6660 - Inverse Genetic Risk Between Vitiligo and Cutaneous Melanoma /Nikolai Klebanov, BS

Objective 1: Identify the most significant melanoma polymorphisms from the results of a genome-wide association study of 500,000 UK Biobank patients.

Objective 2: Analyze the relationship between key risk SNPs associated with vitiligo and those associated with melanoma.

Objective 3: Examine biological pathways that impinge on both phenotypes.

Background: Genotype data on ~500,000 UK Biobank (UKBB) enrollees was recently analyzed and released by research groups, presenting extraordinary opportunity for clinicians to gain knowledge of phenotype-genotype interactions. It has been reported that patients with vitiligo show threefold lower risk of melanoma(1,2), suggesting shared genetic variation linking these disorders of melanocytes. Using a large pool of samples from the UKBB, we sought to test the hypothesis that risk-conferring SNPs for vitiligo also correlate with melanoma risk. Type of Study: Case/control association study using candidate SNPs. Methods: 38 known SNP loci(3) significantly associated with vitiligo were mapped onto loci identified by GWAS(4) of UKBB “self-reported malignant melanoma (2677 cases, 334,482 controls) using p=5x10^-8 genome-wide significance cutoff. STRING(5) was used for unsupervised pathway analysis of candidate SNPs. Results: Of 38 vitiligo risk SNPs, 3 showed genome-wide significance in GWAS for melanoma: SNPs in MC1R, TYR, and ASIP were protective against vitiligo but were positively associated with melanoma risk (ORs > 1 for all; p-values 1.3x10^-22, 1.7x10^-11, 9.8x10^-11 respectively). For the set of 3 loci, STRING revealed significant enrichments in melanin biosynthesis (GO:0042438) and pigmentation (GO:0043473) gene ontology processes (p=1.76x10^-6, 1.02x10^-4 respectively), and in the melanogenesis KEGG pathway (p=2.87x10^-5). Conclusion: UKBB is a novel valuable resource for translational medicine. Using UKBB, we identified 3 loci which showed genome-wide significance for decreased risk of vitiligo and increased risk of melanoma, and which are joined in pigmentation pathways. Observed inverse genetic relationship between melanoma and vitiligo risks associated with pigmentary pathways suggests new avenues for therapeutic pursuit in melanoma.

REFERENCES

Objective 1: To assess the potential of combining gene expression and mutation analyses to identify melanoma risk factors

Objective 2: To introduce non-invasive mutation analyses of pigmented lesions as an option to validate new assays including gene expression tests

Objective 3: To put into perspective how combining non-invasive gene expression and mutation analyses may compare to the well described gold standard of dermatopathology

Background: The diagnosis of early stage melanoma can be challenging histopathologically and can have a discordance rate as high as 27%. Non-invasive gene expression testing for LINC and PRAME via a non-invasive pigmented lesion assay (PLA, 91% sensitivity, 69% specificity) has been validated against histopathology. Mutations in BRAF, NRAS and TERT promoter are found to correlate with melanoma tumor progression and histopathologic criteria. Type of Study and Methods: We sought to validate the PLA against key driver mutations in melanoma. A prospective/retrospective analysis of 103 PLA adhesive patch samples, with consensus panel confirmed histopathologic diagnoses, were analyzed for hotspot mutations in BRAF (non-V600E), NRAS, and TERT. Furthermore, a prospective analysis of mutation frequency in 523 real-world PLA samples was performed. Results: 97% percent of histopathologically confirmed melanoma samples were either PLA positive or mutation positive. Statistically significant differences in mutation frequency were observed between mel(+)/PLA+ and mel(-)/PLA(-) samples for hotspot mutations (75% vs. 15%, p<<0.0001). Mutations in adhesive patch samples were concordant with mutations in FFPE tissue blocks. TERT promoter mutations were the most prevalent (79%). Real-world PLA results showed that 89% of PLA(-) results were mutation negative, while 60% of PLA(+) results were mutation positive. There was no statistical difference in mutation frequency between validation samples and real-world samples. Conclusions: This study confirms the high performance of the PLA. PLA positive tests identify high-risk lesions with driver mutations, while PLA negative test do not harbor these mutations. Gene expression and mutation analyses may enhance pigmented lesion assessment.

REFERENCES

NONE
Objective 1: To describe the clinical utility of the DecisionDx-Melanoma prognostic test for metastasis risk in a large multicenter cohort of melanoma patients.

Objective 2: To provide real world information about the use of primary tumor molecular information for guiding patient management.

Objective 3: N/A

Background: A 31-gene expression profile (GEP) test that identifies cutaneous melanoma tumors as low risk (Class 1) or high risk (Class 2) of metastasis has been clinically validated. A multicenter, prospective clinical utility study to determine clinical impact of the GEP test in patient management plans, including initial workup, follow-up intervals, and referral patterns, was performed. Methods: 243 patients with stage I or II melanoma from 16 dermatology and surgical oncology centers completed study participation. Documented changes in care parameters were categorized as increases, decreases or no change based on comparison of management plans established pre-test and post-test. Fisher’s exact, Chi-squared or F test were used where appropriate. Results: Comparing pre-GEP to post-GEP management plans, 50% (122/243) showed post-test changes in management, including 38% (67/178) of Class 1 and 85% (55/65) of Class 2 cases. Overall, 52 cases had decreased intensity of care, 80 cases had increased intensity of care, and 121 cases had no change (p<0.001). Class 1 accounted for 87% (45/52) of cases with decreases in management, while Class 2 accounted for 64% (51/80) of cases with increases. GEP class was a significant predictor of change in care (p<0.001). Of 66 cases with imaging changes, 45 were Class 2 patients with increased surveillance intensity, with more frequent intervals or a more sensitive imaging modality (i.e., PET/CT vs. chest x-ray). Conclusion: These results from a prospective clinical utility study confirm that the identification of risk provided by the GEP informs appropriate clinical management in accordance with current guidelines.

REFERENCES

6805 - Clinical Utility of a 31-Gene Expression Profile Test to Determine Eligibility for Sentinel Lymph Node Biopsy in Melanoma Patients 65 Years of Age and Older /John Vetto, MD

Objective 1: To evaluate the utility of molecular prognostic tools for guidance of sentinel lymph node biopsy decisions.

Objective 2: To determine if gene expression profiling can identify a population of melanoma patients with low rates of sentinel lymph node biopsy positivity.

Objective 3: To determine long term survival in a population with low risk for sentinel lymph node positivity identified by gene expression profiling.

Background: Older age is associated with a poor prognosis, but these patients show low rates of sentinel lymph node (SLN) biopsy positivity. DecisionDX-Melanoma is a 31-gene expression profile (GEP) test that determines a CM patient’s risk for metastatic disease, classifying patients into low (Class 1) or high (Class 2) risk groups. Patients with a Class 1 tumor profile also have low rates of SLN positivity. Methods: Bioinformatics modeling was performed on a retrospective cohort (n=782) to identify a population with a positive SLNB rate below 5%. GEP Class 1 in patients with AJCC T1-T2 tumors were identified as parameters to achieve a ≥95% negative predictive value (NPV). Validation was performed in a combined contemporary, multi-center, prospective study cohort (n=481). Outcome data was derived from the retrospective cohort. Results: Patients ≥65 years old with Class 1 T1 or T2 tumor, had a SLN positive rate of 4% (NPV=96%). SLN positives were enriched from 13% using current SLNB criteria to 22% if this group of patients was spared the procedure. The 5-year melanoma specific survival (MSS) rate for T1/T2 Class 1 patients was 99% with overall survival (OS) of 97% and distant metastasis free survival (DMFS) of 93%. Conclusion: The 31-gene expression profile can be useful in identifying a patient population with <5% likelihood of a positive SLN and thus has potential utility in guiding SLNB decisions in patients >65 years-old. In this population, the test could potentially reduce the rate of SLN biopsy by up to 52% without affecting patient outcomes.

REFERENCES
**F057 - Late-breaking Research: Basic Science/Cutaneous Oncology/Pathology**

**Saturday, February 17 9:00 AM — 11:00 AM**

**Room 4**

9:48 am - 10:00 am

6671 - The Growing Burden of Melanoma: The Incidence and Mortality of Melanoma in 45 Countries /Emily Dando, BA

Objective 1: To compare the incidence and mortality of melanoma across 45 countries

Objective 2: To assess the change in melanoma incidence among countries between 2000 and 2012

Objective 3: N/A

Background: In many countries, the incidence of melanoma continues to increase while the incidence of other malignancies has stabilized or decreased.1-3 The health burden of melanoma throughout Western Europe, North American, Australia, and New Zealand is well documented, but less is known about its incidence in other regions.

Type of study: Retrospective

Methods: We analyzed incidence and 5-year mortality data for 45 countries in the World Health Organization’s recently released 2012 GLOBOCAN cancer database. We also assessed the change in melanoma incidence compared to data from the GLOBOCAN 2000 dataset.

Results: Of the 45 countries, the top-five countries by incidence per 100,000 were New Zealand (35.8), Australia (34.9), Switzerland (20.3), the Netherlands (19.4), and Denmark (19.2). Melanoma incidence was greatest for males in Australia (40.5) and females in New Zealand (33.1). The top-five countries for melanoma mortality per 100,000 were New Zealand (4.7), Australia (4.0), Norway (3.6), Slovenia (3.1), and Sweden (2.8). Melanoma mortality was highest for males in New Zealand (6.9) and for females in Slovenia (3.1). Compared to data from 2000, the incidence of melanoma has decreased for women in Australia (-6%), Austria (-3%), and New Zealand (-5%), and for men in Brazil (-6%). However, it has increased by over 100% for both sexes in Italy and the United Kingdom, men in Spain and Switzerland, and women in Japan. Conclusion: Although the burden of melanoma is greatest in New Zealand and Australia, it appears to be stabilizing in these countries while increasing in many countries across Europe, Asia, and North America.

**REFERENCES**

6512 - Merkel Cell Carcinoma: Current United States Incidence and Projected Increases based on Changing Demographics / Song Youn Park, MD

Objective 1: Determine MCC incidence in the United States
Objective 2: Project MCC incidence through 2025 in the United States
Objective 3: Increased incidence justifies more MCC awareness

Background: Merkel cell carcinoma (MCC) incidence rates are thought to be increasing and are strongly age-associated. Objective: Determine MCC incidence in the United States and project incident cases through 2025. Methods: Registry data were obtained from the SEER-18 database, containing 6,600 MCC cases. Age and sex-adjusted projections were generated utilizing US census data. Results: Between 2000-2013, there was a 95% increase in the number of reported MCC cases, as compared to 57% for melanoma and 15% increase for cases of all ‘solid’ cancers. Indeed, by 2013 the MCC incidence rate was 0.7 per 100,000 person-years in the US, corresponding to 2,454 cases. MCC incidence increased exponentially with age, from 0.1 to 1.0 to 9.8 (per 100,000 person-years) between age groups 40-44, 60-64, and 85+ years, respectively. Due to aging of the “baby-boom” generation, the projected US MCC incidence is predicted to climb to 2,835 cases in 2020 and 3,284 cases in 2025. Limitations: Projections assume the age-adjusted incidence rate stabilizes and thus may be underestimates. Conclusions: Given upcoming demographic shifts, a significantly larger number of people are likely to be diagnosed with MCC in the US. Given this ongoing increase in the number of cases, the high MCC recurrence risk, and availability of new immunotherapies, more MCC awareness is justified.

REFERENCES

6685 - Type of Organ Transplanted Impacts the Risk of Cutaneous Squamous Cell Carcinoma (CSCC) in Transplant Recipients / Charles Puza, BA

Objective 1: To understand how the type of organ transplanted affects the risk of cutaneous squamous cell carcinoma

Objective 2: To raise the possibility of customized skin screening guidelines by type of organ transplanted and degree of immunosuppression

Objective 3: N/A

Background: Transplant immunosuppression increases the risk of CSCC by 65-200-fold. These CSCC exhibit more aggressive behavior, leaving early excision the best hope for treatment. Understanding how the type of organ transplanted affects the risk of CSCC is critical for proper surveillance. As single center studies are limited, the aim of this study was to investigate the impact of the type of organ transplanted on the risk of CSCC. Methods: IRB approval was received and Duke’s retrospective database was queried to identify patients who underwent an organ transplant from 1/1/1996 to 12/31/16. Data regarding transplant outcomes, CSCC, immunosuppressive regimens, and survival were recorded. An unpaired t-test was used to compare the incidence of CSCC between organ types. Results: Of the 3,652 renal, hepatic, and cardiothoracic transplant patients identified, 142 patients developed at least 1 SCC. The incidence of CSCC varied by type of organ transplanted with 46 of 1684 (2.7%) renal transplant patients developing SCC, 33 of 804 (4.1%) hepatic transplant patients, and 63 of 1164 (5.4%) cardiothoracic transplant patients over the median follow-up time of 6.5 years. The incidence was significantly different between the renal transplant and cardiothoracic groups (p=0.00024). Metastatic SCC was the cause of death in 2 (0.1%) renal transplant patients, 3 (0.4%) hepatic cases, and 3 (0.3%) cardiothoracic patients. Conclusions: The type of organ transplanted confers a unique risk of CSCC. These findings advocate for CSCC-risk stratification of transplant patients by type of organ transplanted and not simply a history of transplantation.

REFERENCES

Objective 1: Explore the relationship between hidradenitis suppurativa and anogenital cancer

Objective 2: Compare the incidence of vulvar cancer among females with HS to that of the general population

Objective 3: Enhance awareness of anogenital cancer incidental to patients with hidradenitis suppurativa

Background Despite reports of anogenital cancer, especially vulvar cancer, in patients with hidradenitis suppurativa (HS), the association between HS and anogenital cancer remains unclear [1-3]. We sought to determine if an association exists between HS and anogenital cancer in females. Type of study Cohort study Methods A large, urban, medical record data repository [4] (> 5 million patients) was searched for females who had an in-clinic dermatology encounter with ≥1 year documentation of follow-up in-clinic encounters (January 2001-October 2017). Patients with HS identified by ICD-9-10 codes (705.83; L73.2) were selected for analysis. Outcomes of interest were a subsequent diagnosis of anal cancer (ICD-9-10 codes:154.2, 154.3, C21), or genital cancer (ICD-9-10 codes:184, C51, C52). The control population consisted of females without HS within the same data repository. Adjusted (for age, gender, race, smoking status, and lichen sclerosus) odds ratio (aOR) was obtained using logistic regression. The Surveillance, Epidemiology, and End Results (SEER) database 2000-2014 was used to calculate the nationwide incidence of vulvar cancer. Results Of 133,936 eligible patients, 716 had a diagnosis of HS of whom 3 (all with GRHS; 2 African American, 1 Caucasian; mean age 53yrs) were diagnosed with vulvar cancer, yielding a highly significant association (aOR 5.56; 95%CI: 1.74-17.76; p=0.004). Moreover, the incidence of vulvar cancer among females with HS (2.6/10,000 x year) in this study population was higher than what is reported in SEER (0.3/10,000 x year). Conclusion Given that GRHS is significantly associated with vulvar cancer in this large patient population, further exploration seems warranted.

REFERENCES
6747 - The X-Ray Crystal Structure of Human Keratin 1 with S233L Mutation Demonstrates Mechanisms of Pathogenic Tonotubular Keratin Formation Leading to Epidermolytic Palmoplantar Keratoderma / Christopher Bunick, MD, PhD

Objective 1: Understand the role of keratin mutations in epidermolytic palmoplantar keratoderma

Objective 2: Understand how keratin 3D structure is altered by protein mutation

Objective 3: Describe how hydrophobicity can cause protein aggregation

Background: Epidermolytic palmoplantar keratoderma (EPPK) is a skin disorder characterized by hyperkeratosis of the palms and soles. While primarily mediated by keratin 9 mutations, a subset of EPPK patients harbor a serine to leucine mutation at residue 233 in the 1B coiled-coil region of keratin 1. This mutation leads to formation of aberrant tonotubular keratin rather than normal intermediate filaments as seen on electron microscopy. We used x-ray crystallography to characterize the affect of the mutant protein on keratin 1/10 structure.

Type of Study: Biomedical research. Methods: 1B coiled-coil regions of keratin 1 (wild-type and S233L mutation) and keratin 10 were expressed in Escherichia coli, purified, and crystallized using vapor diffusion. X-ray data was collected at Argonne National Laboratory, and processed using HKL-2000, Coot, CCP4, and Phenix software.

Results: Two x-ray crystal structures were determined: first, the heterodimer between the 1B segments of wild-type keratin 1 and keratin 10 at 3.0 Å resolution; second, the keratin 1/10 1B heterodimer harboring the S233L keratin 1 mutation at 2.2 Å resolution. The mutation of serine to leucine enhances the exposed hydrophobic surface of the keratin heterodimer, leading to aberrant aggregation between keratin heterodimers. Three aromatic residues (Tyr230, Phe234, Phe314) and one hydrophobic residue (Leu233) from neighboring K1 molecules envelope the primary mutant Leu233 site. Conclusions: Experimentally determined x-ray structures show the change in biochemical properties resulting from S233L mutation in K1 have the ability to drive tonotubular keratin formation through unnatural hydrophobic interactions.

REFERENCES

Objective 1: To assess the relationship of serum endocan levels with the presence of psoriasis.

Objective 2: To assess the relationship of endocan with the severity of psoriasis.

Objective 3: To assess the possible predictive role of endocan regarding endothelial dysfunction in psoriasis vulgaris patients.

Background: Psoriasis is a common multisystem inflammatory disease with several associated co-morbidities. Until present, no serum lab markers have been used to evaluate psoriasis activity although such a marker would be valuable to predict likely serious cardiovascular events. We aimed to assess the relationship of serum endocan levels with the presence and severity of psoriasis and its possible predictive value of endothelial dysfunction. Type of study: A case-control study. Methods: This study was conducted on 30 moderate-severe psoriasis vulgaris patients and 30 healthy controls. A complete physical examination, BMI, body fat percent and PASI assessment were done. Serum endocan and TNF-α levels were measured by ELISA. Endothelial function testing by high-resolution ultrasound to measure the carotid artery intima-media thickness (CIMT) was performed. Results: Psoriasis patients showed statistically significant higher serum TNF-α and endocan levels (P1 = 0.008, P2 = 0.003). There was a statistically significant difference between mean CIMT of both groups (p=0.005). Serum endocan levels positively correlated with PASI score (p = 0.002), serum TNF-α levels (p <0.001) and the average CIMT of common carotid artery (p = 0.001) in the patients group. The BMI and body fat percent were positively correlated with TNF-α (p1 =0.011, p2=0.002), serum endocan (rs = p <0.001) and CIMT (p1 =0.001, p2=0.002). The age of onset of the disease negatively correlated with TNF-α (p <0.001), serum endocan (p =0.003) and CIMT (p =0.001).

Conclusion: Serum endocan is a promising marker of severity of psoriasis with a possible predictive value of endothelial dysfunction in psoriatic patients.

REFERENCES