expression analyses (Genome-Wide GeneChip Human Transcriptome Array 2.0, Affymetrix). Single-sample gene set enrichment analysis was performed for a gene set upregulated in breast tumours with TP53 mutation [Miller et al. Proc Natl Acad Sci U S A. 2005;102(38:13550–5)] and a gene set upregulated in MPNSTs with PR2 inactivation [Lee et al. Nat Genet. 2014;46(11:1227–32)].

**Results and discussions** Both the TP53 network and PR2 activity were down-regulated in MPNSTs compared with the benign neurofibromas, as determined by a significantly higher gene set score (p=3 × 10–10 and p=0.0009, respectively). Furthermore, down-regulation of both processes were associated with inferior survival for MPNST patients (HR=4.1 [95% CI, 1.73–9.79], p=0.001 and HR=4.9 [95% CI, 1.65–14.69], p=0.004, respectively). In multivariable analyses, including the clinical variables NF1 status, sex, age at diagnosis, tumour location, tumour size, and remission status, both gene sets were independent prognostic markers, however the TP53 gene set signature had the strongest prognostic impact. Patients with down-regulation of both processes (n=25, 42%) had a particularly poor survival (HR=9.1, CI:2.1–39.9, p=0.003).

**Conclusion** Dysregulation of the TP53 network and PR2 function distinguish MPNSTs from benign neurofibromas and are independently associated with inferior patient survival.
somatic alterations, including 30 regions with gains (NF1, CCND1, MYC, TP53, DCC, MAPK2, AURKA, IGF1R, PIK3CA, GAB2, NX2-2, BCL2L2, BORF4, BCL2L1, ZNF217, EGF, NCOA3, SKP2, FADD, ORAO1V1, EEF1A2, REL, TERT, AKT3, PRKCI, MAPK7, DCUN1D1, BIRC2, YAP1, MYCN) and 14 losses (FHIT, GPC5, IRS2, BRCA2, RB1, PDGFRα, CDK6, SHH, APC, FOXO1, MET, MTF1, KDR, KIT).

Conclusion The characterisation of a new cervical cancer cell line, HCB-514, will constitute an important in vitro tool for further biological and therapeutic studies of cervical cancer.

PO-343 TARGETED RESEQUENCING IDENTIFIES NOVEL AND ULTRA-RARE HIGH-IMPACT VARIANTS IN BREAST CANCER SUSCEPTIBILITY GENES IN AN IRISH POPULATION

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Introduction Breast cancer (BC) remains the most common female malignancy worldwide (incidence of 89.7/100,000 women). Pathogenic variants in BRCA1 and BRCA2 account for 3% of all BC cases. A further 25% of BCs demonstrate familial clustering that may be accounted for by variants of reduced penetrance in other BC susceptibility genes. Next-generation sequencing facilitates massively parallel sequencing of multiple genes in a cost-effective manner. Multiple expanded gene panels exist, including high- and moderate risk BC susceptibility genes, as well as loci with weak/putative association with disease. Expanded gene panels may increase diagnostic yield, but also increase identification of variants of uncertain significance.

We aimed to investigate the frequency of high impact variants in known or putative BC susceptibility genes in an Irish population using a custom-designed multi-gene panel.

Material and methods Targeted resequencing of 168 gDNA samples (91 patients with BC; 77 unaffected ethnically-matched controls) was performed on an Illumina NextSeq using a Roche-Nimblegen custom 282-gene panel capture. GATK best practices, 2016 were implemented for data analysis. Pplink1.9 was utilised for confirmation and removal of first-/second-degree relationships within our cohort. 1000Genomes data was used in population stratification to confirm ethnicity. Plink1.9 was utilised for confirmation and removal of first-/second-degree relationships within our cohort. 1000Genomes data was used in population stratification to confirm ethnicity. VEP, SnpEff, and Annovar, were used for variant annotation.

Results and discussions 69 high-impact loss-of-function (LoF) variants were identified in 54 genes (including 51 not typically tested in diagnostic setting). 50 patients and 40 healthy controls were heterozygous for ≥one LoF variant. Frequency data for 34 variants was absent from population databases, while 23 variants were reported as ultra-rare (minor allele frequency ≤1.5 × 10⁻³). Two LoF variants were identified in BRCA1; 1 in ATM and 1 CHEK2 (c.1100delG). Considering all variants, enrichment in cases v. controls was not significant (p=0.761). 9 LoF variants were observed in genes that are recurrently somatically mutated in BC.

Conclusion After controlling for ethnicity and relatedness, NGS identified a high-impact variant in 56% of cases and 58% of controls. However, variants in only 3 out of 54 genes in which variants were identified currently impact clinical management.

Our results confirm that NGS increases diagnostic yield, but of variants in genes with moderate-weak association with BC. Further analyses are required to determine contribution and clinical utility of these variants in patients with BC.

PO-344 OSTEOSARCOMA IS CHARACTERISED BY RECURRENT REREARRANGEMENTS OF FOS AND FOSB

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Introduction Osteosarcoma, and the related entity osteoid osteoma, are the most common benign bone-forming tumours. Large, inaccessible, and recurrent tumours can cause considerable morbidity. On occasion, there can be diagnostic uncertainty with osteosarcoma, a malignant tumour that requires multimodal therapy. We sought to define the somatic changes that underpin osteosarcoma.

Material and methods We analysed the whole genomes of 5 osteosarcomas and 1 osteoid osteoma and catalogued all somatic variants. RNA-seq was used to corroborate DNA changes and call gene fusions. FOS fusions were validated with Sanger sequencing. We used FISH and IHC to validate the finding of FOS/FOSB rearrangements in 55 osteosarcomas, 17 angiosarcomas and 183 osteosarcomas. We analysed 55 osteosarcoma and 2652 pan-cancer whole genomes for similar rearrangements.

Results and discussions There was a paucity of somatic alterations in osteosarcoma, with a median mutation burden of 319 substitutions (range 123–700) and 28 indels (range 14–50) per genome. Copy number analyses demonstrated diploid tumours with few aberrations. Only a small number of mutations affected the coding sequence of genes, none of which were plausible driver events.

Analysis of structural variants revealed breakpoints in the AP-1 transcription factor FOS, in 5/6 cases, and its parologue FOSB in the sixth case. All were validated with RNA-seq reads and FOS fusions were validated with Sanger sequencing. FOSB fusion brought expression under the control of the PPP1R10 promoter. FOS fusions were all between exon 4 and intronic or intergenic regions. FOS fusions resulted in the introduction of a stop codon within 30 bp of the breakpoint.

In a validation cohort of 55 tumours, FISH identified FOSB or FOS breakapart signals in 1 and 48 tumours respectively (89%). Osteoblastoma cellularity is low, hampering FISH sensitivity. IHC for the preserved N-terminus of FOS revealed marked immunoreactivity in all FOS rearranged cases, including the 3/6 FOS FISH negative cases with available material. Only 1/183 osteosarcoma cases had comparable FOS immunoreactivity. No osteosarcoma or pan-cancer whole genome harboured similar rearrangements.