

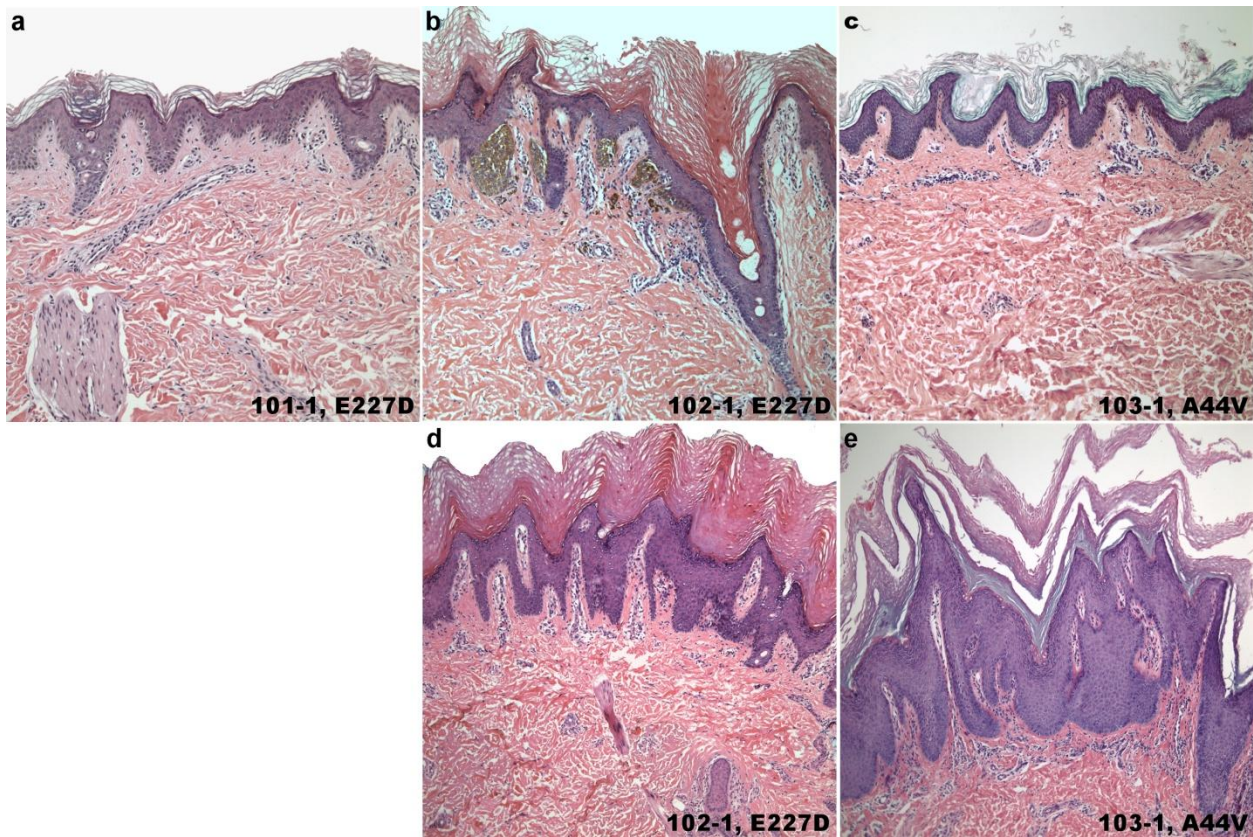
Supplementary Table 1. Exome sequencing coverage.

	<u>101-1</u>	<u>102-1</u>	<u>103-1</u>
Mean coverage:	50x	90x	67x
Median coverage:	42x	77x	54x
Number of reads:	50M	82M	69M
Bases covered \geq 8x:	93%	96%	94%
Bases covered \geq 20x:	79%	91%	84%



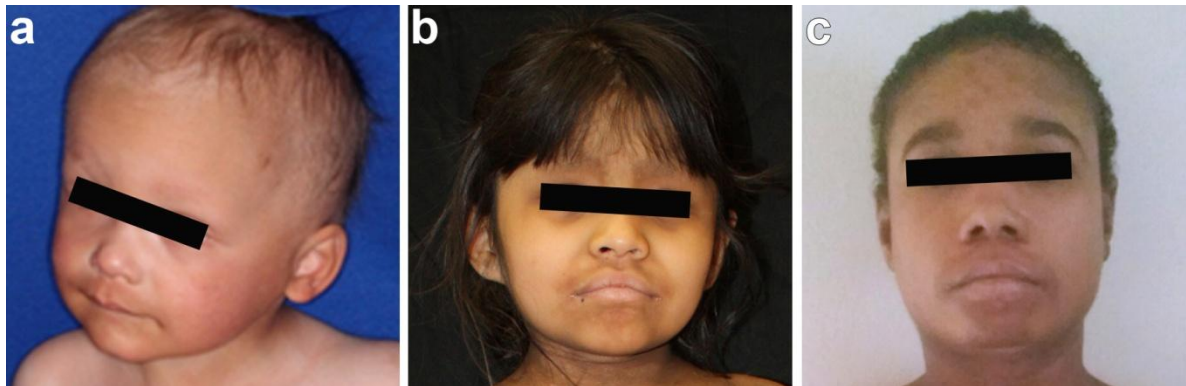
Supplementary Figure 1. EKVP due to *GJA1* mutation has onset in late infancy.

(a) Subject 102-1 is seen at 6 months of age and does not show evidence of skin disease. (b) Subject 103-1 is seen at 3 months of age and does not show evidence of skin disease. In both cases, skin lesions began to appear later in infancy with darkening, scaling, and erythema worsening over time.



Supplementary Figure 2. Histology of EKVP due to *GJA1* mutation.

10X images of tissue sections from less severely affected (a-c) and more severely affected (d,e) skin are shown from EKVP affected individuals, except 101-1, from whom only less severely affected skin was available. (a) Biopsy of the right thigh of subject 101-1 shows mild papillomatosis, basket weave orthokeratosis, and follicular plugging. (b) Biopsy of a compound nevus on the lower back of subject 102-1 shows acanthosis, papillomatosis, orthohyperkeratosis, and follicular plugging as junctional nests of melanocytes. (c) Biopsy from the flank of subject 103-1 shows papillomatosis and orthohyperkeratosis. (d) More severely affected skin on the upper thigh from subject 102-1 shows acanthosis, hypergranulosis, and compact orthohyperkeratosis. (e) Similarly, more severely affected skin on the back of subject 103-1 shows marked acanthosis, hypergranulosis, and compact orthohyperkeratosis.



Supplementary Figure 3. Facial features of subjects with EKVP due to *GJA1* mutation.

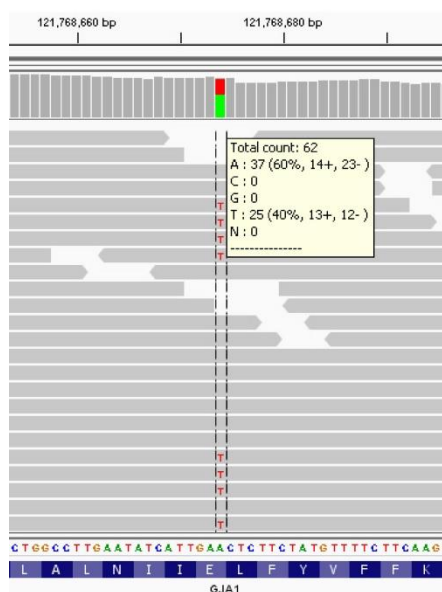
Subjects show hyperkeratosis around the eyes and mouth, and periorificial darkening. All subjects have hair with density appropriate to their age. There is no evidence of nasal or eye abnormalities or other craniofacial defects typically seen in ODDD. (a) 101-1. (b) 102-1. (c) 103-1.



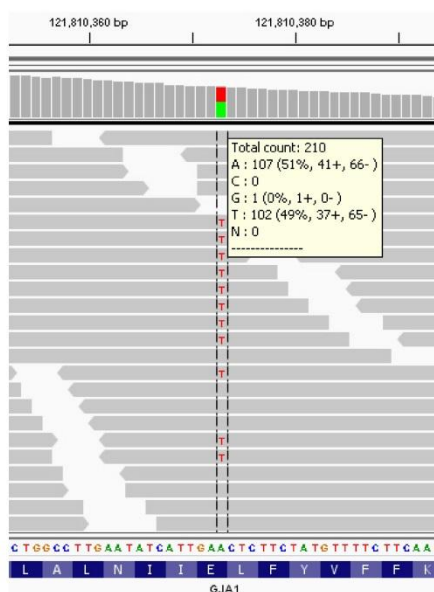
Supplementary Figure 4. Enlarged white lunulae in EKVP subjects with *GJA1* mutation.

Close-up images of the nails of affected individuals are shown. In subjects 101-1 and 102-1, who bear the same E227D *GJA1* mutation, there are enlarged, porcelain-white lunulae extending from the cuticle to the free edge of the nail (**a**, **b**). In subject 103-1, who has an A44V mutation, enlarged white lunulae are present and extend to within 2mm of the nail free edge (**c**).

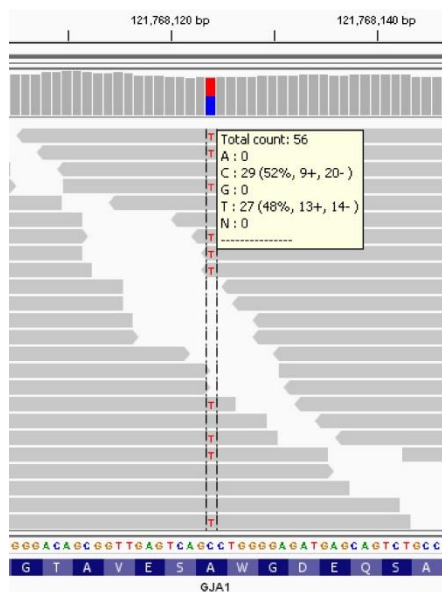
101-1



102-1



103-1



Supplementary Figure 5. Identification of *GJA1* mutations by exome sequencing.

Screen captures from the Integrative Genomics Viewer (IGV) depict aligned reads (gray arrows) from exome sequencing of three subjects. For each, base position on chromosome 6 is shown at the top (hg19 for 101-1 and 103-1, hg18 for 102-1), wild-type DNA and protein sequence is at the bottom, and mutant bases are in colored letters within the aligned reads. The total number of reads at the mutant position and the base count at that position are shown in the yellow box. Mutations are p.E227D, c.A681T (subjects 101-1 and 102-1) and p.A44V, c.C131T (subject 103-1) (NCBI RefSeq NM_000165).

GJA1_Cx43_human	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_orangutan	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_dog	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_elephant	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_mouse	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_chicken	MGDWSALGKLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFRCNTQQPG	60
GJA1_Cx43_frog	MGDWSALGRLLDKVQAYSTAGGK	VWLSVLFIFRILLLGTAVESAWG	DEQSAFV CNTQQPG	60
GJA1_Cx43_zebrafish	MGDWSALGRLLDKVQAYSTAGGK	VWLSVLFIFRILLV LGTAVESAWG	DEQSAFK CNTQQPG	60
GJA1_Cx43_human	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKKEEELKVAQTDG	120
GJA1_Cx43_orangutan	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKKEEELKVAQTDG	120
GJA1_Cx43_dog	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKKEEELKVAQTDG	120
GJA1_Cx43_elephant	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKKEEELKVAQTDG	120
GJA1_Cx43_mouse	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKKEEELKVAQTDG	120
GJA1_Cx43_chicken	CENVCYDKSFPI SHVR	FWVLQIIFVSVPTLLYL AHV FVY	MRKEEKL NKREEEELKV V QNDG	120
GJA1_Cx43_frog	CENVCYDKSFPI SHVR	FWVLQIIFVSTPTLLYL AHV FVY	LMRKEEKLNRKKEEELKMV QNEG	120
GJA1_Cx43_zebrafish	CENVCYDKSFPI SHVR	FWVLQIIFVSTPTLLYL AHV FVY	LMRKEEKLNRKKEEELKVA QNDG	120
GJA1_Cx43_human	VNVDMLHKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSIFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_orangutan	ANVDMHLKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSIFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_dog	ANVDMHLKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSVFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_elephant	ANVDMHLKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSIFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_mouse	VNVEMLHKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSVFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_chicken	VNVDMLHKQIEIKKFKYGI EEHGKVKMRGGLLRT	YIISILFKSVFEVAFLLIQWYIY	GFS	180
GJA1_Cx43_frog	GNVDMHLKQIEIKKFKYGL EEHGKVKMRGGLLRT	YIISILFKSVFEVGFIFIQWYMY	GFS	180
GJA1_Cx43_zebrafish	G D V E L H L K K I E L K K F K H G L E E H G K V K M R G S L L R T	Y I F S I I F K S I C E V V F L V I Q W Y L Y	G F S	180
GJA1_Cx43_human	LSAVYTCRDP CPHQVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	FFKGVKDRV	240
GJA1_Cx43_orangutan	LSAVYTCRDP CPHQVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	FFKGVKDRV	240
GJA1_Cx43_dog	LSAVYTCRDP CPHQVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	FFKGVKDRV	240
GJA1_Cx43_elephant	LSAVYTCRDP CPHQVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	FFKGVKDRV	240
GJA1_Cx43_mouse	LSAVYTCRDP CPHQVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	FFKGVKDRV	240
GJA1_Cx43_chicken	LSA I Y T C E R D P C P H R V D C F L S R P T E K T I	F I V F M L V V S L S L A L N I I E L F Y V	F F K G V K D R V	240
GJA1_Cx43_frog	LSA I Y T C R D P C P H Q V D C F L S R P T E K T I	F I W F M L I V S I V S L A L N I I E L F Y V	T Y K S I K D G I	240
GJA1_Cx43_zebrafish	LSAVYTCERTPCPHRVDCFLSRPTEKTI	FIIFMLVVSLSLALNIIELFYV	LFKR IKDRV	240
GJA1_Cx43_human	KGKSDPYHATSGALSPA KDCGSKYAYFNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			300
GJA1_Cx43_orangutan	KGKSDPYHATSGALSPA KDCGSKYAYFNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			300
GJA1_Cx43_dog	KGKSDPYHATSGPLSPSKDCGSKYAYFNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			300
GJA1_Cx43_elephant	KGKSDPYHATSGPLSPSKDCGSKYAYFNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			300
GJA1_Cx43_mouse	KGRSDPYHATSGPLSPSKDCGSKYAYFNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			300
GJA1_Cx43_chicken	KGKTDPY--HSGTMSPSKDCGSKYAYYNGCSSPTAPLS PMSPPGYKLV TGDRNNSSCR N			298
GJA1_Cx43_frog	KGK K D P Y S A T N D S V V P G K E C G S P K Y A Y F N G C S S P T A - - - P M S P P G Y K L V T G E R N P S S C R N			297
GJA1_Cx43_zebrafish	K - A D K T H I P T - - T L S T P K E L S T T K Y A Y Y N G C S S P T A P L S P M S P P G Y K L A T G E - R T N S C R N			296
GJA1_Cx43_human	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFPDDNQNSKKLAAGHELQPLAIVD			360
GJA1_Cx43_orangutan	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFPDDNQNSKKLAAGHELQPLAIVD			360
GJA1_Cx43_dog	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFPDDNQNSKKLAAGHELQPLAIVD			360
GJA1_Cx43_elephant	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFPDDNENSKKLA TGHELQPLAIVD			360
GJA1_Cx43_mouse	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFPDDSQNAKKVAAGHELQPLAIVD			360
GJA1_Cx43_chicken	YNKQASEQNWANYSAEQNRMGQAGSTISNSHAQPFDFADEHQNTKKLASGHELQPLTIVD			358
GJA1_Cx43_frog	YNKQASEQNWANYSAEQNRMGQAGSTISNTHAQPFDESDEHQNTKKMAPGHEMQPLTILD			357
GJA1_Cx43_zebrafish	YNKQANEQNWANYS TEQNRNLGQNGSTISNSHAQA AFDYFDDTHEHKKLTPGHELQPLAIVD			356
GJA1_Cx43_human	QRPSRRASSRASSRPRPDDLEI			382
GJA1_Cx43_orangutan	QRPSRRASSRASSRPRPDDLEI			382
GJA1_Cx43_dog	QRPSRRASSRASSRPRPDDLEI			382
GJA1_Cx43_elephant	QRPSRRASSRASSRPRPDDLEI			382
GJA1_Cx43_mouse	QRPSRRASSRASSRPRPDDLEI			382
GJA1_Cx43_chicken	QRPPSSRASSRASSRPRPDDLEI			380
GJA1_Cx43_frog	QRPSRRASSRASSRPRPDDLEI			379
GJA1_Cx43_zebrafish	A R P C S R A S S R M S S R A R P D D L D V			378

Supplementary Figure 6. Human Cx43 and orthologs.

Transmembrane domains are outlined, and conserved residues are shaded gray. Cx43 mutation sites A44V and E227D are shaded red.