First WHIM Genetic Screening Study Developed Through a Collaborative Effort Among Academia, Patient Foundation, and Sponsors

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Introduction

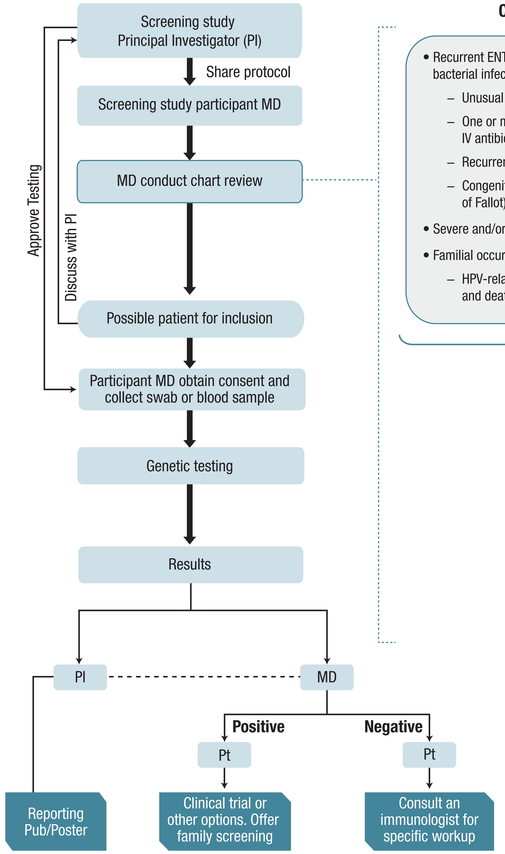
- WHIM syndrome is a rare, autosomal dominant primary immunodeficiency disease caused by a mutation in the *CXCR4* gene leading to abnormal immune cell trafficking.[1,2]
  - The nomenclature for WHIM is derived from the classic phenotype of Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (retention of mature neutrophils in the bone marrow), but this acronym does not reflect the broad spectrum of disease manifestations that patients may experience.[3,4]
- Patients with WHIM have severe chronic neutropenia and lymphopenia which renders them vulnerable to frequent infections that may be severe and life-threatening.[5,6]
  - Patients experience frequent upper respiratory tract and systemic infections, often beginning in infancy.[5]
  - They also show a distinct and disproportionate increase in susceptibility to human papillomavirus (HPV) infections, manifesting as cutaneous and anogenital warts, which may progress to cervical and vulvar cancers.[6]
- The clinical phenotype of WHIM is heterogeneous, and presentation can occur in children and adults.[3,4]
  - Patients with WHIM often face delays in diagnosis and/or misdiagnosis due to the absence of one or more of the four classic characteristics at presentation.[3]
- Patients with WHIM may interact with a range of medical specialists (pediatrician, internist, family physician, hematologist, dermatologist, immunologist), and often go undiagnosed or are classified as having a primary immunodeficiency (PID) of unknown origin.[7]
- Long-term complications of WHIM are severe and include lung damage from recurrent infection and increased risk of cancer, making early identification important for prognosis and prevention.[1,3,6]
- Although targeted investigational therapies are available, the timely identification of patients with WHIM is a challenge among the large group of patients with severe neutropenia where clinical suspicion is generally low.[1,8]
- Genetic testing of known *CXCR4* mutations is the avenue that can lead to definitive diagnosis of WHIM, but it is currently under-utilized.[1,3,8] Patients identified by genetic testing may benefit from targeted investigational therapies.

Objectives

- A partnership between Jeffrey Modell Foundation and X4 Pharmaceuticals resulted in co-sponsoring a genetic screening program for WHIM.
- This study will potentially improve awareness of WHIM, as well as the understanding of incidence and identification of new mutations.
- A multi-stage protocol design will allow cost-effective screening for WHIM in a large pool of potential cases, at no cost to patients or health insurance.

Methods

Figure 1. Genetic screening program study flow and protocol



Clinical History

- Recurrent ENT, airway, and/or skin/skin-structure bacterial infections
  - Unusual frequency and severity for age
  - One or more severe infections that required IV antibiotic
  - Recurrent subcutaneous abscesses
  - Congenital cardiac anomalies (ie, Tetralogy of Fallot)
- Severe and/or chronic recalcitrant warts
- Familial occurrence of similar symptoms including:
  - HPV-related cancers, unexplained early death, and death due to infection

Physical Exam

- Skin: Extensive warts or mollusca
- Oral cavity: Severe gingivostomatitis, periodontitis
- Other:
  - Unexplained bronchiectasis
  - Difficult-to-treat obstructive lung disease
  - Inhibited sense of smell
  - Congenital cardiac anomalies (ie, Tetralogy of Fallot)

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Baseline Blood Test

- Chronic leukopenia (WBC <2000/µL), neutropenia, lymphopenia

Rule out severe antibody deficiency and neutropenia
(blood tests done after clearing/treating infections)

Complete blood count and differential (check absolute neutrophil count [ANC] and absolute lymphocyte count [ALC]). Serum IgG, IgA, IgM, and IgE

- ANC <500/µL or ALC <650/µL (or both), OR
- Hypogammaglobulinemia

Test for known *CXCR4* genotype mutation

- Lymphocyte subpopulations
- Lymphocyte proliferation tests
- Optional bone marrow aspirate for myelokathexis
- B cell maturation analysis in bone marrow

In patients with normal or isolated neutropenia, consult an immunologist to determine a specific workup. Other potential explanations for recurrent infections do not always automatically exclude PID.

Methods (cont'd)

Exclusion Criteria

- All types of medications known to induce neutropenia
- Any prior history of chemotherapy
- Medullary aplasia, irrespective of etiology (idiopathic, Fanconi syndrome, etc)
- Severe anemia (Hgb <7 g/dL) or thrombocytopenia (platelets <10,000/µL)
- Progressive malignant pathology or medical history of malignant pathology
- Any history of HIV diagnosis
- Initial myelodysplasia

Results

- The unique public-private partnership was coordinated, and the grant was awarded in May 2018.
- Up to 300 patients will be tested in the study.
- Findings will provide guidance for more efficient and earlier diagnosis, improving patients' treatment, and will provide insight into the connection between genotype and clinical manifestations.

Conclusions

- This study stands to improve basic knowledge of WHIM genetics and improve diagnostic efficiency for this serious and rare disease, which in turn may improve patient access to appropriate care as well as clinical trials for disease-specific therapies.
- Benefits of this study include promoting efficient diagnosis, but also the potential to improve the efficiency of trials through expediting enrollment, improving knowledge of the disease, and providing an opportunity to raise awareness through publication of study results.
- The establishment of this study illustrates how integrating research efforts and facilitating collaboration between funding entities can be a powerful way to improve patients' care and can serve as a model for how open communication can best serve patients in the rare disease community.
- For more information on this study, contact:
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  IRB Study #: Pro00035468 Hopkins IRB #: IRB00175372

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