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Reference:

Vandamme Timon, Beyens Matthias, Peeters Marc, Van Camp Guy, op de Beeck Ken.- Next generation exome sequencing of pancreatic neuroendocrine tumor cell lines BON-1 and QGP-1 reveals different lineages

Cancer Genetics - ISSN 2210-7762 - New york, Elsevier science inc, 208:10(2015), p. 523-523

Full text (Publishers DOI): <http://dx.doi.org/doi:10.1016/j.cancergen.2015.07.003>

To cite this reference: <http://hdl.handle.net/10067/1287710151162165141>

1 Next-generation exome sequencing of 2 pancreatic neuroendocrine tumor cell 3 lines BON-1 and QGP-1 reveals 4 different lineages

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14 **Key words:** BON-1, QGP-1, PNET, whole exome sequencing

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19 Letter

20 *Ganesh K. Boora* et al.[1] recently published exome sequencing results of several
21 neuroendocrine tumor (NET) cell lines, including BON-1 and QGP-1. We
22 compared their results with our recent exome sequencing efforts of the same
23 pancreatic neuroendocrine tumor (PNET) cell lines (publicly available through
24 the European Nucleotide archive at [http://www.ebi.ac.uk/ena/data/view/](http://www.ebi.ac.uk/ena/data/view/PRJEB8223)
25 PRJEB8223)[2]. In both datasets, BON-1 showed mutations in signaling pathway
26 genes *MAP4K2* and *MAPKBP1*. In QGP-1, mutations in tumor suppressor *TP53*
27 and a p.R2166Q mutation in tumor suppressor *APC* were found in both datasets.
28 However, a number of mutations were unique in each dataset. For instance,
29 *Ganesh K. Boora* et al. did not detect mutations in genes previously found
30 mutated in PNET patient material while our dataset did show mutations in a
31 number of genes found mutated in sporadic tumors [3]. For instance, the PNET-
32 associated gene *ATRX* contained an homozygous *ATRX* p.Q929E missense
33 mutation in BON-1 and an homozygous *ATRX* p.F809S mutation in QGP-1, while
34 three missense mutations, including a heterozygous p.R1306H missense
35 mutation with *in silico* predicted damaging impact, were identified in the PNET-
36 associated tuberous-sclerosis gene *TSC2* in BON-1. *Ganesh K. Boora* et al.
37 identified a mutation in tumor suppressor *MLL2* in BON-1 that was not found in
38 our sequencing data. As the same Illumina platform and a similar bio-informatics
39 approach were used, it is unlikely that this divergence is caused by different
40 methodology. Therefore, we could be looking at different lineages of the same
41 cell lines. Since both cell lines have an abberant chromosome number with a
42 ploidy of 3 in BON-1 and tetraploidy in QGP-1 [2], chromosomal instability could

result in a higher mutation rate. Although we used early passages of BON-1 and QGP-1 (passage 9 and 14, respectively), increasing passage number could result in sub-clonality, explaining the difference between both datasets. Our early passages might have retained more neuroendocrine tumor characteristics, as is demonstrated by the presence of mutations found in PNET patients. Sub-clonality in BON-1 and QGP-1 could have important consequences for experiments with these cell lines, since genetic alterations could lead to phenotypic changes. It is hence vital to confirm genetic identity of the used cell lines and perform mutational analysis of genes of interest. In conclusion, we believe that both papers highlight the importance of performing thorough genetic validation before considering a cell line as a good PNET model.

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