A second locus for Aicardi-Goutiéres syndrome at chromosome 13q14-21

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Key words: Aicardi-Goutiéres syndrome, intracranial calcification, interferon alpha, AGS2, 13q14-21

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Abstract

Introduction:
Aicardi-Goutières syndrome (AGS) is an autosomal recessive, early onset encephalopathy characterised by calcification of the basal ganglia, a chronic cerebrospinal fluid lymphocytosis and negative serological investigations for common prenatal infections. AGS may result from a perturbation of interferon alpha metabolism. The disorder is genetically heterogeneous with approximately 50% of families mapping to the first known locus at 3p21 (AGS1).

Methods:
A genome-wide scan was performed in 10 families with a clinical diagnosis of AGS in whom linkage to AGS1 had been excluded. Following two-point analysis of this data set, we undertook higher-density genotyping in regions of interest using the 10 mapping pedigrees and 7 additional AGS families.

Results:
Our results demonstrate significant linkage to a second AGS locus (AGS2) at chromosome 13q14-21 with a maximum multipoint heterogeneity LOD score of 5.75 at D13S768. The AGS2 locus lies within a 4.7 cM region as defined by a 1 LOD-unit support interval. No obvious phenotypic differences are evident between individuals from families linking to AGS1, AGS2 and other, as yet unmapped, AGS loci.

Conclusions:
We have identified a second AGS disease locus. Our data confirm that at least one further locus exists for this disorder. As in a number of other conditions, genetic heterogeneity represents a significant obstacle to gene identification in AGS. The localisation of AGS2 represents an important step in this process. The cloning of AGS-causing genes will provide novel insights into a neurodegenerative mechanism likely resulting from exposure of the developing human brain to abnormally high levels of interferon alpha.
Introduction:
Aicardi-Goutières syndrome (AGS; MIM 225750) is an autosomal recessive encephalopathy characterised by cerebral atrophy, leukodystrophic changes, intracranial calcification, a chronic cerebrospinal fluid (CSF) lymphocytosis, raised levels of interferon alpha (IFN-α) in the CSF and negative serological investigations for common prenatal infections (MIM 225750).[1][2] Clinically, AGS can usefully be considered as a Mendelian mimic of congenital viral infection. Recognition of the condition is therefore important because of the possibility for misdiagnosis as a non-genetic disorder and counseling of a falsely low risk of recurrence.

The features of AGS may have a prenatal onset or develop over the first few months of life. [2][3] Typically, neurodegeneration is associated with microcephaly, spasticity, dystonic posturing and psychomotor retardation. Death frequently occurs within the first decade. However, we are aware of several children in their teenage years with apparently non-progressive disease. Systemic abnormalities include fever, raised levels of immunoglobulins and autoantibodies, thrombocytopenia, deranged liver function with hepatosplenomegaly and chilblain-like cutaneous lesions.[2] [4][5][6][7]

Levels of CSF IFN-α are consistently elevated in the early stages of AGS and significantly higher than those recorded systemically.[2] [8] Such raised levels of CSF IFN-α are not always accompanied by a CSF lymphocytosis.[9] IFN-α does not cross the blood brain barrier so that when 100 IU/ml of IFN-α is experimentally released into the blood, < 1 IU/ml is detected in the CSF.[10] It is likely then that in AGS, IFN-α is produced intrathecally, possibly by astrocytes or microglia.[11][12]

The pathological finding of wedge-shaped infarctions together with patchy myelin loss and calcified deposits in the media, adventitia and perivascular space of small blood vessels suggests that AGS may represent a genetic cerebral angiopathy.[13] IFN-α is known to have an inhibitory effect on angiogenesis and astrocyte-specific chronic overproduction of IFN-α in transgenic mice recapitulates the neuropathological findings seen in AGS. [14][15][16][17] These observations raise the possibility that the AGS phenotype results from exposure of the developing brain to high levels of IFN-α. Identification of the causative genetic defect in AGS may, therefore, provide novel insights into IFN-α metabolism.

Previously, we identified linkage to an interval on 3p21 in 48% of AGS families tested.[18] Locus heterogeneity was considered the explanation for a failure to identify genetic linkage in a previous study.[19] Since then, we have refined the AGS1 critical interval to a 3.47 cM region by demonstrating that AGS and Cree encephalitis are allelic disorders.[9]

Given that half of the families in our cohort were unlinked to the AGS1 locus, we performed a genome-wide scan using 10 families incompatible with linkage to AGS1. Herein, we report the identification of a second AGS locus at chromosome 13q14-21 resulting from an analysis of this data set.

METHODS:

Subjects:
For inclusion in the study, affected individuals demonstrated a compatible neurological phenotype with intracranial calcification and a CSF lymphocytosis (>5 cells/mm³) and/or raised levels of IFN-α in the CSF (> 2 IU/ml)(measured with a biological assay) as well as negative investigations for common prenatal infections.[2]

17 families (15 consanguineous and 2 non-consanguineous comprising 3 affected siblings) satisfied the inclusion criteria (tables 1 and 2). Blood samples were obtained with consent from affected children, their parents, and unaffected siblings where possible, for DNA extraction, genotyping and subsequent linkage analysis. The study was approved by the Leeds Health Authority / United Teaching Hospitals NHS Trust Research Ethics Committee.
<table>
<thead>
<tr>
<th>Family/Patient (Ethnicity)</th>
<th>Age at presentation</th>
<th>Birth OFC in centiles (gestation in weeks)</th>
<th>Postnatal OFC in centiles (age in months)</th>
<th>Brain calcification</th>
<th>CSF WCC/mm³ * (age in months)</th>
<th>IFN-α IU/ml in CSF/serum† (age in months)</th>
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<tbody>
<tr>
<td>1/IV:3 (Algerian)</td>
<td>Birth</td>
<td>2ᵦ - 9ᵦ (40)</td>
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<td>BG</td>
<td>na</td>
<td>na</td>
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<tr>
<td>2/IV:2 (Algerian)</td>
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<td>75ᵦ - 91ᵦ (40)</td>
<td>NR</td>
<td>BG</td>
<td>43 (10)</td>
<td>16 / 4 (10); &lt;4 / &lt;2 (60)</td>
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<tr>
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<td>50ᵦ (40)</td>
<td>75ᵦ (108)</td>
<td>BG; WM</td>
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<td>&lt;2 / na (108)</td>
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<td>50ᵦ (40)</td>
<td>3ᵦ (21)</td>
<td>BG</td>
<td>8 (7)</td>
<td>6 / &lt;2 (7)</td>
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<tr>
<td>4/IV:1 (Moroccan)</td>
<td>7 months</td>
<td>NR</td>
<td>NR</td>
<td>BG</td>
<td>25 (2)</td>
<td>&gt;100 / na (2)</td>
</tr>
<tr>
<td>5/IV:1 (Italian)</td>
<td>2 months</td>
<td>9ᵦ (40)</td>
<td>&lt;3ᵦ (132)</td>
<td>BG; WM</td>
<td>22 (8)</td>
<td>na</td>
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<tr>
<td>6/II:1 (Dutch)</td>
<td>3 weeks</td>
<td>NR</td>
<td>30ᵦ (84)</td>
<td>BG, WM</td>
<td>13 (4)</td>
<td>18 / na (3)</td>
</tr>
<tr>
<td>6/II:2</td>
<td>3 weeks</td>
<td>9ᵦ (39)</td>
<td>30ᵦ (60)</td>
<td>BG</td>
<td>13 (2)</td>
<td>37 / na (48)</td>
</tr>
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<td>2-3 weeks</td>
<td>25ᵦ - 50ᵦ (38)</td>
<td>NR</td>
<td>BG</td>
<td>0 (78)</td>
<td>&lt;2 / &lt;2 (78)</td>
</tr>
<tr>
<td>7/II:1 (French)</td>
<td>4 months</td>
<td>75th - 91ᵦ (40)</td>
<td>NR</td>
<td>BG</td>
<td>22 (6)</td>
<td>32 / 12 (6)</td>
</tr>
<tr>
<td>7/II:2</td>
<td>5 months</td>
<td>NR</td>
<td>NR</td>
<td>BG</td>
<td>39 (9)</td>
<td>50 / 6 (9)</td>
</tr>
<tr>
<td>7/II:3</td>
<td>8 months</td>
<td>NR</td>
<td>NR</td>
<td>BG</td>
<td>97 (24)</td>
<td>na</td>
</tr>
<tr>
<td>8/IV:1 (Spanish)</td>
<td>1 month</td>
<td>‘Normal’</td>
<td>‘Microcephaly’ (18)</td>
<td>BG</td>
<td>38 (18)</td>
<td>na</td>
</tr>
<tr>
<td>8/IV:3</td>
<td>10 days</td>
<td>‘Normal’</td>
<td>‘Microcephaly’ (18)</td>
<td>BG</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

Table 1. Clinical characteristics of affected individuals from families consistent with linkage to AGS2

OFC = occipito-frontal circumference. CSF = cerebrospinal fluid. WCC = white cell count. BG = basal ganglia. WM = white matter. PV = periventricular. na = not analysed. nr = not recorded.

*Abnormal ≥ 5 cells/mm³ †Normal levels <2 IU/l
<table>
<thead>
<tr>
<th>Family/Patient (Ethnicity)</th>
<th>Age at presentation</th>
<th>Birth OFC in centiles (gestation in weeks)</th>
<th>Postnatal OFC in centiles (age in months)</th>
<th>Brain calcification</th>
<th>CSF WCC/mm³ * (age in months)</th>
<th>IFN-α IU/ml in CSF/serum† (age in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/IV:1 (Pakistani)</td>
<td>Antenatal</td>
<td>9th - 25th (38)</td>
<td>nr</td>
<td>BG; WM; PV</td>
<td>63 (2)</td>
<td>na</td>
</tr>
<tr>
<td>10/IV:1 (Algerian)</td>
<td>Birth</td>
<td>25th - 50th (40)</td>
<td>&lt;0.4th (132)</td>
<td>BG</td>
<td>26 (&lt;1)</td>
<td>60 / 16 (&lt;1); 90 / &lt;10 (2)</td>
</tr>
<tr>
<td>10/IV:3</td>
<td>Birth</td>
<td>9th (40)</td>
<td>&lt;0.4th (72)</td>
<td>BG</td>
<td>10 (&lt;1)</td>
<td>60 / 30 (&lt;1); 30 / 24 (3)</td>
</tr>
<tr>
<td>11/IV:1 (Moroccan)</td>
<td>4 months</td>
<td>nr</td>
<td>&lt;0.4th (72)</td>
<td>BG</td>
<td>23 (6); 11 (12)</td>
<td>6 / &lt;2 (12)</td>
</tr>
<tr>
<td>11/IV:2</td>
<td>Birth</td>
<td>nr</td>
<td>&lt;0.4th (36)</td>
<td>BG</td>
<td>36 (3)</td>
<td>na</td>
</tr>
<tr>
<td>12/IV:1 (Hungarian)</td>
<td>2 months</td>
<td>nr</td>
<td>'Microcephaly' (25)</td>
<td>PV</td>
<td>22 (25)</td>
<td>na</td>
</tr>
<tr>
<td>12/IV:2</td>
<td>&lt; 12 months</td>
<td>nr</td>
<td>'Microcephaly' (48)</td>
<td>PV</td>
<td>80 (48)</td>
<td>na</td>
</tr>
<tr>
<td>13/IV:1 (Pakistani)</td>
<td>6 months</td>
<td>nr</td>
<td>&lt;&lt; 3rd</td>
<td>BG</td>
<td>21 (6)</td>
<td>32 / 4 (6)</td>
</tr>
<tr>
<td>13/IV:2</td>
<td>Birth</td>
<td>30th (40)</td>
<td>nr</td>
<td>BG</td>
<td>nr</td>
<td>200 / 9 (birth); na / 18 (3)</td>
</tr>
<tr>
<td>14/IV:1 (Dutch)</td>
<td>8 months</td>
<td>'Normal'</td>
<td>3rd (60)</td>
<td>BG</td>
<td>14 (13)</td>
<td>na</td>
</tr>
<tr>
<td>14/IV:3</td>
<td>12 months</td>
<td>'Normal'</td>
<td>75th - 95th (36)</td>
<td>BG</td>
<td>550 (30)</td>
<td>na</td>
</tr>
<tr>
<td>15/IV:2 (Pakistani)</td>
<td>8 months</td>
<td>'Normal'</td>
<td>75th - 95th (36)</td>
<td>BG</td>
<td>0 (84)</td>
<td>&lt;2 / &lt;2 (84)</td>
</tr>
<tr>
<td>15/IV:3</td>
<td>6 months</td>
<td>80th (34)</td>
<td>&lt;0.4th (9)</td>
<td>BG</td>
<td>4 (11)</td>
<td>3 / &lt;2 (11)</td>
</tr>
<tr>
<td>16/IV:1 (Belgian)</td>
<td>4 months</td>
<td>25th (38)</td>
<td>nr</td>
<td>BG; PV</td>
<td>38 (4)</td>
<td>na</td>
</tr>
<tr>
<td>17/IV:1 (Spanish)</td>
<td>Birth</td>
<td>&lt;0.4th (37)</td>
<td>&lt;0.4th (84)</td>
<td>BG</td>
<td>25 (&lt;1)</td>
<td>na</td>
</tr>
<tr>
<td>17/IV:2</td>
<td>1 week</td>
<td>&lt;0.4th (40)</td>
<td>&lt;0.4th (13)</td>
<td>BG; WM</td>
<td>52 (1)</td>
<td>70 / na (1)</td>
</tr>
</tbody>
</table>

OFC = occipito-frontal circumference. CSF = cerebrospinal fluid. WCC = white cell count. BG = basal ganglia. WM = white matter. PV = periventricular. na = not analysed. nr = not recorded.

*Abnormal ≥ 5 cells/mm³ †Normal levels <2 IU/l
**Genotyping:**
All included families were initially genotyped across the AGS1 critical region. These families either gave LOD scores of < -2 across this interval or, where the family was too small to allow for statistical exclusion, consanguineous affected individuals showed a number of heterozygous markers within the critical region (data not shown).

A genome-wide scan was performed in 10 pedigrees (families 1, 2, 3, 6, 7, 8, 11, 15, 16, and 17) by the National Heart, Lung and Blood Institute (NHLBI) (http://research.marshfieldclinic.org/genetics/) genotyping facility using 404 polymorphic markers spaced at approximately 10 cM intervals.[20] For higher-density genotyping across the AGS2 interval, information regarding marker order and genetic distance was obtained from the Marshfield Linkage Maps (http://research.marshfieldclinic.org/genetics) and the May 2004 freeze of the Human Genome Browser (http://genome.ucsc.edu/). After individually optimised PCR amplification, markers were analysed using previously described methods.[18]

**Linkage analysis:**
A model of autosomal recessive inheritance with full penetrance was used with a disease allele frequency estimated at 1 in 500. Marker allele frequencies were calculated from transmitted and non-transmitted parental alleles with a minimum marker allele frequency set at 0.05. Genetic map distances were taken from the Marshfield map. Pedigree allele inconsistencies were identified using PedCheck.[21] Two-point analysis was performed with the LINKAGE program.[22] Multipoint LOD scores and heterogeneity testing were computed by means of the GENEHUNTER program, version 2.0 beta.[23]

**RESULTS:**
An initial genome screen was performed using 8 consanguineous families and 2 non-consanguineous pedigrees. Under the hypothesis of locus heterogeneity, the highest HLOD score obtained after two-point linkage analysis of this data set was at D13S768 (HLOD score of 2.41 with recombination fraction \( \theta = 0 \)) for each family at specified markers.

Further genotyping using polymorphic microsatellite markers around D13S768 was undertaken on the original 10 families and an additional 7 consanguineous pedigrees satisfying the inclusion criteria (figs 1 and 2). Two point LOD scores for the individual pedigrees are given in table 3 with the highest individual score obtained in Family 1. Under the hypothesis of locus heterogeneity, a maximum multipoint HLOD score of 5.75 was obtained at marker D13S768 with \( \alpha = 0.43 \) (where \( \alpha \) is the population of linked families) (fig 3). Construction of a 1 LOD-unit support measure suggests the AGS2 critical region encompasses an approximately 4.7 cM interval (fig 3).

**Table 3. Two-point LOD scores (\( \theta = 0 \)) for each family at specified markers**

<table>
<thead>
<tr>
<th>Family Number</th>
<th>D13S325</th>
<th>D13S291</th>
<th>D13S623</th>
<th>D13S284</th>
<th>D13S768</th>
<th>D13S176</th>
<th>D13S1309</th>
<th>D13S634</th>
<th>D13S800</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.75</td>
<td>-0.73</td>
<td>-1.47</td>
<td>2.46</td>
<td>1.19</td>
<td>1.34</td>
<td>0.96</td>
<td>-1.1</td>
<td>1.34</td>
</tr>
<tr>
<td>2</td>
<td>-0.6</td>
<td>-1.20</td>
<td>1.11</td>
<td>1.25</td>
<td>1.67</td>
<td>1.13</td>
<td>-0.61</td>
<td>-0.81</td>
<td>0.52</td>
</tr>
<tr>
<td>3</td>
<td>-1.6</td>
<td>-0.97</td>
<td>-0.88</td>
<td>1.04</td>
<td>0.76</td>
<td>0.68</td>
<td>1.22</td>
<td>1.09</td>
<td>-0.83</td>
</tr>
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<td>4</td>
<td>0.8</td>
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<td>0.89</td>
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<td>0.57</td>
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<td>0.94</td>
<td>0.81</td>
</tr>
<tr>
<td>5</td>
<td>0.23</td>
<td>0.40</td>
<td>0.88</td>
<td>0.79</td>
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DISCUSSION:

Our search for outstanding AGS disease loci was initiated by the previously observed genetic heterogeneity. We report here the mapping of the AGS2 locus to chromosome 13q14-21, with a maximum multipoint HLOD score of 5.75. This exceeds the accepted threshold value of 3.3 for significant linkage of a Mendelian disorder in the presence of locus heterogeneity.[24] On this basis, our data establish the existence of a novel AGS locus, AGS2, on chromosome 13q14-21 and suggest that mutations in at least one other, as yet unmapped, gene produce a similar phenotype.

Based on the minimum region of shared homozygous markers between consanguineous families, the AGS2 critical interval covers a genetic distance of less than 5 cM (D13S284 to D13S1309)(fig 1). However, no single family shows independent linkage to AGS2 (i.e. a LOD score >3)(table 3). Consequently, the AGS2 critical interval is most appropriately defined using a 1 LOD-unit support interval (fig 3).[25] On this basis, the AGS2 locus contains approximately 70 genes and unannotated transcripts. Of note, the majority of these genes are positioned toward the centromeric end of the AGS2 locus. Consequently, refinement of the region may significantly reduce the number of positional candidate genes. To this end, work to identify shared ancestral haplotypes within the critical region is ongoing.

We were unable to discern any obvious differences in the clinical characteristics of those families linking to either AGS1, AGS2 or other, as yet undefined, AGS loci (tables 1 and 2). However, phenotypic differences may become apparent when the genes for AGS are eventually identified. In particular, gene identification will enable the issue of phenotypic overlap of AGS with pseudo-TORCH syndrome to be addressed.[9] Some patients demonstrate elevated levels of CSF IFN-α even when the number of white cells in the CSF is not raised. In the absence of CSF IFN-α measurements, such cases might be inappropriately considered as pseudo-TORCH syndrome. Furthermore, Blau et al. recently described 3 children with intracranial calcification and a neurological phenotype reminiscent of AGS in whom both CSF white cells and IFN-α were consistently normal.[26] A molecular basis for classifying these disorders will therefore be of significant clinical utility.

The mechanism responsible for the elevated levels of CSF IFN-α observed in AGS is not understood. In general terms, such a finding might result from the loss of a negative regulator of IFN-α production or the presence of an IFN-α inducer normally absent from the central nervous system. None of the genes within the AGS2 critical interval are known to have such a role and we have been unable to recognise any obvious paralogs or genes from the same cellular pathway within the AGS1 and AGS2 critical intervals.

AGS is a Mendelian mimic of congenital viral infection that continues to be overlooked in the clinical diagnosis of in-utero infection.[27] The concept of AGS as a primary genetic ‘interferon-opathy’ highlights a possible unifying theme in the neuropathogenesis of AGS, congenital viral infection and cerebral systemic lupus erythematosus.[9] Consequently, identification of the genes responsible for AGS may provide novel insights into a common neurodegenerative mechanism resulting from exposure of the developing human brain to abnormally high levels of IFN-α. As in a number of other disorders such as Joubert syndrome, Walker-Warburg syndrome and Meckel-Gruber syndrome, genetic heterogeneity poses a significant obstacle to defining the molecular basis of AGS. Localisation of the AGS2 locus represents an important step towards gene identification in AGS.

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Conflict of interest; None declared

Figure legends:


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Figure 1. Genotype data for families consistent with linkage to AGS2

Figure 2. Genotype data for families unlikely to be linked to the AGS2 locus

Figure 3. Graph of multipoint HLOD scores across AGS2
REFERENCES


Figure 1. Genotype data for families consistent with linkage to AGS2

**Marker** | **Distance cM** | **Physical distance**
---|---|---
D13S325 | 38.96 | 42,071,250
D13S291 | 41.71 | 43,717,142
D13S623 | 43.9 | 43,191,439
D13S264 | 45.55 | 50,613,202
D13S768 | 47.19 | 54,577,350
D13S176 | 48.26 | 59,411,665
D13S1309 | 50.47 | 66,739,269
D13S634 | 51.57 | 67,542,140
D13S800 | 55.31 | 72,772,650

*Marshfield chromosome 13 map
**May 2004 freeze of the Human Genome Browser

Family 1

Family 2

Family 3

Family 4

Family 5

Family 6

Family 7

Family 8
Figure 2. Genotype data for families unlikely to be linked to the AGS2 locus

See Figure 1 for key

Family 9

Family 10

Family 11

Family 12

Family 13

Family 14

Family 15

Family 16

Family 17
Figure 3. Graph of multipoint HLOD scores across AGS2

- HLOD
- alpha

Distance (cM, Marshfield)

Markers and Distances:
- D1S295: 38.96
- D1S291: 4.11
- D1S293: 13.9
- D1S294: 45.55
- D1S176: 71.19
- D1S176: 82.28
- D1S1309: 50.44
- D1S1304: 51.59
- D1S800: 55.31

*Marshfield chromosome 13 map*
A second locus for Aicardi-Goutiéres syndrome at chromosome 13q14-21


*J Med Genet* published online May 20, 2005

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