Phe)	ENST00000389531	Deleterious	Neutral	Damaging
<i>SYNE2</i>	Chr14:64591831	C/G	Hetero	p.(Thr1120Ser)	ENST00000555002	Neutral	Neutral	Tolerated
<i>SYNE2</i>	Chr14:64588827	A/G	Hetero	p.(Asp1053Gly)	ENST00000555002	Neutral	Neutral	Tolerated
<i>SYNE2</i>	Chr14:64591884	C/G	Hetero	p.(Gln1138Glu)	ENST00000555002	Deleterious	Neutral	Tolerated
<i>SYNE2</i>	Chr14:64520322	C/T	Hetero	p.(Arg3231Cys)	ENST00000344113	Neutral	Deleterious	Damaging
<i>TTLL12</i>	Chr22:43570589	C/T	Hetero	p.(Ser317Asn)	ENST00000216129	Neutral	Neutral	Tolerated
<i>TTLL12</i>	Chr22:43569832	C/A	Hetero	p.(Trp410Cys)	ENST00000216129	Neutral	Neutral	Damaging
Affected VI:21								
<i>AHNAK</i>	Chr11:62299560	C/T	Homo	p.(Asp777Asn)	ENST00000378024	Neutral	Deleterious	Tolerated
<i>ARHGEF26</i>	Chr3:153847426	C/G	Hetero	p.(Ser396*)	ENST00000356448	NA	NA	NA
<i>ARHGEF26</i>	Chr3:153958296	A/G	Hetero	p.(His743Arg)	ENST00000356448	Deleterious	Deleterious	Damaging
<i>BCORL1</i>	ChrX:129148381	C/G	Homo	p.(Pro145Ala)	ENST00000456822	Neutral	Neutral	Damaging
<i>CDH23</i>	Chr10:73270973	G/A	Homo	p.(Gly145Arg)	ENST00000224721	No result	Neutral	Damaging
<i>FER1L6</i>	Chr8:124989691	C/G	Hetero	p.(Pro302Arg)	ENST00000399018	Deleterious	Deleterious	Damaging
<i>FER1L6</i>	Chr8:125072827	G/C	Hetero	p.(Gln1008His)	ENST00000399018	Deleterious	Neutral	Tolerated
<i>GAB1</i>	Chr4:144336904	G/A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging

<i>GLYATL2</i>	Chr11:58602287	A/T	Homo	p.(Phe167Tyr)	ENST00000287275	Deleterious	Neutral	Tolerated
<i>HDAC5</i>	Chr17:42155937	C/T	Hetero	p.(Ser1002Asn)	ENST00000336057	Neutral	Neutral	Tolerated
<i>HDAC5</i>	Chr17:42168769	C/T	Hetero	p.(Ser419Asn)	ENST00000336057	Neutral	Neutral	Tolerated
<i>LRBA</i>	Chr4:151729542	A/G	Homo	p.(Ser1772Pro)	ENST00000357115	Neutral	Neutral	Tolerated
<i>MID2</i>	ChrX:107148811	A/G	Homo	p.(Asn343Ser)	ENST00000262843	Neutral	Neutral	Tolerated
<i>NOD1</i>	Chr7:30491514	C/T	Homo	p.(Gly507Arg)	ENST00000222823	Deleterious	Neutral	Tolerated
<i>SLC7A11</i>	Chr4:139106340	T/C	Homo	p.(Thr284Ala)	ENST00000280612	Neutral	Neutral	Tolerated
<i>STAG2</i>	ChrX:123224495	G/A	Homo	p.(Met1047Ile)	ENST00000354548	Neutral	Neutral	Tolerated
<i>SYNE2</i>	Chr14:64692223	C/T	Hetero	p.(Gln6800*)	ENST00000554584	NA	NA	NA
<i>SYNE2</i>	Chr14:64692067	C/T	Hetero	p.(Leu6748Phe)	ENST00000554584	No result	Neutral	Tolerated
<i>SYNE2</i>	Chr14:64691219	C/T	Hetero	p.(Ser3170Leu)	ENST00000357395	Neutral	Deleterious	Damaging
<i>TMEM140</i>	Chr7:134849260	G/C	Homo	p.(Val23Leu)	ENST00000275767	Neutral	Neutral	Tolerated
<i>TTN</i>	Chr2:179606454	C/T	Hetero	p.(Val3473Met)	ENST00000356127	No result	Neutral	Tolerated
<i>TTN</i>	Chr2:179432791	A/G	Hetero	p.(Ile16956Thr)	ENST00000356127	Neutral	Deleterious	Tolerated
Affected V:1								
<i>ALDOA</i>	Chr16:30078932	C/T	Homo	p.(Arg146Cys)	ENST00000395248	Neutral	Neutral	Tolerated
<i>C4orf27</i>	Chr4:170652863	C/T	Homo	p.(Gly301Ser)	ENST00000393381	Deleterious	Deleterious	Damaging
<i>GAB1</i>	Chr4:144336904	G/A	Homo	p.(Gly116Glu)	ENST00000262994	Deleterious	Deleterious	Damaging
<i>LRBA</i>	Chr4:151729542	A/G	Homo	p.(Ser1772Pro)	ENST00000357115	Neutral	Neutral	Tolerated
<i>OR52E8</i>	Chr11:5878518	T/C	Homo	p.(Thr139Ala)	ENST00000537935	Neutral	Neutral	Tolerated
<i>PTGR1</i>	Chr9:114332484	G/A	Homo	p.(Pro133Ser)	ENST00000238248	Neutral	Neutral	Tolerated
<i>RBMXL3</i>	ChrX:114424906	G/A	Homo	p.(Arg301Gln)	ENST00000424776	Deleterious	Neutral	Damaging
<i>SDK1</i>	Chr7:4006954	C/G	Homo	p.(Ile478Met)	ENST00000389531	Neutral	Neutral	Tolerated
<i>SDK1</i>	Chr7:3678709	C/T	Homo	p.(Lys178Phe)	ENST00000389531	Deleterious	Neutral	Damaging
<i>SHROOM2</i>	ChrX:9900724	G/A	Homo	p.(Arg1134His)	ENST00000380913	Neutral	Neutral	Tolerated

<i>SMOC2</i>	Chr6:169053647	G/A	Homo	p.(Asp19Asn)	ENST00000392101	Deleterious	Deleterious	Damaging
<i>WDR17</i>	Chr4:177058710	G/C	Homo	p.(Gly436Ala)	ENST00000393643	Deleterious	Neutral	Tolerated
<i>ZBTB20</i>	Chr3:114069696	T/A	Homo	p.(Glu337Val)	ENST00000357258	Neutral	Neutral	Damaging
<i>ZNF484</i>	Chr9:95609484	A/G	Homo	p.(Cys493Arg)	ENST00000332591	Deleterious	Deleterious	Damaging

^A Genes for which segregation analysis was performed in family PK-2 are given in bold.

^B Nucleotide locations are according to human reference sequence GRCh37/hg19 assembly.

Supplemental Table 3: Genes with novel changes found in six affected individuals of PK-2 family through WES

Gene	Change	Genotype	Affected 1	Affected 2	Affected 3	Affected 4	Affected 5	Affected 6
<i>ABCA7</i>	p.(Pro455Leu)	Homozygous	-	-	Present	-	-	-
<i>ADCY1</i>	p.(Ala902Thr)	Homozygous	-	-	Present*	-	-	-
<i>AHNAK</i>	p.(Asp777Asn)	Homozygous	-	-	-	-	Present	-
<i>AKAP13</i>	p.(Leu36Ser)	Compound	-	Present	Present	-	-	-
	p.(Met1537Val)	Heterozygous	-	Present	Present	-	-	-
<i>ALDOA</i>	p.(Arg146Cys)	Homozygous	-	-	-	-	-	Present
<i>ANKS3</i>	p.(Gln212Arg)	Homozygous	Present	-	-	-	-	-
<i>ARHGEF16</i>	p.(Ala437Val)	Homozygous	Present	-	-	-	-	-
<i>ARHGEF26</i>	p.(Ser396*)	Compound	-	-	-	-	Present	-
	p.(His743Arg)	Heterozygous	-	-	-	-	Present	-
<i>ATP8B3</i>	p.(Leu381Phe)	Homozygous	-	-	Present	-	-	-
<i>BCORL1</i>	p.(Pro145Ala)	Homozygous	-	-	-	-	Present	-
<i>BTC</i>	p.(Cys46Ser)	Homozygous	-	-	Present	-	-	-
<i>C2ORF69</i>	p.(Gly36Ala)	Homozygous	-	-	Present	-	-	-
<i>C4ORF27</i>	p.(Gly301Ser)	Homozygous	-	-	-	-	-	Present
<i>CCDC137</i>	p.(Pro240Ser)	Compound	-	-	Present	-	-	-
	p.(Arg247Cys)	Heterozygous	-	-	Present	-	-	-
<i>CDCP2</i>	p.(Pro223Ser)	Homozygous	Present	-	-	-	-	-
<i>CDH23</i>	p.(Gly145Arg)	Homozygous	-	-	Present	-	Present	-
<i>CKAP4</i>	p.(Ala121Val)	Homozygous	-	-	Present	-	-	-
<i>DCHS1</i>	p.(Ala1059Glu)	Homozygous	-	-	Present	-	-	-
<i>DIP2B</i>	p.(Pro1150Ser)	Homozygous	-	Present	-	-	-	-

<i>DNAH10</i>	p.(Arg2516His) p.(Arg4352His)	Compound Heterozygous	- -	- -	- -	Present Present	- -	- -
<i>DNHD1</i>	p.(Tyr118Cys)	Homozygous	-	-	Present	-	-	-
<i>FER1L6</i>	p.(Pro302Arg) p.(Gln1008His)	Compound Heterozygous	- -	- -	- -	- -	Present Present	- -
<i>FES</i>	p.(Pro38Ser)	Homozygous	Present	-	-	-	-	-
<i>GAB1</i>	p.(Gly116Glu)	Homozygous	Present	Present	Present	Present	Present	Present
<i>GLYATL2</i>	p.(Phe167Tyr)	Homozygous	-	-	-	-	Present	-
<i>GPR78</i>	p.(His241Tyr) p.(Pro268Ser)	Compound Heterozygous	Present Present	- -	- -	- -	- -	- -
<i>HDAC5</i>	p.(Ser420Asn) p.(Ser1002Asn)	Compound Heterozygous	- -	- -	Present Present	- -	Present Present	- -
<i>HSPG2</i>	p.(Arg2295Cys) p.(Arg485Gln)	Compound Heterozygous	- -	- -	- -	Present Present	- -	- -
<i>IGSF9</i>	p.(Gly71Asp) p.(Ala1149Asp)	Compound Heterozygous	- -	- -	Present Present	- -	- -	- -
<i>VWA8</i>	p.(Ile875Leu) p.(Gln892His) p.(Ser1189Gly) p.(Tyr1214*)	Compound Heterozygous	Present Present - -	- - - -	- - Present Present	- - - -	- - - -	- - - -
<i>LRBA</i>	p.(Ser1772Pro)	Homozygous	Present	Present	Present	-	Present	Present
<i>MAP3K15</i>	p.(Cys191Gly) p.(Cys191Trp)	Compound Heterozygous	- -	- -	Present Present	- -	- -	- -
<i>MID2</i>	p.(Asn343Ser)	Homozygous	-	-	-	-	Present	-
<i>MLL</i>	p.(Asn2276Asp)	Homozygous	-	-	Present	-	-	-
<i>MUC16</i>	p.(Ala3990Thr)	Compound	Present	-	-	-	-	-

	p.(Leu14234Pro)	Heterozygous	Present	-	-	-	-	-
<i>NOD1</i>	p.(Gly507Arg)	Homozygous	-	-	-	-	Present	-
<i>NLRC3</i>	p.(Phe649Leu)	Compound	-	-	Present	-	-	-
	p.(Lys670Glu)	Heterozygous	-	-	Present	-	-	-
<i>OR52E8</i>	p.(Thr139Ala)	Homozygous	-	-	-	-	-	Present
<i>PGAP1</i>	p.(Tyr140His)	Homozygous	-	-	Present	-	-	-
<i>PKHD1</i>	p.(Ala3742Thr)	Homozygous	-	Present	-	-	-	-
<i>PLA2G6</i>	p.(His136Tyr)	Compound	Present	-	-	-	-	-
	p.(Ala199Thr)	Heterozygous	Present	-	-	-	-	-
<i>PRDM16</i>	p.(Val1100Met)	Homozygous	Present	Present	-	-	-	-
<i>PTGR1</i>	p.(Pro133Ser)	Homozygous	-	-	-	-	-	Present
<i>RBMXL2</i>	p.(Pro7Leu)	Homozygous	-	-	Present	-	-	-
<i>RBMXL3</i>	p.(Arg301Gln)	Homozygous	-	-	-	-	-	Present
<i>RPTOR</i>	p.(Val307Ile)	Compound	-	-	-	Present	-	-
	p.(Lys790Arg)	Heterozygous	-	-	-	Present	-	-
<i>SDK1</i>	p.(Leu178Phe)	Compound	-	-	-	Present	-	Present
	p.(Ile478Met)	Homozygous	-	-	-	Present	-	Present
<i>SHROOM2</i>	p.(Arg1134His)	Homozygous	-	-	-	-	-	Present
<i>SLC3A2</i>	p.(Gln18*)	Homozygous	-		Present	-	-	-
<i>SLC7A11</i>	p.(Thr284Ala)	Homozygous	Present	Present	Present	-	Present	-
<i>SMOC2</i>	p.(Asp19Asn)	Homozygous	-	-	-	-	-	Present
<i>SOX7</i>	p.(Val65Gly)	Homozygous	Present	-	-	-	-	
<i>SP6</i>	p.(Phe314Trp)	Homozygous	-	Present	-	-	-	
<i>SPECC1L</i>	p.(Glu617Gln)	Homozygous	-	-	Present	-	-	
<i>STAG2</i>	p.(Met1047Ile)	Homozygous	-	-	-	-	Present	-

<i>STARD9</i>	p.(Ala977Thr) p.(Glu2513Ala)	Compound Heterozygous	Present	-	-	-	-	-
<i>SYNE2</i>	p.(Thr1120Ser) p.(Asp1053Gly) p.(Gln1138Glu) p.(Arg3231Cys) p.(Ser3170Leu) p.(Leu6748Phe) p.(Gln6800*)	Compound Heterozygous	- - - - - - -	- - - - - - -	- - - - - - -	Present Present Present Present - - -	- - - - Present Present Present	- - - - - - -
<i>TMEM140</i>	p.(Val23Leu)	Homozygous	-	-	-	-	Present	-
<i>TTL12</i>	p.(Ser317Asn) p.(Trp410Cys)	Compound Heterozygous	- -	- -	- -	Present Present	- -	- -
<i>TTN</i>	p.(Val3473Met) p.(Ile16956Thr) p.(Gly19936Ser)	Compound Heterozygous	Present Present -	Present - Present	- Present Present	- - -	Present Present -	- - -
<i>UBASH3A</i>	p.(Pro69Arg)	Homozygous	-	-	Present	-		-
<i>VSIG10</i>	p.(Arg389Gln)	Homozygous	-	-	Present	-	-	-
<i>WDR17</i>	p.(Gly436Ala)	Homozygous	-	-	-	-	-	Present
<i>ZBTB20</i>	p.(Glu337Val)	Homozygous	-	-	-	-	-	Present
<i>ZNF7</i>	p.(Thr164Ser)	Homozygous	-	-	Present	-	-	-
<i>ZNF484</i>	p.(Cys493Arg)	Homozygous	-	-	-	-	-	Present

**ADCY1* variant did not co-segregate with hearing loss even within a sibship.

Supplemental Table 4. Transcriptome analysis of *Gab1* and *Mettl13* expression in mouse inner ear

	E16a		E16b		P0		P4		P7		P16	
	<i>Gab1</i>	<i>Mettl13</i>	<i>Gab1</i>	<i>Mettl13</i>	<i>Gab1</i>	<i>Mettl13</i>	<i>Gab1</i>	<i>Mettl13</i>	<i>Gab1</i>	<i>Mettl13</i>	<i>Gab1</i>	<i>Mettl13</i>
Cochlea GFP+ cell (Hair cells)*	725	7	670	15	457	2	366	2	350	3	NA	NA
Cochlea GFP- cell (Supporting cells)	1538	14	668	11	677	14	1185	5	1156	9	NA	NA
Utricle GFP+ cell (Hair cells)	871	4	590	1	161	3	795	4	779	2	294	6
Utricle GFP- cell (Supporting cells)	1531	10	581	2	824	15	1182	15	1934	1	1006	15
	E12		E13		E16		P0		P6		P15	
Spiral ganglion [#]	1824.8 (114.66)	7.94 (3.07)	2674.52 (164.48)	17.27 (7.64)	898.24 (110.81)	26.09 (7.18)	1551.26 (994.33)	16.08 (6)	2522.9 (469.61)	17.17 (7.04)	1283.02 (371.42)	7.02 (9.28)
Vestibular ganglion [#]	2046.33 (73.09)	12.42 (11.95)	2566.03 (20.39)	27.17 (5)	3046.54 (345.95)	17.02 (5.2)	3005.31 (202.3)	4.13 (2.75)	2920.94 (155.09)	7.92 (0.79)	2671.35 (209.27)	20.58 (4.77)

*Read counts; [#]Mean values (standard deviation); NA: Not available.

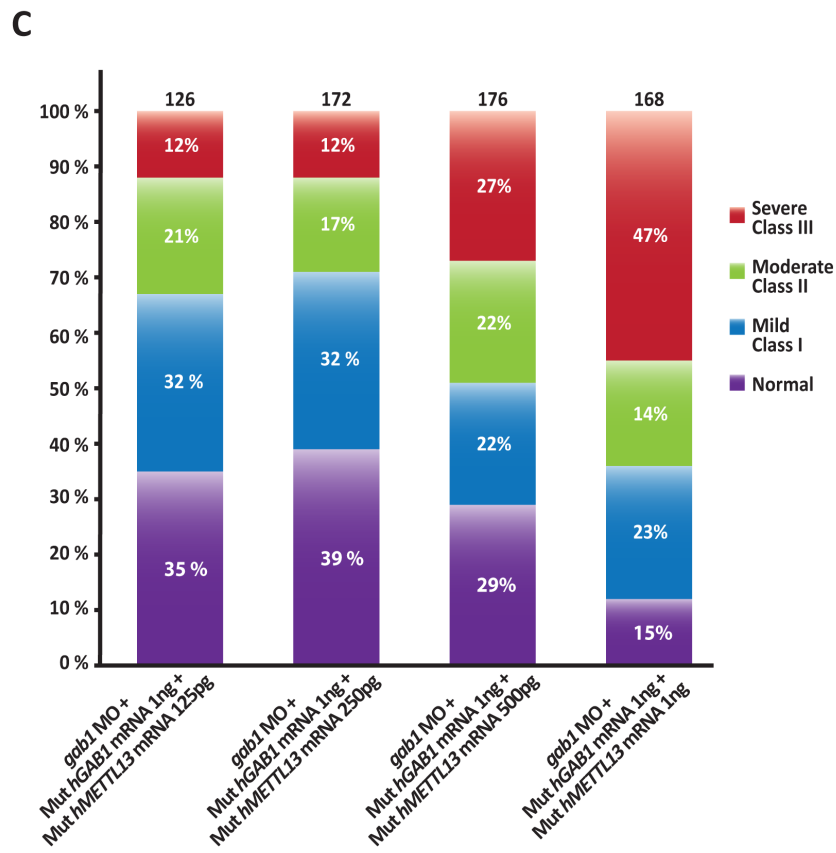
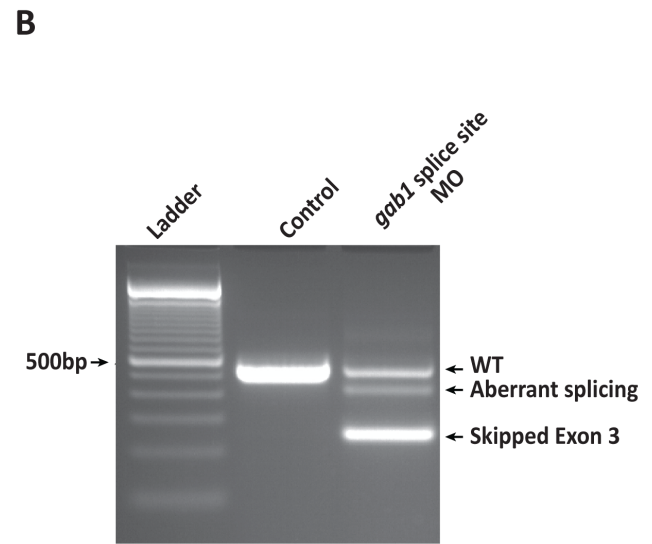
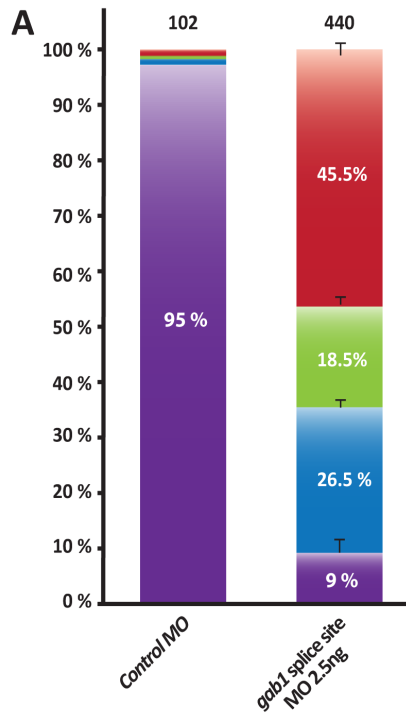
Supplemental Table 5. Primers and TaqMan probe sequences for real time PCR

Gene	Forward primer	Reverse primer	TaqMan Probe
Human			
<i>GAPDH</i>	acatcgctcagacaccatg	tgtagttaggtcaatgaaggg	FAM/AAGGTCGGA/ZEN/GTCAACGGATTTGGTC/IABk
<i>GAB1</i>	gcatagcacaactcaagcag	tgtctccttgggcttgatc	FAM/CTGGACAGGTTTGGGTTCATGGGA/IABk
<i>METTL13</i>	agaaacccagagctactcctag	tcgatctccacagcatcaatg	FAM/CCCCTCTTTGTCCACGATCATTTTCCA/IABk
<i>PI3KR2</i>	ggacaacagagagatcgacaag	ttttaatccccagccactcg	FAM/CATGAACAGCCTCAAGCCGGAC/IABk
<i>SPRY2</i>	actgagcaaggaagatttggg	agtcaatcagttctgggc	FAM/AGGTGTGAG/ZEN/GACTGTGGCAAGTG/IABk
<i>PTPN11</i>	cagggacgttcattgtgattg	aatcgggtactgtgcttctgc	FAM/CAGATGGTGCGGTCTCAGAGGTC/IABk
c-MET			
<i>AKT3</i> ^A	atttgtcgagagagcggggtgttct	tggctgcatctgtgatcccttctt	
Zebrafish			
<i>Gapdh</i> ^A	aattctgggatacacgggagcacca	tcagggtcacatacacgggttgctgt	
<i>gab1</i> ^A	tcgacttggaacctgggaaatcaa	tgctgatccaccagcacatagtct	
<i>mettl13</i> ^A	agacatgcaggctgtccaatcaga	aagcactgagccctcttccaatca	

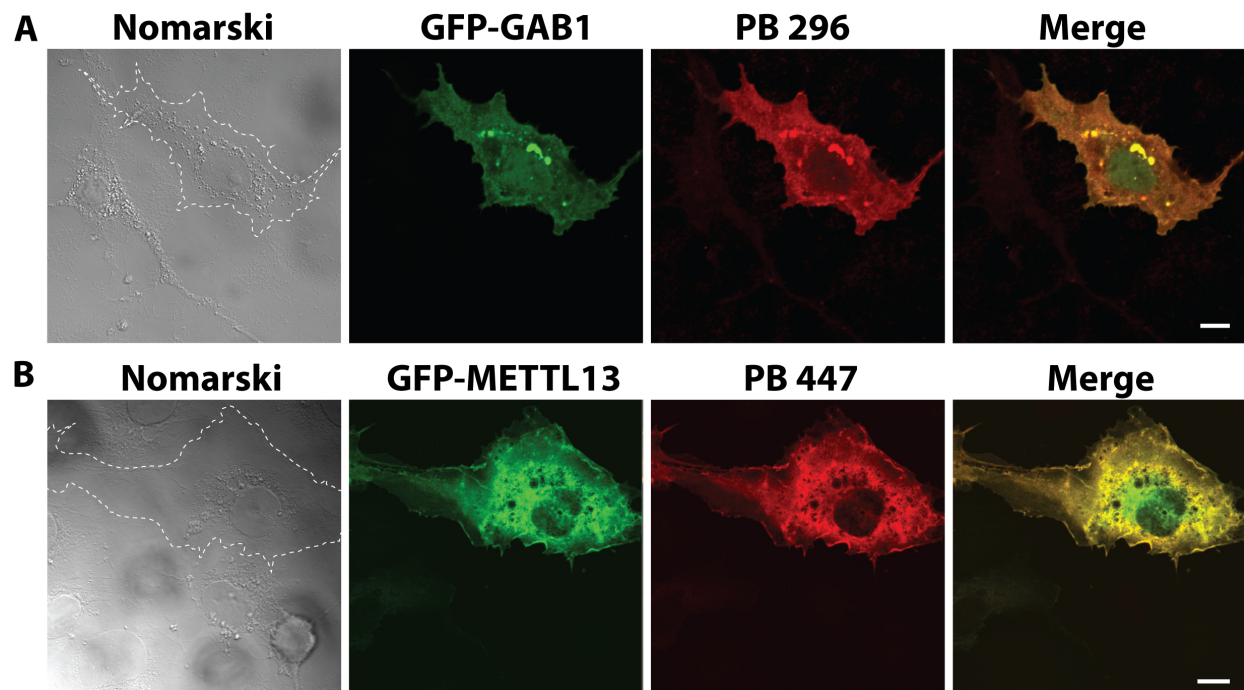
^A PCR was performed using SybrGreen Master Mix.

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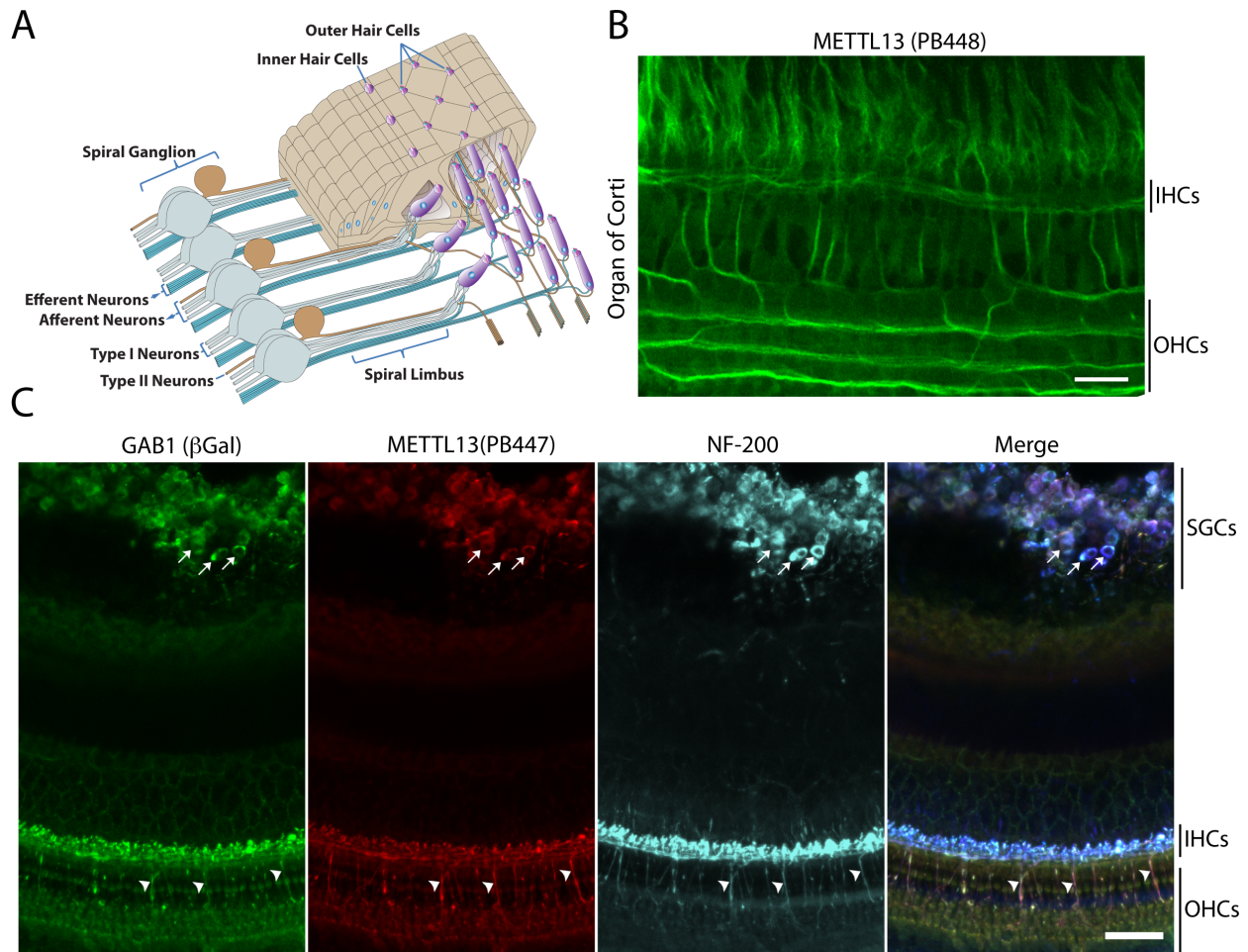
Supplemental Figure 1. ClustalW alignment of GAB family members showed high conservation of p.Gly116 residue of GAB1 substituted in the DFNB26 family. The glycine residue at position 116 of human GAB1 is highly conserved across homologs and paralogs. Asparagine is present at position 116 in GAB3.



Supplemental Figure 2. Human *Mettl13* harboring p.Arg544Gln variant rescues the *gab1* morphant phenotype in a dose dependent manner. (A) Splice site morpholino (MO)-based suppression of *gab1* also results in developmental defects. (B) RT-PCR analysis of *gab1* cDNA from control and *gab1* splice site MO injected zebrafish. (C) *In vivo* rescue assay of *gab1* morpholino (MO) was performed by co-injection of 1 ng of wild type human *GAB1* mRNA and *gab1* mRNA-translation-blocking MO, along with various concentrations of human full length *METTL13* mRNA encoding p.Arg544Gln modifier allele. No rescue was observed with 1000pg of the human full length *METTL13* mRNA encoding p.Arg544Gln modifier allele, however with a decrease in concentration, rescue was observed, with the maximum rescue observed when 250pg of the *METTL13* modifier mRNA with p.Arg544Gln variant was injected.



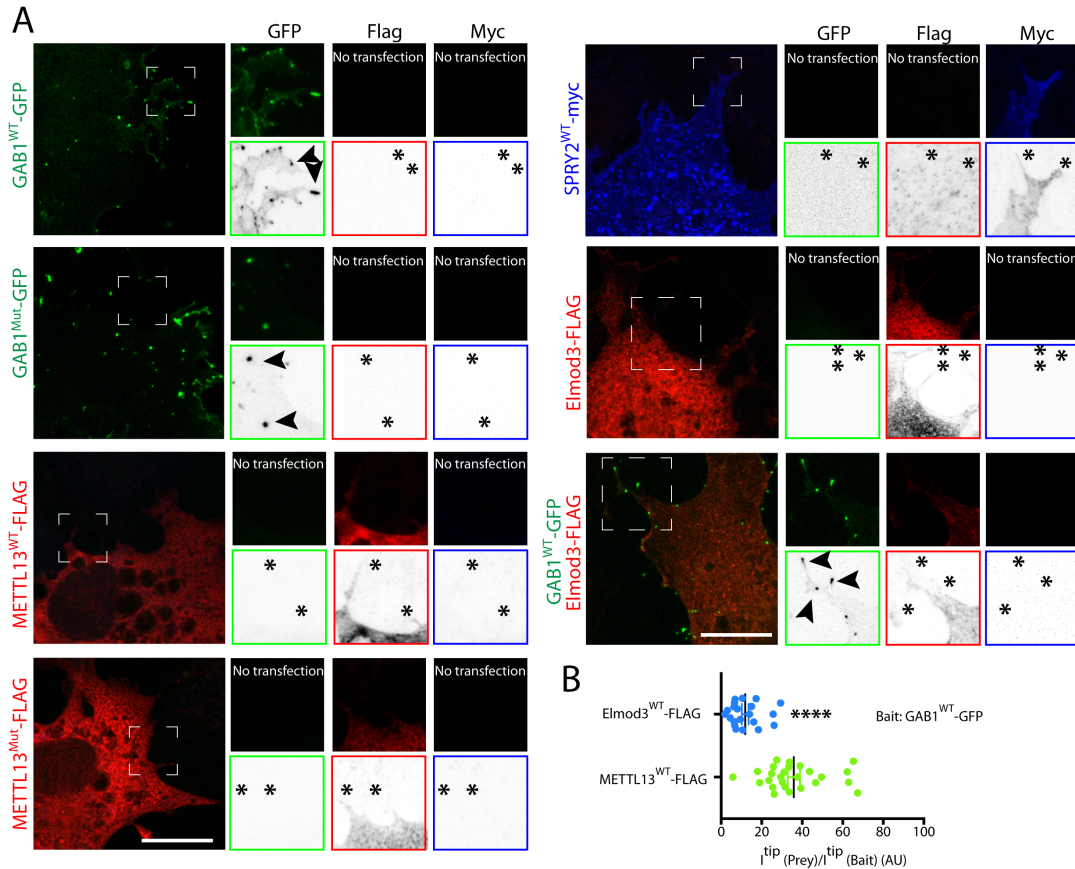
Supplemental Figure 3. Anti-GAB1 and anti-METTL13 antibodies recognize EGFP tagged GAB1 and METTL13 in COS-7 cells. (A) Immunofluorescence signal of GAB1 antibody (PB296) coincided with the signal produced by GFP-tagged full length human GAB1 expressed in COS-7 cells. Non-transfected cells did not show any labeling. (B) Immunofluorescence signal of METTL13 antibody (PB477) coincided with the signal produced by GFP-tagged full length human METTL13 expressed in COS-7 cells. Non-transfected cells did not show labeling.



Supplemental Figure 4. *Gab1* and *Mettl13* are expressed in mouse inner ear. (A)

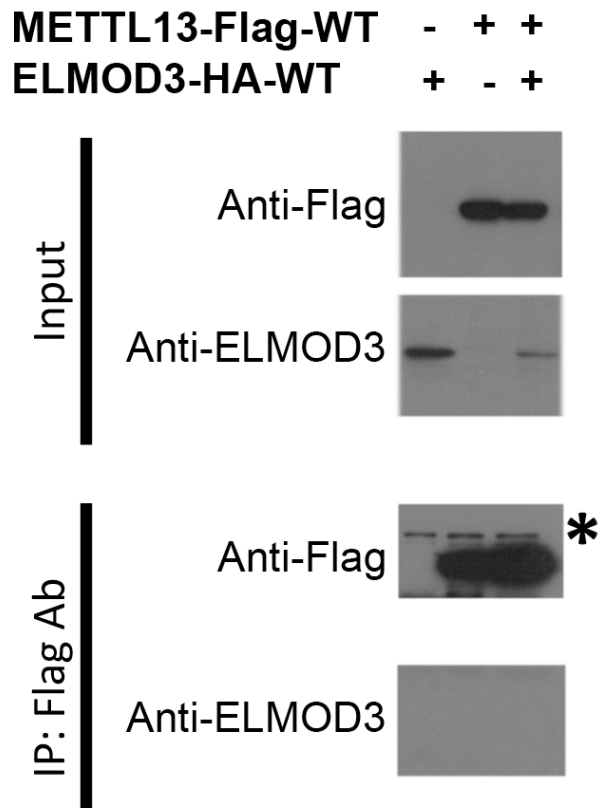
Illustration showing the mouse organ of Corti sensory cells and innervation pattern of efferent and afferent neurons. The inner hair cells are synaptically connected to all type I spiral ganglion neurons (light blue) forming the radial afferent system, while the efferent system (dark blue) neurons bring feedback control to the inner hair cells/type I afferent synapsis. Outer hair cells synapse with a few small endings from type II spiral ganglion neurons, forming the spiral afferent system, while large neurons of the efferent system (dark blue) form synapsis with the outer hair cells as well. **(B)** Maximal projection of confocal images of a mouse organ of Corti immunostained with METTL13 (PB448) antibody. Scale bar: 10 μ m **(C)** Maximal projection of confocal images of a

mouse organ of Corti immunostained with β -galactosidase (GAB1), METTL13 (PB447) and NF-200 antibodies. Arrowheads point nerve fibers, while arrows indicate spiral ganglion nuclei. OHC: outer hair cells; IHC: inner hair cells; SGCs: spiral ganglion cells. Scale bar: 50 μ m.

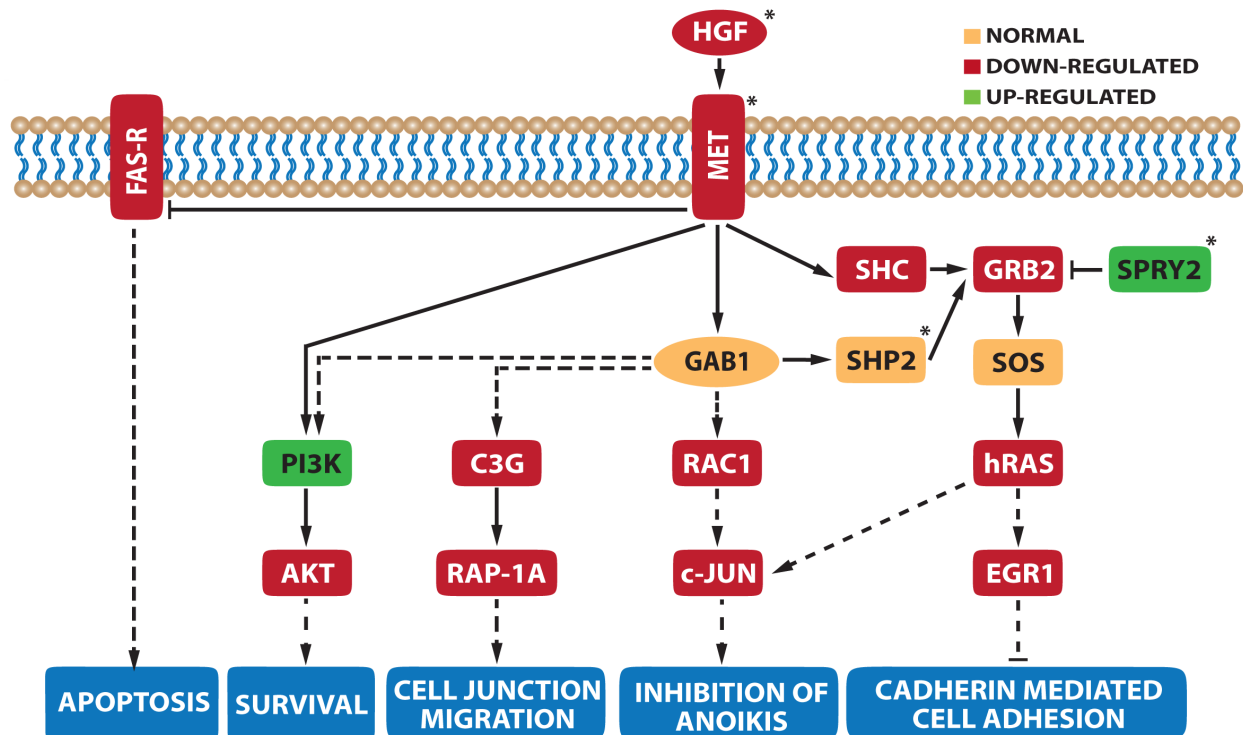


Supplemental Figure 5. Controls used for the nanoscale pull down assay. (A)

COS-7 cells were co-transfected with non-fluorescent MYO10^{NANOTRAP} construct and GAB1^{WT}-GFP, GAB1^{Mut}-GFP (baits, green) or METTL13^{WT}-FLAG, METTL13^{Mut}-FLAG, SPRY2^{WT}-myc, and ELMOD3^{WT}-FLAG (Preys, red) constructs. ELMOD3-FLAG was used as a negative control to rule out the interaction between GAB1-GFP and the FLAG tag. Single channels are shown as inverted grayscale images. Single transfection conditions are shown here. Accumulations at the tip are indicated with an arrowhead. Stars indicate the absence of accumulation at filopodia tips. **(B)** Quantification of fluorescent intensities revealed significant (**** $p < 0.0001$) accumulation of GAB1-GFP and METTL13-FLAG proteins at filopodia tips as compared to the negative control (ELMOD3^{WT}-FLAG). Scale bars: 10 μm .



Supplemental Figure 6. No interaction between METTTL13-FLAG and ELMOD3-HA constructs was observed. Co-immunoprecipitation assay showing no interaction between ELMOD3^{WT}-HA and METTTL13^{WT}-FLAG. ELMOD3-HA was used as a negative control to rule out the interaction between METTTL13-FLAG and the HA tag. The asterisk (*) indicates the IgG used for the pull down.



Supplemental Figure 7. MET signaling pathway genes are dysregulated in the DFNB26 individuals. The expression of many genes in the MET signaling pathway are affected by the *GAB1* p.Gly116Glu substitution, which could affect one or more of the downstream signaling pathways leading to altered cell survival, apoptosis, cell migration or cell adhesion. Four genes (*), *SPRY2*, *SHP2*, *MET* and *HGF*, of this pathway are also known to cause non-syndromic or syndromic forms of deafness in human or mouse.