

# Mapping of the X linked form of hyper IgM syndrome (HIGM1)

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## Abstract

**X linked immunodeficiency with hyper-immunoglobulinaemia M (HIGM1), which is characterised by agammaglobulinaemia together with excess IgM production reflecting an impairment of the immunoglobulin heavy chain class switch of B lymphocytes, has been mapped to Xq26. We report multipoint linkage data in six families with HIGM1 which show that the most likely position for the gene is close to *HPRT* with a maximum lod score of 4.89. The finding of recombinations between *HIGM1* and both *HPRT* and *DXS42* implies that *HIGM1* is not allelic to X linked lymphoproliferative disease. These data will be useful in genetic counselling in families and will also be useful in testing candidate genes.**

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A number of inherited immunodeficiencies mapping to the X chromosome have been described and their chromosomal locations reported.<sup>1</sup> Immunodeficiency with hyper IgM is characterised by raised levels of IgM, normal or raised levels of IgD, and very low levels of IgG, IgA, and IgE in the serum and secretions.<sup>2</sup> Although clinically indistinguishable, several genetic defects may give rise to the same syndrome since it can be X linked, autosomal recessive, or autosomal dominant. All forms are exceptionally rare but the X linked form predominates.<sup>3</sup>

*HIGM1* was shown not to be allelic to Brutons agammaglobulinaemia (*AGMX1*).<sup>4</sup> Using nine X chromosome specific DNA probes recognising RFLPs, Mensink *et al*<sup>5</sup> assigned the *HIGM1* gene to Xq24-27 in a single pedigree. This pedigree, typed for additional markers, has been incorporated into this study. Hendriks *et al*<sup>6</sup> extended the linkage study on the same family and confirmed linkage to *DXS42* (Xq24-q25) with a maximum lod score of 2.29. Three families with *HIGM1* were analysed, and showed linkage to *HPRT* using a VNTR (AGAT) tetranucleotide repeat.<sup>7,8</sup>

Here we extend the number of families and include other probes flanking *HPRT* using both conventional RFLPs and short tandem repeat polymorphisms.

## Materials and methods

### FAMILIES STUDIED

Six families were available for study, most of which have been reported previously. Family

Cou was first described in 1962 (fig 1)<sup>9</sup> and is discussed by McKusick (30823).<sup>10</sup> Subjects IV.4, IV.5, and IV.8 have died since the family was first reported and subjects IV.6, IV.9, and IV.10 have been born since 1962. Surviving family members II.3, II.4, III.3, III.4, III.8, IV.1, IV.6, and IV.10 were typed. An EBV transformed cell line from IV.10 was generously provided by Dr C Roifman. Preliminary linkage data on four families EsX, HB, MM, WG<sup>5,8</sup> has been reported. The same subjects were typed in this study. The sixth family, Tu, is presented in fig 1.<sup>11</sup>

### OLIGONUCLEOTIDE PRIMERS

Primers identifying STRs at the loci *HPRT*,<sup>12</sup> *DXS425*,<sup>13</sup> and *DXS102*<sup>13</sup> were synthesised on an ABI 3801A synthesiser. The sequences used were:

- (1) *HPRT* (AGAT)<sub>n</sub>, forward 5' < TCT CTA TTT CCA TCT CTG TCT CC > 3', reverse 5' < TCA CCC CTG TCT ATG GTC TCG > 3', product size: 159 bp.
- (2) *DXS425* (XL 90A3) (CA)<sub>n</sub>, forward 5' < TCT AGA GTC GAT CAC GTG AG > 3', reverse 5' < TTA GTC ATG ATT CCC CAG AG > 3', product size: 101 bp.
- (3) *DXS102* (Cx38-1) (CA)<sub>n</sub>, forward 5' < GTA GTC TCA GTC GAC ATG CTT TGA > 3', reverse 5' < GCT GAG AAA GTA GAT CCT AAG TGT TC > 3, product size: 157 bp.

### PROBES

The following probes were used for the linkage analysis: 43-15 (from locus *DXS42*)<sup>14</sup> and 36-B2 (from locus *DXS10*).<sup>15</sup>

### SOUTHERN BLOT ANALYSIS

DNA was extracted from the nuclei of peripheral leucocytes by guanidinium hydrochloride extraction.<sup>16</sup> Twenty micrograms of DNA was digested for at least four hours with the appropriate enzyme and the fragments separated on a 0.8% gel by electrophoresis. After denaturation of the gel with 0.4 mol/l NaOH, 1.5 mol/l NaCl, the DNA was blotted directly onto Hybond N+ (Amersham International) and fixed by rinsing with 0.4 mol/l NaOH followed by two washes with 2 × SSC.

DNA probes were radiolabelled to a specific activity of 10<sup>9</sup> to 10<sup>10</sup> cpm/μg with <sup>32</sup>P-dCTP by random hexanucleotide primer extension. Prehybridisation and hybridisation were carried out in 10 × Denhardt's solution, 4 × SSC, 50 μg/ml sonicated salmon sperm

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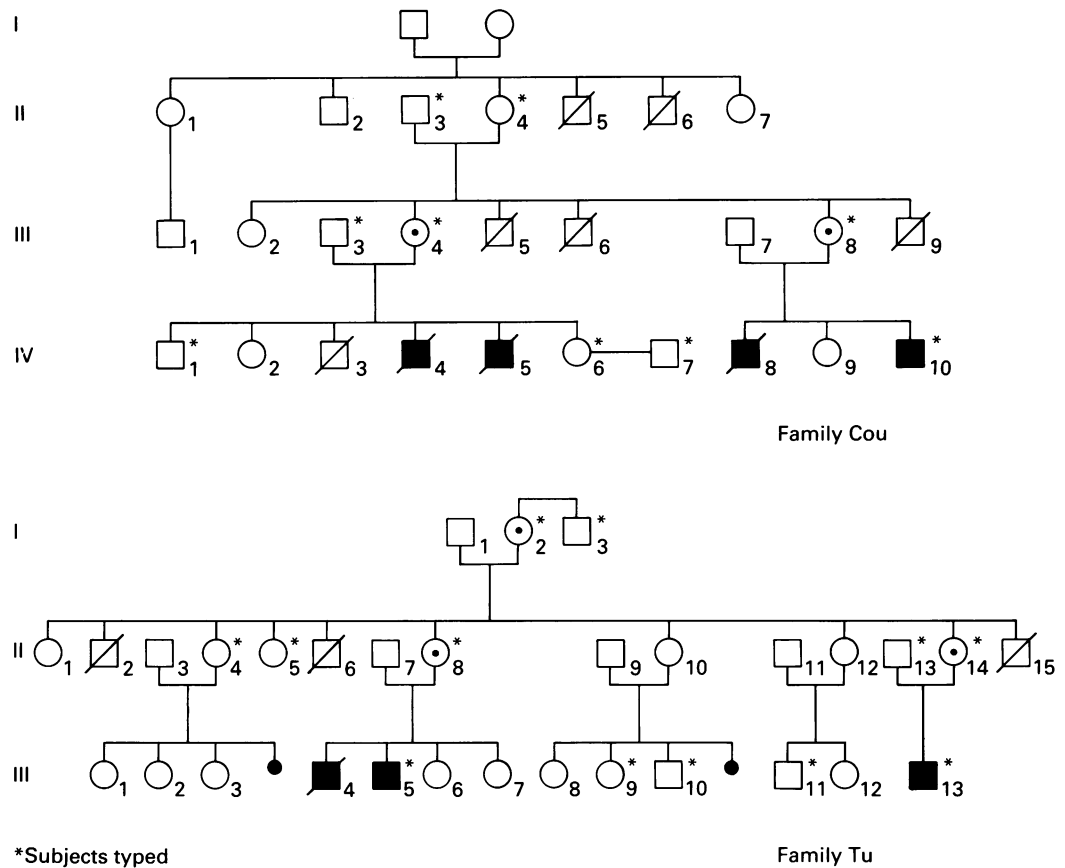


Figure 1 Pedigrees of families Cou and Tu.

DNA, and 0.1% SDS overnight. Filters were washed for  $3 \times 20$  minutes in  $3 \times \text{SSC}$ , 0.1% SDS at room temperature followed by further higher stringency washes at  $65^\circ$ . Autoradiography was performed using  $x$  ray film (Kodak XAR-5) with two intensifying screens at  $-70^\circ$  for 72 hours.

#### PCR ANALYSIS

Reactions were carried out in a 25  $\mu\text{l}$  volume using 100 ng of genomic DNA, 12.5 pmol of each primer, 200 nmol dATP, dTTP, dGTP, 20 nmol dCTP, 0.1  $\mu\text{l}$   $^{32}\text{P}$ -dCTP, in reaction buffer (1.5 mmol/l  $\text{MgCl}_2$ , 50 mmol/l KCl, 10 mmol/l Tris-HCl, pH 9.0, 0.10% gelatin, 0.1% Triton X), and  $10^{-5}$  mol/l tetramethyl ammonium chloride. Reactions were overlaid with mineral oil, denatured at  $94^\circ\text{C}$  for 10 minutes before cooling to  $60^\circ\text{C}$ , and 1.5 to 2 units of *Taq* polymerase (Promega) were added. Twenty-five cycles of  $72^\circ\text{C}$  (one minute),  $94^\circ\text{C}$  (one minute), and  $60^\circ\text{C}$  (30 seconds) were carried out on a Techne PHC-2 machine.

For analysis 1  $\mu\text{l}$  PCR product was diluted five-fold with TE, and stop solution (95% formamide, 20 mmol/l EDTA, 0.05% bromophenol blue, 0.01% xylene cyanol) (USB), denatured for two minutes at  $90^\circ\text{C}$  and 2  $\mu\text{l}$  loaded on a 6% 19:1 acrylamide:bisacrylamide, denaturing polyacrylamide (Acugel) gel and electrophoresed at 55 watts for two hours on BRL sequencing apparatus. The gel was then dried on to 3M Whatman paper. Autoradiography was performed using  $x$  ray film (Kodak XAR-5) at  $-70^\circ\text{C}$  overnight.

#### LINKAGE ANALYSIS

Two point lod scores were analysed using the LIPED programme (version 4.8). A gene frequency of 0.0001 was used. Complete penetrance of HIGM1 was assumed. The allele frequencies that were used are given below. The frequencies for the microsatellites were measured from 90 Caucasian chromosomes. The RFLP frequencies have been published.<sup>17</sup>

- (1) *HPRT* 0.167: 0.396: 0.292: 0.104: 0.041.
- (2) *DXS425* 0.144: 0.333: 0.274: 0.144: 0.105.
- (3) *DXS102* 0.800: 0.050: 0.050: 0.050: 0.050.
- (4) *DXS42* 0.810: 0.190.
- (5) *DXS10* 0.330: 0.670.

Multipoint linkage data were analysed using the LINKMAP program (version 5.04) run via the MRC HGMP Resource Centre. Map distances were set according to published data.

#### Results

Fig 1 shows pedigrees Cou and Tu. The other pedigrees are fully described in Hendriks *et al*<sup>6</sup> and Padayachee *et al*.<sup>8</sup>

Two point lod scores with the loci *DXS42* and *DXS10* and the VNTR polymorphisms *HPRT*, *DXS425*, and *DXS102* are presented in table 1.  $Z_{\text{max}}$  and  $\theta_{\text{max}}$  for each locus are presented in table 2.

A multipoint map from *DXS425* to *DXS102* is presented in fig 2. The order of the markers used is *DXS425-DXS42-HPRT-DXS10-DXS102* based on genetic map evidence for *DXS425-DXS42-HPRT*<sup>18,19</sup> and physical mapping in a YAC contig for *HPRT-DXS10-DXS102*.<sup>20</sup>

The region around *HPRT* has been com-

Table 1 Two point lod scores.

| Marker        | Recombination fraction $\theta$ |       |       |       |       |       |        |          |
|---------------|---------------------------------|-------|-------|-------|-------|-------|--------|----------|
|               | 0.5                             | 0.4   | 0.3   | 0.2   | 0.1   | 0.05  | 0.001  | 0        |
| <i>DXS425</i> | 0                               | 1.37  | 2.202 | 2.976 | 3.041 | 2.284 | -5.506 | -294.927 |
| <i>DXS42</i>  | 0                               | 0.598 | 1.201 | 1.693 | 1.713 | 1.929 | 0.453  | -97.435  |
| <i>HPRT</i>   | 0                               | 0.874 | 1.935 | 3.239 | 4.419 | 4.891 | 3.877  | -94.304  |
| <i>DXS10</i>  | 0                               | 0.216 | 0.601 | 1.020 | 1.419 | 1.606 | 1.780  | 1.783    |
| <i>DXS102</i> | 0                               | 0.337 | 0.623 | 0.868 | 1.065 | 1.267 | 1.142  | 1.142    |

Table 2  $Z_{max}$  and  $\theta_{max}$  for each locus.

| Marker        | $Z_{max}$ | $\theta_{max}$ |
|---------------|-----------|----------------|
| <i>DXS425</i> | 3.157     | 0.14           |
| <i>DXS42</i>  | 1.983     | 0.08           |
| <i>HPRT</i>   | 4.952     | 0.03           |
| <i>DXS10</i>  | 1.783     | 0              |
| <i>DXS102</i> | 1.142     | 0              |

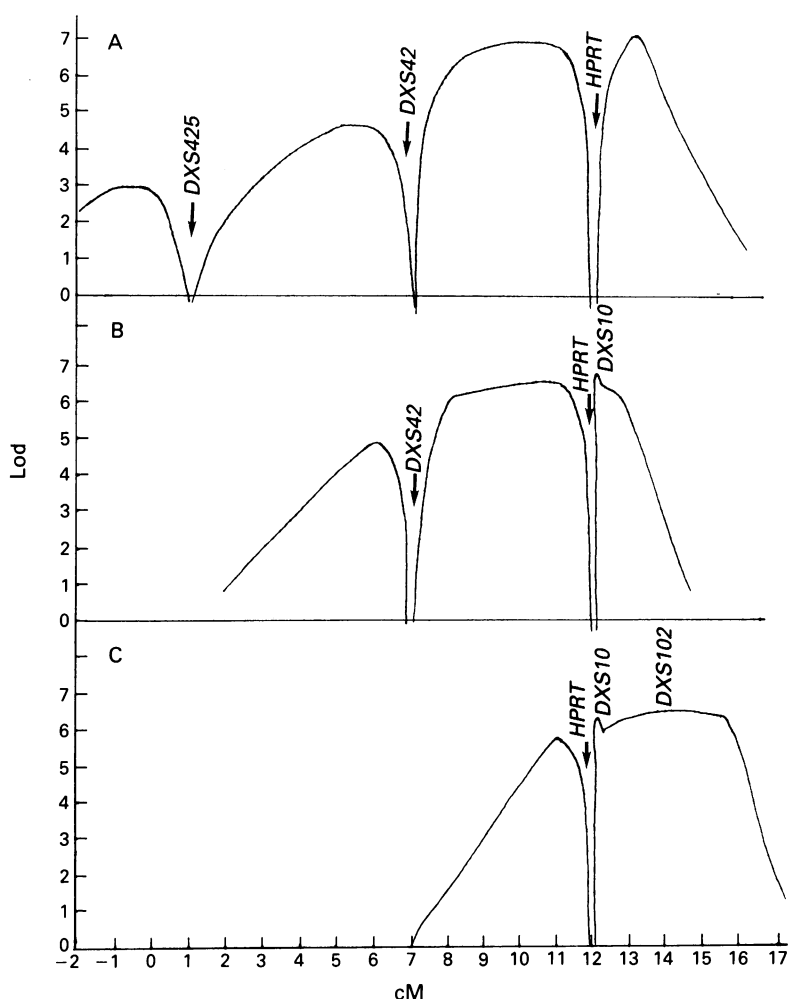


Figure 2 Multipoint linkage analysis of *HIGM1*. The disease plus three markers were analysed in each case. (A) *DXS425-DXS42-HPRT*, (B) *DXS42-HPRT-DXS10*, (C) *HPRT-DXS10-DXS102*.

pletely isolated in a set of YACs covering 8 Mb of DNA.<sup>20</sup> *HPRT* is at the centromeric end of this YAC contig and *DXS10* is 1 Mb distal. *DXS102* is 5.7 Mb distal within 200 kb of factor 9. The genetic distances from *HPRT* to the proximal markers *DXS425* (11 cM) and *DXS42* (5cM) were taken from published work.<sup>18,19</sup> The genetic distance between *HPRT* and *F9* has been measured<sup>18</sup> as 2.5 cM. This is lower than would be expected from the physi-

cal distance between the genes of 5.9 Mb and indicates that this is a region of low recombination. Based on the known physical distances between *HPRT-DXS10-DXS102*, and *F9* the genetic distances were set at *HPRT-0.2 cM-DXS10-2.5 cM-DXS102*.

Recombinations between *DXS425* and the disease locus were found in families Cou, MM, and WG. In family Cou recombinations between *DXS425* and *HIGM1* were found in the meioses between subject II.4 and one of her daughters III.4 or III.8 both of whom are obligate carriers, and between III.4 and her unaffected son IV.1. In the first case *HPRT* also recombines with the disease, but in the second there is a recombination between *DXS425* and *HPRT* with *HPRT* segregating with the disease. This is the only recombinant between *HPRT* and *HIGM1* and the two point lod score is 4.89 at a recombination fraction of 0.05. No definite recombinations were found with *DXS10* or *DXS102* making the exact position of *HIGM1* unclear.

Five of the six families were tested with probe 43-15 (*DXS42*). Family HB showed a recombination between *DXS42* and *HIGM1*. The same meiosis did not recombine with *HPRT* confirming a localisation of the disease gene distal to *DXS42*. The most distal marker tested, *DXS102*, showed no definite recombinations.

## Discussion

Our multipoint linkage analysis in six *HIGM1* pedigrees show that the locus for *HIGM1* is closely linked to the *HPRT* locus on Xq26.1. We found a maximum lod score of 4.89, which makes the *HPRT* polymorphism, together with its high heterozygosity value, useful in genetic counselling. This is important, as the finding of random X chromosome inactivation patterns in B and T cells<sup>1</sup> preclude carrier detection by X chromosome inactivation analyses.

The localisation of *HIGM1* makes testing of candidate genes possible. Unlike X linked agammaglobulinaemia where there is usually a complete absence of circulating B cells, in this disease IgM and IgD expressing B cells are normal or increased while those expressing other isotypes are decreased. However, the finding of random X inactivation patterns in B cells expressing IgM, IgG, and IgA as well as the T cell series, in at least some families, makes it unlikely that the defect is of B cell origin.<sup>6,21</sup>

The clinical features of X linked agammaglobulinaemia and hyper IgM syndrome differ. In both diseases, not surprisingly, bacterial infections predominate and severe mouth

ulcers and neutropenia may occur as presenting features.<sup>3</sup> However, despite no laboratory evidence of any T cell mediated immunodeficiency in either disease, it is only in patients with the X linked hyper IgM syndrome that opportunistic infections such as *Pneumocystis carinii*, *cryptosporidium*, and *aspergillosis*, so characteristic of cell mediated immunodeficiency, occur (Morgan and Levinsky, personal communication).

The genotype of HIGM1 could not be distinguished from XLP as both loci were mapped to Xq25-26 and in both diseases the B and T cell populations manifest random X chromosome inactivation. Our finding of a recombination between *HIGM1* and *HPRT* indicates that *HIGM1* is located distal to *HPRT*. This implies that *HIGM1* is not allelic to *XLP* as linkage data and the finding of Xq25 deletions in *XLP* indicate that *XLP* is proximal to the *HPRT* locus.<sup>22</sup>

Since isotype switching is thought to be under T cell control, a defect in this mechanism would be more likely and this is supported by the description of a Sezary cell derived T cell clone being able to induce B cells from X linked hyper IgM patients to produce IgG in culture.<sup>23</sup> The factor involved has not yet been described but the finding of several new cytokines and their receptor ligands acting on B cells either to induce differentiation or isotype switching make these possible candidate genes.<sup>24 25</sup>

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### For The Blind to support gene mapping of autosomal dominant nystagmus.

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### Corrections

In the paper by Richards *et al* on 'Detailed genetic mapping of the von Hippel-Lindau disease tumour suppressor gene' (*J Med Genet* 1993;30:104-7), an important collaborator, Dr Per Enblad, was inadvertently omitted from the authorship. The correct authorship is as follows.

Richards FM, Maher ER, Latif F\*, Phipps ME, Tory K\*, Lush M, Crossey PA, Oostra B†, Enblad P‡, Gustavson KH‡, Green J§, Turner G||, Yates JRW, Linehan M¶, Affara NA, Lerman M\*, Zbar B\*, Ferguson-Smith MA.

Cambridge University Department of Pathology, Cambridge, UK; \*Laboratory of Immunobiology, National Cancer Institute, Frederick Cancer Research Facility, Frederick, USA; †Erasmus University, Rotterdam, The Netherlands; ‡University of Uppsala, Sweden; §Division of Community Medicine, Memorial University of Newfoundland, Canada; ||Yorkshire Regional Genetics Service and ICRF Genetic Epidemiology Laboratory, Leeds, UK; ¶Surgery Branch, National Cancer Institute, USA.

In the paper by Padayachee *et al* on 'Mapping of the X linked form of hyper IgM syndrome (HIGM1)' (*J Med Genet* 1992;30:202-5), the primer sequence for DXS102<sup>13</sup> under the heading OLIGONUCLEOTIDE PRIMERS was referenced Luty *et al*. This is incorrect and should be:

Gedeon AK, Holmon K, *et al*. Characterization of new pcr based markers for mapping and diagnosis: AC dinucleotide repeat markers at the DXS237 (GMGX9) and DXS102 (cX38.1) loci. *Am J Med Genet* 1992;43:255-60.