Comprehensive Review of BAP1 Tumor Predisposition Syndrome

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Background

- **BRCA1-associated protein-1 (BAP1)** tumor predisposition syndrome (BAP1-TPDS) is a rapidly developing area of medical research.
- Germline mutations in this multifaceted autosomal dominant tumor suppressor gene predispose families to the development of uveal melanoma (UM), mesothelioma (MM), cutaneous melanoma (CM), renal cell carcinoma (RCC), and possibly other cancers.
- The molecular function of the gene as well as the clinical phenotype of the syndrome are still being clarified.
- We sought to conduct a complete review of all published research into BAP1-TPDS to more thoroughly understand the clinical implications of BAP1 mutations.
- This information, in conjunction with phenotypic characteristics such as age of onset, disease aggressiveness and survival, can aid in the management, diagnoses, prognoses, and therapy of these patients and their families.

Methods

- A literature review was conducted on all peer-reviewed published articles on BAP1 and its drosophila homolog, Calypso.
- A search on PubMed was directed with the keywords “BRCA1 associated protein-1,” “BAP1,” and “Calypso.”
- 77 articles pertaining to the human BAP1 gene and its association with cancer were obtained. Of these, 24 articles described patients with germline BAP1 mutations.
- The articles were collated and data were extracted via an article-by-article systematic review.
- Evidence was reviewed on:
  - Cancer types observed
  - Clinical features of cancers
  - Evidence supporting role of BAP1 in tumor suppression

Results

- A total of 167 individuals from 51 families carrying 48 BAP1 mutations have been reported via blood and tumor DNA sequencing, and obligate carriers.
- Researchers focusing only on particular cancers have pursued BAP1 testing, creating an ascertainment bias.
- UM, MM, CM, and RCC are major phenotypes.
- Certain other cancers are also more commonly seen in patients with germline BAP1 mutations (see figure 2).
- Cancers onset earlier in life.
- Atypical Spitz tumors are also associated.
- Tumors exhibit loss-of-heterozygosity.
- Somatic mutations in sporadic tumors indicate BAP1 involvement in tumor development.

Phenotypic Characteristics of BAP1 mutation

Possible highly penetrant gene
- Early age of onset
- Tumors are more aggressive (except MM).
- Patients with MM have lengthened survival.
- Histologically distinct tumors.
- Characteristic atypical Spitz tumors present.

Risk Management Recommendation

RCC: Yearly ultrasound scans and MRI every 2 years starting age 31.

Potential histone deacetylase inhibitor therapies include valproic acid (VPA), trichostatin A (TSA), LBH-589 and Vorinostat (currently in Phase 2 trials for metastatic UM).

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References attached