GENETICS OF SPINOCEREBELLAR ATAXIAS

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Abstract : Over the last decade, more than 25 genes responsible for spinocerebellar ataxias (SCAs) have been isolated. This review classifies hereditary SCAs into two groups: autosomal dominant and recessive ataxias, and summarizes the genetic features of these diseases with some clinical characteristics. The unraveling of the molecular cause of a growing number of ataxia has revealed that these diseases are the consequences of a large variety of different mechanisms, even involving novel, unsuspected molecular pathways. The characterization of these pathways and their roles of the causative proteins will guide research over the next several years.

Key words : autosomal dominant ataxia, autosomal recessive ataxia, polyglutamine disease.

INTRODUCTION

Over the last decade, more than 25 genes responsible for spinocerebellar ataxias (SCAs) have been isolated. Such advances in molecular genetics have allowed better recognition of these diseases. Hereditary SCAs are classified into two groups: autosomal dominant and recessive ataxias. As a general rule early onset (< 20 years) tends to be autosomal recessive, later onset (> 25 years) is usually autosomal dominant. Autosomal dominant form is more frequent than recessive one, and other inheritance is very rare. This review summarizes the genetic features of these diseases with some clinical characteristics.

Autosomal dominant ataxia

The dominant ataxias are a clinically and genetically complex group of neurodegenerative disorders. Most of these diseases are characterized by various combinations of extracerebellar neurological features such as dementia, epilepsy, ophthalmoplegia, optic atrophy, peripheral neuropathy, and pyramidal and extrapyramidal signs. However, some are distinguished by the absence of these extracerebellar features (SCA6) or the presence of pigmentary maculopathy (SCA7). At the time of publication there are over 20 SCA loci identified. Of these, the genes are established for dentatorubral-pallidoluysian atrophy (DRPLA) and SCAs 1, 2, 3, 6, 7, 8, 10, 12, 14, and 17, which are summarized in the Table[1-16].

Polyglutamine diseases. Interestingly DRPLA and SCAs 1, 2, 3, 6, 7, and 17 share a common pathogenic mechanism, expansion of an exonic CAG repeat. The resultant proteins all possess an expanded polyglutamine tract and exert dominant gain of toxic function[17]. A common feature of polyglutamine diseases is genetic anticipation; the CAG repeat is unstable in gametes and increase in the number of repeats is transmitted to the next generation. Because there is an inverse correlation between the expansion size and the age of onset,

Table. Genes for dominant ataxias

name of the genes	chromosomal location	repeat unit	normal size	expanded size	mutation site	function
DRPLA	12p13.13	CAG	7-23	49-80	coding	IGF signaling?
SCA1	6p23	CAG	23-36	37-86	coding	
SCA2	12q24.1	CAG	15-29	35-52	coding	
SCA3/MJD1	14q24-32	CAG	13-36	68-79	coding	
SCA6	19p13	CAG	4-16	21-27	coding	calcium channel
SCA7	3p12-13	CAG	7-17	38-130	coding	
SCA8	13q21	CTG	16-37	110-250	3'UTR?	antisense?
SCA10	22q13	ATTCT	10-22	920-4140	intron	
SCA12	5q31-33	CAG	7-28	66-78	5'UTR	PPP2R2B
SCA14	19q13.4	point mutation	N/A	N/A	coding	protein kinase C-γ
SCA17	6q27	CAG	29-42	47-55	coding	TATA binding protein

IGF, insulin-like growth factor; PPP2R2B, protein phosphatase PP2A; N/A, not applicable

offspring generally develop the disease earlier and more severe. The precise mechanism underlying the instability of repeat is not clear, but in SCA3 we identified a nucleotide polymorphism (C/G) just after the CAG repeat as a possible cause for the instability[18]. The expanded alleles exclusively had the $(CAG)_nC$ configuration, while both $(CAG)_nC$ and $(CAG)_nG$ were seen in normal alleles. Furthermore, the CAG repeat tract in normal alleles was significantly longer in $(CAG)_nC$ than in $(CAG)_nG$. Thus, the $(CAG)_nC$ configuration may increase instability of the CAG repeat.

A unifying pathological feature of polyglutamine disorders is the presence of microscopically discernible inclusions, "aggregation", of the mutant proteins in the nucleus or cytoplasm of affected neurons[19]. The question whether polyglutamine aggregates are deleterious, harmless, or protective remains the most passionately disputed issue in the study of these diseases. Therefore, the therapeutic strategies now aim both to decrease toxicity by soluble form of polyglutamine proteins and to inhibit aggregation formation of insoluble form. We have established a 96-well formatted high throughput assay to explore new therapeutic candidates by measuring both cell viability and formation of aggregation (Figure).

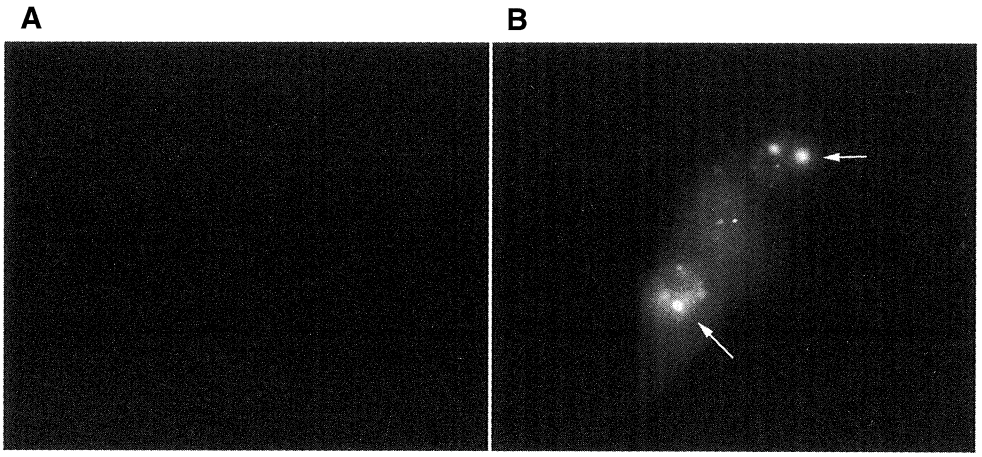

Figure. Fluorescence microscopic detection of inducible polyglutamine aggregation in neuronal PC12 cells. (A) No induction of polyglutamine protein. (B) The induction stimulus increased the expression of the fluorescent protein-fused expanded polyglutamine. Three cells were shown. The aggregations were formed mainly in the nuclei (arrows).

Other forms of dominant ataxias. SCA8 has been reported to link to CTG expansion on chromosome 13q21. However, the gene has not yet been characterized, and many researchers now question the disease-causing property of CTG expansions and advise great caution in genetic testing[20,21]. SCA10 is characterized by cerebellar ataxia and seizures. An expansion of a pentanucleotide (ATTCT) repeat in intron 9 of SCA10 has been identified[11]. There is an inverse correlation between the expansion size and the age of onset[22]. SCA12 is a rare form of ataxia with atypical clinical presentations that include tremor as an initial symptom[12]. An expansion of a CAG repeat in the 5'-untranslated region of a brain-specific regulatory subunit of the protein phosphatase PP2A is the cause of the disorder. Most recently the causative gene for SCA14 is identified and only point mutations are found in this gene encoding protein kinase C-γ[13,14]. Ten members in an American family were available for study and showed a mean age of onset in the third decade, presenting with gait ataxia, dysmetria, dysarthria, abnormal eye movements, and hyperreflexia. There was no cognitive impairment, sensory loss, or myoclonus[23]. However, intermittent axial myoclonus was observed in Japanese patients with early onset[14].

Frequencies. In the Kinki district of Japan, among the dominant families, SCA1 accounted for 3%, SCA2 for 4%, SCA3 for 24%, SCA6 for 31% and DRPLA for 12%[24]. Neither SCA7 nor SCA12 mutations were detected in this district as well as in Japan. Newly identified SCAs 14 and 17 are under investigation, but there have been a few reports in Japan[14-16]. Among the apparently sporadic patients, 15% were found to have expanded triplet repeats. Of these, the SCA6 mutation was most frequently detected.

Autosomal recessive ataxia

Friedreich's ataxia and clinically similar diseases. Friedreich's ataxia (FA) is the most common recessive ataxia in Europe, classically presenting with gait ataxia, but with a number of additional features including dysarthria, and pyramidal tract involvement. A peripheral neuropathy is seen with absent reflexes, large fiber sensory abnormalities, and occasionally distal wasting. Extraneurological abnormalities include skeletal abnormalities, such as scoliosis and pes cavus, cardiomyopathy, and diabetes mellitus. The causative gene encoding frataxin has been cloned and the predominant mutation is a trinucleotide repeat (GAA) expansion in intron 1 of this gene[25]. Expansion of both alleles is found in over 96% of patients. The remaining patients have one of point mutations on one allele and a GAA expansion on the other. The length of the repeat is a determinant of age at onset and therefore to some degree influences the severity in that early onset tends to progress more rapidly[26]. Although the name of this disease is widely recognized, no genetically proven patients have been reported in Japan.

In its classical form, ataxia with isolated vitamin E deficiency (AVED) is quite similar to FA, however, it differs from FA by the absence of cardiomyopathy and diabetes and the presence of low serum vitamin E concentration. This disease is caused by mutations in the α-tocopherol transfer protein gene[27]. AVED patients have an impaired ability to incorporate α-tocopherol, the most active form of vitamin E, into very low density lipoproteins in the

liver, a function attributed to the α-tocopherol transfer protein. We previously reported a splice site mutation on an exon in an AVED patient[28]. The α-tocopherol transfer protein gene naturally produces at least two transcripts by alternative splicing. These encode full-length and truncated proteins. The allele with the exonic mutation produces only the transcript encoding truncated form, which gives rise to the clinical phenotype of AVED. Treatment with high dose vitamin E helps prevent deterioration.

Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH) is the most common recessive ataxia in Japan. Although the clinical picture in neurological abnormalities is similar to that in FA, this disease exhibits the pathological involvement in the cerebellum that is spared in FA. Mental deterioration, peculiar eye movement, and hypoalbuminemia are other distinct characteristics in patients with EAOH. The causative gene encodes aprataxin, possibly responsible for repairing DNA[29, 30]. Other workers and we found mutations in Japanese EAOH families[29-31]. We discovered six new alternatively spliced transcripts that encode three variant proteins[31]. The alternative splicing increases the molecular diversity of aprataxin, possibly relating to the tissue-specific phenotypes. The pathogenic mechanism and treatment are under investigation.

There are a number of rare conditions associated with a reduced capacity to perform repair of DNA damaged by ultraviolet light, radiation, or some chemical carcinogens. The most common is ataxia telangiectasia (AT). This disease shares several clinical features with EAOH, including early onset ataxia, cerebellar atrophy, and ocular motor apraxia, but is mostly characterized by immunodeficiency and predisposition to cancer. The gene for AT has now been cloned and is called ATM, of which product facilitates to repair double-strand breaks of DNA[32]. More recently, the gene coding for tyrosyl-DNA phosphodiesterase 1 (TDP1) is identified as a causative gene for spinocerebellar ataxia with axonal neuropathy (SCAN1) in a Saudi Arabian family[33]. TDP1 repairs covalently bound topoisomerase I-DNA complexes and is essential for preventing the formation of double-strand breaks that result when stalled topoisomerase I complexes interfere with DNA replication in yeast. The authors propose that loss-of-function mutations in TDP1 may cause SCAN1 either by interfering with DNA transcription or by inducing apoptosis in postmitotic neurons.

Other forms of recessive ataxias. The other recessive ataxias are individually rare and often have a metabolic abnormality underlying the pathogenesis.

Cholestanolosis, also called cerebrotendinous xanthomatosis (CTX), is a rare autosomal recessive disorder caused by defective bile salt metabolism, resulting from a deficiency of mitochondrial sterol 27 hydroxylase[34]. It gives rise to ataxia, dementia, spasticity, peripheral neuropathy, cataracts, and tendon xanthomata in the second decade of life. We previously found a missense mutation in triplets, who exhibited an identical phenotypic expression, different from that of a sporadic CTX case with the same mutation[35]. This indicates that environmental or other genetic factors contribute to the clinical phenotype. Treatment with chenodeoxycholic acid appears to improve neurological function.

Refsum's disease was first described in 1946, and was subsequently shown to be due to plasma phytanic acid accumulation. Clinical presentation includes retinitis pigmentosa, peripheral polyneuropathy, cerebellar and sensory ataxia, and elevated cerebrospinal fluid

proteins in the absence of pleocytosis. It usually presents between age 10 and 20 years. Accumulation of phytanic acid is due to the deficiency of the first step of its degradation, which is an alpha oxidation that takes place in the peroxisomes. The causative gene encoding phytanoyl-CoA hydroxilase was initially cloned by us as a lupus nephritis related gene[36]. Later, identification of mutations therein allowed the demonstration of this enzyme's role in Refsum's disease[37, 38]. No patient with this disease has been detected in Japan.

Numerous rare recessive ataxias are not described in this review because of the limited space. Further studies on the newly identified proteins defective in recessive ataxias and identification of the predictably numerous new genes will clarify general pathological neurodegenerative mechanisms that could be amenable to therapy.

Conclusion

We outlined genetic and clinical aspects of common and some rare inherited SCAs. The unraveling of the molecular cause of a growing number of ataxia has revealed that these diseases are the consequences of a large variety of different mechanisms, even involving novel, unsuspected molecular pathways. The characterization of these pathways and their roles of the causative proteins will guide research over the next several years.

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REFERENCES

1) **Koide, R., Ikeuchi, T., Onodera, O., Tanaka, H., Igarashi, S., Endo, K., Takahashi, H., Kondo, R., Ishikawa, A., Hayashi, T., Saito, M., Tomoda, A., Miike, T., Naito, H., Ikuta, F.** and **Tsuji, S.** : Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nat. Genet. **6** : 9-13, 1994.

2) **Nagafuchi, S., Yanagisawa, H., Sato, K., Shirayama, T., Ohsaki, E., Bundo, M., Takeda, T., Tadokoro, K., Kondo, I., Murayama, N., Tanaka, Y., Kikushima, H., Umino, K., Kurosawa, H., Furukawa, T., Nihei, K., Inoue, T., Sano, A., Komure, O., Takahashi, M., Yoshizawa, T., Kanazawa, I.** and **Yamada, M.** : Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p. Nat. Genet. **6** : 14-18, 1994.

3) **Orr, H.T., Chung, M. Y., Banfi, S., Kwiatkowski, T. J. Jr, Servadio, A., Beaudet, A. L., McCall, A. E., Duvick, L. A., Ranum, L. P.** and **Zoghbi, H. Y.** : Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nat. Genet. 4 : 221-226, 1993.

4) **Pulst, S. M., Nechiporuk, A., Nechiporuk, T., Gispert, S., Chen, X. N., Lopes-Cendes, I., Pearlman, S., Starkman, S., Orozco-Diaz, G., Lunkes, A., DeJong, P., Rouleau, G. A., Auburger, G., Korenberg, J. R., Figueroa, C.** and **Sahba, S.** : Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat. Genet. **14** : 269-276, 1996.

5) **Sanpei, K., Takano, H., Igarashi, S., Sato, T., Oyake, M., Sasaki, H., Wakisaka, A., Tashiro, K., Ishida, Y., Ikeuchi, T., Koide, R., Saito, M., Sato, A., Tanaka, T., Hanyu, S., Takiyama, Y., Nishizawa, M., Shimizu, N., Nomura, Y., Segawa, M., Iwabuchi, K., Eguchi, I., Tanaka, H., Takahashi, H.** and **Tsuji, S.** : Identification of the spinocerebellar ataxia type 2 gene using a direct identification of repeat expansion and cloning technique, DIRECT. Nat. Genet. **14** : 277-284, 1996.

6) **Imbert, G., Saudou, F., Yvert, G., Devys, D., Trottier, Y., Garnier, J.-M., Weber, C., Mandel, J.-L., Cancel, G., Abbas, N., Durr, A., Didierjean, O., Stevanin, G., Agid, Y.** and **Brice, A.** : Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. Nat. Genet. **14** : 285-291, 1996.

7) **Kawaguchi, Y., Okamoto, T., Taniwaki, M., Aizawa, M., Inoue, M., Katayama, S., Kawakami, H., Nakamura, S., Nishimura, M., Akiguchi, I., Kimura, J., Narumiya, S.** and **Kakizuka, A.** : CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat. Genet. 8 : 221-228, 1994.

8) **Zhuchenko, O., Bailey, J., Bonnen, P., Ashizawa, T., Stockton, D. W., Amos, C., Dobyns, W. B., Subramony, S. H., Zoghbi, H. Y.** and **Lee, C. C.** : Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha(1A)-voltage-dependent calcium channel. Nat. Genet. **15** : 62-69, 1997.

9) **David, G., Abbas, N., Stevanin, G., Durr, A., Yvert, G., Cancel, G., Weber, C., Imbert, G., Saudou, F., Antoniou, E., Drabkin, H., Gemmill, R., Giunti, P., Benomar, A., Wood, N., Ruberg, M., Agid, Y., Mandel, J.-L.** and **Brice, A.** : Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion. Nat. Genet. **17** : 65-70, 1997.

10) **Koob, M. D., Moseley, M. L., Schut, L. J., Benzow, K. A., Bird, T. D., Day, J. W.** and **Ranum, L. P. W.** An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). Nat. Genet. **21** : 379-384, 1999.

11) **Matsuura, T., Yamagata, T., Burgess, D. L., Rasmussen, A., Grewal, R. P., Watase, K., Khajavi, M., McCall, A. E., Davis, C. F., Zu, L., Achari, M., Pulst, S. M., Alonso, E., Noebels, J. L., Nelson, D. L., Zoghbi, H. Y.** and Ashizawa, T. : Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nat. Genet. **26** : 191-194, 2000.

12) **Holmes, S. E., O'Hearn, E. E., McInnis, M. G., Gorelick-Feldman, D. A., Kleiderlein, J. J., Callahan, C., Kwak, N. G., Ingersoll-Ashworth, R. G., Sherr, M., Sumner, A. J., Sharp, A. H., Ananth, U., Seltzer, W. K., Boss, M. A., Vieria-Saecker, A.-M., Epplen, J. T., Riess, O., Ross, C. A.** and **Margolis, R. L.** : Expansion of a novel CAG trinucleotide repeat in the 5-prime region of PPP2R2B is associated with SCA12. Nat. Genet. **23** : 391-392, 1999.

13) **Chen, D.-H., Brkanac, Z., Verlinde, C. L. M. J., Tan, X.-J., Bylenok, L., Nochlin, D.,** Matsushita, **M., Lipe, H., Wolff, J., Fernandez, M., Cimino, P. J., Bird, T. D.** and **Raskind, W. H.** : Missense mutations in the regulatory domain of PKC-gamma: a new mechanism for dominant nonepisodic cerebellar ataxia. Am. J. Hum. Genet. **72** : 839-849, 2003.

14) **Yabe, I., Sasaki, H., Chen, D. H., Raskind, W. H., Bird, T. D., Yamashita, I., Tsuji, S., Kikuchi, S.** and **Tashiro, K.** : Spinocerebellar ataxia type 14 caused by a mutation in protein kinase C gamma. Arch. Neurol. **60** : 1749-1751, 2003.

15) **Koide, R., Kobayashi, S., Shimohata, T., Ikeuchi, T., Maruyama, M., Saito, M., Yamada, M., Takahashi, H.** and **Tsuji, S.** : A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease? Hum. Mol. Genet. **8** : 2047-2053, 1999.

16) **Nakamura, K., Jeong, S. Y., Uchihara, T., Anno, M., Nagashima, K., Nagashima, T., Ikeda, S., Tsuji, S.** and **Kanazawa, I.** : SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Hum Mol Genet. **10** : 1441-1448, 2001.

17) **Orr, H. T.** and **Zoghbi, H. Y.** : SCA1 molecular genetics: a history of a 13 year collaboration against glutamines. Hum. Mol. Genet. **10** : 2307-2311, 2001.

18) **Matsumura, R., Takayanagi, T., Murata, K., Futamura, N., Hirano, M.** and **Ueno, S.** : Relationship of (CAG)nC configuration to repeat instability of the Machado-Joseph disease gene. Hum. Genet. **98** : 643-635, 1996.

19) **Michalik, A.** and **Van Broeckhoven, C.** : Pathogenesis of polyglutamine disorders: aggregation revisited. Hum. Mol. Genet. **12** Spec No 2 : R173-186, 2003.

20) **Sobrido, M. J., Cholfin, J. A., Perlman, S., Pulst, S. M** and **Geschwind, D. H.** : SCA8 repeat expansions in ataxia: a controversial association. Neurology **57** : 1310-1312, 2001.

21) **Schols, L., Bauer, I., Zuhlke, C., Schulte, T., Kolmel, C., Burk, K., Topka, H., Bauer, P., Przuntek, H.** and **Riess, O.** : Do CTG expansions at the SCA8 locus cause ataxia? Ann. Neurol. **54** : 110-115, 2003.

22) **Rasmussen, A., Matsuura, T., Ruano, L., Yescas, P., Ochoa, A., Ashizawa, T.** and **Alonso, E.** : Clinical and genetic analysis of four Mexican families with spinocerebellar ataxia type 10. Ann. Neurol. **50** : 234-239, 2001.

23) **Brkanac, Z., Bylenok, L., Fernandez, M., Matsushita, M., Lipe, H., Wolff, J., Nochlin, D., Raskind, W. H.** and **Bird, T. D.** : A new dominant spinocerebellar ataxia linked to chromosome 19q13.4-qter. Arch. Neurol. **59** : 1291-1295, 2002.

24) **Matsumura, R., Futamura, N., Ando, N.** and **Ueno, S.** : Frequency of spinocerebellar ataxia mutations in the Kinki district of Japan. Acta. Neurol. Scand. **107** : 38-41, 2003.

25) **Campuzano, V., Montermini, L., Molto, M. D., Pianese, L., Cossee, M., Cavalcanti, F., Monros, E., Rodius, F., Duclos, F., Monticelli, A., Zara, F., Canizares, J., Koutnikova, H., Bidichandani, S. I., Gellera, C., Brice, A., Trouillas, P., De Michele, G., Filla, A., De Frutos, R., Palau, F., Patel, P. I., Di Donato, S., Mandel, J-L., Cocozza, S., Koenig, M.** and **Pandolfo, M.** : Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science **271** : 1423-1427, 1996.

26) **Harding, A. E.** : Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain **104** : 589-620, 1981.

27) **Ouahchi, K., Arita, M., Kayden, H., Hentati, F., Ben Hamida, M., Sokol, R., Arai, H., Inoue, K., Mandel, J.-L.** and **Koenig, M.** : Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein. Nat. Genet. **9** : 141-145, 1995.

28) **Tamaru, Y., Hirano, M., Kusaka, H., Ito, H., Imai, T.** and **Ueno, S.** : α-Tocopherol transfer protein gene: exon skipping of all transcripts causes ataxia. Neurology **49** : 584-588, 1997.

29) **Date, H., Onodera, O., Tanaka, H., Iwabuchi, K., Uekawa, K., Igarashi, S., Koike, R., Hiroi, T., Yuasa, T., Awaya, Y., Sakai, T., Takahashi, T., Nagatomo, H., Sekijima, Y., Kawachi, I., Takiyama, Y., Nishizawa, M., Fukuhara, N., Saito, K., Sugano, S.** and **Tsuji, S.** : Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. Nature Genet. **29** : 184-188, 2001.

30) **Moreira, M.-C., Barbot, C., Tachi, N., Kozuka, N., Uchida, E., Gibson, T., Mendonca, P., Costa, M., Barros, J., Yanagisawa, T., Watanabe, M., Ikeda, Y., Aoki, M., Nagata, T., Coutinho, P., Sequeiros, J.** and **Koenig, M.** : The gene mutated in ataxia-oculomotor apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. Nat. Genet. 29 : 189-193, 2001.

31) **Hirano, M., Nishiwaki, T., Kariya, S., Furiya, Y.** and **Ueno, U.** : Alternative spliced transcripts of aprataxin in early-onset ataxia with oculomotor apraxia and hypoalbuminemia. (Abstract) Ann. Neurol. Suppl **7**: S58, 2003.

32) **Savitsky, K., Bar-Shira, A., Gilad, S., Rotman, G., Ziv, Y., Vanagaite, L., Tagle, D. A., Smith, S., Uziel, T., Sfez, S., Ashkenazi, M., Pecker, I., Frydman, M., Harnik, R., Patanjali, S. R., Simmons, A., Clines, G. A., Sartiel, A., Gatti, R. A., Chessa, L., Sanal, O., Lavin, M. F., Jaspers, N. J., Taylor, A. R., Arlett, C. F., Miki, T., Weissman, S. M., Lovett, M., Collins, F. S.** and **Shiloh, Y.** : A single ataxia telangiectasia gene with a product similar to PI-3 kinase. Science **268** : 1749-1753, 1995.

33) **Takashima, H., Boerkoel, C. F., John, J., Saifi, G. M., Salih, M. A., Armstrong, D., Mao, Y., Quiocho, F. A., Roa, B. B., Nakagawa, M., Stockton, D. W.** and **Lupski, J. R.** : Mutation of TDP1, encoding a topoi-

somerase I-dependent DNA damage repair enzyme, in spinocerebellar ataxia with axonal neuropathy. Nat. Genet. **32** : 267-272, 2002.

34) **Cali, J. J., Hsieh, C. L., Francke, U.** and **Russell, D. W.** : Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. J. Biol. Chem. **266** : 7779-7783, 1991.

35) **Nagai, Y., Hirano, M., Mori, T., Takakura, Y., Tamai, S.** and **Ueno, S.** : Japanese triplets with cerebrotendinous xanthomatosis are homozygous for a mutant gene coding for the sterol 27-hydroxylase (Arg441Trp). Neurology **46** : 571-574, 1996.

36) **Iwano, M., Ueno, S., Miyazaki, M., Harada, T., Nagai, Y., Hirano, M., Dohi, Y., Akai, Y., Kurioka, H.** and **Dohi, K.** : Molecular cloning and expression of a novel peptide (LN1) gene: reduced expression in the renal cortex of lupus nephritis in MRL/lpr mouse. Biochem. Biophys. Res. Commun. **229** : 355-360, 1996.

37) **Mihalik, S. J., Morrell, J. C., Kim. D., Sacksteder, K. A., Watkins, P. A.** and **Gould, S. J.** : Identification of PAHX, a Refsum disease gene. Nat. Genet. **17** : 185-189, 1997.

38) **Jansen, G. A., Ofman, R., Ferdinandusse, S., Ijlst, L., Muijsers, A. O., Skjeldal, O. H., Stokke, O., Jakobs, C., Besley, G. T. N., Wraith, J. E.** and **Wanders, R. J. A.** : Refsum disease is caused by mutations in the phytanoyl-CoA hydroxylase gene. Nat. Genet. **17** : 190-193, 1997.