Table S1: Genes associated with mandibulo-facial and/or ear malformations analysed by next generation sequencing*.

Gene	Target region (bp)	Coverage (%)
B3GALTL	1797	100
CHD7	9778	99,89
DHODH	1368	100
EDN1	739	100
EFTUD2	3459	100
EYA1	2281	100
FGF10	687	100
FGF3	780	100
FGFR2	3324	100
FGFR3	3360	100
GJA1	1169	100
GNAI3	1259	100
NFIX	1847	100
PLCB4	4375	99,73
POLR1C	1348	99,70
POLR1D	825	100
SALL1	4039	100
SALL4	3242	100
SEMA3E	2693	100
SF3B4	1395	100
SIX1	895	100
SIX5	2280	99,82
TCOF1	5159	100
TFAP2A	1897	100
TSHZ1	3119	100
Gene Panel	**63115**	**99,95**

* A custom panel for the targeted enrichment of 25 genes associated with mandibulo-facial and/or ear malformations was designed using the SureDesign software v3.0.3.1 (Agilent Technologies, Santa Clara, CA, United Stated). The gene panel contained 3670 amplicons and the coverage of the target regions (coding sequences and 10 bp flanking sequences) was 99.95 %. The target sequences of the investigated genes were isolated and captured using the HaloPlex Target Enrichment system (Agilent Technologies).

Table S2: Variants identified in patient P1 in genes involved in cranio-facial and/or ear malformations analysed by next generation sequencing.

Gene	HGVS (Genomic)	HGVS (Coding)	HGVS (Protein)	Read Depth	Allele Frequency	HOM/HET	dbSNP	MAF dbSNP
SF3B4	NC_000001.10:g.149898557G>A	NM_005850.4:c.417C>T	NP_005841.1:p.(Gly139=)	408	0.455	HET		
FGFR3	NC_000004.11:g.1803704T>C	NM_000142.4:c.882T>C	NP_000133.1:p.(Asn294=)	778	0.996	HOM	rs2234909	0.2075
FGFR3	NC_000004.11:g.1807894G>A	NM_000142.4:c.1953A>G	NP_000133.1:p.(Thr651=)	337	0.997	HOM	rs7688609	0.0439
TCOF1	NC_000005.9:g.149772280C>G	NM_000356.3:c.3296C>G	NP_000347.2:p.(Pro1099Arg)	465	0.489	HET	rs1136103	0.0815
EDN1	NC_000006.11:g.12294258A>G	NM_001955.4:c.318A>G	NP_001946.3:p.(Glu106=)	428	0.998	HOM	rs5369	0.0986
EDN1	NC_000006.11:g.12296255G>T	NM_001955.4:c.594G>T	NP_001946.3:p.(Lys198Asn)	360	0.446	HET	rs5370	0.2474
SEMA3E	NC_000007.13:g.83029438C>T	NM_012431.2:c.1272G>A	NP_036563.1:p.(Leu424=)	1399	0.999	HOM	rs2722974	0.3395
SEMA3E	NC_000007.13:g.83037751C>A	NM_012431.2:c.603G>T	NP_036563.1:p.(Ala201=)	524	0.998	HOM	rs2722985	0.4437
EYA1	NC_000008.10:g.72111599A>G	NM_000503.5:c.1755T>C	NP_000494.2:p.(His585=)	267	0.481	HET	rs10103397	0.4766
FGFR2	NC_000010.10:g.123239112G>A	NM_001144915.1:c.2107C>T	NP_001138387.1:p.(Leu703=)	186	0.46	HET	rs1047057	0.4143
FGFR2	NC_000010.10:g.123298158T>C	NM_000141.4:c.696A>G	NP_000132.3:p.(Val232=)	484	0.495	HET	rs1047100	0.2047
POLR1D	NC_000013.10:g.28239940G>C	NM_152705.2:c.219G>C	NP_689918.1:p.(Ala73=)	535	0.481	HET	rs11029	0.2578
POLR1D	NC_000013.10:g.28239970G>A	NM_152705.2:c.249G>A	NP_689918.1:p.(Pro83=)	536	0.499	HET	rs14105	0.3718
B3GALTL	NC_000013.10:g.31821240C>T	NM_194318.3:c.347+4C>T		743	0.48	HET	rs9564692	0.496
B3GALTL	NC_000013.10:g.31821992T>C	NM_194318.3:c.348T>C	NP_919299.3:p.(His116=)	356	0.997	HOM	rs4943266	0.0246
B3GALTL	NC_000013.10:g.31891746G>A	NM_194318.3:c.1108G>A	NP_919299.3:p.(Glu370Lys)	119	0.417	HET	rs1041073	0.3333
SALL1	NC_000016.9:g.51171175C>T	NM_002968.2:c.3823G>A	NP_002959.2:p.(Val1275Ile)	429	0.998	HOM	rs4614723	0.0132
SALL1	NC_000016.9:g.51173559G>A	NM_002968.2:c.2574C>T	NP_002959.2:p.(Leu858=)	851	0.998	HOM	rs1965024	0.4613
DHODH	NC_000016.9:g.72042682A>C	NM_001361.4:c.19A>C	NP_001352.2:p.(Lys7Gln)	450	0.488	HET	rs3213422	0.4359
EFTUD2	NC_000017.10:g.42949808G>A	NM_004247.3:c.994+6C>T		310	0.479	HET	rs11654183	0.2426
EFTUD2	NC_000017.10:g.42961009C>T	NM_004247.3:c.426+8G>A		640	0.456	HET	rs2289677	0.4395
PLCB4	NC_000020.10:g.9288522G>A	NM_000933.3:c.61G>A	NP_000924.3:p.(Ala21Thr)	576	0.998	HOM	rs6077510	0.4714
SALL4	NC_000020.10:g.50406630T>G	NM_020436.3:c.2392A>C	NP_065169.1:p.(Ile798Leu)	278	0.534	HET	rs6091375	0.0657
SALL4	NC_000020.10:g.50407162T>C	NM_020436.3:c.1860A>G	NP_065169.1:p.(Thr620=)	459	0.485	HET	rs6021437	0.382
SALL4	NC_000020.10:g.50407502A>C	NM_020436.3:c.1520T>G	NP_065169.1:p.(Leu507Arg)	224	0.493	HET	rs6126344	0.3588
SALL4	NC_000020.10:g.50407966C>T	NM_020436.3:c.1056G>A	NP_065169.1:p.(Ala352=)	213	0.533	HET	rs13038893	0.2093
SALL4	NC_000020.10:g.50408482A>G	NM_020436.3:c.540T>C	NP_065169.1:p.(Asn180=)	304	0.997	HOM	rs6013281	0.0026

Table S3: *In silico* predictions of the effect of the c.417C>T variant in *SF3B4* exon 3 on splicing.

	Predicted Effect	**Wild-type allele**	**Mutant allele**
NNSPLICE v. 0.9	Activation of a cryptic exonic donor site	Splice site not detected	Score: 0.99
NetGene2 v. 2.4	Activation of a cryptic exonic donor site	Splice site not detected	Score: 0.83
Human Splicing Finder	Activation of a cryptic exonic donor site	HSF matrices score: 61.15 MaxEnt score : 0.87	HSF matrices score: 87.99 MaxEnt score: 8.63
	Alterarion of an exonic ESE site		ESE site broken