

Meeting report

Human genetics branches out in Barcelona

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A report of the European Human Genetics Conference, Barcelona, Spain, 31 May-3 June 2008.

The 2,400 attendance at the 2008 conference of the European Society of Human Genetics was a record for this annual meeting - a demonstration of how human genetics research is flourishing in Europe. Particular trends noted at this year's meeting include the role of copy-number variation and noncoding RNAs in human disease, advances in the functional characterization of disease-causing genetic defects and therapeutic strategies based on reversing the effects of gene mutations. Here we report a few of the highlights of the meeting in these areas.

From association studies to the molecular basis of disease

Recent results of genome-wide association scans applied to complex diseases demonstrate the importance of large international collaborative studies and sophisticated statistical analysis of the data. On behalf of the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium, Eleftheria Zeggini (University of Oxford, UK) presented the results of a meta-analysis of three genome-wide association scans to find genes associated with type 2 diabetes. These projects (from the Diabetes Genetics Initiative (DGI), the Finland-United States Investigation of NIDDM Genetics (FUSION) and the Wellcome Trust Case Control Consortium (WTCCC)) encompassed 10,128 individuals of European descent and around 2.2 million single nucleotide polymorphisms (SNPs), either genotyped or imputed. The meta-analysis identified multiple new loci with modest effect on disease risk (odds ratio 1.1), including those for a zinc-finger protein (*JAZF1*), calcium/calmodulin-dependent protein kinase I-delta (*CDC123/CAMK1D*), a metalloproteinase (*ADAMTS9*), and

the thyroid adenoma-associated gene (*THADA*). This study highlighted the value of large sample sizes for understanding the genetics of complex diseases, where many genes of modest effect may play a role, and pointed out the importance of focusing not only on common variants but also on rare ones. Divya Mehta (Helmholtz Zentrum, Munich, Germany) presented an association of *SLC2A9* (which encodes a glucose transporter) with gout, which was obtained by combining the results of genome-wide association studies (WGAs) and gene-expression variation analyses of 350 samples, and using the expression data to prioritize candidate genes from the WGA, thus showing the value of transcriptome analysis in adding resolution to WGAs.

Functional studies showing the molecular mechanisms that link genes with disease were a hot topic. Anita Rauch (Institute of Human Genetics, Erlangen, Germany) presented results showing that biallelic loss-of-function mutations in the pericentrin gene (*PCNT*) cause microcephalic osteodysplastic primordial dwarfism. *PCNT* mutations result in disorganized mitotic spindles, premature sister chromatid separation and mis-segregation of chromosomes. Rauch reported striking similarities between this type of dwarfism and the Late Pleistocene hominid fossils from the island of Flores in Indonesia, and suggested that those fossils might represent modern humans with some similar pathology. Jozef Gécz (Women's and Children's Hospital, North Adelaide, Australia) described his team's identification of protocadherin 19 (*PCDH19*) as the gene related to a rare form of female-limited X-linked epilepsy and mental retardation, where a change in *PCDH19* was identified in the seven affected families studied with this underdiagnosed disorder. He proposed a mechanism in which the disease was caused by the affected individual being a mosaic of *PCDH19*-positive and *PCDH19*-negative cells. Sandra Pasternack (Institute of Human Genetics, Bonn, Germany) reported that the G-protein-coupled receptor P2RY5, which

is expressed in hair-follicle cells, is involved in the maintenance of human hair growth. She and her colleagues have identified homozygous truncating mutations in *P2RY5* for an autosomal recessive form of hereditary non-syndromic human alopecia. It has yet to be seen how these investigations could translate into new therapeutic approaches for hair loss in humans.

Brunhilde Wirth (Institute of Human Genetics, University Hospital, Cologne, Germany) presented the first reported example of a gender-specific protective modifier of a Mendelian disorder - the overexpression of plastin 3 (*PLS3*) as a protection against spinal muscular atrophy in females. Whereas homozygous deletion of the gene *SMN1* generally leads to the disease, some rare individuals carrying the same *SMN1* mutations as their affected siblings are asymptomatic. By comparing the transcriptomes of lymphoblastoid cell lines from unaffected and affected *SMN1*-deleted siblings, Wirth and her colleagues found that *PLS3* was abundantly expressed in the unaffected individuals, but not in their affected siblings. The discovery that *PLS3* protects against spinal muscular atrophy might help to identify novel targets for therapy.

Copy-number variation and noncoding RNAs in human disease

Copy number variation (CNV) and its relation to disease emerged as an increasingly important theme at this year's meeting. Richard Redon (Wellcome Trust Sanger Institute, Cambridge, UK) presented the preliminary results of a comprehensive survey of CNV in the human genome, with the aim of identifying all common copy-number variants larger than 1 kb, noting that current surveys covered only 5-10% of CNVs. His team's analysis showed about 1,500 CNVs per comparison when comparing two random individuals. About half of the total number of CNVs identified were located in genes, and fewer than 1,000 covered entire genes.

Laia Bassaganyas (Center for Genomic Regulation, Barcelona, Spain) presented work on structural variation profiles of 12 ethnic groups from the Human Genome Diversity Panel. Differences observed in the copy numbers of a number of genes involved in common disorders suggest a role for these loci in differential disease predisposition among populations. Most significant CNVs involved genes encoding proteins involved in neurophysiological process, metabolic activity, cellular communication and immune response, and those encoding olfactory receptors. Bassaganyas showed large differences in Asian and Mexican populations for acyl-CoA thioesterase 1, which has a role in chemical detoxification.

Several examples of CNV involvement in autoimmune disease were reported. Tim Aitman (Imperial College,

London, UK) described that a low copy number of the CNV spanning the gene for the low-affinity Fc receptor for IgG (*FCGR3B*) is a risk factor for systemic lupus erythematosus and other autoimmune disorders, such as microscopic polyangiitis and Wegener's granulomatosis. John Armour (Institute of Genetics, Nottingham, UK) has analyzed CNV of the beta-defensin genes and its association with psoriasis. Specifically, they presented a linear model in which each additional copy of *DEFB4* increased the risk for psoriasis, supposedly as a precipitating factor that would lead to an inappropriate inflammatory response after an environmental trigger. One of us (XE) presented the identification of a common *LCE3C* (late cornified envelope 3C) deletion as a risk factor for psoriasis. Loss of *LCE3C* or altered expression of *LCE* genes in individuals harboring the deletion might lead to compromised skin barrier function and psoriasis.

Another emerging topic was the new world of regulatory RNA. Deepak Srivastava (University of California, San Francisco, USA) has analyzed the involvement of the micro-RNA miR-1 in the regulation of cardiac development, and its possible implication in congenital heart disease. He presented work showing that expression of the normally muscle-specific miR-1 and miR-133 in embryonic stem cells can help guide these cells into the cardiac muscle lineage. Such a source of cells could be useful in the search for new cardiac drugs.

Roderick Beijersbergen (Netherlands Cancer Institute, Amsterdam, the Netherlands) described the application of various novel large-scale screening methods involving knockdown of gene expression using small interfering RNAs. Beijersbergen and colleagues have used these methods to search for possible new anticancer drugs as well as for genes involved in drug resistance. As an example of the usefulness of this approach they reported the identification of a tumor suppressor gene, *PTEN* (phosphatase and tensin homolog), as a modulator of trastuzumab sensitivity in breast cancer. Christelle Borel (University of Geneva Medical School, Switzerland) presented work on the regulation of miRNA expression. She described an association of miRNA expression with *cis*-regulatory loci in 16% of the miRNAs studied by her team, for example, miR-100 and miR-16. Association of miRNA expression with *trans*-regulatory loci was found in only 5% of the miRNAs analyzed, for example, miR-134 and miR-221.

MicroRNAs are also being associated with genetic susceptibility to some diseases. Johannes Kapeller (University of Heidelberg, Germany) described the identification of a functional allelic variant in a target site for miR-510 in the serotonin type 3 receptor gene (*HTR3E*) associated with irritable bowel syndrome. A reporter assay demonstrated that this allelic variant affected the binding of miR-510 to

HTR3E and he also presented expression studies showing the co-localization of *HTR3E* and miR-510 in enterocytes.

Towards the treatment of genetic disorders

The disease cystic fibrosis can be caused by several different mutations in the *CFTR* gene, which encodes a chloride channel. Eitan Kerem (Hadassah University Hospital, Jerusalem, Israel) reviewed work by his and other labs regarding the therapeutic possibilities for the different types of mutation. These include the possible use of aminoglycoside antibiotics and PTC124, a small-molecule agent that reduces ribosomal sensitivity to stop codons, to suppress premature termination codons, and the use of chemical and molecular chaperons to stabilize protein structure and avoid degradation of the mutant CFTR protein in the endoplasmic reticulum, for example, the rescue of the $\Delta F508$ mutant by CFcor-325. Kerem reminded the audience that the levels of corrected or mutated CFTR that would be required to achieve normal function are not yet clear.

The use of aminoglycoside antibiotics to suppress termination codons was also described by Annie Rebibo Sabbah (Technion, Haifa, Israel) in the context of type 1 Usher syndrome (USH1), a genetic deficiency associated with both deafness and the development of retinitis pigmentosa. Rebibo Sabbah reported up to 91% suppression of nonsense mutations in the gene for protocadherin 15 (*PCDH15*), the gene responsible for USH1, by commercial aminoglycosides in an *in vitro* translation system, as well as suppression of the R245X mutation in cultured cells by these compounds.

Taking an alternative approach to therapy, Alan Verkman (University of California, San Francisco, USA) described the identification of small-molecule inhibitors of CFTR and of activators of the CFTR mutant $\Delta F508$. Verkman and his team have shown that thiazolidinone and glycine hydrazide CFTR inhibitors block enterotoxin-mediated secretory diarrhea in rodent models for CFTR mutations, and that benzothiophene, phenylglycine and sulfonamide potentiators, which are active at nanomolar concentrations, can correct the defective gating of $\Delta F508$ -CFTR chloride channels, restoring wild-type function. These modulators of CFTR function are being explored for the treatment of cystic fibrosis, secretory diarrhea and polycystic kidney disease.

Annemieke Aartsma-Rus (Leiden University Medical Center, Leiden, the Netherlands) described the use of antisense oligoribonucleotides to induce specific exon skipping during pre-mRNA splicing in mouse models of Duchenne muscular dystrophy and thus restore the reading frame, generating partially functional dystrophins like those produced in Becker muscular dystrophy. She also showed that on systemic injection, the antisense oligos are preferentially taken up by dystrophic muscle fibers. The next step will be clinical trials of this approach.

The use of antisense morpholino oligonucleotides (AMOs) to overcome intronic mutations causing aberrant splicing was presented by Eva Pros (Institut Català d'Oncologia, Barcelona, Spain) for mutations in the neurofibromatosis type 1 gene and by Ana Rincón (Centro de Biología Molecular Severo Ochoa, Madrid, Spain) for mutations causing methylmalonic acidemia. The splicing mutations treated generated cryptic 5' splice donor sites, and antisense morpholino oligonucleotides were designed to target these 5' splice sites and promote the use of wild-type splice sites. Antisense morpholino oligonucleotides were transfected into patient-derived cell lines, and, in both cases, the aberrant splicing was reverted and the normal functionality of the protein - neurofibromin or methylmalonyl-CoA mutase (MUT), respectively - was restored.

Yet another strategy for correcting genetic defects is somatic gene therapy. Randy Chandler (National Human Genome Research Institute, National Institutes of Health, Bethesda, USA) described the rescue of a lethal murine model of methylmalonic acidemia using the *MUT* gene in an adenovirus-associated virus 8 (AAV8) vector. After injection of the construct into the liver of newborn pups genetically lacking the mutase, substantial mutase activity was detected, suggesting that gene therapy could have clinical utility in the treatment of this disease.

The many excellent talks and poster presentations at the meeting were enjoyed by the large audience and we look forward to what new advances next year's conference in Vienna will bring.