



## **Preface**

The Y Chromosome Consortium Newsletter is a forum for communicating progress in the field of evolution of the human Y chromosome. In particular, this Newsletter contains regular updates of the YCC Repository, the YCC Database and other information relevant to Y chromosome evolution (polymorphisms, participants, recent publications, meetings, etc.). The YCC Newsletter is published twice a year. The Editors welcome the submission of letters, research reports, brief communications and other materials suitable for publication in the YCC Newsletter. The next publication deadline is December 1, 1994.

The Y Chromosome Consortium is a group involved in a collaborative effort to study genetic variation on the human Y chromosome. We have i) established a repository of lymphoblastoid cell lines (the Repository) derived from individuals who represent populations from all inhabited continents and ii) we will provide DNAs isolated from these cell lines to investigators searching for polymorphisms on the Y chromosome; iii) the results of typing the same set of DNAs at many Y-specific loci will be pooled into a common database (the Database), in a similar fashion to the CEPH international collaboration.

### Editorial Offices

TUCSON: Department of EEB, Biosciences West, University of Arizona, Tucson, AZ 85721

Tel. (602) 621-9828; Fax: (602) 621-9190.

Editor: Michael F. Hammer

NEW YORK: New York Blood Center, 310 East 67th Street, New York, NY 10021

Tel. (212) 570-3075; Fax: (212) 570-3195

Editor: Nathan A. Ellis

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## RESEARCH INTERESTS

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Research Interests is a feature of the YCC Newsletter wherein different investigators report their research plans and activities. The editors welcome contributions to this section of the newsletter for publication in the next edition of the YCC Newsletter. Please submit by December 1, 1994.

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### Reports

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#### *Report from Mark Jobling and collaborators*

Our interests fall into four areas, all under the broad heading of the isolation and analysis of novel markers for human Y chromosome variation.

- Y-specific minisatellites as digital markers for human Y chromosomes. Minisatellites vary not only in the number of repeat units within an array, but also in their sequence. This variation can be accessed by minisatellite variant repeat PCR (MVR-PCR; 1), which maps the positions of variant repeats within an array, and thus provides a digital DNA typing system. MVR-PCR at autosomal loci reveals an enormously high degree of variability, and has allowed the details of mutation processes to be investigated, showing the importance of interallelic exchange (2). Y-specific minisatellites would be powerful markers for paternal lineages, since they should have many alleles, which can be typed by PCR, and should allow direct investigation of mutation rates and processes by small-pool-PCR in sperm DNA (2). We have identified and characterized an AT-rich minisatellite, MSY1, lying in interval 3 on Yp. Alleles have between 60 and 100 repeats of 25 bp length, which exist in at least 5 variant forms; MVR-PCR at MSY1 shows a high degree of allele diversity. Population studies will use chromosomes studied elsewhere (3,4) as well as samples of Caucasian, Japanese, Malaysian, African, Afro-Caribbean, Surui, and Karitiana origin. A search for Y-specific classical GC-rich minisatellites is also being made, by screening a Y-specific cosmid library with minisatellite core sequences, followed by the exclusion of pseudoautosomal loci, which are not of interest.

- Isolation of Y-specific microsatellite loci by hybridization selection. We are using an efficient hybridization selection strategy (5) to isolate highly informative tri- and tetranucleotide repeat loci from pooled Y-specific cosmid library DNA (with John Armour, University of Leicester).

- Complex polymorphisms of interval 6E of Yq. Interval 6E of Yq is particularly rich in families of chromosome-specific repeats, which are associated with a high degree of polymorphism, including the 49a/f polymorphisms, and deletions encompassing the 50f2/C locus (4). We are studying the population distribution and molecular basis of these deletion polymorphisms; an understanding of these phenomena may also be helpful in defining the roles of genes in this region which are thought to be important in spermatogenesis (6) (with Chris Tyler-Smith, University of Oxford).

- Molecular phylogeny of dispersed low-copy repeat loci of the Y chromosome. The Y is rich in dispersed low-copy repeat sequences, some of which have homologues on autosomes or the X chromosome - the loci detected by 50f2 (DYS7) are good examples. We are using PCR-based cloning and sequencing to investigate how such sequences are related together, with the aim of understanding how they arise and are propagated.

Mark A. Jobling, Neale Fretwell, Nourdine Bouzekri, Barbara Bernasconi, Gabriel A. Dover & Alec J. Jeffreys, Department of Genetics, University of Leicester

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*Report from Chris Tyler-Smith and collaborators*

We have been analyzing the DNA structure of the Y chromosome for several years in order to identify the sequences required for a human centromere. When we investigated the long-range structure of the centromeric alphoid satellite DNA array we discovered an enormous amount of variation in array size and in the presence or absence of some internal restriction enzyme sites. This led to a more general interest in Y chromosome DNA polymorphisms and evolution, and to the work of Rebecca Oakey and Neal Mathias. Currently, our work is directed towards examining as wide a selection of Y chromosomes as possible and looking for new polymorphisms. Specific projects include:

- Mongolian Y chromosomes. High molecular weight DNA was prepared in Ulaanbaatar from 49 Mongolian males and is now being analyzed in Oxford by T. Gerelsaikhan (with B. Dashnyam, Mongolia; Elizabeth Robinson, UK).

- Development of PCR assays for Y alphoid polymorphisms (with Fabricio Santos, Brazil).

- Analysis of deletion/duplication polymorphisms in Yq (with Mark Jobling, UK).

Chris Tyler-Smith, University of Oxford, Oxford, England

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*Report from Michael Hammer and collaborators*

Our research has focused on identifying polymorphisms that are informative for reconstructing phylogeny (i.e., point mutations and small insertion/deletions).

- Determine nucleotide diversity levels on Y chromosome by DNA sequencing. One question of interest is how diversity levels on the Y chromosome compare to other genomic components such as the X chromosome, autosomes, and mtDNA. A 2.6 kb region of the long arm (YAP region) has been sequenced in 16 humans. Four polymorphic sites have been identified in this region: an Alu insertion with variable length poly-A tail, and 3 nucleotide site polymorphisms.
- Score polymorphic sites in YAP region in worldwide populations, construction of Y-haplotypes and evolutionary trees (with Trefor Jenkins, Andrea Novelletto, Satoshi Horai, John Mitchell, Chris Tyler-Smith, Mark Stoneking and Shinji Harihara).
- Search for new polymorphic sites using PCR and mutation detection. For example, we have been amplifying a set of STSs (7) and using single-strand conformation polymorphism, heteroduplex analysis and direct sequencing to detect previously unrecognized point mutations that could be polymorphic sites (with D. Vollrath, Stanford University).
- Examine the utility of hypervariable markers for phylogenetic reconstruction by including microsatellite data in the construction of haplotypes based on slowly evolving sites (i.e., point mutations). We are surveying microsatellite alleles at the Y-27H39 locus (8) and screening for other microsatellite loci.
- Examine Y chromosome markers, along with mtDNA polymorphisms, in native populations of Sri Lanka.
- Examine Y chromosome polymorphisms in native populations of Siberia (with Tatyana Karafet, Institute of Cytology and Genetics, Novosibirsk).

Michael F. Hammer, Al B. Agellon, Agnish Chakravarti, M. Roxane Bonner, Charles Hoeffler, Matthew Kaplan, Arani Rasanayagam, & Elizabeth Wood, University of Arizona, Tucson, Arizona.

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*Report from John Mitchell*

- Examining Y chromosome-specific haplotypes in Mediterranean populations, particularly Greek and Italians. This is being achieved by sampling migrants from these two countries who are now resident in Melbourne, Australia. All subjects

complete consent form questionnaires in their own language, i.e., Greek or Italian. Birthplace information is recorded at the provincial level within each country. The Y-specific markers to be examined (and comprise the Y haplotype) include: p12f, p21A1, pYAP, p49a, 92R7, pYalphaI, pDP34, and microsatellite markers. This study will examine the extent of genetic variation among the regional populations of each country as well as an assessment of male gene flow between these two Mediterranean groups (with Mike Hammer, Mark Jobling, and Amanda Spurdle).

- An investigation of ethnic heterogeneity of present-day Australian populations, which will include analysis of both autosomal and mitochondrial DNA markers in addition to Y chromosome-specific markers. Ethnic groups sampled include Anglo-Celt, Greek, Italian, Slavs, Arabian, Turkish, and Asian. Y markers being examined include p12f, p21A1, 92R7, pYalphaI, pYAP, as well as PCR markers. One question this study hopes to answer is, does the Y-chromosome pattern of variability across ethnic sub-populations reflect, or differ from, the population affinities recorded for autosomal and mtDNA polymorphisms (with Mike Hammer and Mark Jobling)?

John Mitchell, La Trobe University, Bundoora, Victoria, Australia

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*Report from L. Simon Whitfield and Peter Goodfellow*

We are attempting to assess the level of sequence divergence between human Y chromosomes from the Y chromosome repository. We are direct-sequencing PCR products on ABI 373A sequencers; our primers amplify sequences in the region of SRY and the Yp pseudoautosomal boundary. All primers are tailed with either m13 forward or reverse sequences to allow sequencing with standard dye primers. Template is agarose gel purified and recovered by electroelution or from low-melting-temperature agarose with magnetic beads. It is hoped that the development of robust techniques for the generation of high-quality sequencing template will enable the same region of Y chromosome to be sequenced from a large number of individuals.

L. Simon Whitfield and Peter Goodfellow, Department of Genetics, Cambridge

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## **Brief Communications**

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A *Nla*III polymorphism associated with a Y-specific STS

The Y-specific 209 bp sequence tagged site (STS), sY81/DYS271 (7), was sequenced in 38 humans plus 1 chimpanzee. A single nucleotide position was found to be polymorphic for an A to G transition. The base substitution resulted in a

fragment length polymorphism for the enzyme *Nla*III. Additional samples were screened by digestion of the amplified STS with *Nla*III and the products analyzed by agarose gel electrophoresis. We assumed that all individuals which have lost the *Nla*III site, do so because of a transition. It is also possible, however, that a transversion occurred. The STS also contains a conserved *Nla*III site which is a convenient internal control. Individuals with the G allele yielded restriction fragments of 68 and 141 bp. Alternatively, when the A allele was present, products of 39, 68 and 102 bp were resolved. A total of 121 humans, representing 5 continents, and 10 other primates were typed by sequencing and/or restriction analysis. There is a difference between Africans and non-Africans. The STS is polymorphic in Central Africans. The G allele occurred in 19 of 30 Africans typed. Outside Africa, only one sample, a Mayan, had the G allele. As all non-human primates possessed the A allele, this is likely to be the ancestral type.

Joan Hebert, A. Lin, P. A. Underhill, D. Vollrath and L. Cavalli-Sforza. Genetics Department, Stanford University, Stanford CA 94305

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Analysis of three polymorphic DNA markers in circum-Mediterranean populations.

We examined the DNAs from 258 Caucasian males: 20 British, 23 from Veneto (North-eastern Italy), 21 from Puglia (South-eastern Italy), 27 from Calabria (South western Italy), 28 from northern Sardinia, 27 from southern Sardinia, 26 Greeks, 25 northern Egyptians, 22 southern Egyptians, 22 from United Arab Emirates, 11 Omanites, 6 Iranians. The following polymorphisms were studied: The Alu insertion detected by probe pYAP, the T to C substitution in position XY275 of the pseudoautosomal region, the microsatellite at locus Y-27H39. The frequency of pYAP allele 2 shows a North-to-South increasing trend, with a minimum among British (0.0) and a maximum among Egyptians (0.6). Polymorphism at XY275 is only detected among Egyptians (0.12). At locus Y-27H39 allelic differences consist in length variations of an imperfect (GATA)*n* repeat. Allele frequencies at this locus do not display relevant variations among populations, with the exception of Sardinians among whom an unusual 202 bp allele is found with a frequency of 0.2. Although Y-27H39 alleles are not randomly distributed with respect to pYAP alleles the association is not as complete as we observed for RFLPs. We sequenced Y-27H39 alleles with the same length from individuals carrying different pYAP alleles. This analysis did not reveal differences in the placement of (GATA) repeats within the sequence. Thus we conclude that variation at locus Y-27H39 has multiple origins and it adds only a limited amount of information for reconstructing Y chromosome lineages among Caucasians.

Y-27H39

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	178 bp	186 bp	190 bp	194 bp	198 bp	202 bp
pYAP-1	0	5	85	76	29	12
pYAP-2	1	30	7	4	1	0

We are strongly interested in collaborating with people from the following countries to refine this study: Portugal, Spain, Balkan area, Turkey, Lebanon, North-Western Africa.

P. Malaspina, B. Ciminelli, M. F. Hammer, A. Palena, C. Jodice, L. Terrenato and A. Novelletto. Department of Biology, University of Rome, Rome Italy; and Laboratory of Molecular Systematics and Evolution, University of Arizona, Tucson AZ 85721.

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## Y CHROMOSOME WORKSHOP

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*Report on the First Y Chromosome Workshop. Hughes Hall, Cambridge 2<sup>nd</sup> - 5<sup>th</sup> April, 1994. Organized by Nabeel Affara, University of Cambridge and Chris Lau, University of California San Francisco*

This meeting began on Easter Sunday: the day was especially interesting to meteorologists because it started with brilliant sunshine then midway through the day it clouded over and rained; the building was struck by lightning setting off alarms; Simon Whitfield\*, bachelor scientist, who was lecturing on the possibility of 'arms races' being causal in the rapid evolution of the SRY gene, was nearly struck dumb; immediately thereafter a quarter inch of snow fell on the ground. Later on, it hailed.

The purpose of the chromosome workshops is to construct consensus physical and genetics maps of each of the human chromosomes and to make these maps generally available. This workshop stimulated enough intellectual interest to rise above these rather pedestrian goals. The presentations on the Y chromosome at this Workshop were divided into three groups: physical analysis of the Y chromosome, genes situated on the Y chromosome, and evolution and comparative mapping of the Y chromosome.

### **Physical maps of the Y chromosome**

Because the majority of the Y chromosome, one of the smallest of the complement, is unable to recombine with a homologue, Y chromosomal genetic maps rely on the characterization of aberrant chromosomes which bear deletions or translocations of Y material. These chromosomes are detected in certain patients ascertained with disturbances of sexual development. Despite the recombinational limitation, the Y chromosome is one of the most densely and well mapped human chromosomes with an ordered STS (sequence tagged site) on average every 240 kb and a complete 'reference' YAC contig constructed by Page (for information on the Whitehead contig try telnet genome.wi.mit.edu in directory distribution/human\_STS\_releases). The construction of the 'reference' contig relied on an ongoing project to isolate new markers and on ordering the markers prior to construction of the contig: the STSs were binned in a 43-interval map which had been generated on the basis of 96 individuals with aberrant chromosomes carrying Y material.

Using a panel of 96 ordered STSs, David Page rapidly characterizes aberrant chromosomes carrying Y material in newly recognized patients. Later in the meeting, participants expressed the thought that the list of STSs Dr. Page routinely uses should become generally available.

The 'reference' contig was constructed from a library made at the Whitehead using DNA from Oxen, a 49,XYYYY cell line. Additional YACs isolated from CEPH, St. Louis, Oxford, and Cambridge libraries were integrated into the Whitehead contig during the meeting. These YACs were made available at the meeting by Mike Jones.

By a method independent of the construction of the YAC contig, 70% of the Y chromosome has been contiged in cosmids with over 3,100 clones analyzed (for information on cosmid contig try telnet 128.40.82.1, in directory /pub/chrom.Y/.Ychr\_fprints). Jonathan Wolfe foresees difficulty in closing gaps to

form a complete cosmid contig because many of the cosmid contigs have a large block of repeat sequences on each end. STS screening and screening using specific YACs to bridge gaps may be invaluable in the closing process. With the integration of the YACs and cosmids, the complete cloning of Y chromosome will be nearly complete, and these reagents will be good sources for exhaustive isolation of transcribed sequences (see below).

### **Chromosomal functions of the Y chromosome**

Because the Y chromosome must segregate from the X chromosome to generate X- and Y-bearing gametes, regions of homology between the X and Y chromosomes have been maintained during evolution -- the pseudoautosomal regions. The recombination frequency, that is, the probability of a crossover at any base pair, in the short-arm pseudoautosomal region is 20-fold greater than the genome average recombination frequency.

Up to now, the YAC contig of the 2.6 Mb short-arm pseudoautosomal region contains two striking gaps. Gudrun Rappold reported that one is 50 kb in size and the other is 200-300 kb. Quite possibly, these regions are unclonable in yeast; cosmid cloning of the regions is in progress. The 320 kb long-arm pseudoautosomal region is completely cloned in YACs and nearly fully cloned in cosmids. Kirsti Kvaloy described the pseudoautosomal boundary there *PAB2*. Somewhat reminiscent of the short arm pseudoautosomal boundary, which is defined by an Alu repeat sequence inserted on the Y chromosome, *PAB2* occurs at two LINE repeat sequences present on both the X and Y chromosomes. The long-arm pseudoautosomal region was formed possibly by a translocation of distal Xq sequences to distal Yq via recombination between non-homologous LINE repeat sequences on the X and Y chromosomes. The distal segment on the Y chromosome apparently was lost apparently after the translocation event occurred.

Chris Tyler-Smith's interest in centromere structure led him to study the physical arrangement and genetic variability of sequences in this region. A 7 Mb long-range restriction map of the centromeric region, which contains one gap, has been constructed with special attention to six different centromeric or pericentromeric repeat sequences there. Retrofitted YACs containing Y-alphoid sequences have been introduced into a lymphoid cell line (HT1080). In the transfected cells, the site where alphoid sequences inserted forms a constriction -- the cytogenetic sign of a centromere -- and binds CREST (anti-centromeric) antibodies. Anaphase bridges were also observed. These experiments show that Y-alphoid sequences can function as a centromere.

Using a *neo<sup>r</sup>* + telomere "breakage construct" plasmid, WRA Brown introduced telomeres on both arms of the human Y chromosome carried in the hamster x human hybrid cell line 853. He then screened approximately 90,000 *neo<sup>r</sup>* clones in all to isolate two clones, one which had broken at the short-arm plasmid insertion site and the other which had broken at the long-arm plasmid insertion site. With a small exceptional class (< 0.05), the deleted Y chromosomes segregated either 1:1 (about

0.9) or 2:2 (about 0.05). These experiments show that the telomere sequences present in the breakage construct (missing most of the peri-telomeric repeats) are sufficient for most telomere function in CHO cells. The techniques used to break the Y chromosome here should be applicable to other chromosomes.

### Genes on the Y chromosome

On the human Y chromosome, 14 potentially functional genes or gene families have been isolated (see Table 1). Several more have been hypothesized to exist, including stature- or height-promoting genes, the spermatogenesis factor(s) designated *AZF*, and lymphogenesis-promoting genes. The genes controlling some of these functions may be known already, for example, *AZF* may be represented in some way by the *YRRM* genes. A number of pseudogenes have also been identified.

Table 1. Genes, transcribed sequences, and pseudogenes isolated from the human Y chromosome.

Pseudoautosomal region	Y-specific region	Y-specific Pseudogenes <sup>a</sup>
<i>CSF2RA</i>	<i>SRY</i>	<i>XGY-Y</i> <sup>a</sup>
<i>IL3A</i>	<i>RPS4Y</i>	<i>KALY-Y</i>
<i>ANT3</i>	<i>ZFY</i>	<i>STSY-Y</i>
<i>ASMT</i>	<i>TSPY</i>	<i>ASSP-Y6</i>
<i>XE7</i>	<i>AMGY</i>	<i>ACTG-Y2</i>
<i>MIC2</i>	<i>TT221</i> <sup>a</sup>	<i>ADMLY-Y</i>
<i>XG 5'-end</i> <sup>a</sup>	<i>YRRM</i> <sup>a</sup>	<i>RVN-Y2</i>

<sup>a</sup> the Y symbol indicates the gene is non-functional

<sup>b</sup> genes etc. which made Y-chromosome gene-mapping debut

Tsutomu my-friends-call-me-Tom Ogata reviewed recent efforts to map the stature-promoting genes on the Y chromosome, one of which is mapped putatively to the pseudoautosomal region and the other to the proximal Yq region. He then presented a hypothesis that all of the non-stature-related pleiotropic effects associated with the 45,X chromosome constitution and with submicroscopic and microscopically visible deletions of Yp in 46,XY individuals (the so called Turner's syndrome genes) are caused by a X-Y homologous gene or genes involved in lymphogenesis. Hypothetically, when present in a single dose, the Turner's syndrome gene products are insufficient to promote the normal development of the lymphatic system that in turn leads to cystic hygroma and fetal mortality, lymphedema, cubitus valgus, short 4th metacarpal, pigmented nevi, low nuchal hair line, shield chest, widely-spaced nipples, coarctation of the aorta, and horseshoe kidney. This is an interesting hypothesis -- the proof of the pudding is in the eating.

In the short-arm pseudoautosomal region, a previously unrecognized gene was reported that spans the pseudoautosomal boundary. On the X chromosome, the locus encodes a protein product that is 48% homologous to CD99, the *MIC2* gene product (recently renamed from the 12E7 antigen). The gene product appear to carry Xg<sup>a</sup>, the antigen coded by the historical X Grant Falls (XG) blood group gene. On the Y chromosome, transcription that spans the Y-boundary has been observed; however, no functional product appears to exist. A pseudogene of XG has been localized to Y chromosome interval 5.

Jay Ellison reported that the six-exon gene XE7 encodes a 90 kD protein product of unknown function. By immunochemical and Western analyses with a monoclonal antibody, the protein appears localized to the nucleus. Although alternative splicing at the locus has been detected by analysis of transcription products, protein derived from only one transcript (containing exons 1-4 and 6) was observed.

The Howard Cooke-Ann Chandley World AZF-Wrestling Federation (WAWF) tag team presented a molecular and cytological entreechat on the *YRRM* genes (after the RNA recognition motif in exons 2-4 of these genes). There are approximately 15 *YRRM* loci in humans separable into four classes, one of which contains pseudogenes. The genes are localized to the distal Yq euchromatin but also to the pericentric regions. By hybridization analysis, the sequences are conserved to mouse, but there only weakly. Deletion of one or some of these genes is associated with male infertility. By in situ hybridization, *YRRM* and *TSPY* genes are expressed in the germ line only, not in Sertoli cells. In comparisons of expression patterns in testis sections from a normal and an infertile male carrying a deletion of *YRRM* genes, *YRRM* and *TSPY* sequences apparently become expressed at a higher level and in cells that usually have depressed expression of these genes. In the infertile male testis, spermatogenesis subsequently fails. Do deletions of certain Y chromosome regions cause dysfunction of the sex-vesicle? And if so, is it the inappropriate expression of certain genes that causes the dysfunction or the dysfunction that causes the inappropriate expression? Stay tuned!

A cDNA (TT221, an oppressive name for a gene) which contains previously unrecognized Y-specific sequences was reported by Omar Khawaja. The sequences are expressed strongly in brain and in skeletal muscle. The gene is situated in Y chromosome interval 5, and homologous sequences are present also at Xq21.

While the number of expressed Y-chromosomal sequences isolated to date is small, new methods for cloning genes employing genomic sequences are available. A useful discussion of these new methods was presented by Jim Trofatter, Mike Lovett, David Krizman, and Mark Patterson. Chris Lau thinks the chances are high that a complete gene content map of the Y chromosome will be constructed soon.

### **Evolution and Comparative mapping**

Most of the Y-specific sequences originated in evolutionarily recent times (less than 10 millions year old). Moreover, analysis of an ever-expanding database of both expressed and unexpressed sequences in a wide spectrum of mammalian species

suggests that the rate of sequence evolution (as measured by percent of substitutions per millions years) of Y-specific sequences is accelerated over the rate of autosomal and X-specific sequence evolution.

Simon Whitfield, bachelor scientist, presented his seminal work on the rapid evolution of *SRY*. Thinking about 'arms races' waged between evolving cell-surface molecules (especially molecules in the immunological or gametic systems) is difficult to conceive for an intra-cellular molecule like *SRY*. Although *SRY* may interact with other protein or DNA sequences, these interactions would be considered by most to slow evolutionary rate rather than speed it up. However, an analogy may exist with the evolution of *t haplotypes* in mice- segments of chromosome 17 which are selected for high levels of meiotic drive while under attack from suppressors of drive.

Contrary to the rapid evolution of the Y chromosome observed between species, the frequency of sequence differences on the Y chromosome between individuals in the human population seems to be much smaller than those found on the autosomes or X chromosome. Michael Hammer reported on the level of Y chromosome sequence diversity, which is about 4-fold lower than for autosomes, and on a few polymorphisms that are promising for addressing questions on the origin and migration patterns of modern humans. The Y Alu polymorphism (YAP) is an informative marker for migration studies in and out of Africa and testing hypotheses on the peopling of Japan.

Dr. Ellison presented convincing data that pseudoautosomal sequences appear to be evolving at an accelerated rate also. For example, a number of autosomal homologues exist for genes in the pseudoautosomal region, and autosomal genes are conserved generally over a greater span of species than pseudoautosomal genes as determined by hybridization analysis. One possible effect of the accelerated evolutionary rate is that rapid change of pseudoautosomal sequences provides a reproductive barrier between isolated populations. Some documentation for this phenomena exists in Rodentia.

The mouse Y chromosome is at least as interesting as the human Y chromosome, but it is not as well characterized at the genome level. The short of the Y chromosome contains the sex determining region gene *Sry* (most proximal gene known) and two *Zfy* genes. *Zfy1* and *Zfy2* are about 2 Mb apart. Between the *Zfy* genes, ubiquitin activating enzyme 1 on the Y chromosome, *Ube1y*, which is a candidate for a *Spv* gene, a spermatogenesis factor defined by the failure of spermatogenesis in *SxrB*, renamed from *Sxr'*, mice, and *Smcy* (for selected mouse cDNA on the Y chromosome) which is a candidate for a *Hya* gene, a minor histocompatibility antigen determined by rejection of isogenic skin grafts from male by female mice. The long arm contained the pseudoautosomal region, in which a steroid sulfatase gene is situated (homologous to human *STS*? Still a burning controversy!). Colin Bishop reviewed this state of affairs and reminded us that there remains a gap in the YAC contig between *Zfy1* and *Zfy2*, where the interesting expressed *Ube1y* and *Smcy* sequences have been identified.

*Ube1y* is a candidate for being a *Spy* gene. It is expressed in testis only and it has a homologue on the X chromosome, *Ube1x*, which by the way does not escape X inactivation in the mouse whereas in human the homologous locus is partially inactivated. Hybridization studies described by Mike Mitchell has revealed the while *Ube1x* is well conserved up to and including marsupials, *Ube1y* is not found in great apes and Old World monkeys but is found in New World monkeys and lemurs. The studies are not quite finished because some of the bands seen in New World monkeys might be from pseudogenes.

*Smcy* is a candidate for being an *Hya* gene. A 6.5 kb transcript is observed in Northern analysis. The 1810 bp of sequence available contains no genbank homologies. *Smcy* genes are found in humans, mouse, horse, and marsupials but not in goat, sheep, or cattle. Most striking, however, is the observation that the X homologue of *Smcy* escapes X inactivation in mouse, the first gene in mouse to share this distinction with its human X homologue.

Liz Simpson has been introducing into Abelson-transformed T-cell clones from genetically defined mice cosmids and other cloned sequences from the mouse Y-specific region that putatively contains the *Hya* gene. She test these transfectants with antisera against the minor histocompatibility antigen HY by proliferation assays. Cosmids from different segments of the *Hya* region caused stimulation of the cells as well as *Smcy*-containing cosmids. I am totally confused: are there two people on this earth who study HY and who masquerade under the name of Liz Simpson?

Jennifer Marshall Graves delivered her classic lecture on mammalian evolution. The prototherian lineage diverged from meta- and eutherian lineage about 130 million years ago, and the metatherian and eutherian lineages diverged about 100 million years ago. Cytogenetically, the monotreme sex chromosomes (e.g., in platypus) contain visible differential and pairing segments -- the pairing segment being much larger than that found in the most eutherians. Metatherians, on the other hand, have no visible pairing segments, and during male meiosis the sex chromosomes may not pair at all. Given the high rate of sequence evolution of the pseudoautosomal region seen in mouse and man and the cytogenetic differences observed in a wide range of mammals, one might reasonably speculate that the pseudoautosomal region's role in the chromosomal mechanism governing segregation are also subject to rapid change.

Dr. Graves reviewed her extensive data from the study of marsupials and monotremes in which genes known to be present on the short arm of the human X chromosome are in fact autosomal in the non-eutherian animal, an important departure from Ohno's law that is consistent with the growing number of genes on the short arm that escape X inactivation. *ZFY* is autosomal in marsupials and monotremes but sex-linked in eutherians; *Ube1y* is sex-linked in marsupials and autosomal in monotremes. Her model for the evolution of the Y chromosome begins with two homomorphic chromosomes on which the testis-determining gene originates. Thereafter, autosomal segments are translocated to the sex chromosomes that act as pairing partners in meiosis, but the translocations may have occurred in stages in

the different lineages or may be composed of entirely different sequences. As mentioned above, in some marsupials the pairing segments need not be there at all, implying that the whole pairing segment can be lost and its function perhaps replaced by another chromosomal mechanism for segregation. Jenny was happy not to be the last speaker at this meeting, but with her pardon I mention her work here last.

The meeting was a smashing success! The next day we all went our separate way nursing our adult hangovers or proceeding to our adult airplanes or buses or both.

Nathan Ellis, New York Blood Center, New York City

\* Only the individuals who presented lectures are mentioned in this report. For more information about the work summarized here, consult the Abstract which are/will be published in an upcoming issue of Cytogenetics Cell Genetics or that favorite of all rags the Human Genome News.

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## MINUTES

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### *Minutes of the Third International Meeting of the YCC Ad Hoc Committee: Notes from Underground.*

Held in dining room of Chez Whitfield and Mathias in the basement of 8 Melbourne Place, Cambridge, England, at midnight Greenwich mean time on the occasion of the First Y Chromosome Workshop. Attending: Nathan A. Ellis, Michael Hammer, Mark Jobling, Kristi Kvaloy, Chris Tyler-Smith, and Simon Whitfield

In the first order of business, the minutes of the last meeting held at the last meeting of the American Society of Human Genetics in New Orleans in 1993 and published in the Y Chromosome Consortium (YCC) Newsletter Volume One Number One were approved anonymously. In the second order of business, the time and place of the next meeting of the YCC Committee was discussed. Three options were considered: (i) at the University of Arizona, Tucson, Arizona as guests of Dr. Michael Hammer, date to be set; (ii) at the next American Society of Human Genetics Meeting in Montreal in October; (iii) at the next meeting of the Anthropological Genetics Society which is part of the American Society of Physical Anthropology, (March 30 1995, Oakland CA). While everyone wanted to go to Arizona in the winter, it was agreed also that the Anthropological Genetics Society seemed to be the most appropriate venue for the YCC, because the goals of each are parallel. Our contact with the Anthropological Genetics Society is Michael Crawford of the University of

Kansas. This then is the first published announcement for the next meeting of the YCC AD Hoc Committee.

The Committee then addressed matters arising. Simon Whitfield announced that he was an observer at the meeting of a group spearheading the European genome diversity initiative and he thought that Julie Bodmer, Alberto Piazza, Alec Jeffreys, and Svante Paabo would be important connections for the YCC for expanding the number of cell lines in the Repository. At this meeting the issue of informed consent had been raised. Amongst ourselves, this spurred the discussion to consider how ethnic and religious beliefs of different peoples might be affected by the goals and eventual results of anthropological research using polymorphisms on the Y chromosome or indeed how such beliefs might themselves affect anthropological research. Several were in favor of establishing a committee to consider these questions further.

The next discussion revolved around what populations needed to be brought into the YCC Repository and how best to obtain samples. In considering the current status of the YCC Repository, the group thought that a representative sampling of Europeans would be relatively easy to obtain. The European populations considered accessible and appropriate were Basques, Finns, Celts, Lapps, Anglo-Saxon, and Ashkenazi Jewish. Two nice samples of Caucasoid populations have already been donated to the Repository, i.e., the Siberian and Krasnadovian samples from the Kidd laboratory. Mark Jobling volunteered to approach Svante Paabo who is running the cell lines assembly of the European initiative.

Chris Tyler-Smith discussed the possibility of pre-screening European Y chromosome by pulsed-field gel electrophoresis, before admitting cell lines into the Repository, in order to ensure maximum amount of variability of the European sample. For this pre-screening, blocks would have to be made at  $10^7$  cells per milliliter. This will be done when possible.

Samples from Asian, Australoid, and Oceanic populations were discussed in more detail because they are currently under-represented in the Repository. Asian samples that were considered accessible and appropriate were Tibetans, Butans, Mongolians, Japanese, Chinese, Tamils, and Indians. This list was not exhaustive. Australoid and Oceanic populations to be targeted were not specifically listed. Various members of the Committee agreed to make inquiries in order to obtain samples from Papuans, Japanese, Tongans and Hawaiians, Vanuatuans.

The discussion on the Repository closed with exhortation that the Repository contain chimpanzee, gorilla, and perhaps orangutan cell lines as well as Y chromosome containing rodent x human hybrid cell lines and the 49,XYYYY cell line Oxen. Even sorted Y chromosome libraries might be stored in the Repository, but it was pointed out that there is effectively only one good sorted Y-chromosome library, the commercially available (ATCC) Livermore library. Simon will donate a chimpanzee cell line.

All present wanted to receive the Repository's conditions for the shipment of samples. They are published here: five to ten milliliters of blood should be drawn

under sterile conditions into vacutainer tubes containing ACD, EDTA, or heparin as coagulant. The tubes should be sent by express courier (e.g., Federal Express, for the Repository account number please call Nathan Ellis at 1-212-570-3075) and the customs claim should say the material is human blood that is non-hazardous and non-toxic.

The last major discussion centered on the typing of polymorphisms once the DNA from the Repository is available. All polymorphisms presently known should be typed. Nathan Ellis agreed to make bog-standard Southern blots on Hybond-N<sup>+</sup> membrane with the enzymes *StuI*, *TaqI*, *HindIII*, and *EcoRI* which should allow the typing of all the known RFLPs. These membranes will be made available to laboratories familiar with the hybridization conditions for probes that detect RFLPs. Quality control of submitted data was considered essential for the integrity of the polymorphism database, and all agreed that no data should be entered into the polymorphism database unless a copy of the primary data (e.g., autoradiographs) was sent along with the tabulated results. This fact should be made known to investigators when they receive DNA samples from the YCC. Cross-contamination of DNA samples during postage was considered a potential problem for PCR-based tests, and Mike Hammer will investigate the use of different waxes that would seal the DNA into the well of the microtitre dishes in which the DNA will be shipped.

As there was no other business or discussions to pursue, the meeting was adjourned at two o'clock a.m.

Nathan Ellis, Ad Hoc Secretary and Chairman

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## **REPOSITORY UPDATE**

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The YCC Repository is a bank of lymphoblastoid cell lines established from individuals representing populations from all the inhabited continents. DNA will be prepared from these cell lines and distributed to any investigator interested in the evolution of the Y chromosome. Their first purpose is to aid investigators in an exhaustive search for polymorphisms on the human Y chromosome. The second purpose is to provide the source material for a first Y-haplotype-based evolutionary tree. The cell line panel will be made available under certain conditions to collaborative Genome Diversity Projects being considered now in various research communities.

Many cell lines have already been accessioned in the Repository (see Appendix). To achieve the maximum amount of genetic diversity, we need the support of anthropological and Y chromosome research communities. In our sampling of different populations, we plan to have 3-5 individuals from each population, and 4-8

populations from each major continental land mass: African, Eurasian, Australoid, Oceanic, Amerindian. Eurasian, African, and Amerindian population are in the process of becoming well-covered. Our weakest area of collection is in Oceanic and Australoid populations.

We have decided to provide DNA as soon as the Repository has reached half its size. Because the number of cell lines has reached 70 and we plan to have at least 150 cell lines in the Repository, we will soon begin to make cell pellets to be sent to Arizona for DNA preparation. We expect to make these DNA samples available by Christmas.

Any persons wishing to contribute population samples consisting of cell lines or blood to the YCC Repository is asked to contact Nathan Ellis at 212-570-3075 (work) or 212-691-7355 (home). For international shipments, blood is the most convenient form in which to send samples. Either form is welcome.

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## **POLYMORPHISM UPDATE**

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No new Y polymorphisms have been published since the last newsletter (see Table 2), but additional information is available for pDP31 and CRI-J177.

1. pDP31 (DXYS1Y). Spurdle et al. (ref. 45) describe the use of the probe pDP31 to detect polymorphisms at the DXYS1Y locus. *EcoRI* digests show three patterns: (1) a 4.5kb fragment alone, corresponding to one X chromosome fragment and one Y chromosome fragment; (2) the 4.5kb fragment plus a 5.2kb fragment of half the intensity (Y duplication); and (3) the 4.5kb fragment plus a 5.2kb fragment of equal intensity (Y triplication). All three patterns are seen in both pYAP<sup>+</sup> and pYAP<sup>-</sup> chromosomes. There thus appear to have been recurrent mutations at the DXYS1Y locus and this polymorphism is of limited use for evolutionary studies.

2. CRI-J177 (DYS152) was originally described by Bowden & Gravius in 1990 (ref. 2) as detecting multiple Y-specific insertion/deletion polymorphisms but has not been used by others, perhaps because it was initially unavailable from Collaborative Research due to 'quality control' problems. I recently obtained a sample of CRI-J177 phage DNA and report here some further details of the polymorphism.

Eight different *EcoRI* fragments were subcloned and designated CRI-J177a - g. Each fragment was used (with competition if necessary) to probe a small panel of *Hind* III digested DNAs. Fragments CRI-J177c and CRI-J177d produced monomorphic patterns; the other fragments produced polymorphic patterns similar but not identical to one another and to that described by Bowden & Gravius. Fragment CRI-

J177e gave the clearest pattern and was chosen for further work. It detected considerable variation in the number and size of the large *Hind*III bands.

CRI-J177e was further localized on the Y chromosome by hybridization to an array of yOX YACs (ref. 5). Hybridization was seen to yOX 198, 102, 197, 103, 69, 104, 134, 58 and 190: all located in interval 6 on Yq. The probe 49f (DAYS) was known to hybridize to the same set of YACs, although it did not detect yOX 102. CRI-J177e was therefore used to probe *Taq*I digests of genomic DNA. Seven - nine bands were seen in different males and some of these were polymorphic, but they appeared to be a subset of the bands detected by 49a/f.

Conclusions: CRI-J177 (DYS152) detects the complex and polymorphic DYS1 locus. For most purposes it has no advantages over the more widely available 49a/f probes.

Chris Tyler-Smith

## APPENDICES

### Appendix 1. The origins of cell lines contained in the Y Chromosome Consortium Repository

HG#	YCC#	Source code	Language	Geographic origin	Ethnic origin
2214	01	Yale No. 117		North America	Amerindian
2215	02	Yale No. 123		North America	Amerindian
2216	03	Yale No. 139		North America	Amerindian
2217	04	Yale No. 218		North America	Amerindian
2255	05	NASAM	Kung	Namibia	San
2256	06	JK736	Aka	Bagandu, CAR	Biaka Pygmy
2257	07	JK741	Aka	Bagandu, CAR	Biaka Pygmy
2258	08	JK1029	Niger/Kordofanian	Ituri, Zaire	Mbuti Pygmy
2259	09	JK1031	Niger/Kordofanian	Ituri, Zaire	Mbuti Pygmy
2260	10	JK965	Nasioi	Bougainville, Solomon Isl.	Melanesian
2261	11	JK971	Nasioi	Bougainville, Solomon Isl.	Melanesian
2262	12	JK1364	Tupi	Rondonia, Brazil	Karitiana
2263	13	JK1370	Tupi	Rondonia, Brazil	Karitiana
2264	14	JK1493	Tupi	Rondonia, Brazil	Surui
2265	15	JK1498	Tupi	Rondonia, Brazil	Surui
2266	16	JK1504	Tupi	Rondonia, Brazil	Surui
2267	17	JK1624	Yucatec	Campeche, Yucatan	Mayan
2268	18	JK1626	Yucatec	Campeche, Yucatan	Mayan
2486	19	SAIMR01/JR020	!Kung	Namibia	Tsumkwe San
<del>2487</del>	<del>20</del>	<del>SAIMR02/JR031</del>	<del>!Kung</del>	<del>Namibia</del>	<del>Tsumkwe San</del>
2488	21	SAIMR03/JR321	!Kung	Namibia	Tsumkwe San
2489	22	SAIMR04/JR323	!Kung	Namibia	Tsumkwe San
2494	23	TiMu/AR01		Tucson, Arizona	Navaho
2513	24	HaMi/AR02		Tucson, Arizona	Ashkenazi Jewish
2496	25	AnPa/AR03		Tucson, Arizona	Tohono O'Odham
2497	26	RoDa/AR04		Tucson, Arizona	Irish/English
2498	27	McAa/AR05		Tucson, Arizona	Porch Creek
2588	28	SAIMR13/JR354	!Kung	Namibia	Tsumkwe San
2589	29	SAIMR14/JR077	!Kung	Namibia	Tsumkwe San
2590	30	SAIMR15/JR305	!Kung	Namibia	Tsumkwe San
2591	31	SAIMR16/LD148	Bantu	South Africa	Herero
2592	32	SAIMR17/Alb77	Bantu	South Africa	S. Sotho
2593	33	SAIMR18/Alb74	Bantu	South Africa	Pedi
2595	34	SAIMR07/JR306	!Kung	Namibia	Tsumkwe San
2596	35	SAIMR08/JR054	!Kung	Namibia	Tsumkwe San
2597	36	SAIMR19/Alb47	Bantu	South Africa	Tswana
2598	37	SAIMR20/WK122	Bantu	South Africa	Ovambo
<del>2609</del>	<del>38</del>	<del>SAIMR05/JR013</del>	<del>!Kung</del>	<del>Namibia</del>	<del>Tsumkwe San</del>
2610	39	SAIMR06/JR301	!Kung	Namibia	Tsumkwe San
2611	40	SAIMR09/LD156	Bantu	South Africa	Herero
2612	41	SAIMR10/LD145	Bantu	South Africa	Herero
2613	42	SAIMR11/Alb27	Bantu	South Africa	Zulu

2614	43	SAIMR12/Alb55	Bantu	South Africa	Tswana
<del>2632</del>	<del>44</del>	<del>SAIMR22/LD185</del>	<del>Bantu</del>	<del>South Africa</del>	<del>Herero</del>
2633	45	SAIMR23/LD188	Bantu	South Africa	Herero
<del>2634</del>	<del>46</del>	<del>SAIMR21/LD147</del>	<del>Bantu</del>	<del>South Africa</del>	<del>Herero</del>
2643	47	JK3146		Siberia	Yakut
2644	48	JK3149		Siberia	Yakut
HG#	YCC#	Source code	Language	Geographic origin	Ethnic origin
2645	49	JK3150		Siberia	Yakut
2646	50	JK3151		Siberia	Yakut
2647	51	JK3152		Siberia	Yakut
2648	52	JK3158		Krasnador (Black Sea)	Adygeans
2649	53	JK3159		Krasnador (Black Sea)	Adygeans
2650	54	JK3160		Krasnador (Black Sea)	Adygeans
2651	55	JK3161		Krasnador (Black Sea)	Adygeans
2652	56	JK3168		Krasnador (Black Sea)	Adygeans
***a	57	KaMi	Urdu	Kashmir	Pakistani
2734	58	NaHa	Punjabi	Lahore	Pakistani
***a	59	DeKa	Sinhalese	Southern Sri Lanka	
2192	60	IsDe			Ashkenazi Jewish
2707	61	SaGr			Ashkenazi Jewish
1802	62	SaOk	Japanese	Gifu, Honshu	Japanese
1626	63	YoYa	Japanese	Noto Peninsula	Japanese
1778	64	AkKi	Japanese	Kanazawa	Japanese
***a	65	J.A.	German		German
***a	66	C.G.	German		German
***a	67	R.K.	German		German
***a	68	J.B.	German		German
***a	69	A.T.		Iran	Persian
2120	70	HaSa	Turkish	Turkey	

<sup>a</sup> HG numbers are given to establish cell lines or cell lines in the process of being established. The entries marked by "\*\*\*" are currently stored as cryopreserved lymphocytes. They are entered in the Table because the rate of success with lymphocytes from normal individuals is greater than 90%. A strike-through indicates the cell line was entered into the Repository but the cells did not proliferate.

## Appendix 2. Published polymorphisms on the human Y chromosome.

### A. Conventional RFLPs.

locus	probe	enzyme	comments	reference
DYS11	12f2	TaqI, EcoRI	insertion/deletion, probe gives extensive cross-hybridisation	3
DYS1	49f, 49a	TaqI	complex pattern, many variable fragments low stringency conditions required	17, 31
		PvuII		40
		BglII, HindIII, PstI, SstI		44
DYS7	50f2	EcoRI	fragment C absent in one individual	4
		TaqI	novel fragment in two samples low stringency conditions required	13
DYZ3	YalphaI	HindIII	additional site in some subunits of tandem array very high stringency required	48
DXYS5Y	47z	StuI	point mutation	29

DYZ8	21A1	TaqI	complex polymorphism	13
DYS21	116/21	PstI	one individual only	25
DYS150	13/0.9	BglI	one individual only	25
DYS152	CRI-J177	BglII, HindIII, PstI	insertion/deletion	2
DYS287	pYAP	EcoRV, TaqI	Alu sequence insertion	45
DYS27	1/2	TaqI	point mutation in tandem array	14
-	92R7	HindIII	point mutation	26

#### B. Polymorphisms detected by PFGE.

locus	probe	enzyme	comments	reference
DYZ3	YalphaI	several AvaII EcoO109I	array size polymorphism point mutation point mutation	32, 48 48 32
DYZ5	Y-190	XbaI	array size polymorphism	49
-	poxY1	BglII, XbaI	detects one variable DYZ1 fragment	32
-	RBF2	SfiI	detects two independent variable loci	14
DYS1	49f	SfiI	one or two independently variable loci	14
-	RBF4	SfiI	one hypervariable locus	14
-	M911	XbaI	nature of polymorphism uncertain	26
DYZ1	HY10	many	complex hypervariable pattern	26
DYZ2	HY2.1	many	complex hypervariable pattern	26

#### C. Polymorphisms detected by PCR.

locus	locus name	comments	reference
-	27H39LR	GATA repeat	34
-	YCAI	CA repeat	26
-	YCAII	CA repeat, two Y loci amplified	26
-	YCAIII	CA repeat, two Y loci amplified	26

### Appendix 3. Human Y Chromosome Polymorphism References

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## YCC Participants\*

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Luca Cavalli-Sforza/Mark Seielstad  
Department of Genetics  
Stanford University Medical School  
Stanford, CA 94305  
Tel: 415-723-6506  
Fax: 415-725-1534  
Email: "mark@lotka.stanford.edu"

Nathan Ellis  
The New York Blood Center  
310 East 67th Street  
New York, NY 10021  
Tel: 212-570-3378  
Fax: 212-570-3195  
Email: "nellis@server.nybc.org"

Mary Haag  
All Children's Hospital  
Pathology/Cytogenetics  
St. Petersburg, FL 33701  
Tel : 813-892-8687  
Fax:  
Email:

Trefor Jenkins/Erin Dietzsch  
SAIMR, School of Pathology  
Department of Human Genetics  
Hospital Street, P.O. Box 1038  
Johannesburg 2000, South Africa  
Tel: 27-11-725-0511  
Fax: 27-11-725-2319  
Email: "058mrams@witsvma.wits.ac.za"

Judith and Ken Kidd  
Yale University School of Medicine  
Department of Human Genetics  
333 Cedar Street  
New Haven, CT 06510  
Tel: 203-785-2654  
Fax: 203-785-6568  
Email:

John Mitchell  
Dept. of Genetics and Human Variation  
La Trobe University  
Bundoora Victoria  
3083 Australia  
Tel: 61-03-479-2273  
Fax: 61-03-479-2480

Rob Dorit  
Department of Biology/OML  
165 Prospect Street  
New Haven CT 06511  
Tel: 203-432-9919  
Fax:  
Email: "rdorit@beagle.biology.yale.edu"

Peter Goodfellow/Simon Whitfield  
Imperial Cancer Research Fund,  
P.O. Box 123, Lincoln's Inn Fields  
London, WC2A 3PX, United Kingdom  
Tel: 44-71-242-0200  
Fax: 44-71-269-3581  
Email:

Michael Hammer  
Department of EEB, Biosciences West  
University of Arizona  
Tucson, Arizona, 85721  
Tel: 602-621-9828  
Fax: 602-621-9190  
Email: "hammer@brahms.biosci.arizona.edu"

Mark Jobling  
Department of Genetics  
University of Leicester  
University Road  
Leicester LE1 7RH, England  
Tel: 44-533-523-377  
Fax: 44-533-523-378  
Email: "maj4@leicester.ac.uk"

Gerard Lucotte  
International Institute of Anthropology  
1, place d'léna  
Paris (XVI)  
France  
Tel: 47-93-09-73  
Fax:  
Email:

Y. Nakagome  
Department of Human Genetics  
School of International Health  
University of Tokyo  
7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan  
Tel:  
Fax:

Email: "genrjm1@lure.latrobe.edu.au"

Email:

Andrea Novelletto  
Universita Degli Studi di Roma  
Dipartimento di Biologia  
Via Orazio Raimondo  
00173 (La Romanina) Roma, Italia  
Tel: 39-6-249-90  
Fax: 39-6-249-3500  
Email: "terrenato@tovvx1.ccd.utovrm.it"

David Page  
Whitehead Institute  
Nine Cambridge Center  
Cambridge, MA 02142  
Tel: 617-258-5203  
Fax: 617-258-5578  
Email: "page@vax.wi.mit.edu"

Chris Tyler-Smith  
University of Oxford  
South Park Road  
Oxford OX1 3QU, England  
Tel: 44-865-275-259  
Fax: 44-865-275-259  
Email: "chris@bioch.ox.ac.uk"

Jonathan Wolfe  
The Galton Laboratory  
University College London  
4, Stephenson Way  
London, NW1 2HE, UK.  
Fax: 011-44-71-387-3496  
Email:

Gudrun Rappold  
Institut für Humangenetik und Anthropologie  
Universität Heidelberg  
Im Neuenheimer Feld 328  
69120 Heidelberg Germany  
Tel: 49-6221-563-890  
Fax: 49-6221-565-332

Amanda Spurdle  
Department of Genetics and Human Variation  
La Trobe University  
Bundoora Victoria 3083 Australia  
Tel: 61-3-479-2265  
Fax: 61-3-479-2480  
Email:

Harry Ostrer  
Human Genetics Program, Dept. Pediatrics  
NYU Medical Center  
550 First Avenue  
New York, NY 10016  
Tel: 212-873-7220  
Fax: 212- 263-5746  
Email: "ostrer@mcclb0.med.nyu.edu"

A. S. Santachiara Benerecetti  
Department of Genetics and Microbiology  
University of Calabria  
via Abbiategrosso 207  
27100 Pavia, ITALY  
Tel: 39-382-31036  
Fax: 39-382-528-496

Doug Vollrath  
Department of Genetics L321  
Stanford University School of Medicine  
Stanford, CA 94305  
Tel: 415-725-1635  
Fax: 415-723-  
Email: "vollrath@genome.stanford.edu"

Robert Erickson  
Department of Pediatrics  
University of Arizona  
Tucson, AZ 85721  
Tel: 602-626-5483  
Fax: 602-626-  
Email: "erickson@brahms.biosci.arizona.edu"

Jean Weissenbach  
Institut Pasteur  
28, Rue du Dr. Roux  
Paris Cedex, France  
Tel: 33-1-45-68-88-50  
Fax: 33-1-45-67-69-78  
Email:

Frank Schneiders

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\* contributors or those contacted/present at YCC Meetings  
Please send corrections and additions to Michael Hammer.