The inherited ataxias and the new genetics

The powerful new tools of genetic investigation are steadily expanding our understanding of the molecular basis of inherited neurological disease. This is particularly so in the context of the inherited ataxias, in which nosological difficulties are beginning to be resolved by a genetically based classification. Harnessing the new knowledge will bring further rewards, including molecular genetic diagnosis, definition of clinical phenotypes, elucidation of pathophysiology, and the possibility of new treatments. Many metabolic disorders include ataxia as a more or less prominent feature. Traditionally it has been useful to distinguish these disorders from the "idiopathic" inherited ataxias, although the distinction is already seeming artificial as pathological mechanisms are elucidated. This review considers the impact of the new knowledge on the inherited ataxias previously considered idiopathic.

Classification of the idiopathic inherited ataxias

Although pathological study has provided insights into the anatomy and pathophysiology of the ataxias, pathologically based classifications have proved unsatisfactory when clinical features and inheritance (and recently, molecular genetic data) are not considered. With some exceptions, clinical criteria alone are also inadequate, as there may be discordance even between affected ataxic siblings in features such as areflexia or ophthalmoplegia. Harding's classification is based on mode of inheritance together with clinical criteria (table 1) and is increasingly accepted. The principles of this classification have withstood the genetic discoveries of the past decade. This article presents the new genetic data on this framework.

The autosomal recessive ataxias

FRIEDREICH'S ATAXIA

Between 1863 and 1877 Friedreich reported the distinctive clinical syndrome that was to bear his name. It is the commonest genetic ataxia and is of autosomal recessive inheritance, with progressive gait and limb ataxia as the cardinal features. It is associated with lower limb areflexia; dysarthria, pyramidal weakness, and sensory loss manifest later in the course of the disease. In 1981 Harding proposed diagnostic criteria (table 2), which defined a genetically homogenous group; linkage to markers on chromosome 9 was demonstrated in 1988. Further work allowed more precise localisation and identification of candidate genes.

Campuzano et al recently identified one such candidate gene (X25) within the critical region on chromosome 9. One fragment of the gene was noticed to contain an expansion, leading to the discovery of a GAA trinucleotide repeat within intron 1 of the gene. Normal chromosomes contain 10-21 GAA repeats, but nearly 95% of Friedreich's ataxia chromosomes contained between 200 and 900 GAA trinucleotide repeats. Of 79 unrelated patients with typical Friedreich's ataxia Campuzano et al found homozygosity for the expanded allele in 71, and heterozygosity in the remaining eight. Five of the eight had point mutations detected within X25.

The X25 gene product, termed frataxin, contains 210 amino acids. The gene comprises six exons, with evidence of alternate splicing. There is no resemblance to other known genes, and as yet it is not possible to predict the function of frataxin. Northern blots show that X25 expression is high in the heart, with intermediate levels in the liver, skeletal muscle, and pancreas, and minimal levels in other tissues, including whole brain. Comparison between CNS tissues showed high expression in the spinal cord, less in the cerebellum, and very little in the cerebral cortex. Messenger RNA concentrations were undetectable or extremely low in patients with Friedreich's ataxia, suggesting that the mutation causes interference in transcription or RNA processing. Reduced frataxin in the heart and...
spinal cord is probably the primary cause of neuronal degeneration, cardiomyopathy, and increased risk of diabetes. Although trinucleotide repeats are now familiar in autosomal dominant neurological diseases (particularly the ataxias; see below), the repeat within the frataxin gene is the first associated with an autosomal recessive disease. However, it seems to share some characteristics with previously characterised trinucleotide repeats in that the repeat is unstable, showing variation in repeat number within an individual subject as well as on transmission between generations.

The precise range of disease associated with the Friedreich's ataxia genotype will be defined in the near future by the application of direct mutational analysis. However, the use of linkage data has already provided useful information. Harding and Geoffroy et al proposed criteria excluding patients with onset after 25 and 20 years respectively. Yet there are kindreds with later onset of disease who have otherwise similar features (late onset Friedreich's ataxia). These families are linked to the same chromosome 9 markers as in classic Friedreich's ataxia. Comparison between late onset Friedreich's ataxia and classic Friedreich's ataxia showed no differences except a lower incidence of skeletal deformity and a relatively benign course, with patients with late onset Friedreich's ataxia taking five years longer than patients with Friedreich's ataxia to progress from onset to being confined to a wheelchair. Neurophysiology and neuroimaging did not differentiate between the two groups. A further interesting group are those patients who satisfy the criteria for diagnosis of Friedreich's ataxia with the exception of preserved reflexes. Studies of 11 patients from six families with the Friedreich's ataxia phenotype including cardiomyopathy, but with retained reflexes (FARR) confirmed linkage to the Friedreich's ataxia locus. Thus both FARR and late onset Friedreich's ataxia are likely to be allelic variants of Friedreich's ataxia. It is interesting to speculate that severity of phenotype may be related to the GAA repeat numbers within the frataxin allele. These data erode the value of early age of onset and areflexia as essential criteria for Friedreich's ataxia, although these features remain supportive of the diagnosis. The phenotypic range associated with the Friedreich's ataxia genotype clearly extends beyond that of classic Friedreich's ataxia given in Table 2. In clinical diagnosis, particular importance should be attached to confirmation of a sensory axonal neuropathy, which is present even in the variant FARR and late onset Friedreich's ataxia phenotypes. An ECG or echocardiogram consistent with the Friedreich's ataxia cardiomyopathy is also very helpful diagnostically, if present. Nevertheless, it is likely that some patients with the Friedreich's ataxia genotype may have neither cardiomyopathy nor severe sensory axonal neuropathy. Although in many cases a confident diagnosis of Friedreich's ataxia can be made clinically, the arrival of frataxin gene mutational analysis will allow surer diagnosis of atypical patients, with implications for prognosis and genetic counselling.

OTHER AUTOSOMAL RECESSIVE ATAXIAS

Harding described a group of patients with early onset cerebellar ataxia distinguished from Friedreich's ataxia by retained reflexes (EOCARR), less than one quarter as common as Friedreich's ataxia. Clinically, EOCARR differs from Friedreich's ataxia not only with respect to tendon reflexes, but also because of an absence of optic atrophy, cardiac involvement, diabetes mellitus, or severe skeletal deformity. However, the relation of EOCARR to FARR is not well defined, and some patients with EOCARR as originally described may prove to have a frataxin mutation. The absence of sensory neuropathy and MRI findings of cerebellar rather than spinal atrophy supports the diagnosis of EOCARR. Although classification of some patients is difficult, distinction between Friedreich's ataxia and EOCARR is not trivial; patients with EOCARR have a better prognosis than that of patients with Friedreich's ataxia. Inheritance is thought to be autosomal recessive in most cases.

ATAXIA WITH ISOLATED VITAMIN E DEFICIENCY (AVED)

Secondary vitamin E deficiency (precipitated by αβ-lipoproteinaemia or other fat malabsorptive syndromes) is well known to be associated with neurological manifestations including ataxia. In 1981 familial isolated vitamin E deficiency was first described, and this was followed by other reports. In these patients without gastrointestinal disturbance, onset of symptoms occurs between four and 18 years of age, with progressive ataxia, areflexia, sensory loss and pyramidal signs, and sometimes with cardiomyopathy. Thus AVED is a phenocopy of Friedreich's ataxia and estimation of vitamin E is mandatory in all cases of suspected Friedreich's ataxia. However, although AVED is common (relative to Friedreich's ataxia) in north Africa, it seems to be relatively uncommon in northern Europe. It was linked to chromosome 8q13 in 1993. Ouahchi et al subsequently identified mutations in the α-tocopherol transfer protein (TTP) on chromosome 8 in patients with AVED. Patients with AVED have an impaired ability to incorporate α-tocopherol into lipoproteins secreted by the liver, a function attributable to the α-TTP gene. α-Tocopheryl acetate therapy can arrest or reverse the neurological deficit. One exciting possibility is that Friedreich's ataxia is a defect of vitamin E metabolism, allowing the hope of directed therapies in the future.

The autosomal dominant cerebellar ataxias

The ADCAs are heterogenous, both clinically and genetically. They have provided a nosological challenge and many different classifications have been proposed. Pure syndromes are outnumbered by those that include additional features relating to the retina, optic nerves, extrapyramidal pathways, cerebral cortex, brainstem, spinal cord, and peripheral nerve. Harding separated ADCA with pigmented macular dystrophy (ADCA type II) from the other complicated ADCAs, which were classified as ADCA type I (table 1). ADCA type III denotes a
relatively pure, usually late onset (> 50 years) cerebellar ataxia. Type IV indicates the additional features of deafness and neuropathy, but may no longer be a useful concept. Such families were described before mitochondrial encephalomyopathies were recognised, and might now be recognised as having the syndrome of myoclonic epilepsy with ragged red fibres (MERRF)."  

**ADCA TYPE I**

Patients typically present with a progressive cerebellar syndrome with additional features that become more frequent as the disease progresses and include supranuclear ophthalmoplegia, slow ocular saccades, optic atrophy, extrapyramidal features, mild dementia, facial, lingual, or limb fasciculation, increased or decreased tendon reflexes, and sensory loss. Onset may be from childhood to the eighth decade but is most common in middle life. The pathological diagnosis is usually olivopontocerebellar atrophy.

**The SCA1 mutation**

The first step in the genetic analysis of ADCA I was made in 1974 when linkage to HLA loci on chromosome 6 was suspected. Further linkage studies established that some but not all families with ADCA were linked to the disease locus (designated SCA1) on chromosome 6p. A positional cloning approach culminated in the identification of an unstable trinucleotide CAG repeat sequence, confirmed by others. Expansion of the repeat was associated with disease; indeed there is an inverse correlation of repeat number with the age of onset of symptoms. The SCA1 trinucleotide expansion shares characteristics variably manifested in other trinucleotide repeat diseases (for example, Huntington's disease, myotonic dystrophy, X linked bulbospinal neuronopathy). Trinucleotide repeats are unstable, with variation in repeat number within tissues and on gametogenesis. Anticipation refers to the propensity for earlier onset and increased severity of disease in succeeding generations. Moleculary this arises from a propensity for the repeat to expand in gametogenesis. Male gametogenesis is more likely to result in repeat expansion than female gametogenesis, explaining the second finding, of severe phenotypes being more often the result of paternal transmission. In the case of SCA1, paternal transmission results in an average decrease of 0-4 repeats, whereas paternal transmission results in an average increase of 3-3 repeats.

The SCA1 triplet has a further intriguing characteristic. The normal CAG repeat is usually imperfect; about 98% of normal alleles possess an interruption in the CAG repeat (by a CAT sequence) in contrast 30/30 disease carrying chromosomes had a perfect CAG repeat sequence. Repeat numbers seen on normal alleles range from 6 to 39, and from 40-83 on SCA1 alleles. A few cases may therefore lie close to the critical length. Present evidence suggests that a perfect expansion is more likely to indicate an SCA1 carrying chromosome. The size of the SCA1 expansion is not the sole determinant of disease; in terms of age of onset the size of the expansion has been estimated to account for 66% of the variability. Studying one family with a doubly interrupted repeat, Quan et al suggested that the specific CAG repeat configuration may be important, and warned against diagnosis on expansion size alone. Other genetic loci or environmental factors are also likely to play a part.

The CAG triplet lies within the coding region and codes for the amino acid glutamine. The messenger RNA produced from an SCA1 allele is translated; thus the CAG repeat results in a polyglutamine tract. The protein has no hydrophobic region and is probably soluble; there is no homology with previously identified proteins. Because the disease is dominant the increase in length of the polyglutamine tract must in some way result in a deleterious gain in function. Identification of the homologous murine gene showed that the CAG repeat is virtually absent in the mouse. Bursts of gene expression found in early mouse development suggested that the normal murine SCA1 gene has a role at specific stages of both cerebellar and vertebral column development.

Robitaille et al studied 11 patients with SCA1 at necropsy, concluding that SCA1 was associated with a unique neuropathological phenotype characterised by severe degeneration of olivocerebellar and dentatorubrothalamic pathways, extensive loss of Purkinje cells with partial sparing of floculonodular lobes, severe atrophy of the third and 12th cranial nerve nuclei, and extensive loss of motor neurons in anterior horns and Clarke's columns. There was relative preservation of the pars compacta nigra and locus coeruleus, and no oligodendroglial or neuronal cytoplasmic cytoskeletal inclusions.

**The SCA3/MJD mutation**

Machado-Joseph disease (MJD) was initially reported in people of Azorean and Portuguese descent, and has provoked a vigorous debate with respect to its classification. Whereas ataxia is usually the predominant feature, it is maintained that MJD can be distinguished clinically by the features of staring eyes, linguo-facial fasciculations, and dystonia, and pathologically by sparing of the olives. The lumping together of many families under the rubric of ADCA I allowed Harding to include MJD in this group as the features of MJD were also seen in other ADCA I families.

The gene locus for MJD was mapped to chromosome 14q in both Japanese and Portuguese families. However, the SCA3 locus was also linked to the same region in three French families with ADCA I not considered to have MJD on clinical grounds. The underlying mutation, common to patients with MJD or SCA3, is a CAG repeat expansion (table 3). It was first identified in Japanese patients and in other racial groups. With the knowledge that SCA3 and MJD are defined by a single mutation, it is convenient and logical to consider SCA3/MJD as one disease with varying manifestations. It is incumbent on those who would split SCA3 from MJD to justify this clinically or genetically.

Guinti and colleagues found that there was no single clinical feature that differentiated MJD or SCA3 from other ADCA I families. However, it seems that the different SCA loci do have differing phenotypes (table 3), but this is manifest only when considering a group statistically, and does not allow confident individual prediction of genotype, (although racial origins may give a clue). Most patients with ADCA present with a predominantly cerebellar syndrome, but occasionally with predominantly extrapyramidal signs. The second may be more commonly seen in patients carrying the SCA3/MJD mutation; some patients receive partial benefit from levodopa. An ancestor of a family now known to carry the SCA3/MJD mutation was seen by Gowers at the National Hospital, Queen Square. The patient was initially thought to have a diagnosis of paralysis agitans.

Interestingly there is a gap of 21 between the repeat number seen in SCA3/MJD and normal alleles (table 3), by contrast with SCA1. This may indicate a different mutational mechanism. A significant negative correlation has been found between repeat number and age at onset. It is clear that there is a tendency for the repeat number to increase during transmission corresponding to the clinical phenomenon of anticipation. As seen in SCA1
there is also a parental sex effect with paternal transmission showing a larger increase (about three repeats) than female transmission (about one repeat).51 52

At necropsy patients diagnosed as having Machado-Joseph disease have predominant involvement of the spinocerebellar tracts, Clarke’s column nuclei, vestibular nuclei, and pontine base.53 Dürr et al studied two patients with SCA1 and two patients with SCA3/MJD at necropsy.54 Whereas some features were in common they thought that the SCA3/MJD pathology could be distinguished by the presence of lesions in the internal pallidum and interomediolateral columns and lack of inferior olive and Purkinje cell degeneration.

Other SCA loci
Most ADCA I families do not carry either the SCA1 or SCA3/MJD mutations (table 3). To date three further loci have been mapped, and others are not linked to known loci. The best characterised are the SCA2 families linked to markers on chromosome 12.49 55 These families show anticipation, suggesting that the mechanism underlying this disease may also be trinucleotide expansion, but no clear deleterious effect of paternal transmission has been seen. Clinically there is interfamilial and intrafamilial variability, but there is a significantly higher incidence of hyporeflexia in SCA2 families than SCA1 or SCA3 families. Neuropathologically, patients with SCA2 differ from patients with SCA3/MJD, but seem similar to patients with SCA1.56 SCA4 and SCA5 represent loci that have been assigned to chromosomes 16 and 11 by linkage analysis of single families.57 58 It is not clear whether these or other undiscovered loci will account for a substantial proportion of ADCA families.

Use of a monoclonal antibody to detect polyglutamine expansions allows identification of the gene products of the Huntington protein as well as the SCA1 and SCA3/MJD gene products.59 Interestingly, this antibody also detected specific pathological proteins in SCA2 and ADCA II, supporting the hypothesis that these too are trinucleotide repeat diseases. Dentatorubropallidolysian atrophy (DRPLA) is another autosomal dominant disease associated with a trinucleotide repeat, and may present with an ataxic syndrome.60 61 It is most common in Japan, but is also found in the west.62 Although clinical features may overlap with the ADCAs, chorea, myoclonus, epilepsy, or a progressive dementia would favour DRPLA.

ADCA II
Whether using clinical or pathological criteria,63 there is general agreement that this ADCA is distinguished from others by the presence of a pigmentary macular dystrophy. Enevoldson and colleagues described 54 members of eight families.64 The presenting symptom was ataxia in two thirds of patients and visual failure or both in the remainder. The retinal abnormalities are often subtle. Other neurological features include pyramidal signs and a supranuclear ophthalmoplegia. Onset varied between six months and 60 years with more rapid progression usually seen in early onset cases. Some obligate gene carriers were asymptomatic. Anticipation in the offspring of affected fathers was noted; all infantile onset cases resulted from paternal transmission. Therefore, both clinical and laboratory data support the possibility of the gene mutation being an unstable trinucleotide expansion.59

The ADCA type II locus has been mapped to chromosome 3p12-2p1-1 by three different groups indicating that this phenotype corresponds to a genetically homogenous disease entity.65 66

ADCA III
This is described as a relatively benign ADCA with predominant cerebellar features, some pyramidal signs, but no dementia, oculor, or extrapyramidal involvement, with onset over the age of 50 in most patients. The molecular genetic status of this group of ADCA is unclear. In one study none of 30 ADCA type III families had either the SCA1 or SCA3/MJD mutations suggesting that ADCA III may be genetically distinct, and not just a benign variant of ADCA I.69 Ranum et al described a family with a relatively benign ADCA linked to a locus on chromosome 11 (SCA5).68 This could be described as ADCA III, although some members had early onset disease with pyramidal features. Late onset ADCA is not uncommon and further molecular genetic characterisation is keenly awaited.

PERIODIC ATAXIA
Molecular genetic advances have led to the identification of two distinct autosomal dominant disorders characterised by episodic ataxia. In both types the ataxic episodes may be suppressed by acetazolamide. Episodic ataxia type 1 is caused by mutations in the potassium channel gene (KCN1A) on chromosome 12.64 Attacks are brief—seconds to minutes—and are precipitated by startle

Table 3 Autosomal dominant cerebellar ataxias: a clinicogenetic classification

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Gene defect</th>
<th>Frequency*</th>
<th>Associated clinical features†</th>
</tr>
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<tbody>
<tr>
<td>ADCA type I</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SCA1</td>
<td>6p22-p23</td>
<td>(CAG)n</td>
<td>14/87, 5/19, 2/24, 3/29, 4/38</td>
<td>Ophthalmoplegia, pyramidal and extrapyramidal signs, dementia, motor and sensory nerve involvement</td>
</tr>
<tr>
<td></td>
<td>12q23-24</td>
<td>Normal: 6-39</td>
<td>19/73, 13/120</td>
<td>As SCA1 but more frequent hyporeflexia, supranuclear ophthalmoplegia</td>
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<tr>
<td></td>
<td>14q32-1</td>
<td>Normal: 13-41</td>
<td>7/24, 5/29, 19/38, 10/35</td>
<td>As SCA1 but possibly with more frequent extrapyramidal signs (see text)</td>
</tr>
<tr>
<td></td>
<td>16q24-ter</td>
<td>Disease: 62-80</td>
<td>5/42, 28/120</td>
<td>As SCA1 but with prominent sensory axonal neuropathy</td>
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<td></td>
<td></td>
<td></td>
<td>7/48, 28/26</td>
<td>Basal ganglia involvement</td>
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<td></td>
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<td></td>
<td>Benign relatively pure ataxia</td>
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<td>Harding type III</td>
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<td></td>
<td></td>
<td>Pigmentary macular dystrophy (see text)</td>
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<td></td>
<td></td>
<td>Myoclonus, chorea, epilepsy, dementia</td>
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<td></td>
<td></td>
<td>Myoclonus, brief attacks</td>
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<td></td>
<td></td>
<td></td>
<td>Progressive ataxia, myoclonus, longer attacks</td>
</tr>
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</table>

Frequencies vary according to population and with the clinical characteristics of the families surveyed—for example, SCA1 was found in 6/12 British families with ADCA type I; SCA3/MJD constituted 84% of all ADCA in Portuguese patients.56

*Frequencies are expressed as a proportion of all ADCA studied.
†The features of the ADCA overlap; see text.
and exercise. A clue to this disorder may be the presence of interictal myokymia in the periorbital muscles or hands, responsive to phenytoin.

The cause of episodic ataxia type 2 is not yet defined. Episodes of ataxia may be precipitated by emotional stress and exercise but not by startle. Attacks may last several hours or more, with interictal nystagmus or a progressive cerebellar syndrome. Vahedi et al mapped the gene to chromosome 19p.10 Two other groups have found linkage to the same locus, indicating genetic homogeneity.39 42 The same region has been implicated in linkage studies of families with Cadasil (cerebral autosomal dominant arteriopathy with subcortical infarcts and leuкоencephalopathy) and familial hemiplegic migraine. Interestingly, at least three disorders may manifest with ataxia. A recent study suggests that Cadasil and episodic ataxia type 3 are not allelic, but the relation of these two familial hemiplegic migraine remains unclear.72

Conclusion
The pace of genetic advances in this decade is startling. After the identification of the molecular genetic basis of ataxias, the next scientific challenge is to understand the normal and aberrant function of the proteins corresponding to the mutated genes. This is already under way. Eventually this will provide the basis for planning rational treatments. However, the clinician can already use the new advances to help patients.

Direct testing for mutations at the SCA1, SCA3/MJD loci is routinely available and testing for the frataxin expansion is now possible. Analysis of the SCA loci in patients with ADCA allows a precise non-invasive diagnosis (in the minority that have these mutations). In the context of symptomatic patients the physician should obtain consent in the normal manner for any potentially diagnostic procedure. However, testing of presymptomatic subjects in families with known mutations raises complex issues which require full discussion. The situation is similar to that in Huntington’s disease, and testing of at risk subjects should follow the Huntington’s disease protocol, with pretest and post-test counselling.73 The responsible genes at the SCA2, SCA4, and SCA5 loci have not yet been identified. Linkage analysis within families with an adequate family structure is possible, but is not routinely available outside research laboratories.

Several groups have studied patients with sporadic ataxias for the SCA1 and SCA3/MJD mutations. This has been unfruitful. This group of patients will undoubtedly be further investigated as novel SCA mutations are uncovered, but the results to date suggest that such patients do not have SCA mutations causing their disease.

Direct mutation analysis in Friedreich’s ataxia will be helpful diagnostically. Unfortunately, the average age of onset of the disease means that most families are complete before the diagnosis is apparent, preventing prenatal testing. Nevertheless, the availability of direct mutation analysis will aid early diagnosis, make prenatal diagnosis more secure, and will help advise relatives of carrier status. The comparative rarity of the disorder will make screening of the general population impracticable in the foreseeable future.

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