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The Centers for Mendelian Genomics: a new large-scale initiative to identify the genes underlying rare Mendelian conditions

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Abstract

Next generation exome sequencing (ES) and whole genome sequencing (WGS) are new powerful tools for discovering the gene(s) that underlie Mendelian disorders. To accelerate these discoveries, the National Institutes of Health has established three *Centers for Mendelian Genomics* (CMGs): the Center for Mendelian Genomics at the University of Washington; the Center for Mendelian Disorders at Yale University; and the Baylor-Johns Hopkins Center for Mendelian Genomics at Baylor College of Medicine and Johns Hopkins University. The CMGs will provide ES/WGS and extensive analysis expertise at no cost to collaborating investigators where the causal gene(s) for a Mendelian phenotype has yet to be uncovered. Over the next few years and in collaboration with the global human genetics community, the CMGs hope to facilitate the identification of the genes underlying a very large fraction of all Mendelian disorders see http://mendelian.org.

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Keywords

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In science and medicine there are occasional major advances that facilitate transformations of a field. The application of next-generation massively parallel sequencing technologies coupled with powerful computational approaches to discover genes for Mendelian disorders is arguably such a major advance [Biesecker, 2010]. Just three years ago, the strategy of exome sequencing (ES) followed by discrete filtering was introduced and shown to be a potential approach to identify the genes underlying Mendelian conditions [Choi et al., 2009; Ng et al., 2010; Ng et al., 2009]. Since then, ES and whole genome sequencing (WGS) [Lupski et al., 2010] have been used to explain the cause of dozens of disorders [Bamshad et al., 2011; Claudia Gonzaga-Jauregui, 2012; Gilissen et al., 2011] including those transmitted as X-linked, autosomal recessive [Bilguvar and et al., 2010], and autosomal dominant traits [Choi et al. 2011]; as well as phenotypes caused by *de novo* dominant mutations [Choate et al. 2010; O'Roak et al. 2011; Vissers et al. 2010] and somatic mosaicism [Lindhurst et al. 2011]. Given the technical and analytical improvements expected over the next several years, the application of ES/WGS-based strategies will enable the identification of the genes underlying a very large fraction of all known Mendelian disorders for which the genetic basis is not yet known — at a small fraction of the current cost for discovery per disorder.

Based on these advances, exploring all Mendelian disorders should become an imperative for the worldwide human genetics community. The discoveries made through such exploration would be of enormous service to families, and will provide novel entry points to investigate the mechanisms underlying disease development. Such an effort would, however, be very ambitious, requiring an unprecedented degree of cooperation and coordination in the field of medical genetics and the assistance of patients and families from around the world.

A global initiative to explore all Mendelian conditions is now emerging. The initiative, which includes the International Rare Diseases Research Consortium, the Finding of Rare Disease Genes (FORGE) in Canada, and centers in Europe, East Asia and elsewhere, will establish the necessary collaborative framework and physical infrastructure to achieve this goal. In the United States, the National Human Genome Research Institute (NHGRI) and the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) have partnered to support this effort at three *Centers for Mendelian Genomics* (CMGs): the Center for Mendelian Genomics at the University of Washington; the Center for Mendelian Disorders at Yale University; and the Baylor-Johns Hopkins Center for Mendelian Genomics at Baylor College of Medicine and the Johns Hopkins University.

The CMGs have four major goals: (1) to ascertain samples for all Mendelian disorders for which the genetic basis is not yet understood from clinicians and investigators around the world by developing a ‘public list’ of samples and by coordinating submissions to the NIH program with those of other international programs; (2) to improve the efficiency of the sequencing pipeline and quality of exome and genome data through ongoing technology innovation; (3) to determine the genetic basis for as many Mendelian conditions as possible; and (4) to disseminate methods and data to facilitate gene discovery by investigators working independently across the globe. The CMGs will study disorders with age of onset across the entire lifespan including well-delineated, known Mendelian phenotypes as well as novel phenotypes thought to be Mendelian on the basis of their segregation patterns in families.

Initially, the “public list” will be a catalog of collected DNA samples, organized by condition, that have entered the sequencing pipeline at any one of the CMGs. Next, this list will expand to include all of the Mendelian disorders for which the CMGs have solicited DNA samples, sequencing status, and the results obtained to date. Since the availability of a sufficient number of samples from clinically well-characterized cases and families will be critical to the discovery of genes for all Mendelian disorders, one aim of the public list is to facilitate coordination of sample collection and implementation of ES among clinicians and researchers around the world. Ultimately, the CMGs aim to develop the list into a comprehensive community resource that provides information on samples that are available worldwide for concerted disease gene discovery efforts.

With this introduction, we would like to engage the medical genetics community to join with us and collaborate with the CMGs by submitting information about familial conditions, adding samples to the effort from individuals or families with rare Mendelian disorders to stimulate collaborations and eventually new insights. Since many of these conditions are rare, and often with locus heterogeneity, multiple investigators will need to contribute samples from individuals and families with the same diagnosis to improve chances for finding and validating candidate genes and variants. Following sequencing and analysis, the CMGs will return the results to the submitters, and will collaborate with investigators to facilitate further analysis, functional studies, and, ultimately publication. Results will be provided to the collaborating investigators as soon as possible. Collaborating investigators will have data exclusivity for a minimum of six months to ensure ample time to conduct follow up studies and prepare manuscripts for publication. The development of a public list will ensure transparency and facilitate communications about progress within and beyond the medical genetics community; this list will soon be accessible via the CMG website (http://mendelian.org).

While the workflow will vary among CMGs, several key common practices across the CMGs will enable high-quality data production and analysis with partnering contributors. Phenotypic information associated with each sample and family will be collected and evaluated to increase diagnostic precision, identify phenotypic features that clarify genetic heterogeneity and aid in the identification of previously unrecognized disorders. DNA samples will be genotyped using low-cost, genome-wide marker arrays to provide a unique profile for sample tracking, to identify copy number variation (CNVs) and to provide genetic information for subsequent analysis of sequence variations (large and small insertion-deletions) underlying these conditions. These approaches, when applied to well-characterized pedigrees, will aid in finding the genomic intervals shared among all (or nearly all) cases, and reduce the genomic search space and speed the subsequent identification of candidate gene(s) by the collaborating investigators [Sobreira et al., 2010].

The success of this effort will require collaboration at an unprecedented scale in the field of human genetics. The CMGs and their global partners welcome partnering scientists and clinicians with samples or families affected with a Mendelian condition to collaborate with us by submitting inquiries to gmendel@mendelian.org. The CMGs have partnered with Wiley-Liss and the *American Journal of Medical Genetics* (AJMG) to advertise in each issue to its worldwide readership of clinical and medical geneticists. The corresponding author of each manuscript accepted by the *Journal* will be provided with information about the CMGs. This is a welcome and important partnership since the *AJMG* is a well-known forum for the delineation of new syndromes and for reporting the description of novel rare, Mendelian conditions. Similarly, the Online Mendelian Inheritance in Man (OMIM; www.OMIM.org) catalog will provide a means for quickly disseminating summaries of newly discovered genes for known Mendelian disorders and adding newly delineated

disorders to the OMIM catalog. We welcome the possibilities for other scientists, international journals and websites to link to the CMG site (http://mendelian.org).

We ask clinicians and scientists to collaborate with us by submitting cases and families. The key drivers for the CMGs are to serve the scientific community and the individuals and families with rare diseases by improving knowledge about these rare conditions. By making specific diagnoses and exploring on a genome level the relationships between sequence variation and phenotype, collaboratively we can achieve more comprehensive pre-symptomatic or carrier screening. Additionally, the knowledge obtained from these efforts could initiate the exploration of new and/or improved therapeutics for these conditions. The CMG mechanism will eliminate significant financial and technical barriers for clinicians who wish to gain deeper understanding of genetic disorders and will catalyze interactions across the worldwide biomedical community to utilize these genotype/phenotype correlations to drive a deeper understanding of the biology of disease.

The application of powerful new genomic approaches in genetics will provide an unprecedented view into the molecular basis of many, if not most, unexplained Mendelian phenotypes. The CMG will provide the community with access to production infrastructure, bioinformatics support, and analytical expertise. The challenge to the human genetics community is to help initiate this new phase of medical genomics and take advantage of this new opportunity by providing the resources for such studies that obviously cannot occur without finding and characterizing the patients and their families. Please contact us at gmendel@mendelian.org or through the web portals of the individual centers with questions or with samples to submit.

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