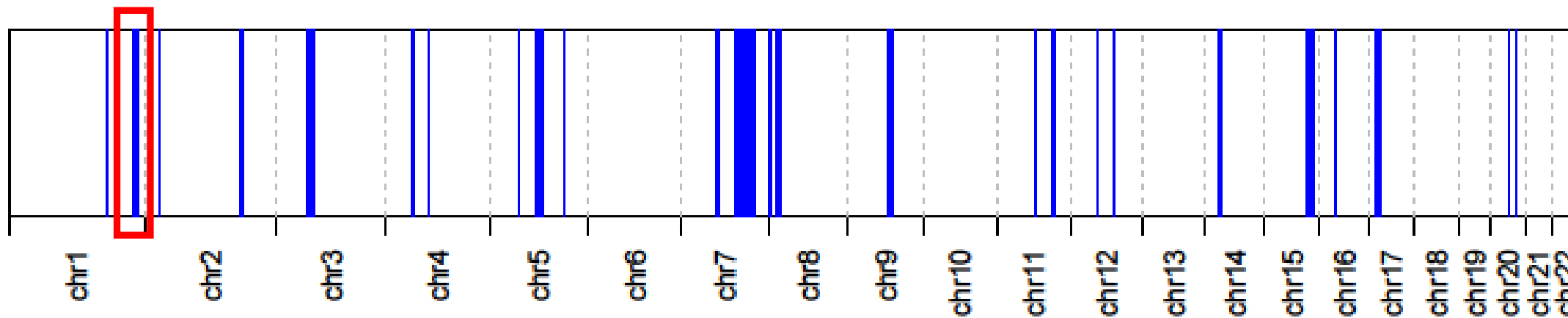


Homozygous Regions for p.(Asn90Ser)

Total = 147.49 Mb (autosomes)

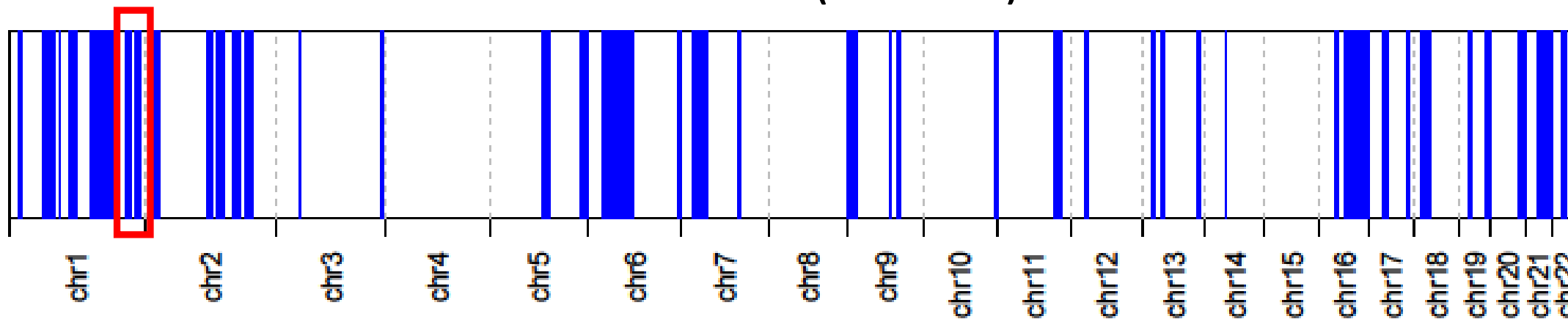
9.77 Mb

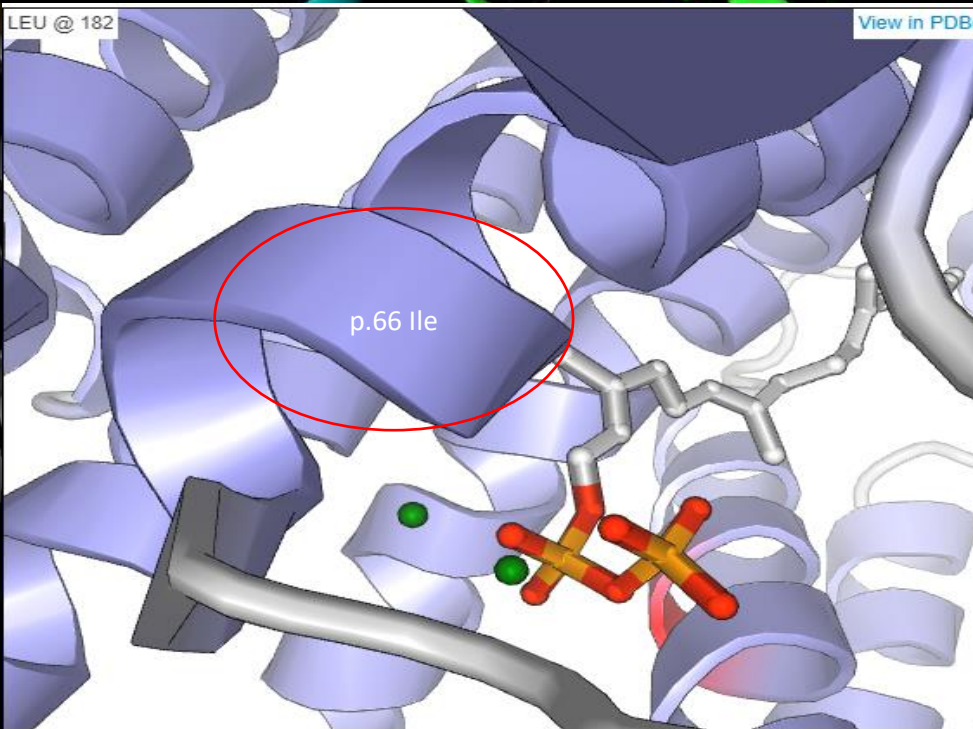
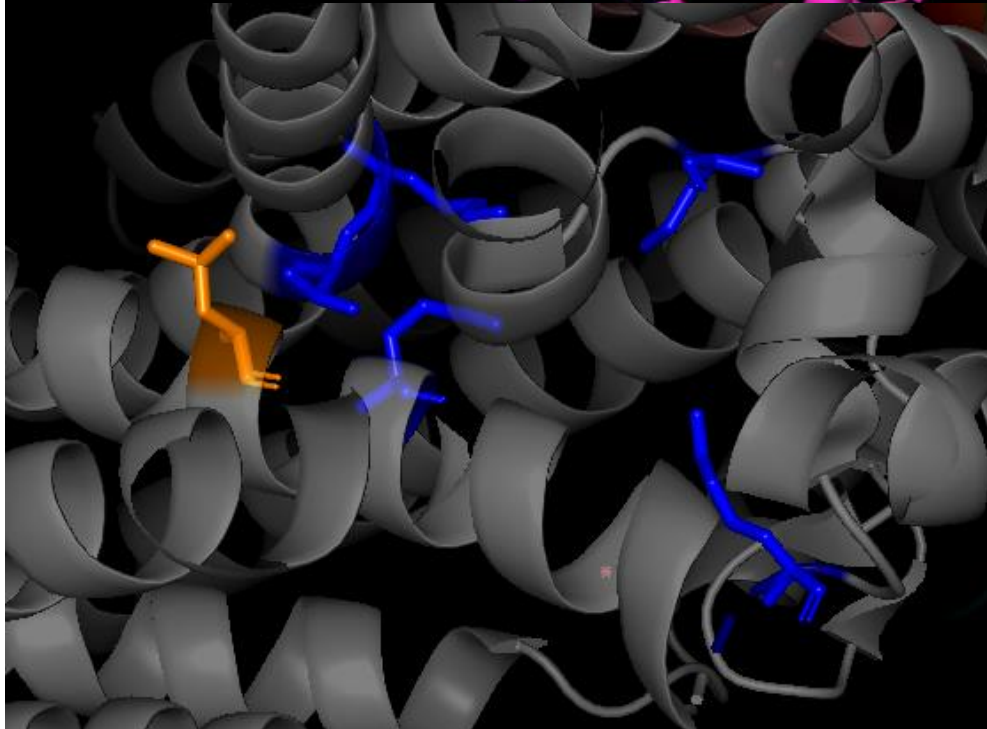
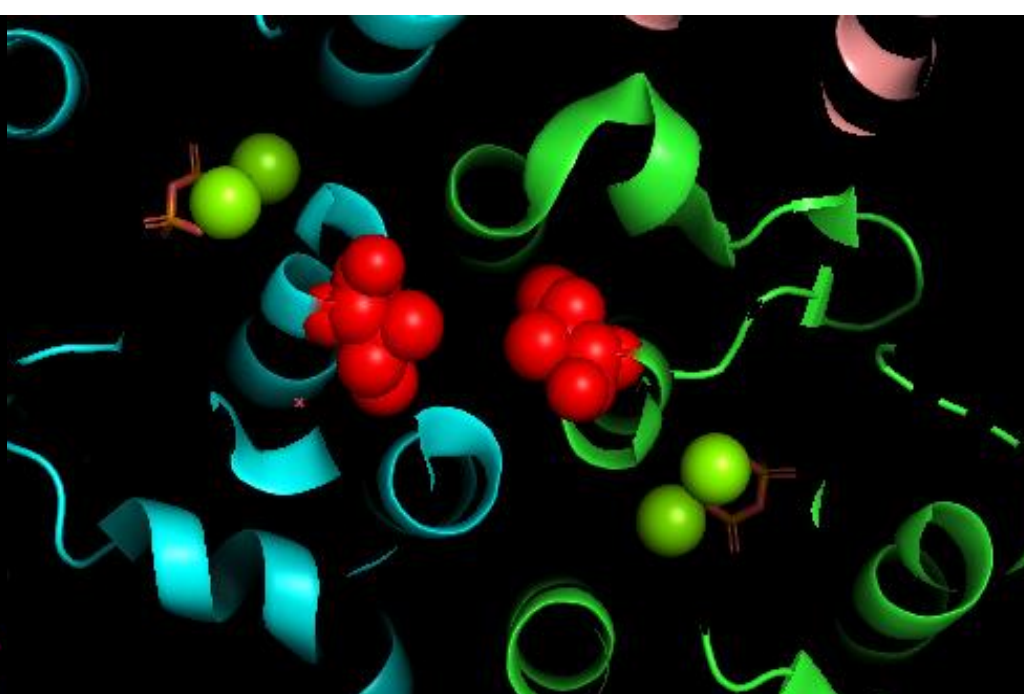
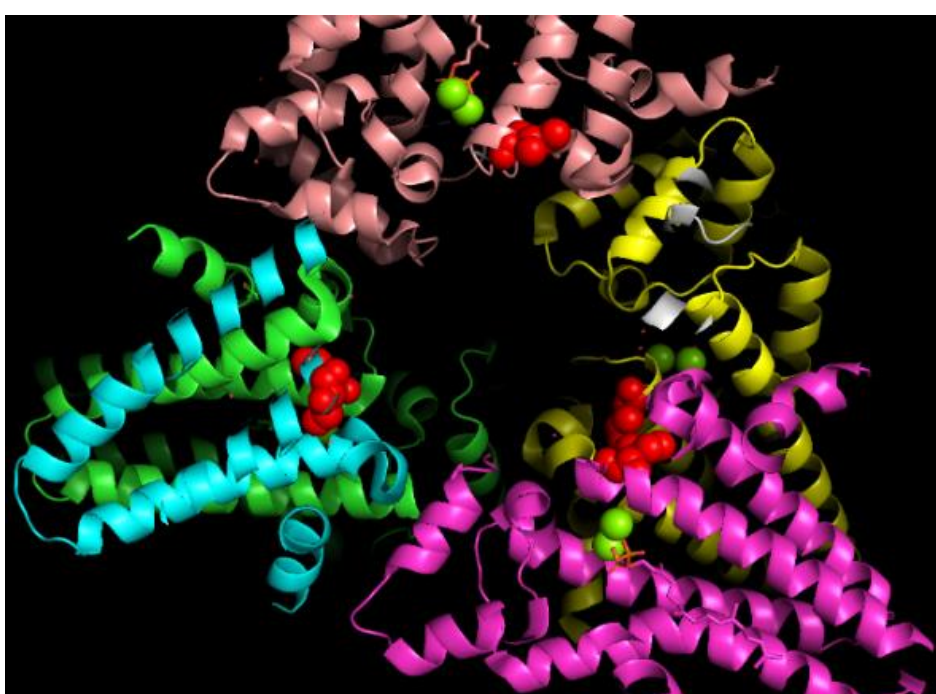


Homozygous Regions for p.(Met147Val)

Total = 461.19 Mb (autosomes)

9.01 Mb

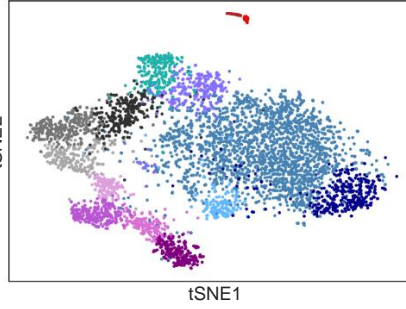
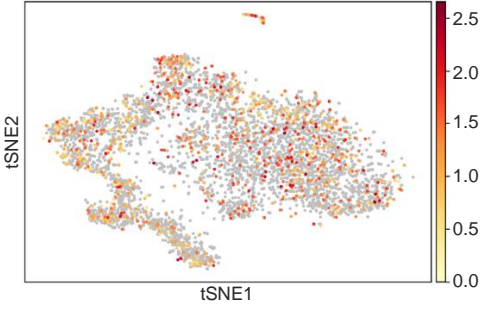




E14 mouse, cochlear epithelium

Ggpsi

cell type

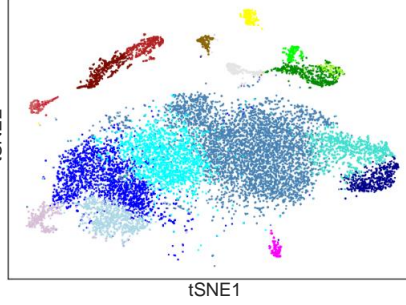
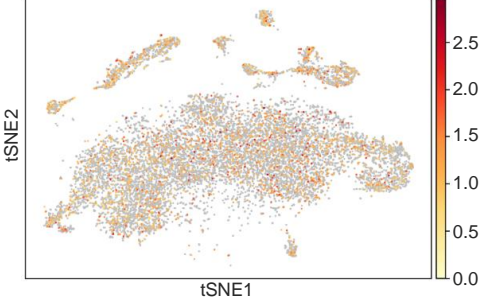


- Greater epithelial ridge
- Greater epithelial ridge expressing *Hmgn2*
- Inner hair cells
- Interdental cells
- Lesser epithelial ridge cells expressing *Bmp4* c1
- Lesser epithelial ridge cells expressing *Bmp4* c2
- Lesser epithelial ridge cells expressing *Fst*
- Lateral prosensory cells
- Medial prosensory cells
- Outer hair cells
- Cells expressing *Oc90* and *Otoa*
- Cells expressing *Oc90* and *Sparcl1*
- Cells expressing *Oc90* c1
- Cells expressing *Oc90* c2

P1 mouse, cochlear epithelium

Ggpsi

cell type

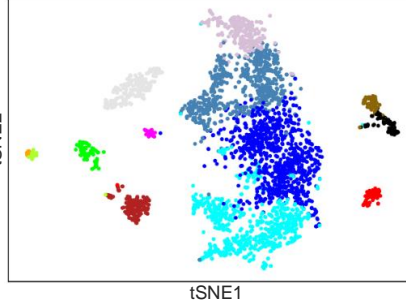
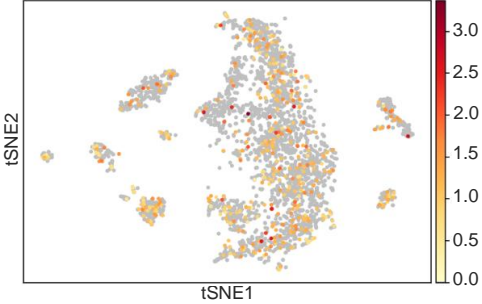


- Deiters' cells rows 1 and 2
- Deiters' cells row 3
- Hensen cells
- Inner hair cells
- Inner pillar cells
- Inner phalangeal cells
- Inner sulcus cells
- Interdental cells
- Lateral greater epithelial ridge cells, group 1
- Lateral greater epithelial ridge cells, group 2
- Lateral greater epithelial ridge cells, group 3
- Medial greater epithelial ridge cells
- Outer hair cells
- Outer pillar cells
- Outer sulcus cells
- Cells expressing *Oc90*
- Less mature developing inner hair cells
- Less mature developing outer hair cells

P7 mouse, cochlear epithelium

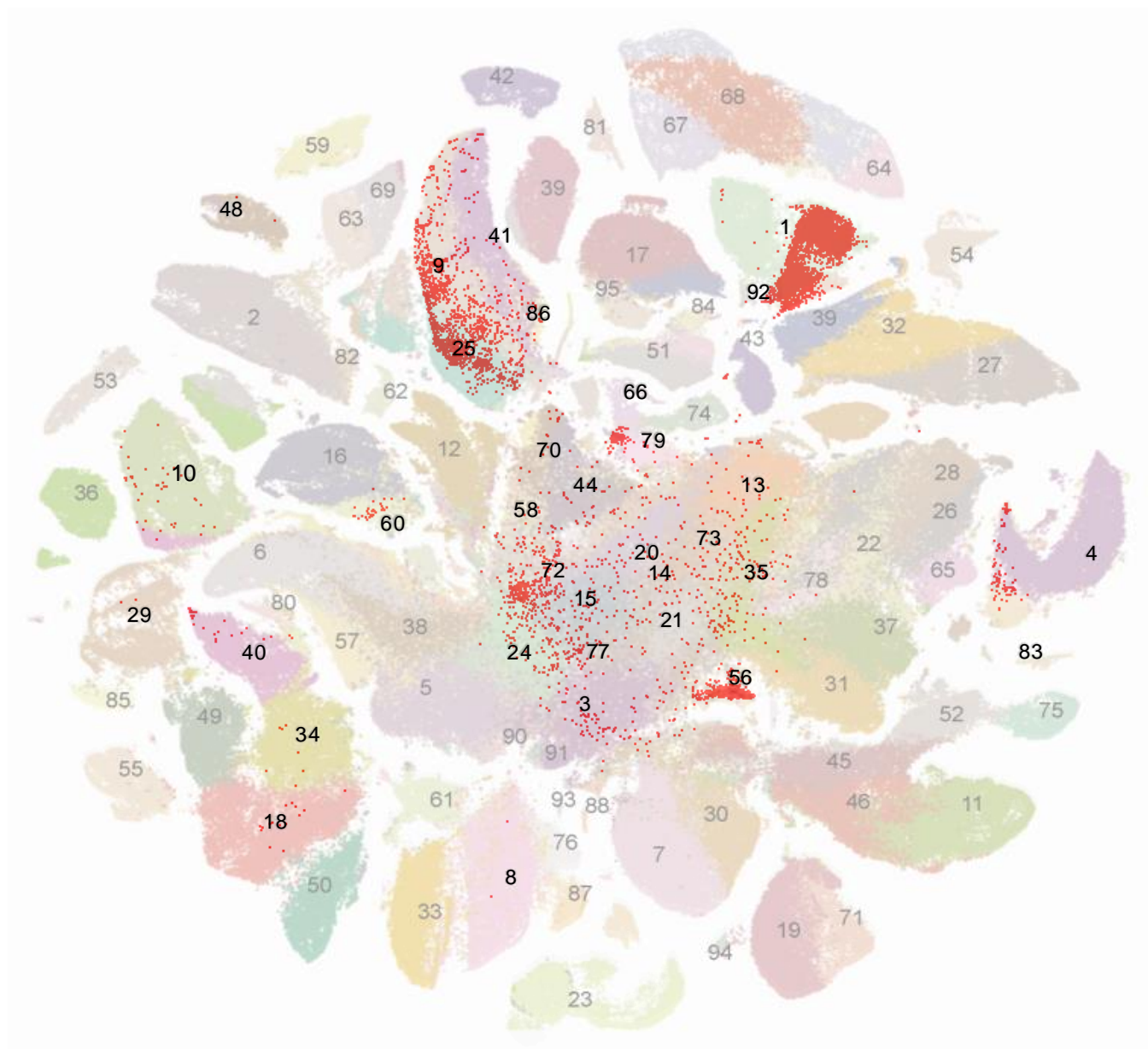
Ggpsi

cell type

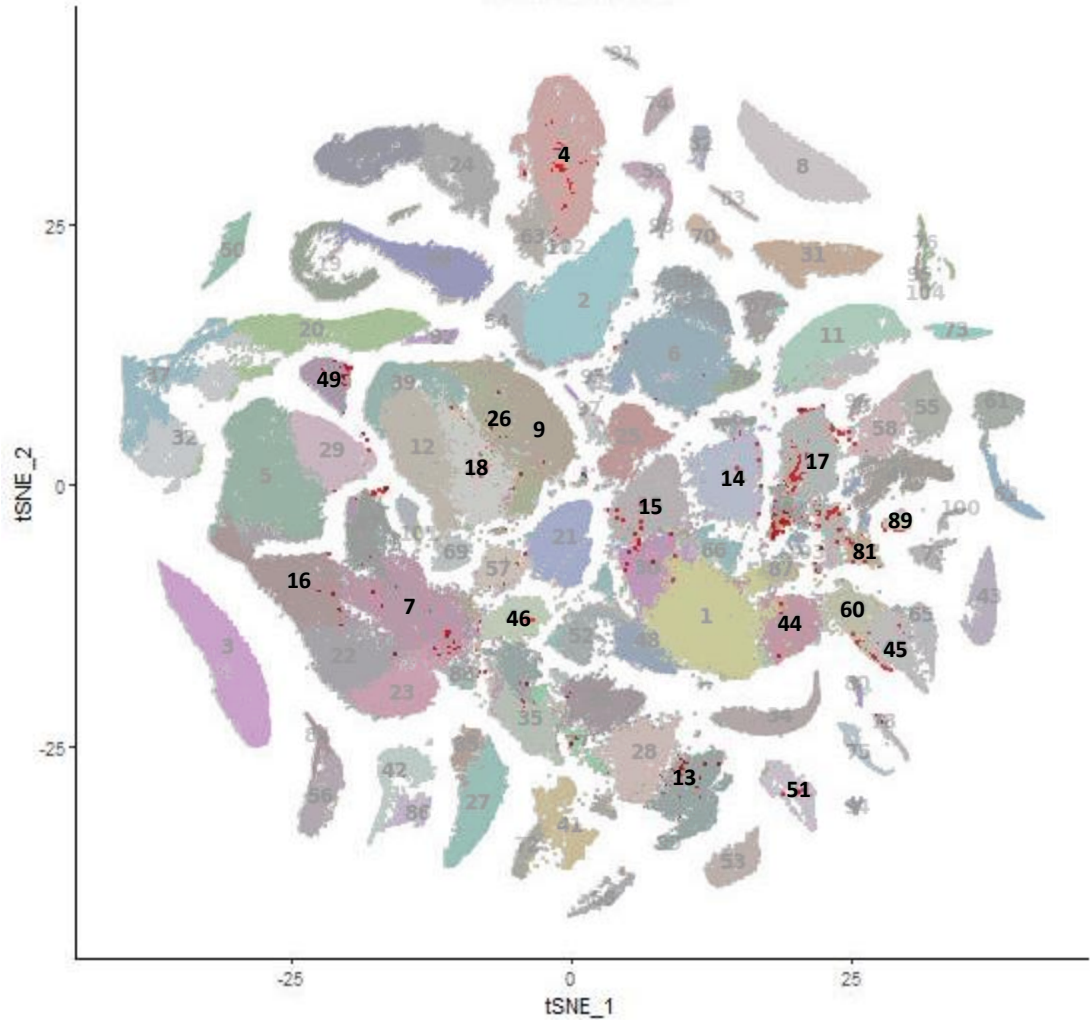


- Basilar membrane cells
- Deiter cells
- Hensen cells
- Inner hair cells
- Inner pillar cells
- Inner sulcus cells
- Lateral greater epithelial ridge cells
- Medial greater epithelial ridge cells
- Medial lateral greater epithelial ridge cells
- Outer hair cells
- Outer pillar cells
- Outer sulcus cells
- Glial cells?

E14.5 mouse female gonad



Neonatal mouse muscle



Supplementary Table 1. Extended clinical features of the affected individuals with biallelic GGPS1 variants

		Family 1			Family 2						Family 3	Family 4	Family 5 (from Tucker et al., 2020)		Foley et al. 2020 (11 persons/6 families)	Tucker et al. 2020 (4 persons/2 families)
	Person	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P 12	P 13		
Variant details	Variant type	Homozygous			Homozygous						Compound heterozygous	Homozygous	Homozygous		Homozygous/compound heterozygous	Homozygous
	Variant at the cDNA level (NM_004837.4)	c.269A>G			c.439A>G						c.196A>C and c.545T>C	c.770T>G	c.269A>G	c.269A>G	(c.860A > G; 865C > G), (c.127C > T; 865C > G), c.866G > A, c.854 T > G	c.782G>A, c.269A>G
	Variant at the protein level	p.(Asn90Ser)			p.(Met147Val)						p.(I166Leu) and p.(L182Pro)	p.(P257Cys)	p.(Asn90Ser)	p.(Asn90Ser)	[p.(Tyr259Cys); p.(Arg261Gly)], [p.(Pro155Ser); p.(Arg261Gly)], p.(Arg261His), p.(Phe257Cys)	p.(Arg261His), p.(Asn90Ser)
Epidemiology	Sex	F	F	F	M	M	M	M	M	F	F	F	M	F	F-6; M - 5	F -3, M -1
	Consanguinity	+	+	+	+	+	+	+	+	+	-	+	+	+	1 family-no, 5 families -NA	NA
	Family history	+	+	+	+	+	+	+	+	+	-	-	-	-	3	+
	Current age	11y.o.	11 m.o. (Died)	8y.o.	23.5 y.o.	4y 8m.o.	5y 7m.o.	4y .o.	5y.o.	30 y.o. (Died)	8 y.o	12 y.o.	20 y.o.	8.5 y.o.	31, 29,22,46,45,44,14,2 1,22,11,8 (y.o.)	36,39,7 (y.o.)
	Age of death	Alive	11 m.o.	Alive	Alive	Alive	Alive	Alive	Alive	30 y.o.	Alive	Alive	Alive	Alive	NA	Alive
Birth	Decreased foetal movements	+	+	+	-	-	-	-	-	-	-	-	-	-	+(1)	NA
	Weeks of gestation	Term	Term	Term	40 weeks	39 weeks	40 weeks	38 weeks	39 weeks	40 weeks	Term	NA	NA	Term	1 - 29 weeks,	NA

	Head circumference at birth	35 cm, 75 th percentile	36 cm, 75 th percentile	33 cm, 25 th percentile	35cm, 50 th percentile	34 cm, 25 th percentile	34.5cm, 25 th percentile	33.5cm, 10 th percentile	35cm, 50 th percentile	33cm, 25 th percentile	NA	NA	NA	33, 25 th percentile	NA	NA
	Birth weight	2.8 kg, 25 th percentile	3.1 kg, 50 th percentile	3.3 kg, 50 th percentile	3.5 kg 50 th , percentile	3.2kg 50 th percentile	3.3 Kg 50 th percentile	2.9kg, 25 th percentile	3.2kg, 50 th percentile	3kg, 50 th percentile	2.6kg (2-9 th centile)	NA	NA	2.7kg, 25 th percentile	NA	NA
	Birth length	52 cm, 75 th percentile	52 cm, 75 th percentile	51 cm, 50 th percentile	50cm, 50 th percentile	49.5 cm, 50 th percentile	50 cm, 50 th percentile	48cm, 25 th percentile	49cm, 25 th percentile	48cm, 25 th percentile	NA	NA	NA	47cm, 25 th percentile	NA	NA
	Neonatal with a weak cry and a poor suck	+	+	+	-	-	-	-	-	-	-	-	-	-	+ (1)	NA
Medical history	Age at onset	Prenatal	Prenatal	Prenatal	1y 8m.o.	8 m.o.	6 m.o.	1y 6m.o.	2y.o.	3y.o.	7 months	18 m.o.	Motor delay noted at 18 months	4 months	Prenatal	Childhood
	First presentation	Weak cry	Weak cry	Weak cry	Delayed walking	Delayed motor milestones	Muscle weakness /flaccidity /Delayed walking	inability to stand well from sitting position	Delayed walking	Muscle weakness	Hypotonia, muscle weakness. Respiratory insufficiency	Motor delay	Motor delay noted at 18 months	Motor delay	Hearing loss in cases with milder motor phenotypes, manifestations with motor delay in 2 persons	Hearing loss
	Type of progression (rapid, moderate, slow)	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow	Slow (progressive scoliosis with improvements in motor and swallowing function).	Slow	Moderate	Slow	Slow (11)	Slow (4)
	Failure to thrive	+	NA	+	-	-	-	-	-	-	-	-	-	+	+ (8)	NA

[illegible]

	Hypotonia	-	-	-	+	+	+	+	+	+	+	+	+	+	+	NA	NA				
	Muscle weakness	+	NA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	(1)	+	(2)
	Body distribution of muscular weakness	Leg/foot, pelvic girdle, trunk	Poor head control	Leg/foot, pelvic girdle, trunk	Pelvic girdle /shoulder girdle / back	Shoulder girdle/ Pelvic girdle	Shoulder girdle and pelvic girdle	Shoulder girdle and pelvic girdle	Shoulder girdle and pelvic girdle	Generalized	Four limb proximal and axial muscle weakness	Axial and proximal	LL>UL	LL>UL	NA	NA					
	Pattern of muscular weakness	NA	NA	NA	Generalized	Proximal	Proximal	Proximal	Proximal	Generalized	LL>UL	Axial and proximal	LL > UL	LL>UL	NA	NA					
	Muscle hypertrophy	-	NA	-	-	Mild calf muscles	Calf muscles	Calf muscles	Calf muscles	-	-	-	-	-	NA	NA					
	Peripheral neuropathy	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	NA	NA				
	DTRs	0	NA	0	0	↓	↓	↓	↓	0	↓	↓	↓↓	↓↓	NA	NA					
	Muscular atrophy	+	NA	+	+	+	+	+	+	+	+	+	+	+	+	NA	NA				
	Myalgia	-	NA	-	+	+	+	+	+	+	-	NA	NA	-	NA	NA	+	(2)			
	Stiffness	+	NA	+	+	-	-	-	-	+	-	NA	+	+	NA	NA					
	Gait	Broad-based	NA	Broad-based	Non ambulant	Waddling gait	Waddling gait	Normal gait	Waddling gait	Non ambulant	Unsteady	Non ambulant	NA	Waddling gait	Non-ambulant (5), NA (6)	NA					
Details on Hearing loss	The age of onset	11 m.o.	6 m.o.	6 m.o.	Intact	Intact	Intact	Intact	Intact	Intact	Normal new-born hearing screening. Abnormal hearing test at 4 years old	Not sure - childhood	Intact	From birth	From neonatal to childhood	Childhood					
	The type of hearing loss	SNHL	SNHL	SNHL	-	-	-	-	-	-	SNHL	SNHL	-	SNHL	SNHL	SNHL					

	The laterality and symmetry of the hearing loss	Bilateral	NA	Bilateral	-	-	-	-	-	-	Bilateral	Bilateral	-	Bilateral	Bilateral	Bilateral
	The degree of hearing loss	Severe	NA	Severe	-	-	-	-	-	-	Severe	Severe	-	80 dB on each side	NA	NA
Investigations	Elevated CK (age)	NA	NA	NA	14y.o.: 2000	4y.o.: 6000	5y.o.: 6600	3y.o.: 27000	3y.o.: 12000	11y.o.: 5000	+(7m.o 1594U/L, 4y.o 5490U/L)	19m.o.	7000	2000	+ (9)	NA
	FSH	NA	NA	NA	na	na	na	na	na	NA	NA	High	NA	NA	88.2IU/l, 50.3IU/l, 53.2IU/l	60 IU/l, 35.8 IU/l
	EMG	Normal	Normal	Normal	Myopathic picture	Myopathic picture	Myopathic	Myopathic	Myopathic	Myopathic	Myopathic	Myopathic	Normal	Normal	NA	NA
	Muscle biopsy/ histochemistry	NA	NA	NA	Not done	No done	No done	No done	No done	No done	(8m.o) Type 1 fibre predominance, central nuclei, Z line streaming, mini-cores.	Fatty infiltration with mitochondrial changes	Dystrophic pattern	Dystrophic pattern	+ (9) Dystrophic, with evidence of degeneration	NA
	Muscle MRI	NA	NA	NA	Not done	Done	Done	Done	Done	Not done	(8m.o) generalised muscle atrophy without fatty infiltration.	NA	NA	NA	+ (3) Fatty infiltration consistent with an underlying muscular dystrophy.	NA

Abbreviations: P- Person; NA – not available; na- not applicable; y.o. – years old; m.o. – months old; LL- lower limbs; UL – upper limbs; SNHL – sensorineural hearing loss; FSH -follicle stimulating hormone; EMG- electromyography; MRI – magnetic resonance tomography; m – male; f- female; CK – creatine kinase; DTRs – deep tendon reflexes. dB – decibel.

Supplementary Table 2. Population frequencies and *in silico* pathogenicity predictions for *GGPS1* variants reported in this study

Gene	<i>GGPS1</i>	<i>GGPS1</i>	<i>GGPS1</i>	<i>GGPS1</i>	<i>GGPS1</i>
Variant	c.269A>G p.(Asn90Ser)	c.439A>G p.(Met147Val)	c.196A>C p.(Ill66Leu)	c.545T>C p.(Leu182Pro)	c.770T>G p.(Phe257Cys)
Transcript	NM_004837.4	NM_004837.4	NM_004837.4	NM_004837.4	NM_004837.4
Rs-ID	rs1012843795	rs1237799550	Absent	Absent	Absent
gnomAD	Absent	1 heterozygous allele out of 251328	Absent	Absent	Absent
Iranome and GME	Absent	Absent	Absent	Absent	Absent
UK Biobank	Absent	2 heterozygous alleles out of 537358	Absent	6 heterozygous alleles out of 537358	Absent
Queen Square Genome database (23 000 exomes)	Absent	Absent	Absent	Absent	Absent
Centogene database	1 heterozygous allele Centogene AF ~5.6 x 10 ⁽⁻⁶⁾	2 heterozygous alleles	Absent	Absent	Absent
TOPMed	1 heterozygous allele	1 heterozygous allele	Absent	Absent	Absent
ClinVar	Not reported	Not reported	Not reported	Not reported	Not reported
CADD PHRED score	26.4	25.8	25	26	27.3
GERP	6.17	6.17	5.05	6.17	6.17
SIFT score	0.02 (Deleterious)	0.00 (Deleterious)	0.01 (Deleterious)	0.00 (Deleterious)	0.00 (Deleterious)
PolyPhen score	0.964 (Probably damaging)	0.946 (Probably damaging)	1 (Probably damaging)	0.999 (Probably damaging)	0.994 (Probably damaging)
PROVEAN	-5.0 (Damaging)	-3.73 (Damaging)	-1.88 (Neutral)	-6.55 (Damaging)	-6.98 (Damaging)
FATHMM PRED	Tolerated	Tolerated	Tolerated	Tolerated	Damaging
LRT PRED	Deleterious	Deleterious	Deleterious	Deleterious	Deleterious
MetaLR score	0.5429 (Damaging)	0.5090 (Damaging)	0.4605 (Tolerated)	0.6008 (Damaging)	0.5524 (Damaging)
MutPred score	0.859	0.728	0.776	0.734	0.751

MutationAssessor score	3.42 (High functional impact)	3.765 (High functional impact)	2.845 (Medium functional impact)	3.19 (Medium functional impact)	3.38 (Medium functional impact)
REVEL score	0.624	0.570	0.50	0.7039	0.7179
ACMG	PS4, PP1 (moderate), PM2, PP3 Likely pathogenic	PS4, PP1 (moderate), PM2, PP3 Likely pathogenic	PM2, PP3, PP4 VUS	PM2, PP3 VUS	PM2, PP3 VUS