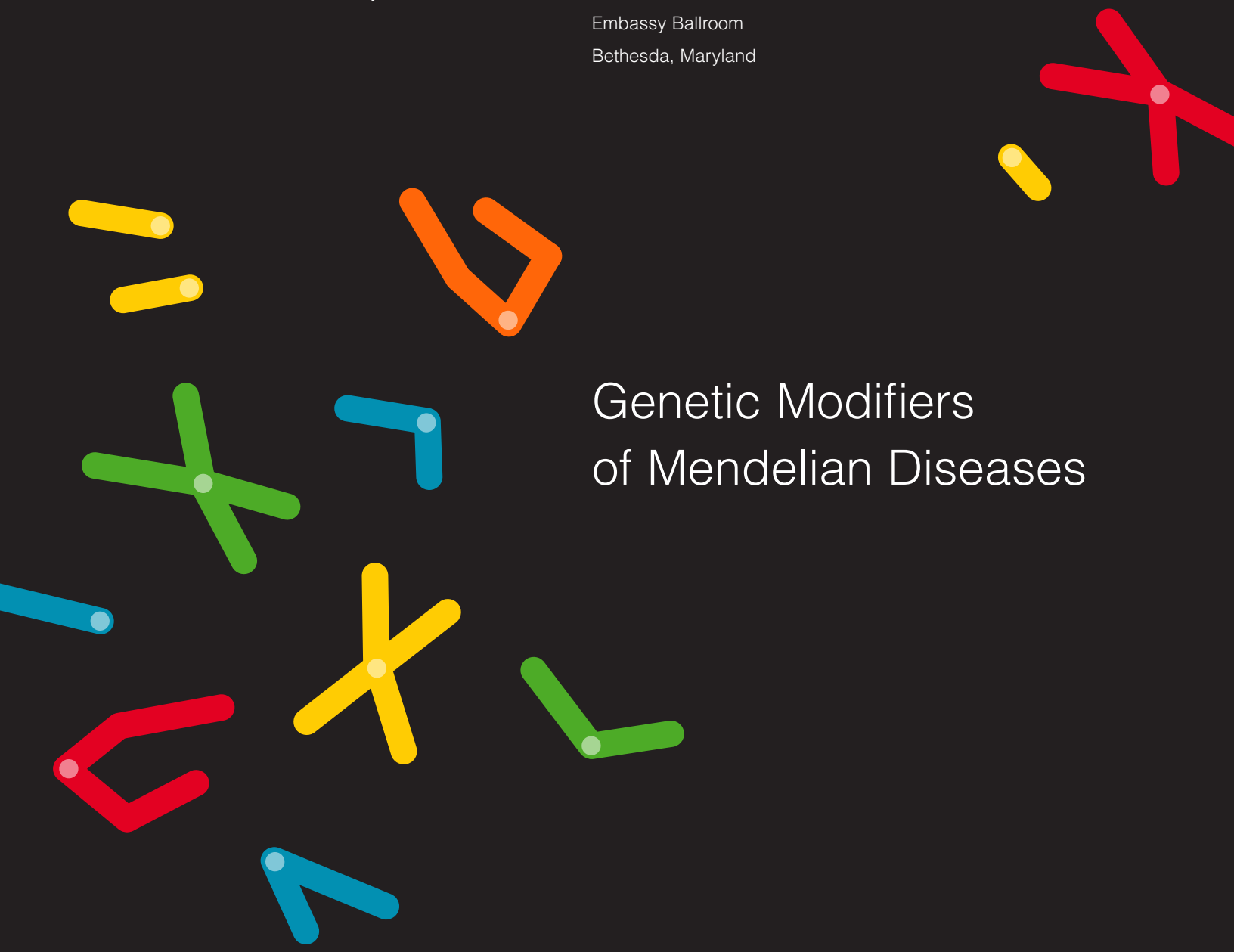
September 9-10, 2002

Four Points Sheraton
Embassy Ballroom
Bethesda, Maryland



Genetic Modifiers of Mendelian Diseases

Sponsors

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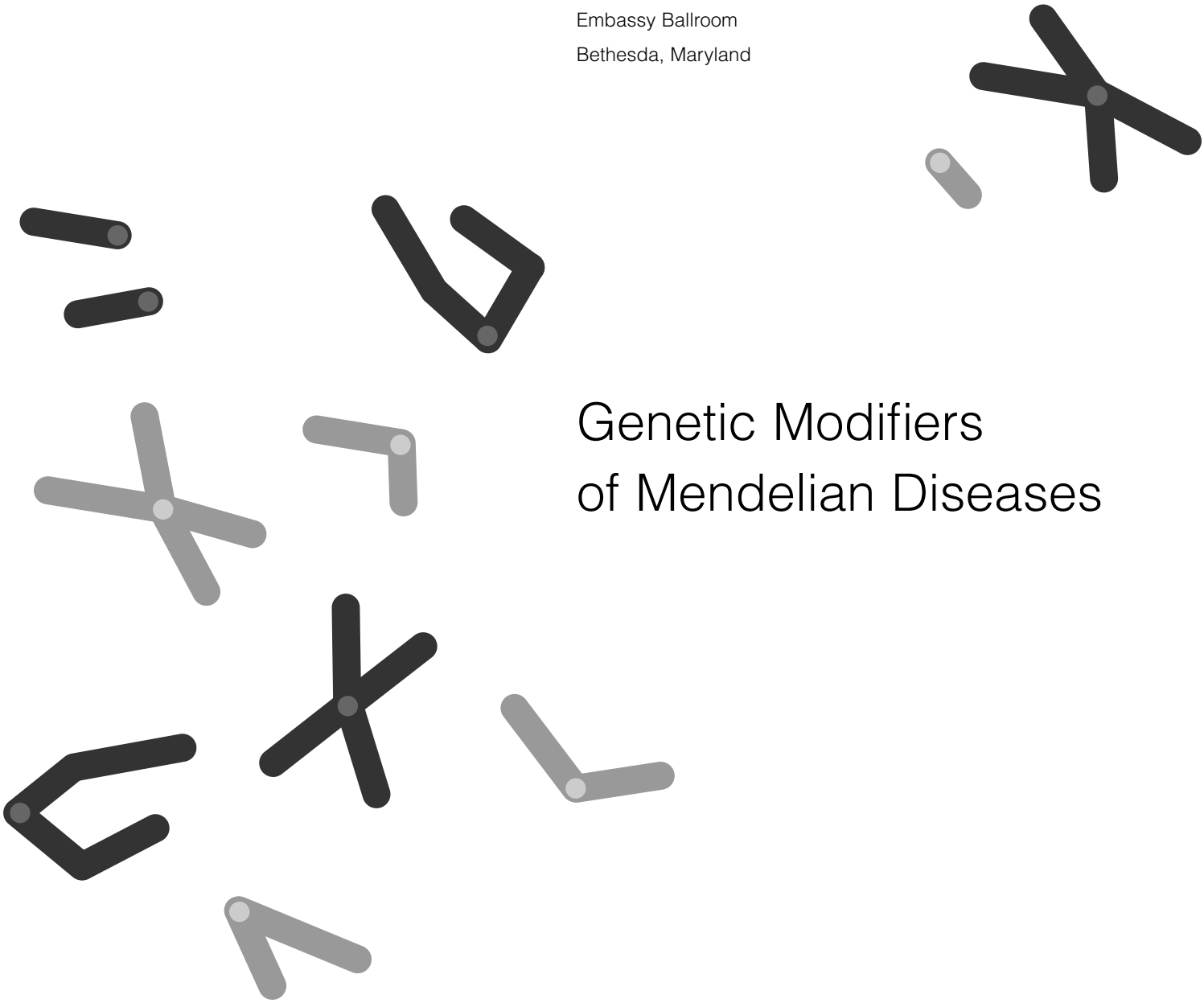

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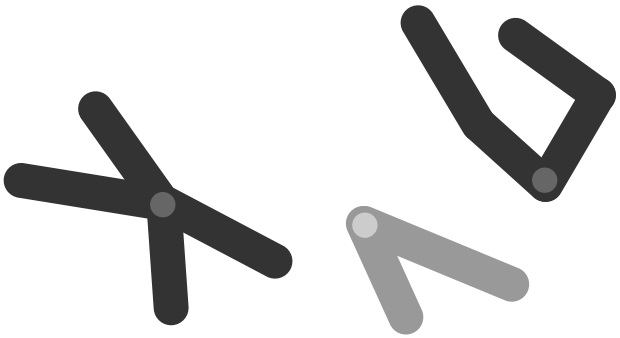
Workshop Co-Chairpersons	
Lap-Chee Tsui, PhD	*Vice Chacellor* *University of Hong Kong*
Sir David Weatherall, MD, FRS	*Professor, Weatherall Institute of Molecular Medicine* *University of Oxford, John Radcliffe Hospital*

Workshop Organizers	
Catherine McKeon, PhD	*Senior Advisor for Genetic Research* *Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK*
David Badman, PhD	*Hematology Program Director* *Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK*



Genetic Modifiers of Mendelian Diseases

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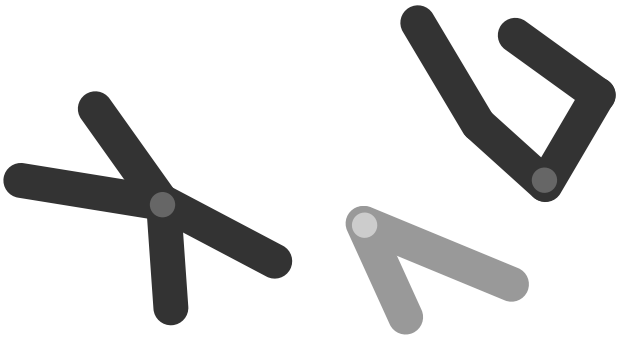

Genetic Modifiers of Mendelian Diseases

Agenda

Monday, September 9, 2002

1:00 pm	Welcome	*Dr. Allen Spiegel, Director, NIDDK* *Dr. Steve Groft, Director ORD, OD, NIH*

AFTERNOON SESSION – IDENTIFICATION OF GENETIC MODIFIERS OF HUMAN DISEASE

1:15 pm	Genetic Modifiers in CF	*Lap-Chee Tsui*
2:00 pm	Genetic Modifiers in Human and Rodent PKD	*David Woo*
2:45 pm	Splitting Multigenic Hirshsprung Disease	*Aravinda Chakravarti*
3:30 pm	**Coffee Break (15 mins)**	
3:45 pm	Complexity in Two Disorders Mapping to Xp21: Glycerol Kinase Deficiency and Adrenal Hypoplasia Congenita	*Ed McCabe*
4:30 pm	Genetic Modifiers of Sickle Cell Disease	*Griffin Rodgers*
5:15 pm	Discovery Strategies of Genetic Modifiers in Mendelian and Polygenic Diseases	*Andreas Braun*
6:00 pm	**Social Hour (1 hour)**	
7:00 pm	Keynote – Hemoglobin E/beta Thalassemia	*Sir David Weatherall, Professor*

Agenda

Tuesday, September 10, 2002

MORNING SESSION – ANIMAL MODELS FOR IDENTIFICATION OF MODIFIERS

8:30 am	Strategies for Finding Modifiers in Mouse Models of Human Diseases	*Joe Nadeau*
9:15 am	Genetic Modifiers Influencing Multiple Intestinal Neoplasia in the Min Mouse Model	*Linda Siracusa*
10:00 am	**Coffee Break (15 mins)**	
10:15 am	A Mouse Model of Alagille Syndrome	*Thomas Gridley*
11:00 am	Zebrafish for Identifying Genetic Modifiers	*Iain Drummond*
11:45 am	Short Talks from Submitted Abstracts	
12:30 pm	**Lunch Break (1 hour)**	

AFTERNOON SESSION – MECHANISMS FOR GENETIC MODIFIERS

1:30 pm	Genetic Modifiers of Hemochromatosis	*Ernest Beutler*
2:15 pm	Synergistic Heterozygosity	*Jerry Vockley*
3:00 pm	Modifiers of Non-Syndromic Deafness	*Thomas Friedman*
3:45 pm	Gaucher Disease: Complex Genotypes and Atypical Phenotypes Implicate the Role of Modifier Genes	*Ellen Sidransky*
4:30 pm	Discussion	
4:45 pm	Adjourn	

Speaker Abstracts

Genetic Modifiers of Human and Rodent PKD

David Woo, PhD

David Geffen School of Medicine at UCLA, Los Angeles, CA

The age of onset of renal failure among autosomal dominant polycystic kidney disease patients is known to be highly variable and can range from 0.5 to over 80 years of age. This variability can be due to genetic factors or environmental factors or both. Genetic factors that can influence the severity of PKD include PKD1 vs PKD2, 5' vs 3' mutant alleles in PKD1, somatic mutations and modifier genes.

Variance component analyses of clinical data collected from 222/430 PKD1 patients from 23 PKD1 families and from 7/22 MZ twin pairs, showed that inter-familial, intra-familial and intra-person variance accounted for 13%, 84% and 3% of the total observed ESRD age variance respectively. These results suggest that genetic modifier(s) are responsible for the majority of the variation in disease severity in ADPKD.

Our understanding of PKD is greatly enriched by several spontaneous and induced genetic models of PKD in mice and rats. For example, the recent discovery of the cilia localization of the gene products polaris and cystin in the orpk and the cpk mice lead to the finding that polycystin-1 and polycystin-2 are also present in cilia.

Using standard quantitative trait loci (QTL) mapping approaches, we have successfully mapped genetic modifiers of PKD severity in cpk mice, in pcy mice, in Cy/+ rats and in Cy/Cy rats. Results from these mapping studies suggest that modifiers of PKD severity common to several PKD models may exist. Identifying the nature of genetic modifiers common to several PKD models may be especially useful in elucidating the factor(s) governing the severity of PKD. Our results comparing PKD modifiers in Cy/+ and in Cy/Cy rats indicated that different modifiers are involved in heterozygous vs homozygous state of the same PKD mutation. This finding suggested that studying PKD modifiers in PKD1 +/- mice and in PKD2 +/- mice may be more relevant to human PKD than studying PKD modifiers in PKD1 -/- and PKD2 -/- mice. In addition, our data also indicated that extra-ranal complications of PKD are under the control of genetic modifiers that are distinct from modifiers of the renal phenotype.

Splitting Multigenic Hirschsprung Disease

Aravinda Chakravarti, PhD

Johns Hopkins University, Baltimore, MD

Hirschsprung disease (HSCR), the most common hereditary cause of intestinal obstruction, shows considerable variation and complex inheritance. Coding sequence mutations in *RET, GDNF, NTRN, EDNRB, EDN3, ECE1, SOX10* and *SMADIP1* lead largely to long-segment and syndromic HSCR but fail to explain the transmission of the much more common short-segment (S-HSCR) form. We conducted a genome scan in S-HSCR families and identified susceptibility loci at 3p21, 10q11 and 19q12 which appear to be necessary and sufficient to explain recurrence risk and population incidence. The gene at 10q11 is likely *RET*, proving its critical role in all forms of HSCR; however, coding sequence mutations are present in only 40% of linked families demonstrating the importance of non-coding variation. We demonstrate oligogenic inheritance of HSCR, the 3p21 and 19q12 loci as RET-dependent modifiers, and a parent-of-origin effect at RET.

We also conducted a genome-wide association study in Mennonite family trios to search for association arising from common ancestry. We identified susceptibility loci at 10q11, 13q22 and 16q23; the gene at 13q22 is the G-protein coupled receptor (GPCR) EDNRB and that at 10q11 is the receptor tyrosine kinase (RTK) RET. Statistically significant joint transmission of *RET* and *EDNRB* alleles in Mennonites and non-complementation of aganglionosis in mouse intercrosses between *Ret* null and *Ednrb* hypomorphic piebald alleles implicates epistasis between a GPCR and RTK.

Thus, genetic interaction between mutations in the RTK *RET* and the GPCR *EDNRB* is an underlying mechanism for this complex disorder. We also demonstrate, by a complete genetic dissection, why the inheritance pattern of HSCR is non-Mendelian.

Complexity in Two Disorders Mapping to Xp21: Glycerol Kinase Deficiency (GKD) and Adrenal Hypoplasia Congenita (AHC)

ERB McCabe[1], David Geffen[2]

[1] *Mattel Children's Hospital at UCLA*
[2] *School of Medicine at UCLA, Los Angeles, CA*

Phenotypes of "simple" Mendelian disorders are complex traits influenced by protein activity thresholds, modifier genes, systems dynamics and network architecture[1-6]. Robust biological systems are scale-free networks with a characteristic hub-and-spoke structure and a high tolerance for failure of individual components, because most nodes are peripheral and have low connectivity. The more highly connected nodes, however, represent sites of vulnerability within these robust networks.

Many of us began our investigations of rare "single gene" disorders with the naïve assumption that identification of patients' mutant genotypes would improve our abilities in prognosis and management. We have learned, however, that genotype does not reliably predict phenotype.

We will describe our recent investigations and considerations involving two disorders that map to Xp21: an inborn error of metabolism, GKD, and an inborn error of development, AHC. Despite our ability to map specific point mutations to three-dimensional structural models for the proteins involved in these diseases, GK and DAX1, respectively, and, for GK, to measure enzymatic activity extremely accurately, we found that neither mutation site nor residual activity was a reliable predictor of phenotype.[5, 7-10]

In addition to identification of modifier genes, we must also elucidate additional functions for proteins, since disruption of these other functions may contribute to phenotype. For example, GK is also involved in the ATP-dependent movement of the glucocorticoid-receptor complex from the cytoplasm across the nuclear membrane.[11]

The challenges we face in understanding the relationships between the individual's genome and their phenotype involves not only the full elucidation of all of the functions and modifiers for each protein, but also the organization of these proteins within their proteomic networks, and ultimately the influence of this functional organization on flux through the metabolome.

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Discovery Strategies of Genetic Modifiers in Mendelian and Polygenic Diseases

A. Braun[1], S. Fucharoen[2], K. Abel[1]

[1] *SEQUENOM, Inc., San Diego, CA USA;*
[2] *Mahidol University, Nakornpathom, Thailand*

Completion and availability of the entire human genome sequence is enabling for the discovery of genes and gene products involved in human complex disorders. Successful identification of these genes is dependent on available sample sets, a high-throughput scoring technology, and an underlying scientific hypothesis on how best to combine both these resources. SEQUENOM has developed a chip-based mass spectrometry approach (MassARRAY) for analyzing single nucleotide polymorphisms, complemented by fully automated SNP assay design and development as either uniplexes or multiplexes. Taking advantage of MassARRAY's capability for quantitative analysis, allele frequencies can be estimated in pools containing large numbers of individual DNAs. Comparing frequencies between two or more pools as a first-pass "filtering" step represents a tremendous throughput advantage over individual genotyping, and permits the cost effective testing of virtually all variations for association with various phenotypes or diseases. Fueling this technology, we have developed the world's most comprehensive set of screening reagents consisting of almost 400,000 SNP assays. Depending on required SNP density, assays for gene-based SNPs evenly spaced throughout the genome have been organized including from 1,000 to more than 100,000 SNPs, with all frequency classes represented.

We're employing a genomewide, non-hypothesis driven approach to identify modifiers of severity in HbE/β-thalassemia disease patients. Despite similar genotypes (HbE/ beta-0 alleles), patients display an extreme range of severity, suggesting additional genetic factors. Patients controlled for these genotypes are being collected and stratified by mildest versus most severely affected. DNAs from individuals in each group will be pooled, and frequencies of up to 100,000 SNPs will be compared to identify variations associated with disease severity. An exciting candidate modifier is the recently described AHSP gene, and SNP assays for characterizing this gene in the patients have been developed. Another objective is characterizing the β-globin complex for mutation-linked haplotypes, and for possible influence by other beta-like genes in the disease. Toward a higher density SNP map of this ~80 Kb region, resequencing has identified nearly forty new putative SNPs. As for monogenic diseases, it's hoped this approach can be extended to common diseases with probable polygenic involvement. Genes associated with Alzheimer's disease, including ApoE, likely don't account for all genetic contribution. However, genomewide screens with patients stratified by reported susceptibility or protective alleles may reveal other genes influencing onset or progression. Such a screen is envisioned using AD patients stratified by presence or absence of ApoE ε4, hopefully revealing susceptibility alleles influencing disease either cooperatively or independently of ε4.

Hemoglobin E-ß Thalassemia

D.J. Weatherall

Weatherall Institute of Molecular Medicine, University of Oxford

The β thalassemias show remarkable phenotypic variability. Homozygotes or compound heterozygotes have a spectrum of disorders ranging from severe anemia requiring lifelong transfusion to a mild anemia which is compatible with a completely normal life. And while most heterozygotes have very mild anemia some are completely normal while others have a level of anemia similar to that observed in more severely affected homozygotes. It has been possible to ascribe much of this heterogeneity to the action of primary, secondary and tertiary genetic modifiers together with environmental factors.

Globally, the most important application of these findings is directed at trying to understand the phenotypic heterogeneity of the intermediate forms of β thalassemia, that is those that lie between a severe, lifelong requirement for blood and extremely mild, symptomless anemia.

The commonest form of β thalassemia intermedia is Hb E-β thalassemia which is producing a major public health problem throughout the Indian subcontinent and Southeast Asia. Over the last five years over 100 patients with this condition in Sri Lanka have been followed closely and both their phenotypes and genotypes analysed in detail. A preliminary analysis of these studies indicates that it is extremely difficult to define “severity”, a pre-requisite to any analysis of genotype/phenotype relationships, but a number of secondary and tertiary genetic modifiers are of particular importance in establishing the clinical phenotype, and that there are important areas of study, which hitherto have been neglected, which are still required to understand why many of these patients can adapt to life remarkably well in the face of severe anemia. These observations have important implications for the study of other monogenic and multigenic diseases.

Genetic Modifiers Influencing Multiple Intestinal Neoplasia in the Min Mouse Model

Linda D. Siracusa, Revati Koratkar, Karen Silverman, Marina Markova, and Arthur M. Buchberg

Kimmel Cancer Center, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, USA

The study of genes that influence cancer susceptibility is a rapidly evolving field. Our laboratories use the mouse as a model system to identify and characterize genes that influence the development of *APC*-induced neoplasia. Apc^{Min} mice develop many polyps throughout their intestinal tract when the mutation is carried on the "susceptible" C57BL/6J (B6) background. In contrast, F1 hybrids resulting from crosses of B6 Apc^{Min} mice to "resistant" inbred strains develop few polyps. Quantitative trait loci (QTL) analyses had identified a locus, called Modifier of Min 1 (*Mom1*), which maps to distal chromosome 4 and modifies the number and size of intestinal polyps. We reported that the secretory type II Phospholipase A2 (*Pla2g2a*) gene was a strong candidate for most of the *Mom1* phenotype. We recently identified a second modifier locus, called Modifier of Min 2 (*Mom2*), that is another potent suppressor of intestinal tumorigenesis in Apc^{Min} mice. We have also established congenic lines and demonstrated that some "resistant" strains can significantly suppress polyp number and size, even in the absence of a resistant *Mom1* locus, suggesting that additional modifier loci (*Mom#*) are present. Examination of newly identified loci should reveal the relationship between the effects of modifier genes and tumor initiation, growth and progression. These studies are a critical step to understand the role of these genes in human cancer, their predictive value in treatment outcome, and their potential use as preventive agents. Research supported in part by NCI PO1 CA72027 to LDS and AMB.

A Mouse Model of Alagille Syndrome: *NOTCH 2* as a Genetic Modifier of *JAG 1* Haploin Sufficiency

B. McCright, L. Krebs, J. Lozier and T. Gridley *The Jackson Laboratory, Bar Harbor, Maine, USA*

Alagille syndrome is a human autosomal dominant developmental disorder characterized by heart, liver, eye, skeletal, craniofacial and kidney abnormalities. More than 95% of Alagille syndrome patients exhibit congenital heart defects, including peripheral pulmonic stenosis, pulmonic valve stenosis, atrial and ventricular septal defects, coarctation of the aorta, and Tetralogy of Fallot. Alagille syndrome is caused by mutations in the Jagged1 (*JAG1*) gene, which encodes a ligand for Notch family receptors. The majority of *JAG1* mutations seen in Alagille syndrome patients are null alleles, suggesting *JAG1* haploinsufficiency as a primary cause of this disorder. *JAG1* mutations can also cause congenital heart defects without accompanying defects in the liver or most of the other tissues typically affected in Alagille syndrome patients.

Mice homozygous for a *Jag1* null mutation die during embryogenesis, and *Jag1* heterozygous mice exhibit eye defects but do not exhibit other phenotypes characteristic of Alagille syndrome patients. However, mice doubly heterozygous for the Jag1 null allele and a *Notch2* hypomorphic allele exhibit developmental abnormalities characteristic of Alagille syndrome. *Jag1/Notch2* double heterozygous mice exhibit multiple cardiac defects, including right ventricular hypoplasia, pulmonary artery stenosis, and atrial and ventricular septal defects. Double heterozygous mice also exhibit jaundice, growth retardation, impaired differentiation of intrahepatic bile ducts, and defects in eye and kidney development. These results demonstrate that the *Notch2* and *Jag1* mutations interact to create a more representative mouse model of Alagille syndrome, and provides a possible explanation of the variable expressivity observed in Alagille syndrome patients. The phenotype exhibited by the *Jag1/Notch2* double heterozygous mice is indicative of a broader role for the Notch signaling pathway in regulating vascular development in mice. The role that the Notch signaling pathway plays during vascular development and the phenotypes of several mutants affecting these processes will be described.

Zebrafish as a Tool for Discovering Genetic Modifiers

Iain Drummond *MGH Renal Unit, Charlestown, MA*

Large scale mutagenesis screens using the zebrafish have generated over 2000 mutants that reveal essential gene functions in embryonic patterning, organogenesis and behavior. Interactions between mutants, for instance those affecting the BMP and nodal signaling systems, have already defined key elements of cellular signaling pathways in early dorsal-ventral patterning. The molecular characterization of *squint*, a spontaneously arising recessive enhancer of the *cyclops* phenotype, demonstrated the possibility of discovering new elements of signaling pathways by screening for enhancers or suppressors of existing mutants. Now the focus is on making such screens feasible with a variety of mutants. A key consideration in undertaking enhancer/suppressor screens in fish is the tester phenotype: ideally a hypomorphic mutant allele that is 1) viable as a homozygote and 2) whose phenotype can be reliably scored as enhanced or suppressed. Achieving viability of homozygotes has in some cases been engineered by complementing mRNA injections, isolating temperature sensitive mutations, or bypassing gene function by providing downstream activities or metabolites. Currently, the highest throughput screens are aimed at identifying dominant suppressors or enhancers in Fo or F1 generation mutagenized fish. In addition to using ENU mutants, other screening approaches propose using antisense “morpholino knock-downs” as a starting point for isolating dominant suppressors of loss of function phenotypes. Combining genetics with small molecule chemical library screens is another promising approach to pathway discovery. So although zebrafish do not exist as inbred strains, this does not limit their usefulness in modifier screens. Advantages such as the ability to make and screen haploids, embryo transparency, the ability to collect large numbers of embryos for mapping, and the existence of many mutants remain key strengths of the system and justify the effort to extend the use of this model organism for discovery of genetic pathways.

Genetic Modifiers of Hemochromatosis

Ernest Beutler *The Scripps Research Institute, La Jolla, CA*

Hereditary hemochromatosis, once considered to be a rare disease, has been more recently regarded as the most common genetic disorder of Northern Europeans. It has been suggested that many patients with this disease die unnecessarily because of the failure to recognize that the cirrhosis, diabetes, and cardiomyopathies from which they suffer are due to easily-treated iron overload. Indeed, some five persons per thousand have the hereditary hemochromatosis genotype and many of them also manifest the characteristic blood findings, viz., elevated transferrin saturation and increased serum ferritin.

To determine the actual clinical penetrance of the *HFE* mutation we genotypedmore than 41,000 subjects attending the Health Appraisal Clinic at Kaiser Permanente in San Diego, California for the C282Y and H63D mutation. We found 156 homozygotes for the common 845G6A (C282Y) mutation of the *HFE* gene. There were 630 compound heterozygotes for the C282Y and 187C6G (H63D) mutation. Laboratory studies including serum iron, transferrin saturation, ferritin, and SGOT were compared with ethnically and age-matched wt/wt controls. Participants recorded responses to 400 questions concerning symptoms and medical history. Although there was a strong relationship between *HFE* genotype and transferrin saturation and serum ferritin, we found no statistically significant increases in the symptoms commonly associated with hemochromatosis: diabetes, cardiac arrythmias, impotence, darkening of the skin, or arthropathy in homozygotes or compound heterozygotes. The only significant differences in the responses of homozygotes was that more of them had been told by physicians that they had "liver trouble". There was also a small but statistically significant increase in prevalence of elevated SGOT and serum collagen IV (a surrogate for hepatic fibrosis) in the homozygous group. Importantly, the number of homozygotes among the white patients exceeded slightly the Hardy-Weinberg expectation and there was no significant effect of homozygosity or compound heterozygosity on age distribution.

It is clear from these investigations that the clinical penetrance, in contrast to the biochemical penetrance, of the *HFE* mutations is extremely low, and we have therefore tried to identify genes that may modify the expression of *HFE*. We have sequenced genes encoding the following proteins in 5 expressing homozygotes, 5 non-expressing homozygotes, 5 *wt/wt* subjects with iron overload, and 5 *wt/wt* subjects without iron overload: transferrin, transferrin receptor-1, transferrin receptor-2, ferroportin, NRamp1, DMT-1, $2-microglobulin, ferroportin, USF-2, hepcidin, ceruloplasmin, TNF promoter, haptoglobin, ferritin heavy chain, and ferritin light chain. We have not found a polymorphism in any of these genes that incline patients toward iron overload. We are attempting to clone the juvenile hemochromatosis gene on chromosome 1q with the hope that it may be a modifier of *HFE* hemochromatosis.

Synergistic Heterozygosity

Jerry Vockley

Mayo Clinic Rochester, Rochester, MN

Regulation of flux through a metabolic pathway is often viewed in terms of rate limiting enzymes. *In vivo*, the situation is almost certainly more complicated than this. Metabolic control analysis describes flux through a biochemical pathway in quantitative terms related to the relative (additive) effects of all component enzymes and transporters involved in the pathway, along with changes in metabolic states. For example, metabolic control analysis studies indicate that, while the potential for carnitine palmitoyl transferase I (CPT I) to control flux through mitochondrial β-oxidation is high, the ability of malonyl-CoA (an inhibitor of CPT I) to regulate flux through the pathway is dependent on several factors. Thus to understand the full clinical effects of partial reductions of components in a metabolic pathway, one must consider them in combination rather than individually. For example, a reduction in activity of one or more of the mitochondrial matrix enzymes involved in β-oxidation might lead to the defective step(s) becoming rate limiting in the pathway, thus removing control from the step most adapted for this role. This in turn might lead to an aberrant response to increased energy demands.

Defects in energy metabolism, especially those of mitochondrial oxidative phosphorylation (oxphos) and β-oxidation, show pleiotropic and variable symptoms including hypoglycemia, myopathy, neuropathy, and cardiomyopathy. A significant number of patients with episodic symptoms suggestive of a defect in energy metabolism remain without a diagnosis after extensive biochemical and enzymatic evaluation. Predominant among these symptoms are recurrent fasting or stress-induced episodic muscle pain with or without rhabdomyolysis, and sudden life threatening events (presumably due to hypoglycemia). Increasingly, we have been identifying concurrent partial defects at multiple loci in energy metabolism in this population. We have suggested that such patients are exhibiting clinically significant reductions in energy metabolism related to these partial defects, a phenomenon we have termed synergistic heterozygosity. Synergistic heterozygosity, the accumulated effects of alterations at more than one locus in a patient, can be thought of as a specific example of multifactorial inheritance, where the influence of multiple loci (heterozygosity for deleterious mutations in two or more genes encoding enzymes involved in energy metabolism) and the environment (fasting and physiologic stress) interact to produce a final phenotype (episodic muscle symptoms or hypoglycemia).

Modifiers of Non-Syndromic Deafness

Thomas B. Friedman

Laboratory of Molecular Genetics, Section on Human Genetics, National Institute on Deafness and Other Communication Disorders, NIH, Rockville, MD

Transduction of sound presents an unparalleled requirement for precise biomechanical properties within the cochlea of the inner ear. Given this structural complexity and specialization, it is not surprising that hereditary deafness is remarkable for its genetic heterogeneity. Mutant alleles of at least sixty loci are associated with non-syndromic hearing loss. Individuals with hereditary hearing loss show a wide variety of phenotypes ranging from profound, congenital deafness to slowly progressing, adult-onset hearing loss. Parsing out the sources of variation in disease phenotype has been challenging. Phenotypic variation may be due to an amalgam of locus and allelic heterogeneity, environmental factors, stochastic developmental events or modifier genes (genetic background). An allele of a modifier gene may or may not express an obvious mutant phenotype on its own, but is detected by its effects on the expression of other genes. Alleles of modifier genes can be classified as either enhancers or suppressors and can reveal unexpected gene interactions that mediate normal and abnormal function. I will present three examples, which suggest or illustrate a genetic underpinning for the variation in clinical presentation. (1) Variation due to the inheritance of different mutant alleles of *CDH23* and *PCDH15* can result in non-syndromic hearing loss or Usher syndrome type 1, which is characterized by severe to profound hearing loss, vestibular dysfunction and retinitis pigmentosa leading to blindness (Bork et al. 2001; Astuto et al. 2002; Ahmed et al. 2002). (2) Variation in hearing loss is found within and between families in individuals who are homozygous for the same recessive null allele of *GJB2* (gap junction beta), which encodes connexin 26, suggesting the existence of modifier loci. (3) Non-penetrance of profound, congenital deafness *DFNB26* is due to the inheritance of a dominant suppressor allele at the modifier locus *DFNM1*. Individuals who are homozygous for the recessive deafness allele at the *DFNB26* locus (4q31) and who also inherit the dominant suppressor allele of *DFNM1* (1q24), have normal hearing (Riazuddin et al. 2000, Nature Genetics 26: 431-434). Identification and functional studies of modifier genes of hearing loss loci will refine our understanding of sound transduction and may guide the rational design of medical therapies for hearing loss. Appropriate mouse models will be essential to functionally dissect modifiers of the major deafness loci.

Gaucher Disease: Complex Genotypes and Atypical Phenotypes Implicate the Role of Modifier Genes

N. Tayebi, B. Stubblefield, E. Orvisky, M.E. LaMarca, O. Goker-Alpan, E. Sidransky

Section on Molecular Neurogenetics, NIMH, NIH, Bethesda, MD

Gaucher disease, the inherited deficiency of glucocerebrosidase (GC) manifests with vast phenotypic variation. While over 200 mutations in GC have been identified, our understanding of genotype/phenotype correlation is incomplete. Some mutations, i.e. N370S, have prognostic implications. However, patients with diverse disease manifestations can share the same point mutations and conversely, clinically similar patients have many different genotypes. Siblings and even identical twins can manifest with very different symptoms.

Accurate genotype/phenotype studies have been limited by the incomplete ascertainment of both genotype and phenotype. The glucocerebrosidase gene locus is complex, containing 7 genes and 2 non-processed pseudogenes in close proximity. The GC gene has a highly homologous pseudogene only 16 kb downstream, and the metaxin pseudogene and gene are located contiguously to the 3` ends of GC and pseudoGC, respectively. The presence of two highly homologous pseudogenes increases the likelihood of recombination and mutation in the functional genes, and such recombinant alleles have been identified in 59 to 240 patients. Using Southern blots and direct sequencing, possible mechanisms and crossover sites were identified, and included gene fusions (18 alleles), duplications (7 alleles) and gene conversions (34 alleles). Thus, genotyping which relies solely on PCR-based screening for individual point mutations will not fully characterize many mutant alleles, and alterations to contiguous genes could potentially contribute to phenotype differences.

As our appreciation of the complexity of the GC locus has expanded, so too has our awareness of the spectrum of associated clinical manifestations. Gaucher disease is classified into 3 types based on broad phenotypic groupings, but there is overlap and variation in the kind and severity of symptoms in all 3 types. A subset of patients has neonatal lethal type 2 Gaucher disease with hydrops fetalis and/or congenital ichthyosis. Some of these infants are homozygous for recombinant alleles. Another fascinating group is adult patients with early onset, treatment refractory parkinsonism. Our studies of 15 such patients identified 11 different genotypes. Several of these probands had relatives with a family history of parkinsonism without Gaucher disease, suggesting a modifier or pathway shared by the two phenotypes. A group of patients with cardiac valve involvement and oculomotor apraxia all carried mutation D409H, while a series of 16 patients with myoclonic epilepsy had multiple genotypes. Another group of 9 children was identified with an intermediate phenotype which falls between what is classically considered type 2 and type 3 Gaucher disease. Both discordant patient groups sharing the same genotype, and phenotypically similar patients sharing atypical manifestations, provide fertile grounds for the identification of other factors that modify phenotype in this disorder.

Poster Abstracts

Hereditary Amyloidosis: Variations in Expression

Merrill D. Benson, MD

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Hereditary amyloidosis can be caused by mutations in a number of genes including transthyretin (TTR), apolipoprotein A-I, fibrinogen A -chain, lysozyme, cystatin C and apolipoprotein A-II. These are all inherited as autosomal dominant traits and cause systemic disease. In addition, amyloidosis localized to the Central Nervous System (Alzheimer Disease) may result from mutations in the amyloid producing APP protein or genes which impact on APP metabolism, including presenilin 1 and 2.

The most common form of hereditary systemic amyloidosis is the result of mutations in transthyretin, and greater than 80 disease causing mutations have been described. While each form of amyloidosis shows obvious Mendelian inheritance, the degree of penetrance varies between disease caused by different mutations, and age of onset and organ involvement of clinical disease varies within kindreds with the same mutation.

A prime example is the amyloidosis of TTR Val30Met. Members of Portuguese families have disease onset at age 32, whereas subjects with the same mutation in Sweden have a mean onset of 56 to 58 years of age. Within the Portuguese families approximately 10% have late-onset, and within the Swedish population approximately 10% have early-onset. Similar variations are found with fibrinogen A chain and apolipoprotein A-I amyloidosis.

Results to date: Haplotype analysis of patients of English origin with TTR Val30Met show late- onset of disease associated with TTR haplotype III; however, this does not explain the disparity between Portuguese and Swedish subjects since both have TTR haplotype I. Conclusion: The hereditary amyloidoses, in particular transthyretin amyloidosis, offer an excellent opportunity to search for genetic modifers of Mendelian diseases.

Heme-Regulated eIF2α Kinase: A Modifier Gene of Erythropoietic Protoporphyria in Mice

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Heme-regulated eIF2α kinase (HRI), is essential for translational regulation and survival of erythroid precursors in the setting of iron deficiency. Because iron is an essential component of heme, iron deficiency necessarily leads to heme deficiency. To address the question whether it is heme or iron that directly regulates HRI *in vivo*, $HRI^{-/-}$ mice were crossed with *fech* mice which have a severe defect in ferrochelatase, the last enzyme of heme biosynthesis, required to insert iron into protoporphyrin IX (PPIX) to form heme. Homozygous *fech* mice are heme-deficient, but not iron-deficient, with elevated PPIX and a mild anemia. $HRI^{-/-}$ *fech/fech* double mutant mice were born at a frequency of 5.0%, slightly less than the expected 6.25%. Although, these mice readily survive to >8 months old, they are much smaller in size, very sensitive to light and profoundly anemic. The anemia is characterized by the unusual combination of normocytic, hyperchromic red blood cells, and is similar to that seen in $HRI^{-/-}$ mice maintained on an iron deficient diet. This indicates that HRI is regulated *in vivo* by heme and not iron. PPIX levels in $HRI^{-/-}$ *fech/fech* erythrocytes are 20-50 times higher than those seen in $HRI^{+/+}$ *fech/fech* controls, leading to an exacerbation of the hepatic PPIX deposits that are seen in mice deficient in fech alone. Thus, HRI is important not only for regulating globin synthesis, but also for regulating heme biosynthesis, serving to retard the accumulation of toxic intermediates such as PPIX. Deficiency of ferrochelatase activity in humans is associated with erythropoietic protoporphyria (EPP). A small fraction of EPP patients develop fatal hepatic pathology. Our study of $HRI^{-/-}$ *fech/fech* mice indicates that HRI may be a modifier gene that affects the severity of EPP.

Analysis of Candidate Gene Modifiers in the Complex Multigenic Mechanisms Underlying Severe CF Liver Disease

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The CFTR genotype has limited predictive value in forecasting the disease severity a given CF patient will develop. CFTR genotype correlates poorly with the risk for developing severe CF liver disease (*CFLD*), defined as portal hypertension with splenomegaly and/or esophageal varices, except for a general requirement for "severe" CFTR mutations. Our preliminary data suggest complex genetic interaction involving the alpha-1-antitrypsin (*PI*), transforming growth factor beta (*TGFB1*), and mannose binding lectin (*MBL2*) genes. Comparison of allele frequencies at these loci between 71 Caucasian CFLD patients and 150 CF patients without LD (all Caucasians homozygous for ΔF508) has detected an increased risk for CFLD conferred by *PI* gene mutations (odds ratio (OR) 2.9, 95%CI 1.3-6.3, P=.007). This effect is compounded by a high expression *TGFB1* promoter variant (OR 3.2, 95% CI 1.2-8.2, P=.01) and *MBL2* mutations (OR 4.6, 95%CI 1.2-16.9, P=.038). Strikingly, combination of mutations/variants in all three genes (*PI, TGFB1, MBL2*) confers the greatest risk (OR 11.4, 95%CI 1.3-104, P=.01).

Additional genes likely contribute to development of CFLD. We have identified 180 single nucleotide polymorphisms (SNPs) within 85 candidate modifier genes that underlie inherited liver disorders, mediate fibrogenesis, inflammation, or immunity, involve the oxidative stress response and/or metabolism of the ECM, or play a role in hepatocellular proliferation. The majority of these SNPs (123) are functional in that they alter gene expression or protein function. The remaining SNPs (57) are anonymous, but have been validated (reported by more than one group to have a carrier rate >10%). The anonymous SNPs will permit detection of risk-conferring haplotypes associated with candidate modifier genes lacking known functional variants. High-throughput analysis of these SNPs is currently underway on 120 CFLD patients and 200 CF controls without clinically relevant liver disease. We anticipate these association studies will identify additional genes that influence CFLD. Multicenter collaborations have identified >300 additional CFLD patients likely to meet our criteria, which will permit identification of subtle genetic influences.

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Gene Modifiers for Cystic Fibrosis (CF) Lung Disease: Clinical Phenotype of Homozygous Patients (ΔF508/ΔF508) with "Mild" Versus "Severe" Lung Disease

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The variability of pulmonary disease in CF is not explained by intragenic mutations in *CFTR*, and likely reflects environmental effects and genetic heterogeneity at other loci. To identify non-*CFTR* genetic contributions to the heterogeneity of CF lung disease, a multi-center study has been initiated to enroll 700 patients with the same *CFTR* genetic background who have "severe" (lowest 20th percentile for age) or "mild" (highest 20th percentile) lung disease. To date, we have enrolled 350 patients, and report here on clinical data on the first 268 subjects, segregated into three groups: 1) 110 subjects with "mild" lung disease (age 15-28 yrs), 2) 80 older subjects with "mild" disease (≥age 29 yrs), and 3) 78 subjects with "severe" disease (age 8-25 yrs). Longitudinal analysis (~21 measures/patient) shows the intercepts (at birth) for the FEV1 (% Pred.) for these 3 groups are 117, 107, and 103, respectively. The rates of decline (%/year) for the mild subject cohorts (1.3 and 1.6%) are less than severe subjects (3.4%). The body mass index (BMI) percentile (50% is "normal") was 48% and 34% for the "mild" cohorts, but lower (20%) for severe patients. The age at diagnosis (0.9 years) was earlier for "severe" patients, as compared to milder disease (2.6 and 4.3 years). Sweat Cl- values did not differ among the 3 groups (104-106 mM/L). The prevalence of *Pseudomonas aeruginosa* was similar for three groups (84-87%). The prevalence of S. *aureus* was greater in the males of all 3 groups (67-74%) than for females (43-58%). In summary, CF patients in this protocol are discriminated as "mild" and "severe" by pulmonary function, BMI, and age-at-diagnosis. These subjects are being genotyped (~100 candidate alleles) to test for association with pulmonary phenotype. *Reporting for the CF Lung Gene Modifier Study Group.

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The Common Polymorphism Pro11Leu as an 'Intragenic' Modifier of Primary Hyperoxaluria Type I (PH1) Due to Ile244Thr Mutation

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Primary hyperoxaluria type I (PH1) is an inborn error of metabolism due to a deficiency of alanine-glyoxylate amino transferase (AGXT). Most of the PH1 alleles detected in the Canary Islands carry the Ile244Thr mutation in the *AGXT* gene, with 14 out of 16 patients being homozygous for this mutation. Four polymorphisms within AGXT (Pro11Leu, intron1ins, C386T, Ile340Met), as well as D2S125 and D2S140 markers were also shared in their haplotypes (AGXT*LTM), consistent with a founder effect.

The consequences of these amino acid changes were investigated in various expression systems. While Ile244Thr alone did not affect AGXT activity or subcellular localization, when present in the same protein molecule as Leu11Pro it resulted in loss of enzymatic activity in soluble cell extracts. Like its normal counterpart, the AGXT*LTM protein was present in the peroxisomes but it was essentially insoluble in detergent-free buffers. The common polymorphism Leu11Pro (allelic frequency = 0.2) behaved as an intragenic modifier of the Ile244Thr mutation with the resulting protein undergoing stable interaction with molecular chaperones and aggregation. This aggregation was temperature-sensitive, with higher proportion of soluble protein being detected at 30C than at 37C. AGXT*LTM protein expression in both E.coli, as a GST- fusion protein, and Sf9 insect cells allowed the purification of soluble mutant protein that retained significant enzymatic activity, compared with the wild type form. Using the differential solubility as an indicator, various chemical chaperones were tested in cell culture. In particular, betaine substantially improved the solubility of the mutant protein and the enzymatic activity in cell lysates. In summary, Ile244Thr, the second most common mutation responsible for PH1 is a protein conformational disease which may benefit from new therapies with pharmacologic chaperones or small molecules to minimize protein aggregation.

Validation of Circulating Immunoreactive Trypsinogen as a Heritable, Biochemical Marker of Variation in Early Pancreatic Injury in Cystic Fibrosis (CF)

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Pancreatic injury in cystic fibrosis (CF) results in significant morbidity. Identification of modifier genes for pancreatic injury may lead to development of new treatments but requires the validation of appropriate phenotypic markers. To determine whether circulating immunoreactive trypsinogen (IRT), an important pancreatic enzyme precursor, may serve as a biochemical marker of heritable variation in early pancreatic injury in CF, we examined longitudinal IRT determinations in 288 infants with CF identified through a statewide newborn screening program. This program is based on elevation of circulating IRT in CF newborns compared to normals. In infants with CFTR mutations generally considered pancreatic insufficient (Class I, II, or III), IRT declined monotonically over the first five years of life to undetectable levels, indicating severe, progressive exocrine pancreatic destruction. In infants with CFTR mutations generally considered pancreatic sufficient (Class IV or V mutations), IRT remained elevated over the first five years of life, indicating ongoing pancreatic injury but with preservation of some exocrine pancreatic function. IRT decline in individual infants correlated with increased coefficients of fecal fat excretion, confirming the clinical relevance of IRT in the CF pancreatic phenotype. Significant variation in IRT decline was observed in infants homozygous for the ΔF508 deletion suggesting the presence of modifier genes. “Rapid” and “slow” decliners could be identified. Squared trait difference testing of initial IRT in 22 sibling pairs strongly indicated heritability. There was no difference between IRT decline in infants homozygous for the ΔF 508 mutation or heterozygous for the ΔF508 mutation with another Class I, II or III mutation, further indicating that CFTR mutation alone does not explain variation in IRT decline in pancreatic insufficient patients. Controlling for genotype, infants with meconium ileus had significantly lower IRT levels at every age than infants without meconium ileus, suggesting coupling between intestinal and pancreatic disease in CF and raising the possibility that genetic modifiers of intestinal disease may also modify pancreatic injury. We conclude that circulating IRT is a heritable, biochemical marker of variation in early pancreatic injury in CF that may be useful in identification of modifier genes. Examination of pancreatic injury in CF for modifier genes offers several advantages compared to examination of lung injury in that 1) pancreatic destruction occurs over the first few years of life compared to the much longer course of lung destruction and 2) pancreatic injury may be tracked through a biochemical marker, IRT, whereas there are no accepted biochemical markers of the lung disease.

Gaucher Disease and Parkinsonism: From a Simple Mendelian Disorder to a Complex Disease

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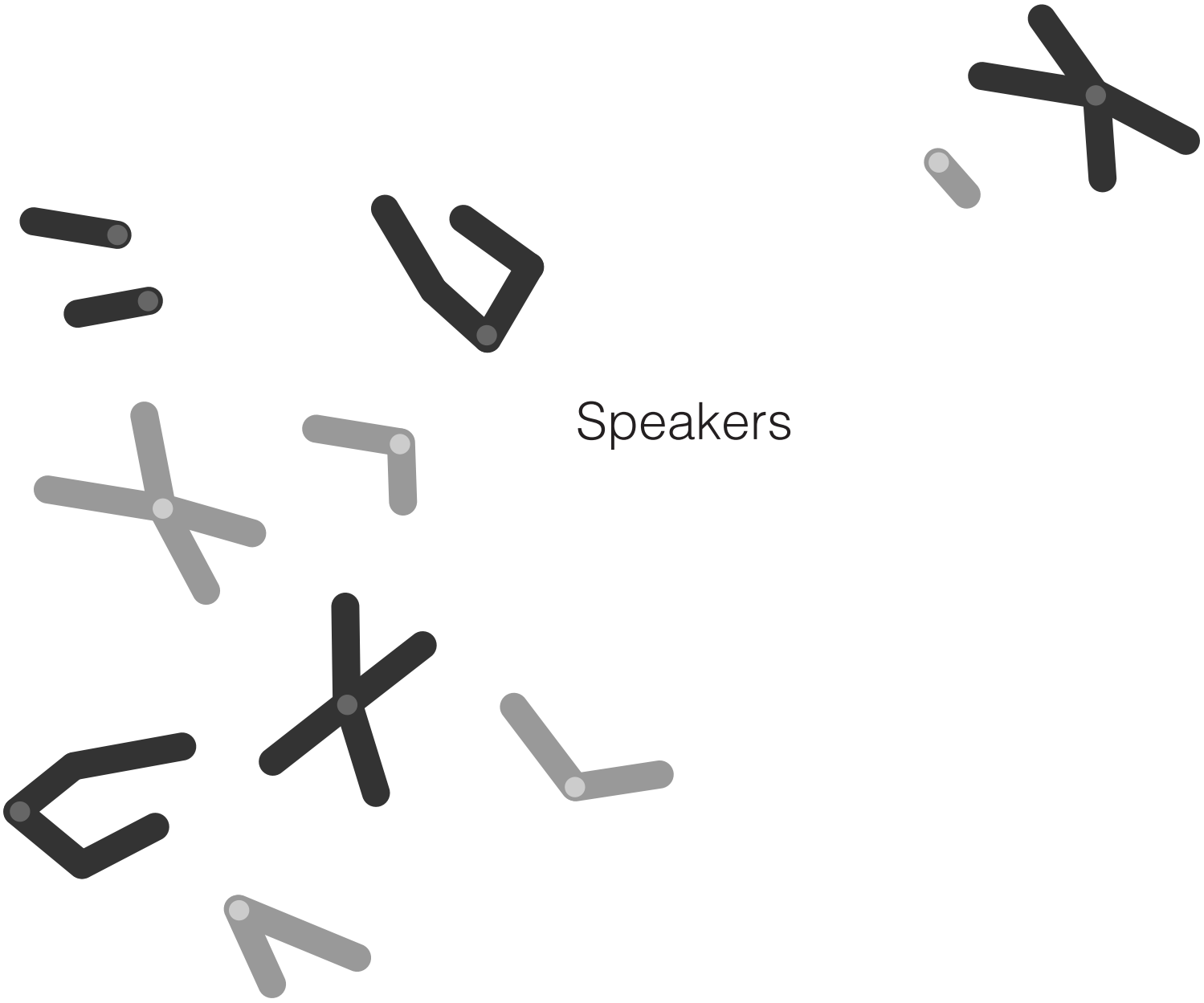
Among the many phenotypes associated with Gaucher disease, the inherited deficiency of lysosomal glucocerebrosidase (GC), are reports of patients with parkinsonian symptoms. These patients have an early onset, treatment-refractory form of parkinsonism and often have mild Gaucher manifestations. Several actually had a family history of parkinsonism.

We performed genotypic analyses on 15 patients with Gaucher disease and parkinsonism from eight different nations including Ashkenazi and non-Jewish individuals. Sequencing of the GC gene demonstrated at least ten different genotypes. The common N370S mutation, which is not associated with neuronopathic Gaucher disease, was encountered in 11 of the patients studied. One patient carried mutation L444P on the paternal allele and D409H on the maternal allele, but Southern blot analyses showed that the maternal allele had an additional 15 kb fragment resulting from a recombination between metaxin and its pseudogene. Metaxin, a convergently transcribed gene located adjacent to the GC pseudogene, encodes for a 317 protein, believed to be part of a preprotein import complex in the outer membrane of the mammalian mitochondrion. Sequencing of the gene for metaxin revealed that 11 patients had an alteration in the metaxin gene which was subsequently found to be a polymorphism linked to mutation N370S. No other mutations in the gene for metaxin, as well as the genes for parkin and alphasynuclein, were detected. Because Parkinson disease is a relatively common disorder, thought to result from multiple etiologies, there may be different genes contributing to this phenotype among our patients or there may be a shared modifier.



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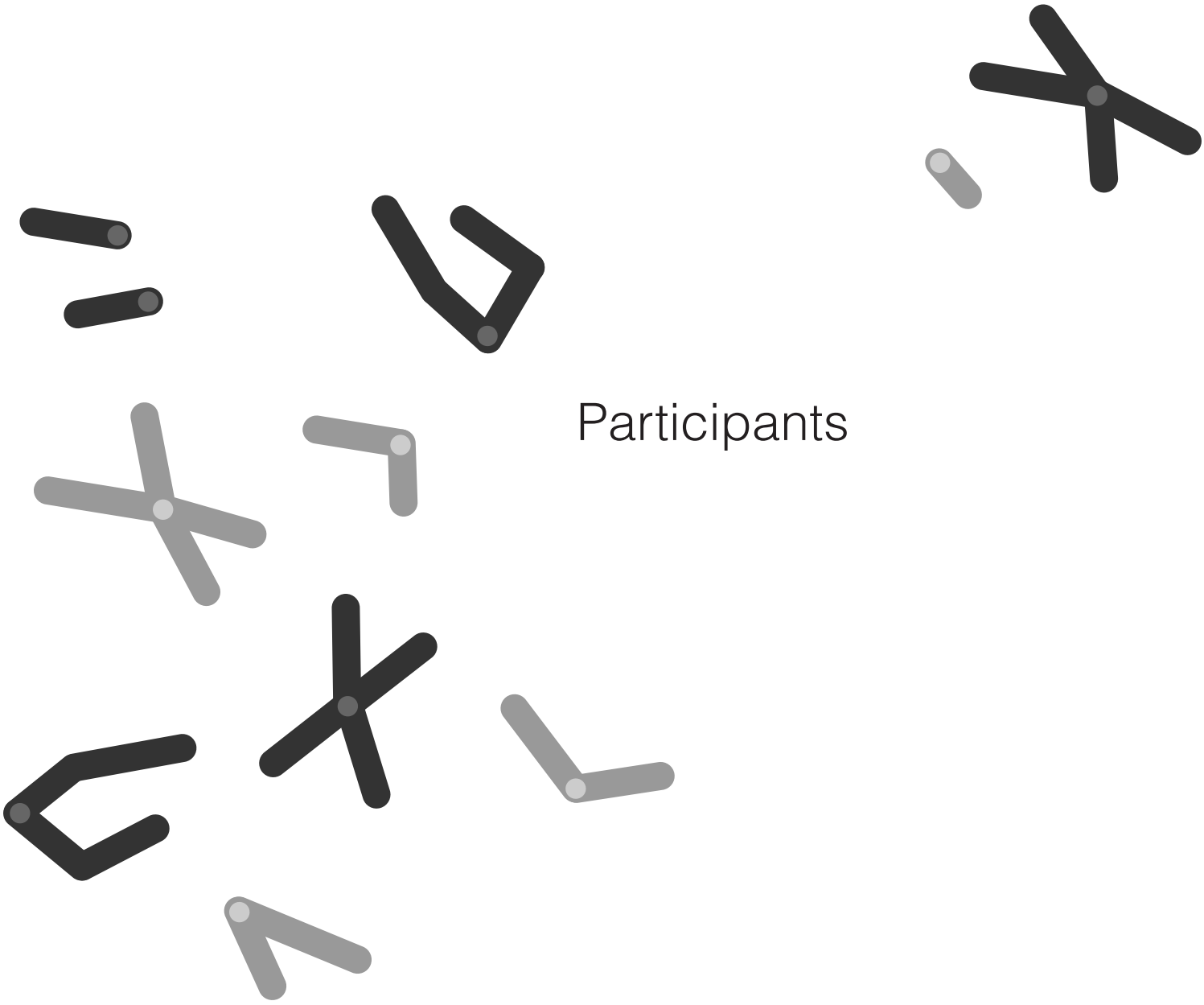

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