Cutaneous malignant melanoma is one of the most deadly skin cancers in Caucasian populations. Mutations in \textit{BRAF} and \textit{NRAS} are demonstrated to lead to constitutive mitogen-activated protein kinase (MAPK) pathway, which represents a critical event in melanoma growth and progression. Initially, a series of paired primary melanomas and melanoma metastases at different sites (lymph nodal, subcutaneous, visceral, and/or cerebral) from the same patients (N=97) were analyzed for somatic mutations in \textit{BRAF/\textit{NRAS}} genes, through direct automated DNA sequencing. Confirming previously reported data, \textit{BRAF} and \textit{NRAS} mutations were found to be mutually exclusive; with the exception of subcutaneous metastases, no difference in rates of mutations in \textit{BRAF} and \textit{NRAS} was observed between primary and secondary tumor tissues from same patients. Conversely, about 25\% subcutaneous metastases presented a discontinuous pattern of \textit{BRAF/\textit{NRAS}} mutations in comparison to primary melanomas, suggesting that independent subclones might be generated at subcutaneous level. Therefore, a linear progression model does not always account for melanoma progression and tumor heterogeneity may lay in cell population at early stage of tumorigenesis. Successively, we performed next-generation sequencing (NGS) analysis of main genes participating in melanoma pathogenesis and progression among paired primary and metastatic lesions of melanoma patients, with the aim to evaluate levels of discrepancies in mutational patterns. Paraffin-embedded tumor tissues of the paired lesions were retrieved from the archives of the institutions participating in the study. NGS was performed using a specific multiple-gene panel to explore the mutational status of selected regions (343 amplicons; coverage 100\%) within the main 25 genes involved in melanoma pathogenesis. In >40 patients with available tissue samples from metastatic and primary lesions, we detected 829 genetic non-synonymous variants; among them, 101 (12.2\%) were pathogenic mutations. Overall, a high level of concordance in mutational patterns between primary and metastatic melanoma lesions was found (76\% for all pathogenic mutations); consistency was higher for \textit{BRAF} and \textit{NRAS} mutations (95\% and 86\%, respectively). Our aims are to accurately classify melanoma patients into different molecular subtypes in order to define the more appropriate paths for patients' management, using comprehensive NGS assays. On the other hand, we intend to study molecular mechanisms of melanocytic transformation by evaluating the progression steps from benign Deep Penetrating Nevi (DPN) to melanoma. DPN are melanocytic lesions characterized by atypical histological features that can lead to misdiagnosis as melanomas. While melanocytes become smaller and less pigmented as the thickness increases in common nevi, DPN cells maintain size and pigmentation level. Although considered benign lesions, DPN with atypical features can occasionally metastasize and have unfavorable outcome. Previous data identified molecular alterations in beta-catenin pathway as characteristic feature of DPN together with mutations in MAPK pathway. Actually, we screened 22 atypical DPN by NGS with a 400 tumor-related genes panel and found beta-catenin activating mutations in 19/20 (95\%) of the samples analyzed; 14 out of 20 DPN presented additional alterations in genes involved in MAPK pathway: \textit{BRAF} (7), \textit{NRAS} (2), \textit{HRAS} (4), \textit{MAP2K1} (5). Pathogenic alterations were found with lower frequency in additional genes in our cohort. Same pattern of alterations in beta-catenin and MAPK pathways genes was found in a control group of typical DPN, confirming the driver role of these genes in DPN pathogenesis. Further analyses are required to establish the involvement of pathogenic mutations in non-driver genes and the correlation with histological features.

\textbf{Keywords:} MAPK pathway, NGS, melanomagenesis