Pathogeneses of the Rare Phakomatoses: Advances in Understanding

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Purpose
Recent advances in genetics and molecular biology provide a vastly improved understanding of the pathogeneses of hereditary diseases. The purpose of this exhibit is to illustrate the application of these advances to the detection and classification of the rare phakomatoses.

Materials & Methods
The case files of the authors' institutions were searched to identify examples of vascular phakomatoses including hereditary hemorrhagic telangiectasia (HHT) (Osler-Rendu-Weber syndrome) and ataxia-telangiectasia; hypomelanotic melanophakomatoses including hypomelanosis of Ito, incontinentia pigmenti, and Waardenburg syndrome; hypermelanotic melanophakomatoses including neurocutaneous melanosis and McCune-Albright syndrome, and the basal cell nevus syndrome (Gorlin-Goltz syndrome).

Results
Hemorrhagic telangiectasia results from genetic defects designated HHT 1, HHT 2, and HHT 3, which lead to dysfunction of the receptors for transforming growth factor. Ataxia-telangiectasia results from dysfunction of the ATM gene that is involved in DNA repair and cell cycle checkpoint control following DNA damage. Incontinentia pigmenti Types I and II result from mutations in the NEMO gene. This gene encodes a critical regulatory component of the NFkappa-beta signalling pathway, which regulates gene expression in inflammatory responses, cell proliferation and apoptosis. Waardenburg syndrome Type I results from dysfunction of Pax3, a gene that plays a central role in neural development and neural crest-derived pigmentation. Neurocutaneous melanosis likely is related to dysfunction of hepatocyte growth factor (a multifunctional cytokine and angiogenesis factor) and its receptor cMet. It is an excellent example of an otherwise lethal gene that survives by mosaicism. McCune-Albright syndrome comprises polyostotic fibrous dysplasia, hyperpigmented macules, and diverse endocrinopathies. The fibrous dysplasia results from replacement of arginine by cysteine or histidine at the 201 codon of the GNAS 1 gene. The hyperpigmentation likely results from overactivation of adenylate cyclase by gain of function mutation in GNAS 1 in affected...
melanocytes. Basal Cell Nevus syndrome results from mutation in the sonic hedgehog receptor gene PATCHED, a tumor suppressor gene. The sonic hedgehog signalling pathway helps to regulate embryonic patterning and cell fate determination.

**Conclusion**
Molecular biology provides the proper basis for understanding the nature and manifestations of the rare phakomatoses, and for their improved classification. Those familiar with the pathogeneses can screen family members appropriately, search efficiently for concurrent conditions, and approach the diverse manifestations of these kaleidoscopic anomalies with greater confidence.