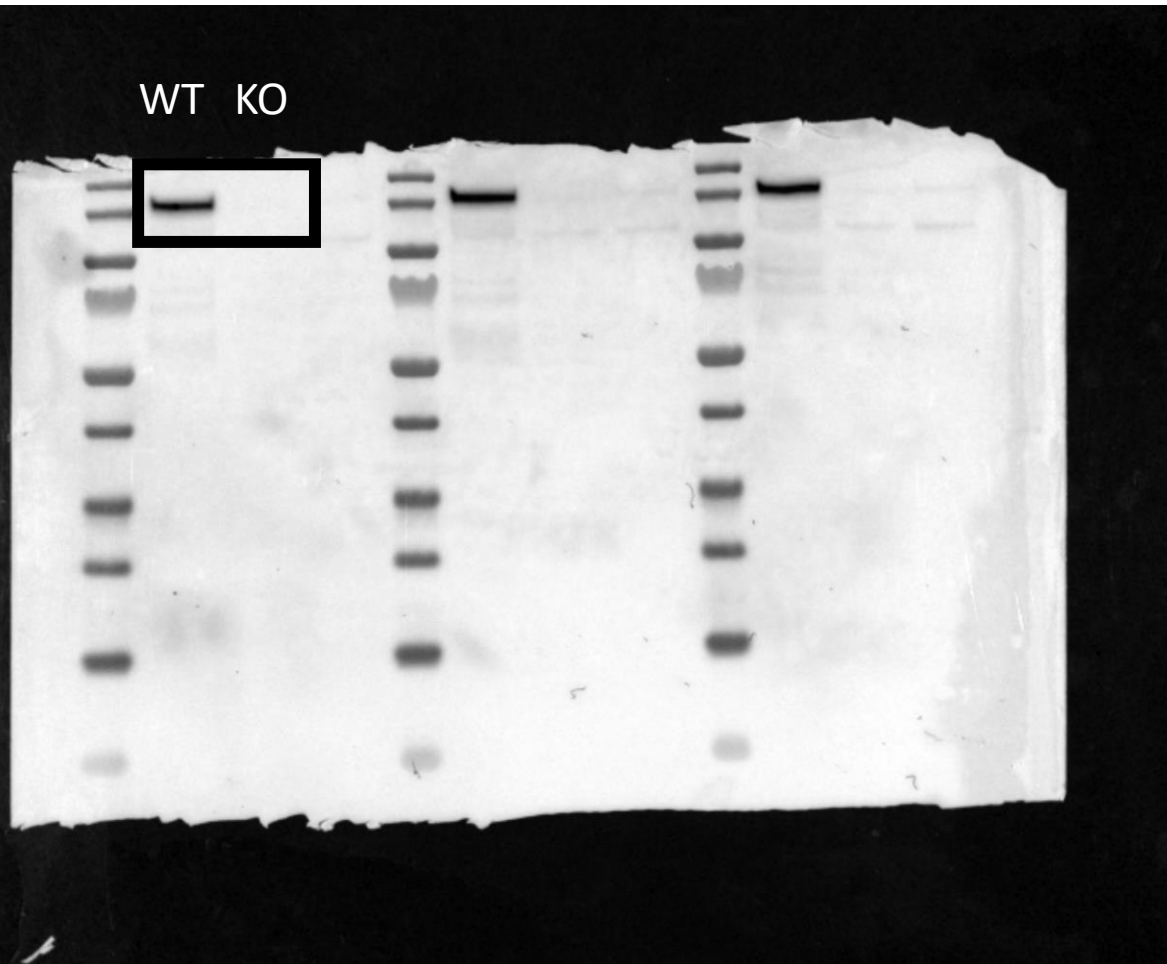
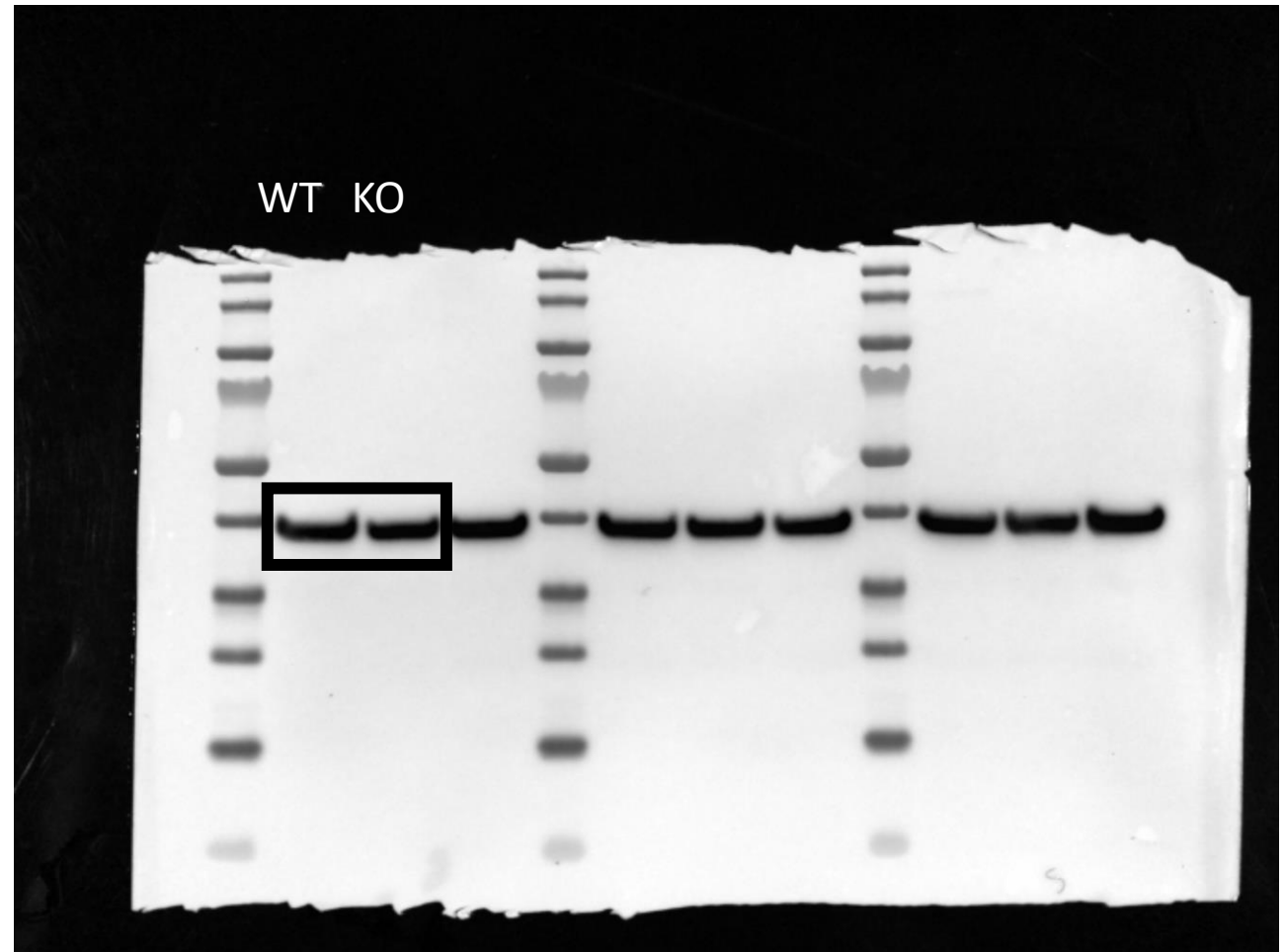


XPC (125 kDa)



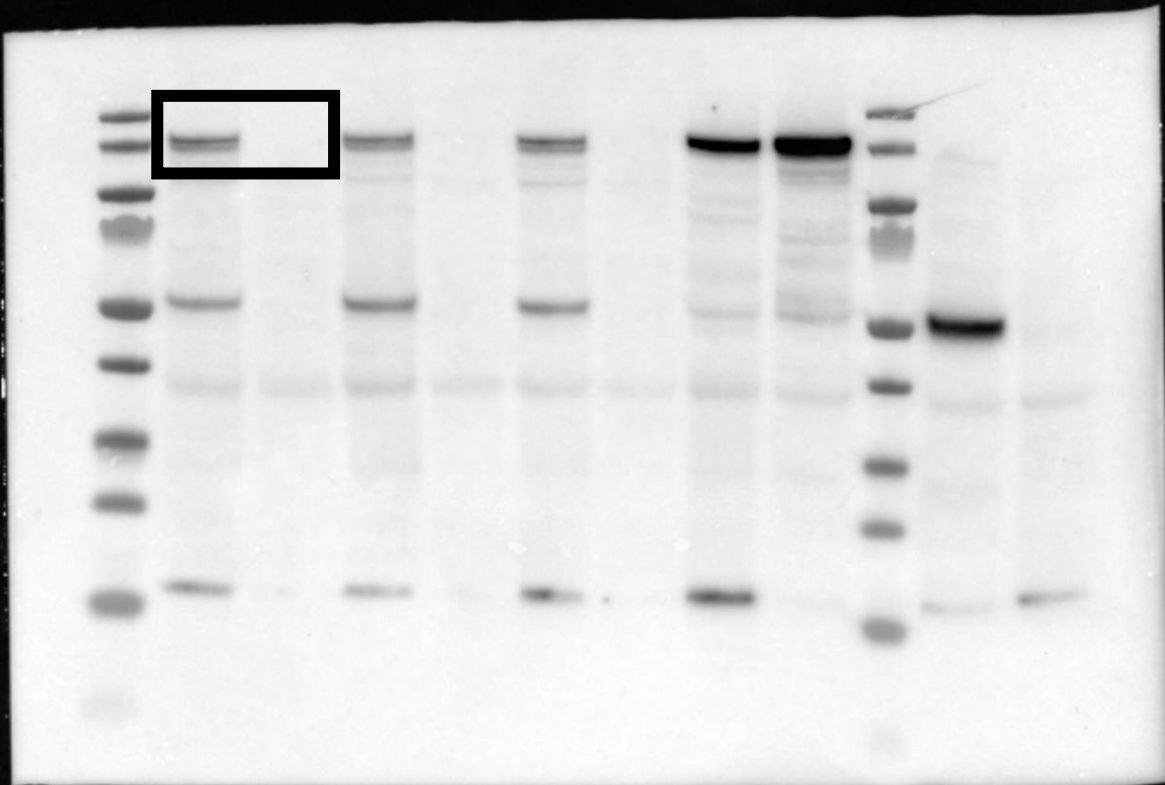
GAPDH (37 kDa)



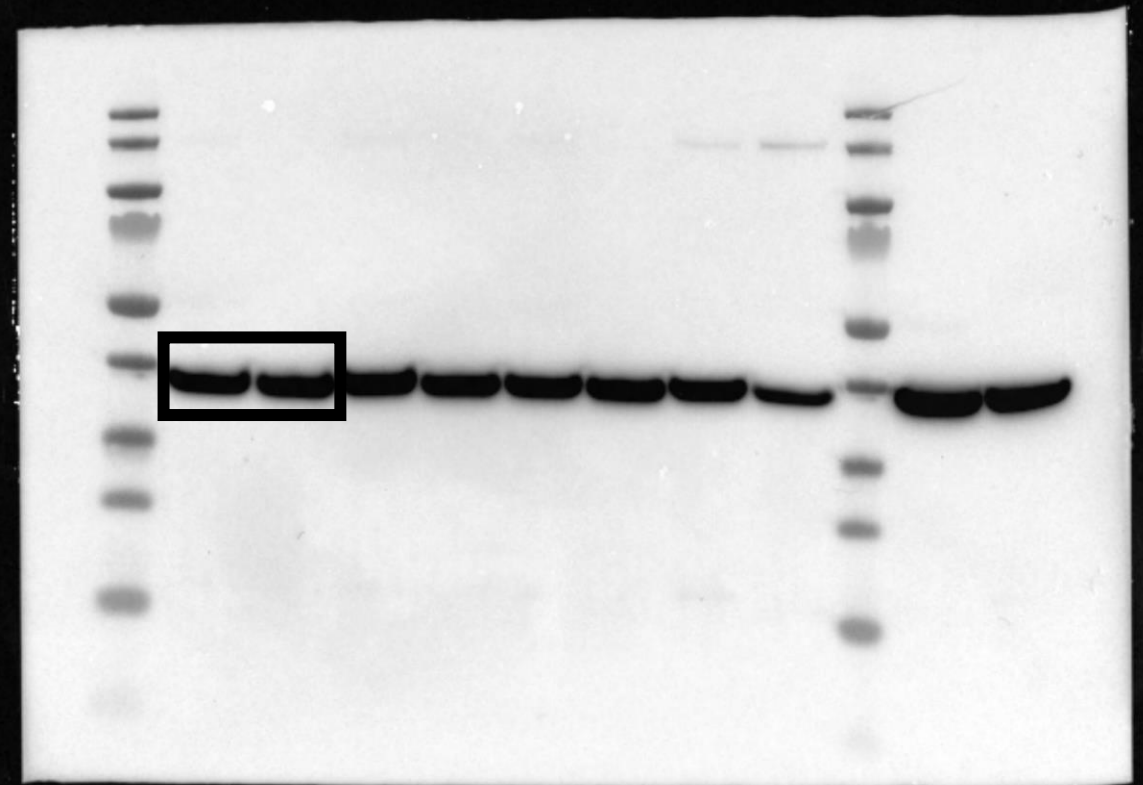
XPC (125 kDa)

GAPDH (37 kDa)

WT KO

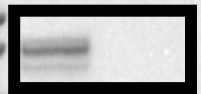


WT KO



XPC (125 kDa)

WT KO



GAPDH (37 kDa)

WT KO



XPC KO Keratinocyte clone final Sequencing

2 nucleotides deletion

WT	3	ATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGTCTAATTAGCTCAAAAGAA	62
KO	3	ATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGTCTAATTAGCTCAAAAGAA	62
WT	63	AACAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatcaacacaaaaaacacag	122
KO	63	AACAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatcaacacaaaaaacacag	122
WT	123	aaccaaacagttctgaaacaaagaaaGATGTTTCACCTTCAACCTCTTCCCAATCATTT	182
KO	123	AACCAACAGTCTGAAACAAAGAAAGATGTTTCACCTTCAACCTCTTCCCAATCATTT	182
WT	183	TCACTTTCTCCTCTTCTTCATTGCTGTCTTCATTATGCTGAGCCCTCTCTTCAGATGG	242
KO	183	TCACTTTCTCCTCTTCTTCATTGCTGTCTTCATTATGCTGAGCCCTCTCTTCAGATGG	240
WT	243	TGTGCTTCTTGAGGTCACCTGGAAAGTCCCTGTGTAAGACACAGGAAGGAAGATGAA	302
KO	241	TGTGCTTCTTGAGGTCACCTGGAAAGTCCCTGTGTAAGACACAGGAAGGAAGATGAA	300
WT	303	GAAGACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAATTTTAAACCCCTCCTA	362
KO	301	GAAGACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAATTTTAAACCCCTCCTA	360

Keratinocytes (N/TERT-2G cell line)

XPC KO Fibroblast clone final Sequencing

5 nucleotides deletion

WT	7	ATGAGTTTTTCCATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGTCTAATT	66
KO	1	ATGAGTTTTTCCATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGTCTAATT	60
WT	67	AGCTCAAAAGAAAAAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatcaacaaa	126
KO	61	AGCTCAAAAGAAAAAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatcaacaaa	120
WT	127	aaaaacaacagaacccaacagttctgaaacaaagaaaGATGTTTCACCTTCAACCTCT	186
KO	121	AAAAACAACAGAACCAACAGTTCTGAAACAAGAAAGATGTTTCACCTTCAACCTCT	180
WT	187	TCCCAATCATTTTCACTTTCTTCTCTTCTTCATTGCTGTCTTCATTATGCTGAGCCCT	246
KO	181	TCCCAATCATTTTCACTTTCTTCTCTTCTTCATTGCTGTCTTCATTATGCTGAGCCCT	239
WT	247	CTCTTCAGATGGTGTGCCTTCTTGAGGTCACCTGGAAAGTCCCTGTGTAAGACACAGG	306
KO	240	CTCTTCAGATGGTGTGCCTTCTTGAGGTCACCTGGAAAGTCCCTGTGTAAGACACAGG	295
WT	307	AAGGAAGATGAAGAAGACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAATTTT	366
KO	296	AAGGAAGATGAAGAAGACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAATTTT	355
WT	367	AAACCCCTCCTATTTATTGAGAATCTGTTGCAACTATTTAAAG	409
KO	356	AAACCCCTCCTATTTATTGAGAATCTGTTGCAACTATTTAAAG	398

Fibroblasts (S1F/TERT-1 cell line)

XPC KO Melanocyte clone final Sequencing

238 nucleotides deletion

WT	1	TTGGCCATGAGTTTTTCCATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGT	60
KO	6	TTGGCCATGAGTTTTTCCATATATATCAAAGCAAGTCCCTAGTACAACCTTATCTGTGGT	65
WT	61	CTAATTAGCTCAAAAGAAAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatc	120
KO	66	CTAATTAGCTCAAAAGAAAAAAGGATTGCAATTAGTGATCTGACTCcaaacagaatc	86
WT	121	aaacacacacacacacacacacacagttctgaaacaaagaaaGATGTTTCACCTTCA	180
WT	181	ACCTCTTCCCAATCATTTTCACTTTCTTCTCTTCTTCATTGCTGTCTTCATTATGCTGA	240
WT	241	GCCCCCTCTTTCAGATGGTGTGCCTTCTTGAGGTCACCTGGAAAGTCCCTGTGTAAGAC	300
WT	301	CACAGGAAGGAAGATGGAAGACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAA	360
KO	79	AAGAAACTCAGACATCCTAGTGTTCCATTCAAGCTAAATGGAA	122
WT	361	TTTTTAAACCCCTCCTATTTATTGAGAATCTGTTGCAACTATTTAAAGATGATTAGTAA	420
KO	123	TTTTTAAACCCCTCCTATTTATTGAGAATCTGTTGCAACTATTTAAAGATGATTAGTAA	182
WT	421	GCTCTGAGCCTCACTTCTCCATCAACATGTGTTCCAAATCTCATCAAGATGTGCTCTGA	480
KO	183	GCTCTGAGCCTCACTTCTCCATCAACATGTGTTCCAAATCTCATCAAGATGTGCTCTGA	242
WT	481	TCATCTGTCTAATTACTACCAGATGTGCTGTTAAAAACCTACAATCTAGATCGTGTA	540
KO	243	TCATCTGTCTAATTACTACCAGATGTGCTGTTAAAAACCTACAATCTAGATCGTGTA	302
WT	541	AGAAAACATAGCTG	554
KO	303	AGAAAACATAGCTG	316

Melanocytes (Mel-ST cell line)

Figure supplementary 1. Validation of the XPC gene knockout in the three skin cell types

The exon 3 target site of the XPC gene was sequenced to validate the type of edit introduced. BLAST bioinformatic alignment analysis of the control versus the XPC KO clone has shown 2 nucleotide deletion for keratinocytes, 5 nucleotide deletion for fibroblasts, and 238 nucleotide deletion for melanocytes in the target site, which induced a frameshift disruption of the gene.

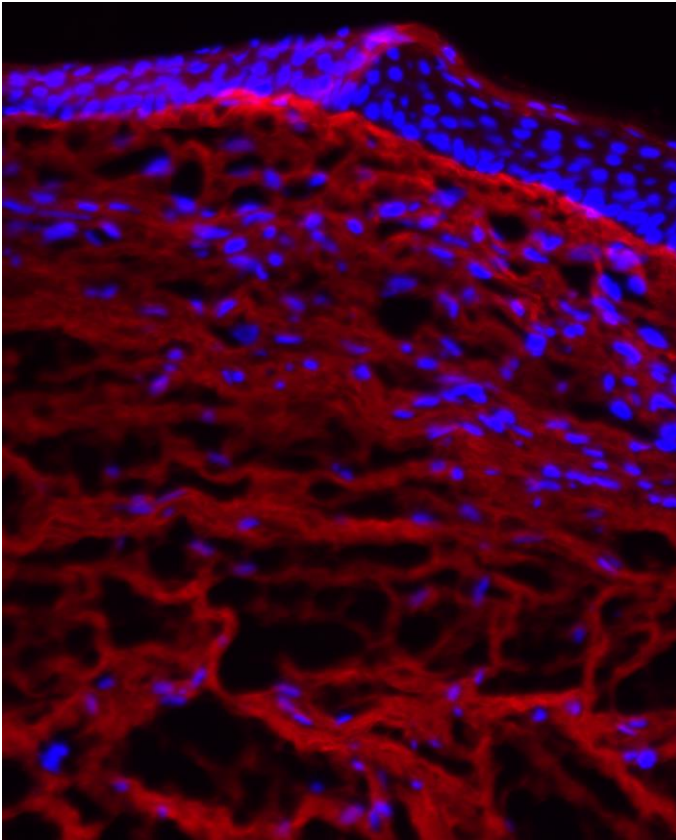
Gene Name	Function	Mismatch Number
POLR1A	The protein encoded by this gene is the largest subunit of the RNA polymerase I complex. The encoded protein represents the catalytic subunit of the complex, which transcribes DNA into ribosomal RNA precursors.	3
PGGT1B	The protein encoded by this gene catalyzes the transfer of a geranyl-geranyl moiety from geranyl-geranyl pyrophosphate to a cysteine at the fourth position from the C-terminus of proteins having the C-terminal sequence Cys-aliphatic-aliphatic-X.	4
UPRT	The protein encoded by this gene catalyzes uracil phosphoribosyltransferase, which catalyzes the conversion of uracil and 5-phosphoribosyl-2-R-diphosphate to uridine monophosphate (UMP). This reaction is an important part of nucleotide metabolism, specifically the pyrimidine salvage pathway.	4
MED24	The protein encoded by this gene is a component of the mediator complex (also known as TRAP, SMCC, DRII, or ARC), a transcriptional coactivator complex thought to be required for the expression of almost all genes.	4
DSG2	The protein encoded by this gene is a member of the desmoglein family and cadherin cell adhesion molecule superfamily of proteins. Desmogleins are calcium-binding transmembrane glycoprotein components of desmosomes, cell-cell junctions between epithelial, myocardial, and other cell types.	4
HUWE1	This gene encodes a protein containing a C-terminal HECT (E6AP type E3 ubiquitin protein ligase) domain that functions as an E3 ubiquitin ligase. The encoded protein is required for the ubiquitination and subsequent degradation of the anti-apoptotic protein Mcl1 (myeloid cell leukemia sequence 1 [BCL2-related]).	4
BOD1L1	This gene encodes a protein which is predicted to enable protein phosphatase 2A binding activity and protein phosphatase inhibitor activity. Involved in cellular response to DNA damage stimulus and replication fork processing.	3
IRF3	This gene encodes a protein which is a member of the interferon regulatory transcription factor (IRF) family. The encoded protein is found in an inactive cytoplasmic form that upon serine/threonine phosphorylation forms a complex with CREBBP. This complex translocates to the nucleus and activates the transcription of interferons alpha and beta, as well as other interferon-induced genes.	4
PATL1	This gene encodes a protein which enables poly(G) binding activity and poly(U) RNA binding activity. Involved in P-body assembly and deadenylation-dependent decapping of nuclear-transcribed mRNA.	4
KMT2D	This gene encodes a protein encoded which is a histone methyltransferase that methylates the lys-4 position of histone H3. The encoded protein is part of a large protein complex called ASCOM, which has been shown to be a transcriptional regulator of the beta-globin and estrogen receptor genes.	4
KPNA4	This gene encodes a protein where the nuclear import of karyophilic proteins is directed by short amino acid sequences termed nuclear localization signals (NLSs). Karyopherins, or importins, are cytoplasmic proteins that recognize NLSs and dock NLS-containing proteins to the nuclear pore complex.	4
MAML1	This gene encodes a protein which is the human homolog of mastermind, a Drosophila protein that plays a role in the Notch signaling pathway involved in cell-fate determination. There is in vitro evidence that the human homolog forms a complex with the intracellular portion of human Notch receptors and can increase expression of a Notch-induced gene.	4
LSP1	This gene encodes a protein which is an intracellular F-actin binding protein. The protein is expressed in lymphocytes, neutrophils, macrophages, and endothelium and may regulate neutrophil mobility, adhesion to fibrinogen matrix proteins, and transendothelial migration.	4
AP1G2	This gene encodes a protein belonging to adaptins that are important components of clathrin-coated vesicles transporting ligand-receptor complexes from the plasma membrane or from the trans-Golgi network to lysosomes. The adaptin family of proteins is composed of four classes of molecules named alpha-, beta-, beta prime- and gamma- adaptins. Adaptins, together with medium and small subunits, form a heterotrimeric complex called an adaptor, whose role is to promote the formation of clathrin-coated pits and vesicles.	4
NDFUF3	This gene encodes a protein involved mitochondrial complex I assembly protein that interacts with complex I subunits.	3

Supplementary figure 2. List of predicted possible off-target genes by CRISPOR bioinformatic tool

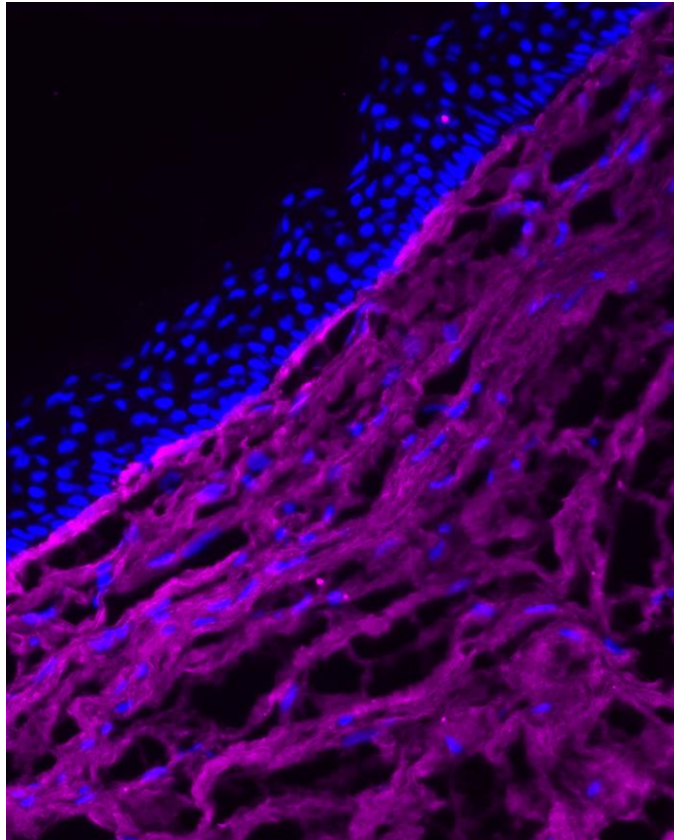
Majority protein IDs	Gene names	Protein names	#observable peptides	Razor + unique peptides	Unique + razor sequence coverage [%]	Mol weight [kDa]	Sequence length	Score	log2FC (XPC_vs_WT)	Enrichment	p-value (XPC_vs_WT)	-log10(p-value)	is Differential (XPC_vs_WT)
O95602;B9	POLR1A	DNA-directed RNA polymerase I subunit RPA1	110	26	21.6	194.81	1720	103.52	-0.036136	1.025364	0.250975	0.60037	0
P53609	PGGT1B	Geranylgeranyl transferase type-1 subunit beta	21	6	20.7	42.368	377	13.886	0.113299	1.081699	0.008905	2.050385	0
Q96BW1;A	UPRT;RP11	Uracil phosphoribosyltransferase homolog	15	2	16.8	33.786	309	25.17	0.139738	1.101705	0.00793	2.100748	0
O75448;A0	MED24	Mediator of RNA polymerase II transcription subunit 24	59	3	3.5	110.3	989	6.4466	0.022	1.02	0.6212	0.2068	0
Q14126	DSG2	Desmoglein-2	52	15	20.3	122.29	1118	150.84	-0.209849	1.156567	1.72E-05	4.765178	0
Q726Z7;A0	HUWE1	E3 ubiquitin-protein ligase HUWE1	208	78	25.7	481.89	4374	323.31	-0.091	1.07	0.0037	2.4373	0
Q8NFC6	BOD1L1	Biorientation of chromosomes in cell division protein 1-like 1	156	11	4.6	330.46	3051	47.952	-0.03024	1.021182	0.415879	0.381033	0
Q14653;A0	IRF3	Interferon regulatory factor 3	19	7	25.5	47.219	427	34.19	0.155	1.11	0.0002	3.8185	0
Q86TB9;B7	PATL1	Protein PAT1 homolog 1	46	8	15.5	86.849	770	150.28	0.056	1.04	0.2247	0.6484	0
O14686;A0	KMT2D	Histone-lysine N-methyltransferase 2D	241	4	1.2	593.38	5537	15.771	0.050	1.03	0.5298	0.2759	0
O00629;A0	KPNA4	Importin subunit alpha-3	20	18	44.1	57.886	521	319.24	-0.002152	1.001493	0.927061	0.032892	0
Q92585;Q5	MAML1	Mastermind-like protein 1	37	1	1	108.05	1016	2.3278	0.086	1.06	0.5146	0.2885	0
P33241;C9	LSP1	Lymphocyte-specific protein 1	22	1	4.4	37.191	339	4.2307	0.494	1.41	0.0001	4.0109	1
O75843;Q5	AP1G2	AP-1 complex subunit gamma-like 2	45	14	26	87.116	785	110.86	0.042964	1.030228	0.169176	0.771662	0
Q9BU61;Q1	KFZp564J0	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex assembly factor 3	10	4	34.2	20.35	184	51.431	-0.039	1.03	0.4971	0.3036	0

Supplementary figure 3. The protein expression of the possible predicted off-targets was validated using MS-based proteomic profiling in XPC KO and associated control cells.

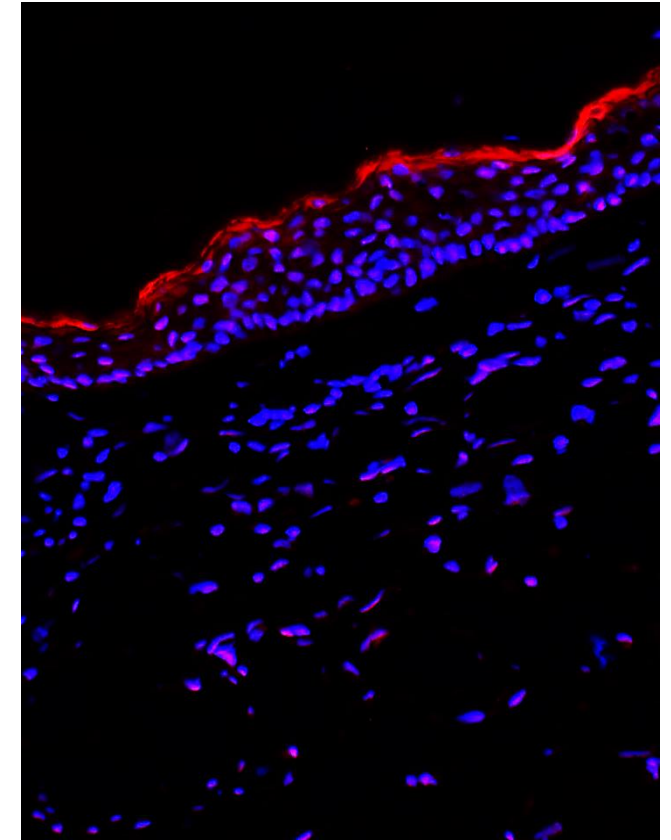
Collagen type I



Collagen type III



Involucrin



Supplementary Figure 10B. Control skin keratinocytes (N/TERT-2G), fibroblasts (S1F/TERT-1), and melanocytes (Mel-ST) embedded in a fibrin scaffold express collagen Type I (in red), Type III (in purple), and involucrin (in red).