Our Lady's Children's Hospital
Crumlin, Dublin 12, Ireland
Tel + 353 1 409 6739
Fax + 353 1 456 0953
www.genetics.ie

National Centre for **Medical Genetics**
Ionad Náisiúnta **Gineolaíocht Leighis**
Director: Professor Andrew J Green, MB, PhD, FRCPI, FFPath(RCPI)

Annual Report of the National Centre for Medical Genetics 2005

Compiled by Sally Ann Lynch

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Introduction

The framework, within which this annual report is set, is the Harper report of 1998, commissioned and subsequently accepted by the Department of Health and Children. The Harper report states that the National Centre for Medical Genetics should follow the model of service delivery for other European countries. It recommended that a single integrated genetic service provides for a population of 4 million people. The report recommends that there should be a centralised laboratory service which analyses samples from the whole country, and a clinical service which provides clinics on the basis of need on a "hub and spoke" model, with a central administrative base at the National Centre.

This comprehensive report was produced by the staff of the National Centre for Medical Genetics, and endorsed and adopted by the Director and Laboratory Heads of the National Centre for Medical Genetics. In reading this report, the large increases in workload of all three branches of the Centre since 2000 should be taken into account.

Clinical Section

The National Centre for Medical Genetics offers genetic counselling to all residents of the Republic of Ireland. As a national service, the clinics are free. Patients can be seen privately if requested. We hold clinics in two major paediatric hospitals in Dublin; Our Lady's Children's Hospital, where we are based, and The Children's University Hospital, Temple Street. Peripheral clinics in Cork, Galway and Limerick are held regularly throughout the year. Our waiting times are approximately three to four months for most clinics. Some peripheral clinics have longer waiting times.

We see families with all types of genetic disorders ranging from single gene disorders such as cystic fibrosis, Huntington disease, Duchenne muscular dystrophy, neurofibromatosis through to families with a history of breast or bowel cancer. We are also asked to see many children with birth defects such as cleft lip/palate, cardiac defects, kidney problems and limb anomalies. In addition, a large part of our workload includes seeing children with developmental delay of unknown cause. Our remit is to see if we can make a diagnosis in these difficult cases. Clinical Genetics, as a speciality, involves dealing with both children and adults. Over 50% of our referrals are adults. Historically, Clinical Genetics arose from paediatrics and is still thought of as a paediatric speciality. However, the service had changed and adult genetics disorders such as Huntington disease, Charcot-Marie-Tooth, Spino-cerebellar ataxias and cancer genetics forms an important part of our remit.

At the start of 2005 the clinical team comprised three full time consultants, three full time and one part-time genetic counsellor, three full time and one half time administrative staff. One of the counsellors took maternity leave in February and the vacancy was filled by full-time locum counsellor for a three month period from April-July. We appointed another locum counsellor to help with the increased workload generated over a temporary timeframe following the recommendation of R Elles et al for follow up of Fragile X referrals. This post was financially supported by the University of Galway for a twelve month period and ceased at the beginning of 2006. We appointed two new counsellors at the end of 2005 and one of the successful candidates took up the post with immediate affect having been in one of the locum positions. The other candidate is expected to take up the position in 2006.
We are allocated a Registrar in Paediatrics on a six-month rotational basis at Our Lady's Children's hospital. Their remit is to keep an eye on ward referrals and they also help out in clinics at Our Lady's and at some of the peripheral clinics. At Temple Street, we are allocated a part-time registrar who is also responsible for working as a senior registrar attached to the community paediatric team. This forms part of their paediatric training. We do not, as yet, have a dedicated Senior Registrar training in Clinical Genetics. We are aiming to push this forward as recruitment to consultant posts will remain difficult without in-house training.

Like many other sectors of the Irish health service, we are seriously under-resourced. The UK recommendations are that there should be at least 4 whole-time-equivalent consultants per million of population for both cancer and general Genetics with two genetic counsellors per consultant. In order to be fully staffed we require a further 14-15 extra full-time consultants and a further 28 counsellors. {From RCP consultant physicians working with patients latest version (page 84)
http://www.rcplondon.ac.uk/pubs/books/cpwp/ConsPhys2.clingenetic.pdf }

In Northern Ireland, where there are 1.69 (UK 2001 census) million residents, there are five full time consultants and 6.5 counsellors. In the Republic, we have three full-time consultants and 4.3 counsellors for 4.5 million residents and this inevitably leads to a compromise in the service. We cannot offer joint specialist clinics or even specialist clinics within Genetics unlike our European counterparts. Other activity that is affected by this staff shortage includes allowing time for staff to undertake clinical audit and/or research. This shortcoming was highlighted across all sections of specialities in the recent accreditation process of both OLCHC and Temple Street hospitals.

Although based in Our Lady's Children's Hospital, Crumlin, 50% of our referrals are seen off site. The Harper report recommended peripheral clinics to facilitate families and to help increase the profile of the department so that we truly fulfil our remit to be a National Centre. Our biggest off-site clinical commitment is to Temple Street Hospital where we saw over 400 families in 2005. We also offered approximately 160 appointments to families who were seen at the University Hospital Galway, the Limerick Regional Hospital and St Finbarr's Hospital in Cork. We saw approximately 130 families in each of these three venues in 2005. Unfortunately, we still have a 30% failure to attend and/or cancellation rate. Each appointment is given 45 minutes to one hour. A missed appointment is therefore very costly to our service. Efforts have been made to reduce this following an audit carried out in our department by our genetic counsellor, Debby Lambert.

We also saw a number of sick neonates (>40) in the three Dublin maternity hospitals. Whilst we have a formal arrangement with Holles Street, we do not have the same with the other two hospitals. The split site location of these three hospitals proves problematic. This, together with the split location of the three paediatric hospitals, means that consultant cover can be difficult, particularly when not all three consultants are on duty.
Our genetic counsellors work autonomously within the Centre. The counsellors see families with known genetic disorders such as cystic fibrosis, Duchenne muscular dystrophy and Huntington disease. They also are largely responsible for managing the cancer referrals to the department. They also deal, to a large extent, with urgent requests during pregnancy.
The consultants see individuals referred for help with diagnosis. They would also see children and adults with birth defects. All ward referrals are seen by the consultants. For those referrals that need to be seen by a Doctor, ours is very

much a consultant-led service, the registrars help the initial assessment but the consultants will also need to see the child or adult.

Genetics, as a speciality involves seeing families. Many appointments involve several family members. Therefore, we hold family charts. We also record both the number of appointments and the number of patients seen.

Clinical Activity for the Period From

01/01/2005 To: 31/12/2005

No. OPD Appointments

Attended	2000
Cancelled	453
Not attended	238
Unknown	137
Total	2828

Unfortunately, clinical activity on 137 appointments was not recorded on the genetics database.

No. Patients seen in OPD

Attended	4068
Cancelled	454
Not attended	241
Unknown	150
Total	4913

Unfortunately, clinical activity on 150 patients was not recorded in our database.

Ward referrals 2005	No. patients seen
OLCHC	394
TSCH	97
Holles Street	34
Coombe	27
Rotunda	7

Clinical links with other Genetics departments

We maintain close links with the Genetics department in Belfast. We met on the 15th June 2005 in Dublin. This was one day meeting and involved presentations of audits carried out in both centres plus the days ended with case discussions. This meeting involves both the consultants and genetic counselling staff.

Multi-disciplinary meetings.

We have close links with the dermatology department and had two meetings in 2005 (1/5/2005 & 21/12/2005) for case discussion.

We held an away day at the Conway Institute in UCD in October. The purpose of the meeting was to finalise clinical protocols and smooth out some administrative issues within the department. We invited four outside professionals from three specialities who came to talk to us about issues relating to both their speciality and ours on the day. Vicky Lee a cancer nurse specialist from Tallaght hospital who works with Mr James Geraghty, Consultant Surgeon. She talked to us about setting up a family history clinic from scratch to provide services to the women in her area. We discussed how we can improve the process of referral both from us to the Tallaght team and vice versa.
Dr Fionnuala McAuliffe and Prof Peter McParland talked to us about the foetal assessment unit in Holles street hospital. We discussed a wide range of issues concerning antenatal procedures that they can offer.
Dr Joe Galvin, a cardiologist from both Blanchardstown and the Mater Hospital, talked to us about the management and treatment of long QT syndrome.

The paediatric endocrine department held the first of what shall be regular multidisciplinary meetings in Dec 2005 which Dr Lynch attended.
Prof Green has attended a number of Dublin foetal pathology meetings hosted in rotation by one of the three Dublin maternity hospitals.

Training
First aider Lisa Malone
Access course D Lambert & SA Lynch

Audit
Cliona de Baroid and Claire Gibbons, both genetic counsellors in our department, reviewed the records of families known to our department with Duchenne muscular dystrophy. It was clear that there were a number of females in these pedigrees who were at risk of being a carrier of DMD. At our request, the muscular dystrophy support group highlighted the availability of genetic testing by publishing a paragraph written by us in their information leaflet. We invited any families who were concerned to contact our department for further information and testing if requested.
Debbie Lambert & Sally Ann Lynch looked at the problem of non-attendance at genetic clinics. Debby sent a questionnaire to non-attenders and attenders at our clinic to see what were the barriers to attendance at genetic clinics. It was clear that parents struggle attending multiple appointments for their children with complex disorders. Many other families stated that they did not know who had referred them to the genetics clinic and didn't know what the appointment was for. Others were concerned that they would incur a fee for the consultation.

We re-designed our information leaflets and now include a small business card asking people to confirm or cancel their appointment to reduce the inefficiencies in our system.

Conferences

Conferences attended by staff throughout the year included:
The Irish Society of Human Genetics, Belfast, September
British Society of Human Genetics meetings in March (London) and September (York)
European Society of Human Genetics meeting, Prague May
The 5th International Neural Tube defects meeting, September, USA.
The Association of Genetic Nurses and Counsellors meeting, April London.
The Canadian Association of Genetic counsellors Sept Montreal.

Molecular Genetics Department

The Molecular Genetics division of the National Centre comprised a Head of Department (Dr David Barton), one Principal Scientist (Dr Shirley McQuaid), 2.5 Senior Clinical Scientists, 5 Basic Grade Clinical Scientists and 3 Medical Laboratory Assistants as of January 2005. We were fortunate to be allowed recruit towards the end of the year and in November 2005 we appointed 4 Genetic Technologists.
Requests for molecular analysis have increased exponentially since our inception. We have seen an increase of 133% in sample numbers since 1999. Unfortunately, our staffing numbers have not risen in the same fashion. The Molecular Genetics Laboratory operated a nation-wide service but has been unable to take the extra case load following the closure of the NDC laboratory in Galway. Reduced staff numbers means that there are still serious concerns about the Laboratory's ability to deliver a high-quality, safe service to its users.
We offer molecular testing for eleven genetic conditions; cystic fibrosis, Duchenne muscular dystrophy, Huntington chorea, spinal muscular atrophy, fragile X, haemochromatosis, Angelman syndrome, Prader-Willi syndrome, Friedreich ataxia, uniparental disomy and torsion dystonia (DYT1).
In addition, we extract DNA and act as a send-out service for genetic testing to other laboratories worldwide. We exported close to 1000 DNA samples for molecular testing in 2005 to over 50 laboratories world-wide.

Demand for Molecular Genetics (DNA) testing continued to increase in 2005 with annual sample numbers up 16%. Growth is being seen in all areas of demand, from the high-volume tests such as Fragile X syndrome, cystic fibrosis and haemochromatosis to the lower-volume, high-cost tests such as breast and colorectal cancer syndromes.

Service downgraded as samples are sent abroad for testing
We had to drop tests for several genetic disorders from our in-house service repertoire in 2001 and 2002 because we did not have the resources to maintain them. More than a third of our testing repertoire has now been dropped. These samples are now being sent to UK laboratories, leading to a loss of hard-won expertise from the Laboratory and making us very much less of a National Centre. It is certain that these tests could be performed more cheaply in-house, if the money was used to hire staff instead of paying for testing abroad.
In the past we used to offer testing for myotonic dystrophy, Familial polyposis coli, X inactivation, zygosity testing, UPD for chromosome 11 (one cause of Beckwith–Wiedemann syndrome), hereditary motor and sensory neuropathy, spino-cerebellar ataxias, dentatorubral-pallidoluysian atrophy (DRPLA), spinal bulbar muscular atrophy and breast-ovarian cancer (the latter on a research basis).

Disease	No. of reports issued 2005
Haemochromatosis	747
Fragile X	699
Cystic fibrosis	520
Prader-Willi Syndrome	118
Friedreich ataxia	52
Angelman syndrome	27
Spinal muscular atrophy	20
Duchenne muscular dystrophy	17
Torsion Dystonia	13
Uniparental disomy 7	6
Huntington disease	41

Total Sample Numbers:

Received	Extracted	Sent out	Analysed in house
5327	**4598**	**1385**	**3119**

Send out data
893 samples received in 2005 were sent out for analysis. The disease for which the most common requests for testing were received included:

Disease	Samples exported for testing
Breast cancer genes 1&2	95
Hereditary colorectal cancer	91
Hereditary motor and sensory neuropathy	39
Myotonic dystrophy	38
Spino-cerebellar ataxia	26
Rett syndrome	24
Beckwith-Wiedemann syndrome	23
Mitochondrial disorders	23
DMD (if deletion screen negative)	19
CF (if 11 mutation kit negative)	19
134 other disorders	496

Analysis

NCMG – Fragile X Referrals

As one can see, 699 reports for Fragile X testing were issued in 2005. Dr Liz Donohoe, the scientist working on Fragile X samples, performed an audit to assess the percentage pick up rate of positive cases and compare our figures with other genetic centres. Her results show a very poor pick-up rate of positive

Fragile X cases. It is well known that Fragile X syndrome is not as common as was originally thought. It has now become part of the routine work up in all children presenting with developmental delay despite the fact that many of the samples sent in are from children with features one does not normally associate with Fragile X syndrome such as microcephaly and or malformations. The pick-up rates in the other centres was low but better than our own.

Table 1: Pick-up rates based on samples received on a query affected basis where there was no known family history of Fragile X (L Donohoe)

Year	No. of samples	Positive results
2005	682	25 → 21 Premutations 4 Full Mutations → All rec'd on basis of +ve Family Hx ∴0/551 = **0% pick-up rate**
2004	648	20 → 12 Premutations 8 Full Mutations → 5 with no family history ∴5/648 = **0.8% pick-up rate**
2003	520	7 → 4 Premutations 3 Full Mutations → 1 with no family history ∴ 1/520 = **0.2% pick-up rate**
2002	456	10 → 4 Premutations 6 Full Mutations → 3 with no family history ∴3/456 = **0.7% pick-up rate**

New Diagnosis: Clinical Indications / Referring Clinician

In 2005, no new case of Fragile X picked up.

In 2004, five new cases of Frax picked up.

Case 1 Acute onset of ataxia, encephalopathy, seizures, comatose. Dev delay, ?macro-orchidism, **Referrer:** Consultant Paediatrician
Case 2 Speech delay **Referrer:** Consultant Paediatrician
Case 3 Global Developmental delay, **Referrer:** Cons. Neonatologist
Case 4 Familial developmental delay **Referrer:** Consultant Geneticist
Case 5 Developmental delay **Referrer:** Consultant Rheumatologist

- In 2003, one new case of Fragile X picked up.

Case 1 Speech delay **Referred By:** Consultant Rheumatologist

- In 2002, three new cases of Frax picked up (case 1 excluded, probable FHx)

Case 1 Speech and language delay, probable low IQ, no FHx. **Referrer:** Cons. Child Psychiatrist
Case 2 Atypical Autism, language & intellectual disability, obesity. **Referrer:** Cons. Paediatrician
Case 3 Gross developmental delay, seizures, big head and ears. **Referrer:** Cons. Neonatologist

Table 2: Summary of NCMG Pick-up rates 1995 - 2006

Year	Total no. of samples	New Full Mutations	Pick-up rate (%)
2005	682	0	0
2004	648	5	0.8
2003	520	1	0.2
2002	456	3	0.7
2001	486	4	0.8
2000	412	2	0.5
1999	391	3	0.8
1998	328	4	1.2
1997	288	4	1.4
1996	162	1	0.6
1995	103	2	1.9
Combined Total	**4755**	**29**	**0.6**

External Laboratory Figures:
Positive Fragile X Cases In Patients With No Family History

Newcastle Fragile X Figures

	Sample No.*	Positive results (full expansion)	Pick-up rate (%)
Male	747	7	0.94
Female	197	0	0
Total	944	7	0.74

*Frax Referrals from April 2002 to November 2003

Belfast Fragile X Figures

	Sample No.	Positive results (full expansion)	Pick-up rate (%)
Male	932	13	1.4
Female	233	3	1.3
Total	1166	16	1.4

We are trying to be stricter on acceptance criteria for Fragile X. For example, Asperger's syndrome on its own is not an indication for testing unless there is co-existing developmental delay. It is clear that further education of our referrers is important to highlight those cases that require testing. In contrast, Rett syndrome, due to mutations in MECP2 gene, is probably as common as Fragile X but requests for testing are much lower and the pick up rate much higher. We

sent out 30 query affected samples for testing in 2005 and 7 (23%) were positive. In a further case a “variant” was identified. It was unclear if this was a polymorphism or a mutation.

As part of a data audit required in order to maintain testing and reporting standards, we correlated CFTR mutations in 105 patients with borderline/equivocal sweat test (ST) results, who were referred to the NCMG from 1995 to 2005 inclusive. If not originally provided, ST levels were sought retrospectively for the purpose of the audit. ST levels were thus obtained for 77/105 (73%) of referrals. Forty three percent (33/77) of referrals with “borderline” STs actually had normal levels according to the accepted reference ranges. None of the referrals with normal STs had two CF mutations. Forty five percent of referrals (45%, 35/77) were confirmed to have borderline ST levels. Of these, 77% (27/35) had no mutation, 14% (5/35) had one classic mutation and 9% (3/35) had 2 mutations (one classic and one mild). Twelve percent (12%, 9/77) had ST levels in the diagnostic range. The high proportion of referred “borderline” STs that actually had normal levels indicates a problem with interpretation of, or use of, different guidelines by clinicians. The clinical implication of this audit is that actual ST results should be provided with requests for genetic testing to allow best interpretation of results for the patient. The implications for a genetic testing service are: (1) data audit is required in order to maintain testing and reporting standards (2) ST levels must be sought if not already provided with a referral (3) a ST must be performed before comprehensive mutation screening. The value of extended CF genetic testing in cases of borderline STs is limited as DNA sequence variants found may be difficult to interpret. The identity of mutations is more important for the family than for the patient as the diagnosis of CF is ultimately clinical, based on experience and weight of evidence.

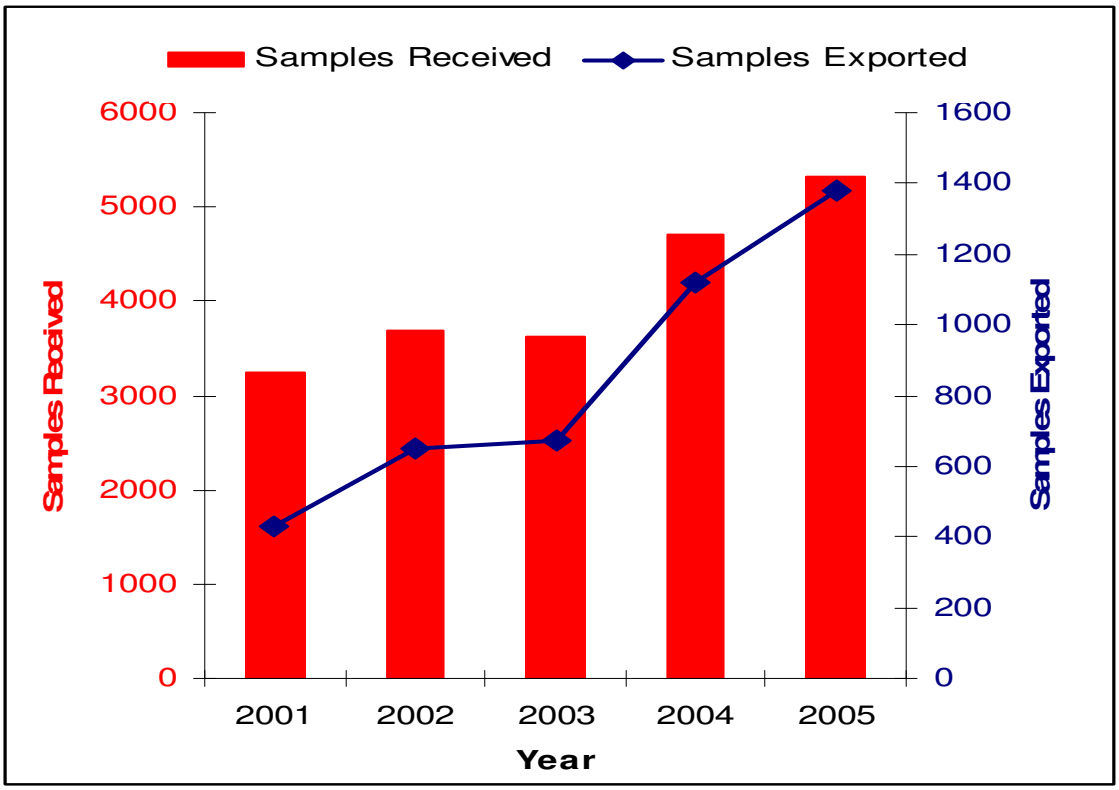
Moving forward:

Despite the chronic staffing issue, some incentives have taken place in order to improve patient sample through-put and reporting times. A new method for CF was investigated, which utilises xMAP Technology together with the Luminex® 100IS bead array platform. The work was conducted in collaboration with Ambion Diagnostics (now Asuragen Inc), Austin, Texas. Aside from increasing the number of mutations screened for from 11 to 25, the method is robust and facilitates greater sample through-put with potential for robotic integration and report generation interfacing. It is hoped to launch the new assay for routine use in 2006. Combined with the introduction of stricter testing criteria for hereditary haemochromatosis in 2003, streamlining of sample processing and reporting this year, should result in decreased reporting times while the same new technology being introduced for CF was assessed for use with haemochromatosis also. Further assay development work is planned for 2006. An improved bisulphite modification kit is being validated for PWS/AS which should allow mosaicism to be detected and make the overall procedure quicker and easier. With the intake

of new staff in late 2005 and 2006, it is hoped to develop and introduce MLPA (multiplex ligation-dependent probe amplification) technology for DMD/BMD. This will allow all 79 exons of the dystrophin gene to be analysed, SMN copy number to be ascertained and facilitate carrier testing for both disorders which has previously been sent out to UK laboratories. MLPA has application in many other dosage related disorders so extension of this technology to these disorders should follow pending staff allocation and resources. This would enable us to take back some of the disorders previously tested for in-house. Assessment of a kit for detecting maternal contamination of CVS and amniocyte samples is also proposed for 2006.

Trends and responses

The dramatic increase in sample numbers observed between 2001 and 2005 is illustrated below:



Conferences

Conferences attended by staff during the year included:
The Irish Society of Human Genetics, Belfast, September
Clinical Molecular Genetics Society, Salisbury, April
British Human Genetics Conference, York, September
European Society of Human Genetics meeting, Prague May
European Cystic Fibrosis Conference, Crete, June
American Society of Human Genetics, Salt Lake City, October (Who?)

Cytogenetics Department

The Harper report recommended that genetic laboratory services be provided on a fair and equal basis to all clinics throughout Ireland. Despite being a National service, the Cytogenetics department serves the Eastern half or the Republic of Ireland; the laboratories are not staffed adequately to enable them to serve the entire nation, much to our regret.
We have been unable to provide services to a number of hospitals that have requested that the National Centre for Medical Genetics analyse samples for constitutional cytogenetic abnormalities from their patients. These include Galway Regional Hospital, Tralee General Hospital, Cavan General Hospital, Limerick Regional Hospital, St Finbarr's Hospital, Cork and Wexford General Hospital. Up until 2005 a private laboratory operated on the NUI Galway campus. This has now closed. Samples from these hospitals are being analysed by private laboratories abroad, at additional cost to the health boards concerned. To provide a National service to include these hospitals would require an additional senior clinical and an additional basic grade clinical scientist, as well as equipment, and approximately 10sqm of additional laboratory space.

Rod Howell took up his position as head of the Cytogenetic department at the start of January 2005. He joined us from Bristol, UK. The haematology section of the cytogenetic laboratory moved towards a national service from June 2005. This has been a great achievement. Towards the end of 2005, we were allowed employ a number of new scientists and laboratory technicians and we hope to improve the service including bringing down reporting times from what it has been.
We receive a range of tissue for analysis including blood, marrow, skin biopsies, amniocytes and chorionic villus biopsies.
There is also an increasing demand from all of the maternity hospitals, especially in Dublin, for rapid interphase FISH testing to allow rapid diagnosis of trisomy in babies with multiple malformations. Such analysis currently has to be sent abroad, although the technology could be implemented in the NCMG, with additional resources. The provision of this test would require one additional clinical scientist.
The Association of Clinical Cytogeneticists (ACC) in the UK carried out a study (July 2000) and gave the following annual average workload per member of staff (unweighted and **excluding FISH**) as follows:

Constitutional samples workload 258 samples
Leukaemia samples workload ★ 186 samples

It is important to note that these workload figures include all members of staff and is not representative of an individual's analytical workload, which will be much higher in many cases. In practice, the proportion of time that a member of staff can allocate to analysis will depend on the organisational requirements of the laboratory. It will not be evenly distributed between different grades of analyst.

There are also limits on attention span and also on the length of time over which visual acuity, and hence accuracy, can be sustained.
★ *This applies to specialist leukaemia laboratories.*

With the upsurge in FISH activity which is not included in the ACC workload figures; there is clearly a requirement for additional clinical scientists at both Basic and Senior grades. To include the total constitutional workload from the Galway region alone will require an additional 30% in staffing.

Cytogenetics, achievements 2005
RH March 2006

2005 Activity

Total samples		**abnormal**
Blood	3102	254
Bone marrow	1526	316
Haem. Blood	156	9
Amniotic fluid	214	51
CVS	88	15
Tissue	129	
Other samples	90	
Total	5305	

FISH tests

Total constitutional and oncology **886**

Microdeletions	***total***	***abnormal***
22q	258	14
Prader Willi	71	3
Williams	20	1
Miller D/Smith M	15	1
Wolf H	11	0
1p36	11	0
Kallman	9	1
Steroid sul	6	4
Angelman	4	1
Cri du chat	4	0
2q	2	0
Total microdels	411	25

Multitelomeres	39
Other tests	65
Total constitutional	**515**

Oncology	
BCR/ABL	112
X/Y	61
MLL	47
TEL/AML1	28
IgH (alone or combi)	25
CLL2	22
CLL1	19
7q	14
CBFB	13
AML1/ETO	12
TLX3	4
SIL/TAL	4
E2A	4
PML/RARA	3
Others	3
Total oncology	**371**

New work

Until May 2005 the oncology service did not cover the whole country. The service was only national for seven months. Since then the mean weekly number of samples has been about 40, so the projected oncology activity for 2006 is approximately 2100 samples

Staffing

Recruitment of 1 senior scientist, 3 basic grade scientists, and 3 MLAs brings the total establishment to 29.4 staff, comprising 23.8 scientists, 5 MLA, and 0.6 technical analyst

All staff received an appraisal / performance review in 2005

Training

The department was visited by representatives of the Shire Management computer system, and a number of staff received training and updating in use of the system.

Q-pulse training was delivered by an external consultant

Two staff (AD and HOS) involved in quality management attended an advanced Word course

AM was given the role of Cytovision manager and visited Applied Imaging in Newcastle for two days intensive training

JK, ZA, MS received training to become qualified First Aiders

RH attended the OLH Management training course

Conferences attended by staff include

- EuroGentest information management, Leuven (AD)
- BSHG, York (RH)
- CML update meeting (CB, SMcC, SR)
- European Cytogeneticists, Madrid (AD, SL)
- UKCCG, London (PC, SMcC)
- Mol diagnostics in acute leukaemia, Rotterdam (JK, HOS)
- Leukaemia Research fund study Day (CB)
- Microarrays in haematology, Portugal (JK)
- European myeloma network (JK)
- NCRI annual review of leukaemia (JK)

Quality issues

The laboratory participated in the UKNEQAS EQA scheme with full compliance and satisfactory performance in all areas of prenatal, postnatal and oncology assessment

An Incident Logging system was introduced. Incidents are regularly discussed at laboratory meetings and an annual report was circulated to all staff. 133 incidents were reported including 19 that resulted in an incorrect report leaving the department

New equipment

- Hybrite FISH processing system
- Flat screens replace old monitors on three Cytovision stations
- Cytovision server
- Class 1 Safety Cabinet
- Charcoal filter workstation for slide making
- 5 new analytical microscopes
- Prep room microscope
- 2 second-hand microscopes for Prep room, gifted from Birmingham
- Coulter cell counter

Scientific staff undertook trials of cytogenetics slide-making apparatus from Euroclone and Hanabi with a view to the possibility of purchase at a later date

Building works

Revisions to benching have permitted more staff to be accommodated

Installation of wash hand basins and the Class 1 hood, and revisions to benching mean that the main culture room (Cyto2) now operates to full category 2+ standard and is thus CPA compliant for the type of culture work undertaken

Laboratory Accreditation for the National Centre for Medical Genetics

A priority for the laboratory is the acquisition of laboratory accreditation. As a national centre, the National Centre for Medical Genetics must be internationally recognised, and provide a service of the highest standard. Laboratory accreditation is an essential part of ensuring national and international standards in the Centre. As in all laboratories, there is a considerable amount of work that needs to be done to establish standards, and prepare both laboratories for accreditation by the UK CPA organisation. To that end, a plan for such accreditation was established and it has been submitted for funding. In addition to the new recruits recently appointed, permanent scientific staff will be needed, upon attaining accreditation, as a Quality Manager / Training Officer / Health & Safety Officer per laboratory (total of two permanent posts) to maintain accreditation status and fulfil CPA requirements. These posts would start upon accreditation, and would be a necessary part of accreditation.

Administrators

There are 7½ administrative staff based at the National Centre for Medical Genetics - this is divided between the Clinical section (where Consultants see patients) and the genetics laboratory.
During 2005 2 fulltime administrators were employed – one to assist the genetic counsellors in their service and the other in the genetics laboratory. These positions arose following the increase in referrals to the unit for genetic cancers and the influx of Clinicians in house and an increase in outside providers requesting genetic testing on children and adults.
Liam Farrell joined us from Human resources in the summer of 2005 as a business manager. His was a welcome addition to an increasingly busy department.
On the clinical side 3 administrators works with and is responsible for the workload of a Genetic Consultant and genetic counsellor. The other 2 work administrators work with and for a team of genetic counsellors. There would also be a lot of telephone queries into our centre.
Our centre is expanding rapidly it is essential that we continue our education. We hope to have an Education co-ordinator support person who will be drive the training and education forward in the department. We hope to have training in Microsoft Access and the other computer packages by the end of the year. One of our administrative team has been on a specialised training course in Cyrillic Pedigree Drawing – which would assist the Consultants and Genetic Counsellors in collating genetic information on computers using graphics e.g. drawing of family trees etc.
Another part of our team is seeking to work on our website. We are hoping training courses in desktop publishing and web design will be sanctioned shortly.
Another one of our administrative staff will be pursuing an in house management course in 2006.
Due to the continuing increase in new staff members to both laboratories during the year a committee was set up which worked on an induction package. This was introduced in 2005. This has taken place twice over the past six months and has been very successful. The new staff members gain an overall awareness of what takes place in the other areas of the department and the hospital as a whole.

Departmental groups:

We have a number of multidisciplinary groups within our department. These were set up as a mandatory requirement of the accreditation process.

Management/Accreditation Group.

The remit of this group is to monitor the Centre's growth and development. The group, which meets monthly, is made up of senior representatives from all three sections. The group contributes to the service plans that are submitted on an annual basis. A representative from the other groups, (Health & Safety, Training and Education, Quality), contribute any outstanding issues. Monthly statistics from each section are submitted and discussed. Staffing issues are also discussed.

Health and Safety

The remit of this group is to implement health and safety procedures to ensure that there is a safe working environment in accordance with current safety guidelines and legislation. The group meets monthly and is comprised of staff from all three divisions, across all grades. Health and safety issues are discussed and procedures for all aspects of safety (e.g. fire, major spillages of dangerous chemicals or clinical material, reporting and monitoring of accidents and incidents, risk assessments etc) are developed and implemented.

Training and Education
The remit of this group is to facilitate and enhance activities within the department relating to initial staff training and ongoing education. As Medical Genetics in a dynamic and rapidly expanding discipline maintaining professional development activity is fundamental to ensuring a high standard of patient care. The group meets once every 2 months and is comprised of staff from all three divisions, across all grades. The group considers issues arising in relation to the travel and training budget, induction & training programmes for new staff, ongoing staff training procedures, IT training, library & journal access, Journal Clubs, seminar programmes, research & development, access to scientific meetings, clinical/laboratory liaison meetings, MRCPath training, continuing professional development, staff appraisal and relationships with HR. All staff members were initially given an opportunity to express their training and education concerns and comments via a questionnaire. Initiatives which have been successful this year include the implementation of a journal club for the molecular genetics division, Clinical Laboratory liaison meetings (detailed below under education) and piloting of an induction program for new staff. We plan in 2006 to introduce an induction day for all new staff which would give an overview of the divisions within the department, introduce them to issues relating to health & safety, training & education and quality. We also plan to educate our users more so that accessing the service can be more effective.

Quality
The remit of this group is to and establish and oversee the implementation of a quality management system in a way that is sympathetic to attainment of CPA laboratory accreditation. The group ensures that all procedures and practices comply with international standards and guidelines, and that substantiating documentation exists. The group has established policies and procedures for document preparation, review and revision, and control.

Education

Clinical/laboratory liaison meetings
We held the first Clinical/laboratory liaison meeting in May 2005 and had three in total in 2005. The aim of these meetings was that ongoing audits or any research and developmental projects within a section of the NCMG could be discussed throughout the department. These meetings were enthusiastically received by all staff members as they give a forum for discussion across the different disciplines. The structure involves one member of each of the sections presenting an interesting topic for 15 minutes. We have tried to have a common theme at most meetings. They have stimulated interesting debate and also encouraged people to start similar projects within their own section. The titles of the talks given at these three meetings are listed below:

15th June 2005
Clare Gibbons & Cliona deBaroid - Clinical audit of Duchenne Muscular Dystrophy families
Linda McArdle & Adam Dunlop - Cytogenetic case presentations for Iso Y
Liz Donohue - Molecular case study of a female with a full expansion & premature ovarian failure

22nd September 2005
Theme: Sub-telomeric rearrangements in patients with Mental retardation
Sally Ann Lynch - Overview of the patient group
Marice Mullarkey - Cytogenetics FISH update

Sean Ennis - MLPA update

14th December 2005
Trudi McDevitt - Incidence of BRCA1 & BRCA2 mutations in Irish Breast Cancer Families
Nuala Cody – Cancer families from the Counsellor's perspective

Teaching

We have a broad teaching remit in the Department. Professor Green holds a UCD contract. Sean Ennis is also employed by UCD and so both are committed to teaching UCD students. Prof Green also lectures to both RCSI and TCD students.
Dr David Barton
- UCD Pathology module for Medical Students, Genetics Tutorial
- UCD Pathology module for Medical Students, Lecture on Molecular Genetics Diagnostic Tests
- TCD MSc in Molecular Medicine, Lecture on Triplet Repeat Disorders

Dr Caitriona King- UCD Pathology module for Medical Students, Genetics Tutorial
Dr Trudi McDevitt – UCD Pathology module for Medical Students, Genetics Tutorial
Dr Alana Ward- UCD Pathology module for Medical Students, Genetics Tutorial
Dr Shirley McQuaid - UCD Pathology module for Medical Students, Genetics Tutorial
Dr Sally Ann Lynch. MRCP Paediatric teaching to post-graduate students in Temple Street.
Dr Sally Ann Lynch Teaching commitment to NCHDs, Temple Street
Prof Andrew Green Teaching commitments to Medical students in UCD, RCSI and TCD.
Dr Sean Ennis. Teaching commitments to Medical students in UCD.
Ms Rose Kelly. Tallaght hospital Paediatric nursing students & midwifery students in Holles Street
Ms Cliona deBaroid. Midwifery students Coombe hospital & paediatric nurses OLHSC.
Debbie Lambert. Paediatric nurses Temple Street hospital
Ms Nuala Cody. Higher diploma in oncology Mater hospital,
Nuala Cody Irish cancer society Annual support group meeting Dublin
Ms Debby Lambert: Paediatric Nurses Temple Street Hospital. Graduate Nurses' course in Inherited Metabolic Disease, Temple Street Hospital.
Ms Debby Lambert. National PKU support group planning meeting.
Ms Debby Lambert. MSUD national support day.

Audit

1. Debby Lambert & SA Lynch. Improving the failure to attend rate in Genetics.
2. Dr Caitriona King, An Audit of Genotypes and Borderline Sweat Tests in CF.
3. Cliona de Baroid/Claire Gibbons. Duchenne Muscular Dystrophy families known to NCMG.
4. Rodney Howell. An audit of failed blood samples and transit time, Jan - Aug 2005.
5. Adam Dunlop. An audit of specimen reception and receipt data, Jan – Aug 2005.

Oral Presentations

1. Incidence of BRCA1 and BRCA2 Mutations in Irish Breast Cancer Families. T. McDevitt, B. O'hIci, N.Cody , M. Adams , N. Miller, W.Ormiston, E.Berkeley , C.Nolan, R. Clarke; P.A.Daly

E.McDermott, D.E.Carney A.J.Green, D.E.Barton[1,2]. Irish Society of Human Genetics, Belfast Sept 2005
2. The Complexity of Hereditary Non-Polyposis Colon Cancer (HNPCC) Diagnosis in the Irish Population. Solvig Roring, Shirley McQuaid, D Grehan*, J O'Brien*, Michael McDermott*, David Barton and Andrew Green. Irish Society of Human Genetics, Belfast Sept 2005
3. Elizabeth Donohoe, Workshop on Fragile X Syndrome, BSHG Annual Conference, York, 2005
4. Dr Sally Ann Lynch Cephalocoele in Oculoauriculovertebral spectrum (OAVS). Neural Tube Defects Meeting. Palm Springs, California, USA
5. Dr Caitriona King; Genotypes & Borderline Sweat Tests: The NCMG Experience, Temple Street Grand Rounds Dec 2005
6. Dr Caitriona King, Luminex-based Cystic Fibrosis Assays, European CF Conference Crete June 2005
7. Debby Lambert. Why do people fail to attend Genetics clinics? Temple Street Grand Rounds
8. Dr David Barton: EU Policy Forum on Genetic Testing, European Commission, Brussels, 9 March, 2005
9. Dr David Barton: First International Meeting on Clinical and Laboratory Genomic Standards in Paris, May 2005
10. Dr David Barton: Workshop on Quality Control in Genetic Testing at the European Society for Human Genetics Conference in Prague, May 2005
11. Dr David Barton Workshop on Cystic Fibrosis at the European Society for Human Genetics Conference in Prague, May 2005: "Survey on Commercial Assays for Cystic Fibrosis Testing"
12. Dr David Barton: European Commission IVD Technical Group, Brussels, June 2005
13. XIX International Congress of Clinical Chemistry on "Quality Networks for Genetics Testing: A European Perspective" Orlando, July 28, 2005
14. Dr David Barton: Meeting at Life Knowledge Park on the use of telomerase technology to produce Reference Materials for genetic tests Sept 30, 2005
15. Stephen Lalor, Louise Gallagher, Geraldine Kearney, Michael Fitzgerald, David E Barton, Andrew J Green, Michael Gill and Sean Ennis. Mutation screening of a break-point candidate gene for autism, UBE2E3, on chromosome 2q31.3. Conway Institute opening Festival, Sept 2005

Meetings organized:
Dr David Barton
Workshop on Fragile X Syndrome PCR at BSHG meeting, York, September 2005
International Symposium on Reference Materials for Genetic Testing, Geel, Belgium, November 2005
OECD Expert Group on Genetic Test Results Reporting, Washington, DC, 19 September, 2005

Administrative research activities

Ennis S.
DMMC (Dublin Molecular Medicine Centre) SAC (Scientific Advisory Committee) review talk of collaborative scientific activities within the NCMG/UCD site.
Co-coordinator of the Irish Autism Genetics Collaboration (IAGC)
Shared IAGC representation on the Executive Committee of AGP International Autism Genome Project
Sat on the Committee of Senior Investigators (CSI) for the AGP International Autism Genome Project
Member of the Molecular Committee of the AGP International Autism Genome Project

Poster presentations

1. C. King, T. McDevitt, T. Yeomans, D. Barton, A Luminex-based Cystic Fibrosis Assay, Irish Society of Human Genetics, Belfast Sept 2005
2. T. McDevitt, C. King, B. O'hIci, S. McQuaid, C. Le Maréchal, C. Férec, D. E. Barton. Increasing complexity of the CF mutation spectrum in the Republic of Ireland, Irish Society of Human Genetics, Belfast Sept 2005
3. Elizabeth Donohoe, DM Lambert, DE Barton and C Clabby. Expansion of the Fragile X Phenotype, British Society of Human Genetics, York, Sept 2005 & Irish Society of Human Genetics, Belfast Sept 2005.
4. T. McDevitt, C. King, T. Yeomans, B. O'hIci, A. Butler, D. Barton, Luminex-based Cystic Fibrosis Assays, ESHG Conference, Prague, May 2005 and European CF Conference Crete June 2005 and HUGO Mutation Detection Symposium Santorini May 2005
5. D Lambert & SA Lynch. Why do people fail to attend Genetics clinics? British Society of Human Genetics, York, England Sept 2005 & Irish Society of Human Genetics, Belfast, Northern Ireland Sept 2005
6. Analysis of sub-telomeric aberrations suspected in unknown causes of mental retardation via Multiplex Ligation-dependent Probe Amplification (MLPA). Robert J. Goldsmith[1, 3], Sean Ennis[1, 2] and Sally-Ann Lynch[1] Irish Society of Human Genetics, Belfast, Northern Ireland Sept 2005
7. Accuracy of a Clinical Diagnosis of Marfan Syndrome. AM Murphy, SA Lynch, AJ Green* Irish Society of Human Genetics, Belfast, Northern Ireland Sept 2005
8. Quality assurance of novel diagnostic technologies: a collaborative effort towards the generation of "generic SOPs" for DHPLC analysis. Matthijs G, Dequeker E, Schollen E, Michils G, Vankeirsbilck B, Harvey J, McQuaid S, van Schooten R, van den Akker E, Merle O, Schrooten S, Clark S. American Society for Human Genetics, Salt Lake City, Oct 2005 & European Society for Human Genetics, Prague, May 2005
9. Greenway M, Russ C, Ennis S, Traynor B, Green A, Brown RH, Hardiman O. Hypoxia-inducible genes in motor neuron degeneration. Biochemical Society 2005
10. Greenway M, Ennis S, Green A, Hardiman O. Association of the H63D polymorphism in the hemochromatosis gene with sporadic ALS. Proceeding of the Irish Neurological Association 2005
11. Hughes J, Clark A, Geoghan O, O'Toole J, Hendroff U, Rogers Y, Walsh O, O'Regan M, Stetson C, Lambert D, Yap S, Manning R, Treacy E. A study on Outcomes in Siblings with Classical Galactosemia in Ireland. SSIEM 2005

External Quality Assessor

Dr Shirley McQuaid - Assessor for European Molecular Quality Network HNPCC scheme
Dr Shirley McQuaid – Scheme Organiser UK NEQAS
Dr David Barton - Scheme Organiser for European Molecular Quality Network Hereditary Friedreich Ataxia scheme
Dr Caitriona King – Assessor for European Molecular Quality Network Hereditary Haemochromatosis scheme

Publications by National Centre for Medical Genetics Staff

1. Developing a Sustainable Process to Provide Quality Control Materials for Genetic Testing.
   Chen B, O'Connell CD, Boone DJ, Amos J, Beck JC, Chan MM, Farkas DH, Lebo RV, Richards CS, Roa BB, Silverman LM, **Barton DE** *et al.* Genetics in Medicine 7(8): 534-549, 2005
2. Fragile X-associated tremor/ataxia syndrome presenting in a woman after chemotherapy
   O'Dwyer JP, **Clabby C**, Crown J, **Barton DE**, Hutchinson M. Neurology 65: 331-33, 2005
3. Reference Materials for Human Disease Molecular Genetic Test Kits:
   Overcoming 'black box' Diagnostics. **Barton DE**, Klein C, Dequeker E. Bioworld Europe, 2005

4. Uroplakin III Is Not a Major Candidate Gene for Primary Vesicoureteral Reflux. **Kelly H, Ennis S**, Yoneda A, **Bermingham C** , Shields DC, Molony C, **Green AJ**, Puri P, **Barton DE**. European Journal of Human Genetics 13:500-502, 2005
5. Quality Control in Mutation Detection. **Barton DE** *in* Guide to Mutation Detection, Taylor GR and Day INM eds, Wiley, Hoboken, New Jersey, 2005 pp75-78
6. Certified Reference Materials for Genetic Testing **Barton DE**, Stacey G, Klein C. in Encyclopaedia of Medical Genomics & Proteomics, Dekker, New York, 2005 pp226-231
7. Denaturing High Performance Liquid Chromatography (DHPLC) using the WAVE DNA Fragment Analysis System **E Donohoe** *in* Hypertension: Methods and Protocols, Fennell, J.; Baker, A. H. eds., Humana Press inc. 2005, chap 13, pp173-187
8. **Lynch SA.** Non-multifactorial neural tube defects. Am J Med Genet C Semin Med Genet. 2005 May 15;135(1):69-76.
9. Myers A, Kay LJ, **Lynch SA**, Walker DJ. Recurrence risk for psoriasis and psoriatic arthritis within sibships. Rheumatology (Oxford). 2005 Jun;44(6):773-6. Epub 2005 Mar 9.
10. Bond J, Flintoff K, Higgins J, Scott S, Bennet C, Parsons J, Mannon J, Jafri H, Rashid Y, Barrow M, Trembath R, Woodruff G, Rossa E, **Lynch S**, Sheilds J, Newbury-Ecob R, Falconer A, Holland P, Cockburn D, Karbani G, Malik S, Ahmed M, Roberts E, Taylor G, Woods CG.The importance of seeking ALMS1 mutations in infants with dilated cardiomyopathy. J Med Genet. 20105 ;42(2):e10.
11. 3'CBFB deletion associated with inv(16) in acute myeloid leukaemia. **Kelly J**, Foot NJ, Conneally E, Enright H, Humphreys M, Saunders K, **Neat MJ**. Cancer genetics and cytogenetics 162 (2005) 122-126.
12. Schollen E, Dequeker E, **McQuaid S**, Vankeirsbilck B, Michils G, Harvey J, van den Akker E, van Schooten R, Clark Z, Schrooten S, Matthijs G; DDQA Collaborative Group. Diagnostic DHPLC Quality Assurance (DDQA): a collaborative approach to the generation of validated and standardized methods for DHPLC-based mutation screening in clinical genetics laboratories. Hum Mutat. 2005 Jun;25(6):583-92.
13. Stephen Lalor, Louise Gallagher, Geraldine Kearney, Michael Fitzgerald, **David E Barton, Andrew J Green**, Michael Gill and **Sean Ennis**. Mutation screening of a break-point candidate gene for autism, UBE2E3, on chromosome 2q31.3. Ulster Med. J. 2006: 75(1) 97-107.
14. Robert J. Goldsmith, **Sean Ennis** and **Sally-Ann Lynch**. Analysis of subtelomeric aberrations suspected in unknown causes of mental retardation via Multiplex Ligation-dependent Probe Amplification (MLPA). Ulster Med. J. 2006: 75(1) 97-107.
15. Conroy J, Cochrane L, Segurado R, Meally E, **Green A, Ennis S**, Gill M and Gallagher L. Further evidence supporting the role of ITGA4 as a candidate gene for Autism. Am. J. Med. Genet. 2005 Sept 138B (1) 66
16. **Matthew Greenway**, Peter M. Andersen, Carsten Russ, **Sean Ennis**, Susan Cashman, Colette Donaghy, Victor Patterson, Robert Swingler, Karen E. Morrison, **Andrew Green**, K. Ravi Acharya, Robert H. Brown Jr & Orla Hardiman. The genetics of VEGF and Angiogenin. European FALS Group Meeting 7 Dec 2005
17. Russ C, **Greenway M, Ennis S, Green A**, Swingler R, Hardiman O and Brown Jr RH. Analysis of Vascular endothelial growth factor (VEGF) haplotypes and risk for ALS in North American, Irish and Scottish populations. ALS and other motor neuron disorders 2005:6 Suppl 1; 83
18. **Greenway M**, Russ C, **Ennis S**, Cashman S, Neng L, Raman V, Anderson P, **Green A** and Hardiman O. Segregation of the TAU haplotype in ALS. ALS and other motor neuron disorders 2005:6 Suppl 1; 50.
19. Dolan C, Shields DC, Stanton A, O'Brien E, **Lambert DM**, O'Brien JK, Treacy EP. Polymorphisms of the Flavin containing monooxygenase 3 (FMO3) gene do not predispose to essential hypertension in Caucasians. BMC Med Genet. 2005 Dec 2;6:41
20. Interstitial deletion of chromosome 21q and schizophrenia susceptibility. Murtagh A, McTigue O, **Hegarty AM**, **Stallings RL, Green AJ**, Ramsay L, Corvin A. Schizophr Res. 2005 May 23
21. SALL1 mutation analysis in Townes-Brocks syndrome: twelve novel mutations and expansion of the phenotype. Botzenhart EM, **Green A**, Ilyina H, Konig R, Lowry RB, Lo IF, Shohat M, Burke L, McGaughran J, Chafai R, Pierquin G, Michaelis RC, Whiteford ML, Simola KO, Rosler B, Kohlhase J. Hum Mutat. 2005 Sep;26(3):282.
22. Genetic Conditions in the Irish Roma Gypsy Population **S O'Connell**, K Butler, J McMenamin, M Waldron, **AJ Green** Irish Medical Journal 2005 98 (10)