

The official journal of

INTERNATIONAL FEDERATION OF PIGMENT CELL SOCIETIES · SOCIETY FOR MELANOMA RESEARCH

# PIGMENT CELL & MELANOMA Research

## Genomic characterisation of acral melanoma cell lines

Simon J. Furney, Samra Turajlic, Kerry Fenwick, Maryou B. Lambros, Alan MacKay, Gerda Ricken, Costas Mitsopoulos, Iwanka Kozarewa, Jarle Hakas, Marketa Zvelebil, Christopher J. Lord, Alan Ashworth, Jorge S. Reis-Filho, Meenhard Herlyn, Hiroshi Murata and Richard Marais

DOI: 10.1111/j.1755-148X.2012.01016.x

Volume 25, Issue 4, Pages 488-492

If you wish to order reprints of this article, please see the guidelines [here](#)

Supporting Information for this article is freely available [here](#)

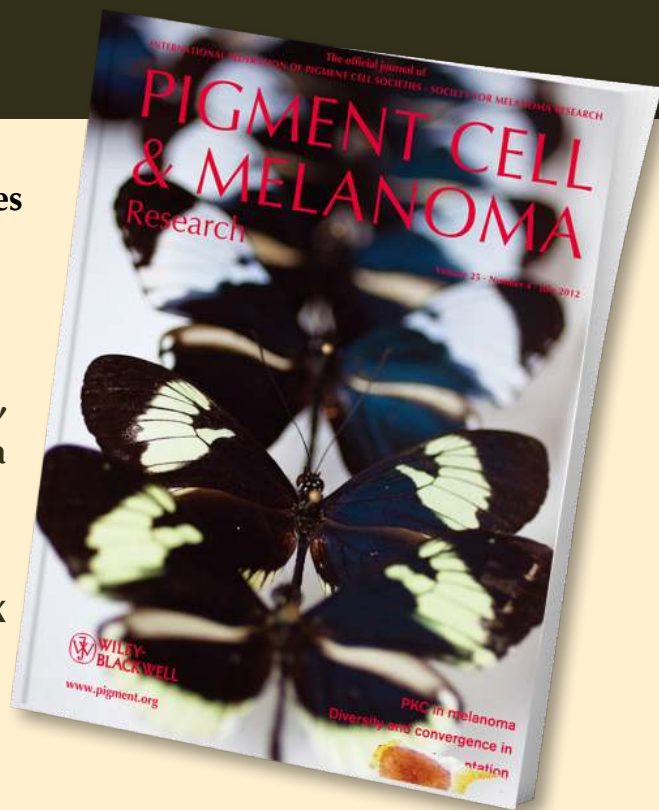
### EMAIL ALERTS

Receive free email alerts and stay up-to-date on what is published in Pigment Cell & Melanoma Research – [click here](#)

Submit your next paper to PCMR online at <http://mc.manuscriptcentral.com/pcmr>

Subscribe to PCMR and stay up-to-date with the only journal committed to publishing basic research in melanoma and pigment cell biology

As a member of the IFPCS or the SMR you automatically get online access to PCMR. Sign up as a member today at [www.ifpcs.org](http://www.ifpcs.org) or at [www.societymelanomaresearch.org](http://www.societymelanomaresearch.org)



To take out a personal subscription, please [click here](#)

More information about Pigment Cell & Melanoma Research at [www.pigment.org](http://www.pigment.org)

# Genomic characterisation of acral melanoma cell lines

Simon J. Furney<sup>1,\*</sup>, Samra Turajlic<sup>1,\*</sup>, Kerry Fenwick<sup>2</sup>, Maryou B. Lambros<sup>2</sup>, Alan MacKay<sup>2</sup>, Gerda Ricken<sup>1</sup>, Costas Mitsopoulos<sup>2</sup>, Iwanka Kozarewa<sup>2</sup>, Jarle Hakas<sup>2</sup>, Marketa Zvelebil<sup>2</sup>, Christopher J. Lord<sup>2</sup>, Alan Ashworth<sup>2</sup>, Jorge S. Reis-Filho<sup>2</sup>, Meenhard Herlyn<sup>3</sup>, Hiroshi Murata<sup>4</sup> and Richard Marais<sup>1,5</sup>

**1** Signal Transduction Team, Division of Cancer Biology, Institute of Cancer Research, London, UK **2** The Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, Institute of Cancer Research, London, UK **3** The Wistar Institute, Philadelphia, PA, USA **4** Department of Dermatology, Shinshu University School of Medicine, Asahi, Matsumoto, Japan **5** The Patterson Institute for Cancer Research, The University of Manchester, Manchester, UK

**CORRESPONDENCE** R. Marais, e-mail: rmarais@picr.man.ac.uk

\*These authors contributed equally to this work.

**KEYWORDS** acral melanoma/cell lines/exome sequencing/genomics/mutational signature

**PUBLICATION DATA** Received 13 March 2012, revised and accepted for publication 11 May 2012, published online 12 May 2012

doi: 10.1111/j.1755-148X.2012.01016.x

## Summary

Acral melanoma is a rare melanoma subtype with distinct epidemiological, clinical and genetic features. To determine if acral melanoma cell lines are representative of this melanoma subtype, six lines were analysed by whole-exome sequencing and array comparative genomic hybridisation. We demonstrate that the cell lines display a mutation rate that is comparable to that of published primary and metastatic acral melanomas and observe a mutational signature suggestive of UV-induced mutagenesis in two of the cell lines. Mutations were identified in oncogenes and tumour suppressors previously linked to melanoma including *BRAF*, *NRAS*, *KIT*, *PTEN* and *TP53*, in cancer genes not previously linked to melanoma and in genes linked to DNA repair such as *BRCA1* and *BRCA2*. Our findings provide strong circumstantial evidence to suggest that acral melanoma cell lines and acral tumours share genetic features in common and that these cells are therefore valuable tools to investigate the biology of this aggressive melanoma subtype. Data are available at: [http://rock.icr.ac.uk/collaborations/Furney\\_et\\_al\\_2012/](http://rock.icr.ac.uk/collaborations/Furney_et_al_2012/).

Primary cutaneous melanoma most commonly occurs on sun-exposed hair-bearing skin, but in rare cases, it also occurs on the non-hair-bearing (i.e. acral) skin of the palms, soles and nail beds. Notably, although the *BRAF* gene is mutated in approximately 50% of melanomas from hair-bearing skin, *BRAF* is only mutated in approximately 16% of acral melanomas, and whereas *KIT* is not mutated in melanoma from hair-bearing skin, it is mutated in approximately 20% of acral melanomas (Curtin et al., 2006). Furthermore, focal gene amplifications involving the regions that encode *GAB2* (Chernoff

et al., 2009), *CCND1* (Sauter et al., 2002) and *CDK4* (Curtin et al., 2005) in particular appear to be more prevalent in acral melanoma than in hair-bearing skin melanoma. These studies have demonstrated that cutaneous melanomas from hair-bearing and acral skin are genetically distinct diseases, and accordingly, at least in some studies, it has been shown that acral melanoma is inherently more aggressive and has a poorer prognosis than melanoma from hair-bearing skin (Bradford et al., 2009).

Notably, melanoma from hair-bearing skin is almost entirely restricted to Caucasians and is associated with

## Significance

The treatment of rare melanoma subtypes remains challenging as the majority of driver genetic alterations remain unknown. This study represents a genomic analysis of six of the seven available acral melanoma cell lines. We present the coding sequence mutations and copy number alterations detected in these lines and an analysis of the mutational burden and mutational signatures. The data provide a reference for studies on acral melanoma in particular, but will be of value to the entire melanoma research community.

intermittent or chronic exposure to ultraviolet (UV) light, whereas acral melanoma occurs with equal frequency in all racial groups and does not appear to be causally linked to UV light exposure. These differences have been ascribed to the fact that acral skin is UV-protected by a thickened stratum corneum or the nail matrix and is further protected by habitual under-exposure to UV light. We have recently reported a somatic mutation rate in acral melanomas that was substantially lower than that seen in hairy-skin melanomas and more similar to that seen in cancers that are not associated with known mutagens (Pleasant et al., 2010a; Wei et al., 2011; Turajlic et al., 2012). Surprisingly, despite this, we observed a mutation pattern that was consistent with UV-induced DNA damage (Turajlic et al., 2012). This suggests that the protection of acral skin from UV light is not absolute and that although UV light exposure to acral skin is qualitatively and quantitatively different from that of hairy skin, UV light may play a role in acral melanomagenesis.

Common cutaneous melanomas tend to lend themselves to establishment as immortalised cell lines, whereas acral melanoma cell lines are more difficult to establish. To date, only seven immortalised acral melanoma lines have been described (Satyamoorthy et al., 1997; Murata et al., 2007; Ashida et al., 2009). The SM3, SMYM-PRGP, MMG1 and WM3211 lines were derived from primary lesions, whereas the SM2-1 and Mel-2 lines were derived from in-transit metastases, and the Mel18 line was derived from a lymph node metastasis (Table S1). SM3, SMYM-PRGP, MMG1, SM2-1, Mel-2 and Mel18 cells were from Japanese patients, but the racial origin of WM3211 cells is unknown. Given the importance of these lines as models of a distinct and aggressive melanoma subtype and the uncertainty of the role of UV in acral melanomagenesis, we sought to define whether these cell lines are representative of the molecular features of primary and metastatic acral melanomas. We therefore subjected the SMYM-PRGP, MMG1, SM2-1, Mel-2, Mel18 and WM3211 cells to microarray-based comparative genomic hybridisation (aCGH) and next generation sequencing to characterise their genomic landscape and mutational profiles. Unfortunately, SM3 cells could not be included in this analysis owing to their poor growth properties.

Short tandem repeat (STR) typing authenticated the identity of WM3211 cells and demonstrated that SMYM-PRGP, MMG1, SM2-1, Mel-2 and Mel18 cells had unique identities (Table S2). All lines were confirmed as mycoplasma-free. We used array CGH profiling of the cell lines to characterise somatic copy number alterations (Figures S1–S6; Krzywinski et al., 2009). Previously, it has been shown that acral melanomas display a higher degree of overall genomic aberrations and of amplicons than melanomas from sun-exposed hair-bearing skin (Curtin et al., 2005). In the line with these observations, we identified an average of 9.2 amplifications and 4.7 dele-

tions in each cell line using previously described thresholds (Natrajan et al., 2010). Several regions typically amplified in acral melanoma, including 5p15 and 12q14, were identified (Figures S1–S6). The focal amplifications of *CCND1* (11q13) and *hTERT* (5p15) previously described (Murata et al., 2007) in SMYM-PRGP cells were confirmed by aCGH (Figures S1–S6).

We also performed exome capture and sequencing of genomic DNA derived from these cell lines and obtained approximately 7.8 Gb of high-quality mapped sequence per cell line with mean on-target coverage of 79× (Table S3). The paired-end reads were aligned to the NCBI build 37 reference genome, which revealed approximately 15–18 000 single nucleotide variants (SNVs) and approximately 800–1300 small insertions or deletions (indels) in each line (Figures S1–S6, Table 1). Unfortunately, we did not possess reference germline DNA for these cell lines, so to identify candidate driver events, we first removed known human polymorphisms present in the dbSNP 135 database. This revealed 287–1078 putative novel SNVs and 83–130 putative novel indels in each line (Figure S1–S6; Table 1; Li and Durbin, 2009; McKenna et al., 2010; Koboldt et al., 2009; McLaren et al., 2010). To benchmark this approach, we re-analysed the exomes from the acral tumours we previously described but without their reference germline DNA (Turajlic et al., 2012). Pleasingly, this revealed very similar numbers of mutations, with 278 novel SNVs and 148 indels in the primary tumour and 259 novel SNVs and 80 indels in the metastasis (Table 1).

It is intriguing that WM3211 cells carry two to three as many SNVs as the Japanese lines (Table 1). WM3211 cells were derived from a tumour arising on the ankle (<http://www.wistar.org/lab/meenhard-herlyndvm-dsc>), a near-acral site. However, as WM3211 cells carry a mutation in *KIT* and *KIT* mutations are rare in hairy-skin melanomas (Beadling et al., 2008), they were likely derived from a *bona fide* acral melanoma. Other explanations for the higher mutation burden in WM3211 cells could be environmental (geographic) or ethnic differences, or related to the fact that these cells have *TP53* and *BRCA2* mutations that could have affected DNA repair (Table S4).

We checked for the presence of all SNVs, including those in dbSNP, in the COSMIC database (<http://www.sanger.ac.uk/genetics/CGP/cosmic/>) and validated likely oncogenic mutations by Sanger sequencing (Table 1). We prioritised the non-dbSNP variants according to their likelihood of being deleterious using in-silico approaches (Gonzalez-Perez and Lopez-Bigas, 2011). Cross-referencing these deleterious SNVs and indels with the Cancer Gene Census (<http://www.sanger.ac.uk/genetics/CGP/Census/>) identified 24 variants at novel residues in the genes previously reported as mutated in cancer (Table S4).

The L576P *KIT* mutation previously described in WM3211 cells (Woodman et al., 2009) was confirmed

**Table 1.** Summary of mutations in acral melanoma. The data show a summary of single nucleotide variants (SNVs) and small insertions and deletions (indels) detected in the six acral melanoma cell lines and the primary acral melanoma and metastasis. For each of the cell lines or tumours, the data show the total number of variants (Total SNVs), the number of novel variants not present in the dbSNP 135 database (Novel SNVs), the number of those novel variants that are predicted to be deleterious (Del. Novel SNVs), the SNVs validated by Sanger sequencing and described as being mutant in COSMIC (Validated SNVs present in COSMIC), the total number of indels (Total indels), the number of novel indels (Novel indels) and the number of novel indels predicted to be deleterious (Del. Novel indels).

Cell line	Total SNVs	Novel SNVs	Del. novel SNVs	Validated SNVs present in COSMIC	Total indels	Novel indels	Del. novel indels
Mel18	16662	450	127	<i>BRAF</i> V600E <i>PTEN</i> T167A <i>APC</i> S130G	1029	110	26
Mel-2	18280	287	65	<i>NRAS</i> G12D <i>GRK7</i> V398F	1291	130	26
MMG1	14945	330	84	<i>BRAF</i> V600E	903	83	18
SM2-1	16756	305	69	<i>BRAF</i> V600E <i>PTEN</i> C136Y	1055	94	28
SMYM-PRGP	17074	304	87	<i>GPR179</i> V1969I	1157	102	20
WM3211	16187	1078	361	<i>TP53</i> C242G <i>KIT</i> L576P <i>CBL</i> F418L	805	83	21
Primary acral melanoma	19975	278	60	n/a	1435	148	23
Acral melanoma nodal metastasis	18069	259	50	n/a	1031	80	19

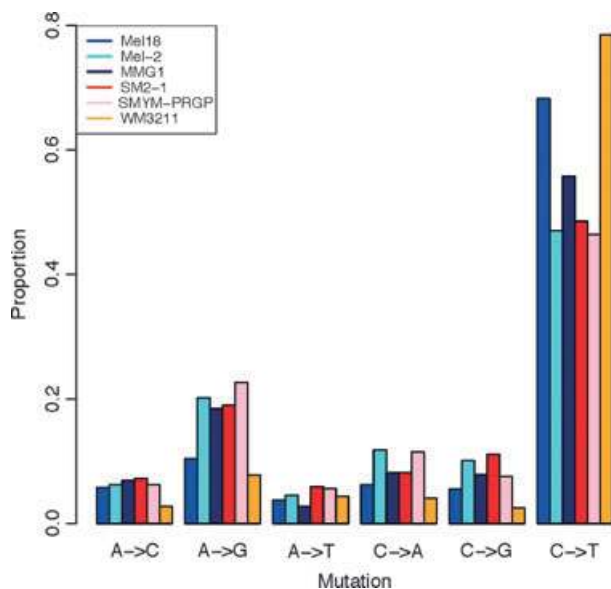
by exome sequencing (Figure S7). We also confirmed that MMG1, SM2-1 and Mel18 cells all harboured *BRAF* V600E mutations and that Mel-2 cells carried an *NRAS* G12V mutation (Figure S8). *BRAF* mutations occur in <20% of acral melanomas (Curtin et al., 2005), so a mutation rate of 50% (3/6) in the lines is an over-representation. The enrichment of *BRAF* mutations in the cell lines presumably occurs because cells expressing oncogenic *BRAF* are easier to establish in culture than cells expressing other oncogenes, or because these mutations are acquired during in vitro culture. Of note, *BRAF*<sup>V600E</sup> mutations also appear to be over-represented in uveal melanoma cell lines (Griewank et al., 2012).

Although the mutant forms of *KIT*, *BRAF* and *NRAS* are likely to be driver events in some of the cancers from which these lines were derived, we also identified additional potential driving and cooperating lesions in these cells (Table S5). We report homozygous mutations in known melanoma tumour suppressors (Sparrow et al., 1995; Aguisa-Toure and Li, 2011), including T167A and C136Y in *PTEN* in Mel18 and SM2-1 cells, respectively, C242G in *TP53* in WM3211 cells and L650\* in *NF1* in SMYM-PRGP cells (Figure S9A–D). We also report a P793L mutation in *MAP3K9* in WM3211 cells (Figure S9E) and note that this residue was recently reported as mutated in a study that described *MAP3K9* as being mutated in 15% of melanoma cell lines (Stark et al., 2011). The S130G mutation observed in *APC* in Mel18 cells (Figure S9F) was previously reported in SKMEL-28 melanoma cells (<http://www.sanger.ac.uk/genetics/CGP/cosmic/>).

In addition to the mutations described above, we observed novel mutations in genes that may be related to microsatellite instability and DNA repair. We describe a Q723\* mutation in *ARID1A* (Figure S3G), a gene that encodes a member of the SWI-SNF chromatin-remodelling family and mutations, which have been reported in

association with microsatellite instability (Jones et al., 2012). Similarly, microsatellite instability is associated with mutations in *ERCC5*, and we previously reported a truncating mutation in this gene in acral melanoma (Turajlic et al., 2012). We also observed novel heterozygous *BRCA1* and homozygous *BRCA2* variants in SMYM-PRGP and WM3211 cells, respectively (Table S4), and although of unknown significance (<http://brca.iarc.fr/LOVD/home.php>) they are predicted to be deleterious. These findings suggest that defects in DNA repair may play a role in acral melanomagenesis, at least in some cases.

The previously published lung cancer and melanoma cell line genomes (Plesance et al., 2010a,b) exhibited characteristic mutational signatures associated with UV and tobacco. To investigate the mutational processes in acral melanoma, we first assessed the pattern of all novel single-base substitutions in the exomes of the cell lines (Figure 1). We observed that the predominant mutations in each cell line were C>T (G>A) transitions consistent with the mutational signature we previously reported in human acral tumour samples (Turajlic et al., 2012). Whole-genome sequencing of a cutaneous melanoma cell line revealed a high proportion of C to T transitions, 92% of which occurred at the 3' base of a pyrimidine dinucleotide (Plesance et al., 2010a). These mutations are characteristic of DNA damage induced by UVB light (Pfeifer and Besaratinia, 2012). Two of the cell lines we examined, Mel18 and WM3211, exhibit higher proportions of C to T transitions (68 and 79%, respectively; Figure 1; Table S10). Hence, we examined the sequence context in each of the cell lines (Figure S10; Table S10) and detected an enrichment for C>T (G>A) at the 3' base of TpC or CpC dinucleotides in Mel18 (82%) and WM3211 (90%) cells, but not in the other cells, which had lower rates of C>T (G>A) transitions. It is possible that these mutations were the result of



**Figure 1.** Mutational signature analysis in acral melanoma cell lines: The proportion of novel SNVs (non-dbSNP) by class in each cell line.

fluorescent light-induced DNA adducts acquired during in vitro culture (Ritter and Williams, 1981). However, this seems unlikely as the pattern was not seen in all cell lines, and these results therefore suggest a role for UV light in the induction of the tumours from which the Mel18 and WM3211 cells were derived. We note that the differences in the degree of UV mutational signature correlated with the variation in mutation rate. There was no correlation between the mutational status of the major melanoma oncogenes and the mutational signature.

In conclusion, we present the first comprehensive profiling of the currently available acral melanoma cell lines. We show that the copy number alterations, mutational burden and mutational signature are similar to those of published acral melanoma tumour samples and we have catalogued all the coding mutations in these cells, providing a list of variants that may constitute disease drivers. We provide lists of all SNVs, indels and regions of copy number alteration discovered in the cell lines as supplementary data available at [http://rock.icr.ac.uk/collaborations/Furney\\_et\\_al\\_2012/](http://rock.icr.ac.uk/collaborations/Furney_et_al_2012/) as a resource for the melanoma research community.

## Acknowledgements

This work was supported by a Career Development Award from The Harry J Lloyd Charitable Trust (S.T.), Cancer Research UK (ref: C107/A10433) and The Institute of Cancer Research. J.R.-F. is in part funded by Breakthrough Breast Cancer and is a recipient of the 2010 CR-UK Future Leaders Prize. We acknowledge NHS funding to the NIHR Biomedical Research Centre and thank Ms Alice Smith for technical assistance with Sanger sequencing.

## References

- Aguissa-Toure, A.H., and Li, G. (2011). Genetic alterations of PTEN in human melanoma. *Cell. Mol. Life Sci.* **69**, 1475–1491.
- Ashida, A., Takata, M., Murata, H., Kido, K., and Saida, T. (2009). Pathological activation of KIT in metastatic tumors of acral and mucosal melanomas. *Int. J. Cancer* **124**, 862–868.
- Beadling, C., Jacobson-Dunlop, E., Hodi, F.S. et al. (2008). KIT gene mutations and copy number in melanoma subtypes. *Clin. Cancer Res.* **14**, 6821–6828.
- Bradford, P.T., Goldstein, A.M., McMaster, M.L., and Tucker, M.A. (2009). Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986–2005. *Arch. Dermatol.* **145**, 427–434.
- Chernoff, K.A., Bordone, L., Horst, B. et al. (2009). GAB2 amplifications refine molecular classification of melanoma. *Clin. Cancer Res.* **15**, 4288–4291.
- Curtin, J.A., Fridlyand, J., Kageshita, T. et al. (2005). Distinct sets of genetic alterations in melanoma. *N. Engl. J. Med.* **353**, 2135–2147.
- Curtin, J.A., Busam, K., Pinkel, D., and Bastian, B.C. (2006). Somatic activation of KIT in distinct subtypes of melanoma. *J. Clin. Oncol.* **24**, 4340–4346.
- Gonzalez-Perez, A., and Lopez-Bigas, N. (2011). Improving the assessment of the outcome of nonsynonymous SNVs with a consensus deleteriousness score. *Condel. Am. J. Hum. Genet.* **88**, 440–449.
- Griewank, K.G., Yu, X., Khalili, J., Sozen, M.M., Stempke-Hale, K., Bernatchez, C., Wardell, S., Bastian, B.C., and Woodman, S.E. (2012). Genetic and molecular characterization of uveal melanoma cell lines. *Pigment Cell Melanoma Res.* **25**, 182–187.
- Jones, S., Li, M., Parsons, D.W. et al. (2012). Somatic mutations in the chromatin remodeling gene ARID1A occur in several tumor types. *Hum. Mutat.* **33**, 100–103.
- Koboldt, D.C., Chen, K., Wylie, T., Larson, D.E., McLellan, M.D., Mardis, E.R., Weinstock, G.M., Wilson, R.K., and Ding, L. (2009). VarScan: variant detection in massively parallel sequencing of individual and pooled samples. *Bioinformatics* **25**, 2283–2285.
- Krzywinski, M., Schein, J., Birol, I., Connors, J., Gascoyne, R., Horsman, D., Jones, S.J., and Marra, M.A. (2009). Circos: an information aesthetic for comparative genomics. *Genome Res.* **19**, 1639–1645.
- Li, H., and Durbin, R. (2009). Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–1760.
- McKenna, A., Hanna, M., Banks, E. et al. (2010). The genome analysis toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res.* **20**, 1297–1303.
- McLaren, W., Pritchard, B., Rios, D., Chen, Y., Flicek, P., and Cunningham, F. (2010). Deriving the consequences of genomic variants with the Ensembl API and SNP effect predictor. *Bioinformatics* **26**, 2069–2070.
- Murata, H., Ashida, A., Takata, M., Yamaura, M., Bastian, B.C., and Saida, T. (2007). Establishment of a novel melanoma cell line SMYM-PRGP showing cytogenetic and biological characteristics of the radial growth phase of acral melanomas. *Cancer Sci.* **98**, 958–963.
- Natrajan, R., Weigelt, B., Mackay, A. et al. (2010). An integrative genomic and transcriptomic analysis reveals molecular pathways and networks regulated by copy number aberrations in basal-like, HER2 and luminal cancers. *Breast Cancer Res. Treat.* **121**, 575–589.
- Pfeifer, G.P., and Besaratinia, A. (2012). UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer. *Photochem. Photobiol. Sci.* **11**, 90–97.

- Pleasant, E.D., Cheetham, R.K., Stephens, P.J. et al. (2010a). A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* **463**, 191–196.
- Pleasant, E.D., Stephens, P.J., O'Meara, S. et al. (2010b). A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature* **463**, 184–190.
- Ritter, M.A., and Williams, J.R. (1981). Fluorescent-light-induced lethality and DNA repair in normal and xeroderma pigmentosum fibroblasts. *Biochim. Biophys. Acta* **655**, 18–25.
- Satyamoorthy, K., DeJesus, E., Linnenbach, A.J., Kraj, B., Kornreich, D.L., Rendle, S., Elder, D.E., and Herlyn, M. (1997). Melanoma cell lines from different stages of progression and their biological and molecular analyses. *Melanoma Res.* **7**(Suppl 2), S35–S42.
- Sauter, E.R., Yeo, U.C., von Stemm, A. et al. (2002). Cyclin D1 is a candidate oncogene in cutaneous melanoma. *Cancer Res.* **62**, 3200–3206.
- Sparrow, L.E., Soong, R., Dawkins, H.J., Iacopetta, B.J., and Heenan, P.J. (1995). p53 gene mutation and expression in naevi and melanomas. *Melanoma Res.* **5**, 93–100.
- Stark, M.S., Woods, S.L., Gartside, M.G. et al. (2011). Frequent somatic mutations in MAP3K5 and MAP3K9 in metastatic melanoma identified by exome sequencing. *Nat. Genet.* **44**, 165–169.
- Turajlic, S., Furney, S.J., Lambros, M.B. et al. (2012). Whole genome sequencing of matched primary and metastatic acral melanomas. *Genome Res.* **22**, 196–207.
- Wei, X., Walia, V., Lin, J.C. et al. (2011). Exome sequencing identifies GRIN2A as frequently mutated in melanoma. *Nat. Genet.* **43**, 442–446.
- Woodman, S.E., Trent, J.C., Stemke-Hale, K. et al. (2009). Activity of dasatinib against L576P KIT mutant melanoma: molecular, cellular, and clinical correlates. *Mol. Cancer Ther.* **8**, 2079–2085.

## Supporting Information

Additional Supporting information may be found in the online version of this article:

**Data S1.** Methods.

**Figure S1.** Circos plot of Mel2 cell line.

**Figure S2.** Circos plot of Mel18 cell line.

**Figure S3.** Circos plot of MMG1 cell line.

**Figure S4.** Circos plot of SM2-1 cell line.

**Figure S5.** Circos plot of SMYM-PRGP cell line.

**Figure S6.** Circos plot of WM3211 cell line.

**Figure S7.** IGV browser representation of the reads mapping to chr4 5593661 in WM3211 cells.

**Figure S8.** IGV browser representation of the reads mapping to particular genomic coordinates in each of the cell lines.

**Figure S9.** Sanger sequencing traces showing mutations detected and validated in various cell lines.

**Figure S10.** Frequency of bases  $\pm 5$  bp of C>T/G>A transitions in acral melanoma cell lines.

**Table S1.** Acral melanoma cell lines used in this study.

**Table S2.** Short Tandem Repeat (STR) profiling of the cell lines used in this study.

**Table S3.** Whole exome sequencing summary.

**Table S4.** Summary of mutations in acral melanoma cell lines in genes previously reported in the Cancer Gene Census.

**Table S5.** Driver and cooperating lesions in acral melanoma.

**Table S6.** Details of PCR and sequencing primers used in validation by Sanger sequencing.

**Table S7.** Candidate deleterious somatic SNVs identified in the cell lines passing thresholds and not present in dbSNP 135.

**Table S8.** Candidate deleterious somatic indels identified in the cell lines passing thresholds and not present in dbSNP 135.

**Table S9.** Segmentend aCGH data for all cell lines.

**Table S10.** The percentage of all mutations that are C>T (G>A), the percentage of C>T(G>A) mutations occurring at the 5' base of a pyrimidine dinucleotide, and, the percentage of C>T(G>A) mutations occurring at the 3' base of a pyrimidine dinucleotide.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.