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About 25,000 DNA samples from families with different genetic disorders are stored in the Human Genome Research Center

The Human Genome Research Center (HGRC)

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THE HUMAN GENOME RESEARCH CENTER
HGRC

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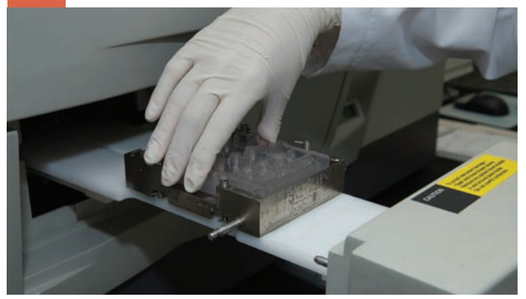


The Human Genome Research Center, in addition to genetic research and counseling, has set up and currently maintains a core facility for DNA sequencing, microsatellites analysis and diagnostic tests for genetic disorders

The Human Genome Research Center (HGRC) at the University of São Paulo is dedicated to the study of genetic disorders. Since its beginning, about 40 years ago, more than 100,000 patients have been referred and investigated by different groups of the Biosciences Institute always in a mutually beneficial interaction: patients generating research and research helping patients. The establishment of the HGRC enhanced integration between the Principal Investigators (PI) responsible for the different research groups, resulting in optimization of resources and know how for scientific investigation on the human genome and consequently a better service to patients as well.

The aim of the HGRC is to enhance comprehension of gene function with focus on neuromuscular, craniofacial and brain development mainly through the study of genetic disorders, which is the ultimate goal of the Human Genome Project. It is also our aim to contribute to the development of new approaches to treat genetic or acquired conditions. These are ambitious avenues of research, which draw upon the combined expertise of our research team. To achieve these goals, the identification of disease genes as well as studies on genotype-phenotype correlations through the analysis of the effect of different mutations on protein expression and phenotypic variability remain a major challenge behind all research on the Human Genome. In terms of pathological variation, recent molecular studies have shown for a great number of genetic disorders that patients, who present the same underlying mutations, may have strikingly different phenotypes. These observations highlight the importance of other genetic and/or non-genetic factors in determining phenotypic expression. The possibility to treat affected patients in the future, also one of our main goals, is being approached through cell and gene therapy investigations by using different animal models.

MAIN RESEARCH TOPICS

Molecular basis of genetic disorders through:

Identification of genes associated with human genetic disorders, particularly neuromuscular and developmental disorders.

Functional and protein analysis

Genotype-phenotype relationship

Association studies in complex disorders

Development of future therapeutic approaches to genetic diseases through research related to:

Analysis of stem-cells from different sources and therapeutic trials with animal models

Gene therapy based on RNA interference and on adenovirus

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Research
Identification of genes associated with human genetic disorders

Mapped disease genes:
- Amyotrophic lateral sclerosis, *Als*8
- A form of X-linked spinal muscular atrophy
- A new form of autosomal dominant *Lgmd-Lgmd*1G
- A new autosomal recessive syndrome, with spastic paraplegia, optic atrophy, and neuropathy –*Spoan*
- A form of X-linked spastic paraplegy
- Aurycular condylar syndrome
- Autosomal recessive form of craniometaphyseal dysplasia
- A new locus for deafnesss
- A new locus for ectrodactily/tibial hemimelia syndrome
- A new locus for Angelman-like syndrome

The genes involved in the pathogenesis of the following diseases were identified:
a) Limb-girdle muscular Dystropy 2G: telethonin
b) Knobloch syndrome: mutations in *Col*18A1
c) Amyotrophic lateral sclerosis: *Vap*-B
d) A new form of syndromic X-linked mental rertardation: *Ube*2A
e) Carpenter Syndrome: *Rab*23
f) Spastic paraplegia type 8: *Kiaao*196 gene

Functional and Protein analysis
For neuromuscular disorders, one important result was the observation that VAP-B (vesicle-associated membrane protein-associated protein b) involved in the fusion of membranes and the transport of intracellular proteins is responsible for ALS8, a dominant form of amyotrophic lateral sclerosis with great clinical variability. More recently it has been suggested by other groups that VAP-B is apparently also involved in sporadic forms of ALS, which opens new avenues of research of worldwide interest. This outlines the importance of investigating the cause of apparently rare disorders.

The analysis of more than 10 muscle proteins was done in about 600 patients affected by different forms of MD. We developed new methods for protein studies, and evaluated the interaction among several proteins of the muscle sarcolemma.

Genotype-phenotype relationship
Many important findings have been achieved through this approach as summarized below.

Screening of mutations for different disorders showed that a strict genotype-phenotype correlation is not the rule. For most disorders, patients with the same mutation may show discordant clinical courses. Identifying the responsible mechanisms, and particularly what "protects" some individuals from the deleterious effects of pathogenic mutations, remains a great challenge, still under investigation, which may have important impacts in future treatments.

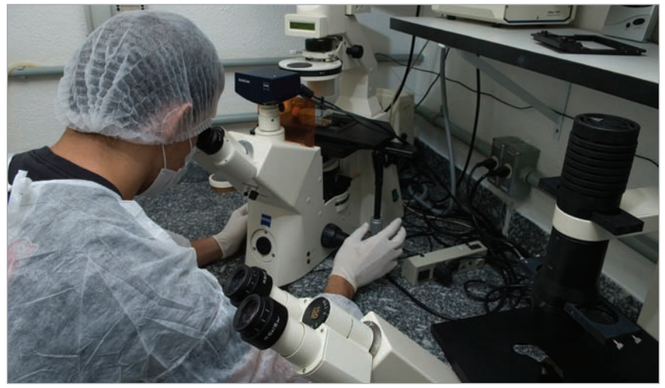
The characterization of the most prevalent mutations in our population for some disorders allowed us to develop molecular tests extremely important for diagnosis and identification of asymptomatic carriers in "at-risk" families.

Function of different isoforms as well as identification of important protein functional domains have been identified for some genes involved in neuromuscular and developmental disorders.

The genetic studies of a large cohort of patients with Prader-Willi and Angelman syndromes (genomic diseases) pointed out that the phenotypic variability are due to the different mechanisms involved in the etiology of these syndromes (deletion, uniparental disomy) and that the most severe phenotype of AS results from larger deletions occurring in chromosome region 15q11-13.

The use of expression profile array in a Mendelian bone disorder led to the identification of new proteins involved in osteogenesis, which might provide new targets for the action of drugs that can accelerate bone ossification.

Complex disorders (unknown mechanisms and multifactorial inheritance)
In chromosomal studies, the introduction of the technique of comparative genomic hybridization based on arrays (array-CGH) allowed the detection of chromosomal losses and gains below the microscope resolution. This led to the identification of microrarrangements underlying the etiology of congenital malformations, unexplained mental retardation and deafness. We have shown that microchromosomal rearrangements are important mutational mechanisms in syndromic craniosynostosis and syndromic obesity associated with behavioral disturbances. New candidate gene regions have been identified for these phenotypes.



The Human Genome Center (HGRC) is the largest center for the study of genome disorders in Latin America and is an important contributor in stem cell research

In the group of multifactorial inheritance diseases of, one of our major contributions has been the finding that maternal and fetal genotypes might interact in the predisposition to cleft lip and/or palate.

We also showed that functional analysis of a gene can be achieved through case-control studies in common disorders for which a candidate gene might play a major causative role. For example, we showed that variations in *Col*18A1, in which null mutations cause Knobloch syndrome, is associated to common diseases, such as cancer and obesity. This once again shows that functional analysis of genes associated to rare Mendelian disorders can contribute to the understanding of the human genome.

Future Therapeutic approaches
a) Stem cells investigation
Our main results relate to the differentiation of human adult stem-cells from different sources and pre-clinical therapeutic trials in animal models. Our preliminary results showed the possibility to restore faulty muscle proteins in animal models with muscular dystrophy as well as bone reconstruction. We have also published a paper pointing out that the richest source of mesenchymal stem-cells in umbilical cord units is not the blood but rather the cord, which is usually discarded.

b) Gene therapy
In an effort to start work that may be related to gene therapy, we have been employing cell culture and animal models as recipients of gene transfer. For that we developed recombinant adenovirus vectors to transfer genetic information directly to cells that are from human patients and analyzed their ability to correct the cells' genetic defects. Our data achieved some success correcting the DNA repair deficiency in xeroderma pigmentosum cells, providing hope for these patients to face their skin problems when exposed to sunlight. Moreover, our studies have also been able to propose a new strategy, monitoring DNA repair of tumor cells, to battle aggressive tumors such as glioblastomas.

c) Transfer of technology and genetic counseling
Our results are critical in GC for the estimation of genetic risks, identification of "at-risk" carriers, management and follow-up of patients. Our Center also interacts with patients/parents associations such as the Brazilian Muscular Dystrophy Association (ABDIM), Fragile X Prader-Willi, Angelman associations and Cleft lip/palate Associations. Through ABDIM we established an important partnership with Secretaria da Saúde de São Paulo and more recently with Petrobras for diagnostic tests and management of patients with neuromuscular disorders. The Center also performs genetic services, sequencing and genetic tests, for other members of the scientific or medical community.

The HGCR is also involved in the identification of strategies to ameliorate the suffering of some genetic diseases, in particular neuromuscular, craniofacial and deafness. Recently, a patent application has been done regarding use of a new source of stem cells for bone reconstruction.