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REVIEW

12q24 locus association with type 1 diabetes: *SH2B3* or *ATXN2*?

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Abstract

Genetic linkage analyses, genome-wide association studies of single nucleotide polymorphisms, copy number variation surveys, and mutation screenings found the human chromosomal 12q24 locus, with the genes *SH2B3* and *ATXN2* in its core, to be associated with an exceptionally wide spectrum of disease susceptibilities. Hematopoietic traits of red and white blood cells (like erythrocytosis and myeloproliferative disease), autoimmune disorders (like type 1 diabetes, coeliac disease, juvenile idiopathic arthritis, rheumatoid arthritis, thrombotic antiphospholipid syndrome, lupus erythematosus, multiple sclerosis, hypothyroidism and vitiligo), also vascular pathology (like kidney glomerular filtration rate deficits, serum urate levels, plasma beta-2-microglobulin levels, retinal microcirculation problems, diastolic and systolic blood pressure and hypertension, cardiovascular infarction), furthermore obesity, neurodegenerative conditions (like the polyglutamine-expansion disorder spinocerebellar ataxia type 2, Parkinson's disease, the motor-neuron disease amyotrophic lateral sclerosis, and progressive supranuclear palsy), and finally longevity were reported. Now it is important to clarify, in which ways the loss or gain of function of the locally encoded proteins SH2B3/LNK and ataxin-2, respectively, contribute to these polygenic health problems. SH2B3/LNK is known to repress the JAK2/ABL1 dependent proliferation of white blood cells. Its null mutations in human and mouse are triggers of autoimmune traits and leukemia (acute lymphoblastic leukemia or chronic myeloid leukemia-like), while missense mutations were found in erythrocytosis-1 patients. Ataxin-2 is known to act on RNA-processing and trophic receptor internalization. While its polyglutamine-expansion mediated gain-of-function causes neuronal atrophy in human and mouse, its deletion leads to obesity and insulin resistance in mice. Thus, it is conceivable that the polygenic pathogenesis of type 1 diabetes is enhanced by an SH2B3-dysregulation-mediated predisposition to autoimmune diseases that conspires with an ATXN2-deficiency-mediated predisposition to lipid and glucose metabolism pathology.

Key words: Diabetes mellitus type 1; 12q24; *ATXN2*; Obesity; *SH2B3*; Autoimmune

Core tip: Within the multifactorial pathogenesis of type 1 diabetes mellitus (T1D), a genetic risk mediated by the chromosome 12q24 locus was consistently observed. Mutations in the *ATXN2* gene there trigger the pathogenesis of obesity, while mutations in the SH2B3 gene there trigger the pathogenesis of autoimmune processes. Given that both genes show co-regulated expression, their combined effects may drive these two core aspects of T1D. Tissue and phenotype studies of mouse mutants will identify molecular targets for causal therapies.

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INTRODUCTION

The pathogenesis of many common multifactorial diseases was successfully elucidated over the past years, principally through genome-wide association studies (GWAS) in many thousands of sporadic patients *vs* control individuals. For diabetes mellitus type 1 (T1D), more than 40 chromosomal loci were uncovered to modulate disease risk[1,2]. However, now the challenge consists in establishing causality between one of the multiple genes contained in any locus and one of the disease features. One promising approach is the careful consideration of phenotypes and pathology caused by disruption or overexpression of any candidate gene, *e.g.*, in mouse, and the subsequent comparison with relevant traits that occur within the first years of the disease course. Thus, clinical information may help to guide the characterization of mutant animals, while conversely the tissue analysis of mutant animals may help to elucidate presymptomatic stages of disease. A particularly complex example is the subject of this review-the association of T1D and many other medical conditions with mostly two single nucleotide polymorphisms (SNPs) on chromosome 12q24-rs3184504 and rs653178.

THE EXCEPTIONALLY PLEIOTROPIC DISEASE SUSCEPTIBILITY LOCUS ON CHROMOSOME 12Q24 EXTENDS FROM THE *SH2B3* GENE ACROSS THE *ATXN2* GENE, BUT MAY STRETCH BEYOND THESE BORDERS

Chromosome 12q contains one of the largest blocks of linkage disequilibrium (LD) in the human genome[3]. It was observed early on in European/Asian/African populations and found to span > 1 Megabase pairs (Mbp) across several genes including the growth repressor *SH2B3*, the RNA processing factor *ATXN2*, the nuclear localization inhibitor *BRAP*, the mitochondrial fatty acid beta-oxidation enzyme *ACAD10*, the alcohol metabolism enzyme *ALDH2*, and the stress kinase *MAPKAPK5*[4]. The core LD block was localized to exon 1 of the *ATXN2* gene in a population of European ancestry, and was explained by positive selection of the (CAG)-repeat size in this exon[4]. Indeed, the most frequently observed disease associations at this 12q24 locus are within a 200000 basepairs (bp) fragment, which comprises the *ATXN2* gene and the immediately adjacent *SH2B3* gene (Figure 1). According to the United States National Center for Biotechnology Information reference sequences, human *SH2B3* is transcribed in orientation from the centromere, covering about 46000 bp, and spans 9 predicted exons to constitute an mRNA of 5425 nucleotides, which encodes a protein of 575 amino acids. *ATXN2* is transcribed in orientation from the telomere, covering about 147000 bp, and spans 24 predicted exons with several splice-isoforms, of which the longest constitutes an mRNA of 4712 nucleotides and encodes a protein of 1313 amino acids. The missense SNP rs3184504 in *SH2B3* open reading frame (resulting in the substitution W262R) was observed in perfect cosegregation ($r^2 = 1$) with the SNP rs653178 deep within intron 2 of the *ATXN2* gene[5], in spite of a physical distance of 123148 bp. Since rs653178 is far away from *ATXN2* splice sites and since the W262 codon in SH2B3 is not conserved between human and mouse[6], both of these polymorphisms are probably innocent bystanders and are noticed only through their frequency, depending on their random distribution within population stratifications. They are presumably coinherited with other rare sequence variants, *e.g.*, within the promoters or within the mRNA 3'-untranslated regions, which alter the transcript expression levels slightly upwards or downwards. Indeed, both of these cosegregating *SH2B3* and *ATXN2* variants correlated with significant changes in the expression of both *ATXN2* and *SH2B3* mRNAs[7]. This coinheritance together with correlated expression changes makes it inherently difficult to establish causality between any of the individual traits within a complex disease and any of the neighbouring genes. This is exemplified by the allocation of six hematologic and three blood pressure traits to the region from *SH2B3* to *ATXN2* by genome-wide studies, reflecting the exceptional pleiotropy of this locus[8]. The 12q24 linkage disequilibrium block in some studies of restricted populations included further genes, namely *CUTL2*, *FAM109A*, *SH2B3*, *ATXN2*, *BRAP*, *ACAD10*, *ALDH2*, *MAPKAPK5*, *TMEM116*, *ERP29*[9], *NAA25/C12orf30*, *TRAFD1*, *HECTD4/C12orf51*, *RPL6*, *PTPN11*[10-12], thus extending across 1.5 Mbp. For these reasons it is crucial to consider monogenic mutants for each gene and their phenotypic effects, so as to decide which of them might contribute to each of the diseases. However, for most of these genes the relevant mouse mutants are not yet characterized.

NULL MUTATIONS IN MOUSE AND HUMAN DEMONSTRATE *SH2B3* TO REPRESS THE PROLIFERATION OF WHITE BLOOD CELLS, IN PARTICULAR B-LYMPHOCYTES

The generation of mice with deletion of SH2B3 (also called Lnk) demonstrated primary splenomegaly and extramedullary hematopoiesis with progenitor hypersensitivity to various cytokines[13]. It caused the accumulation of pre-B and immature B-lymphocytes in enlarged spleens as well as an increase in B-lineage cells in the bone marrow, in parallel to unimpaired T-cell de-

SH2B3-ATXN2 genomic locus

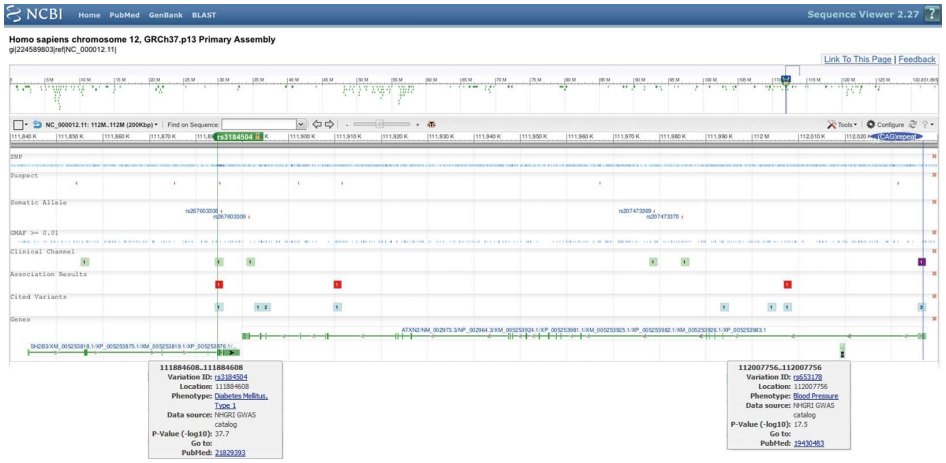

Figure 1 The core 200000 bp region of the chromosome 12q24 locus covering the immediately adjacent *SH2B3* and *ATXN2* genes, with an illustration of the single nucleotide polymorphism rs3184504 encoding the W272R missense variant of the SH2B3/LNK protein (as shown in the United States National Center for Biotechnology Information database) as well as the (CAG)-repeat structure encoding the unstable polyglutamine domain of the ataxin-2 protein.

velopment in thymus[14]. It accelerated and exacerbated oncogenic JAK2-induced myeloproliferative diseases through an expansion of myeloid progenitors, accelerated myelofibrosis and finally features of chronic myeloid leukemia (CML). These murine data supported notions that SH2B3 directly inhibits oncogenic JAK2 and cooperates with the *BCR/ABL* oncogene in the development of CML[15]. Deletion of SH2B3 was also observed in a genomic and transcriptomic study of patients with BCR-ABL1-positive acute lymphoblastic leukemia with poor outcome (Ph-like ALL), together with promising therapeutic benefits from tyrosine kinase inhibitors[16]. Human germline homozygous *SH2B3* mutations including a frameshift with translation stop resulted in growth retardation, high white cell counts in parallel to anemia and thrombocytopenia, splenomegaly and liver cirrhosis, autoimmune Hashimoto thyroiditis, speech delay and ALL. In addition, this study identified homozygous somatic *SH2B3* frameshift mutations in ALL cases[17]. A 5 bp deletion of SH2B3, which was predicted to affect both the PH domain and the SH2 domain, manifested clinically as primary myelofibrosis. In contrast, a somatic *E208Q* missense mutation in the PH domain was observed in a patient with essential thrombocythemia[18]. SH2B3 was also shown to interact with platelet-derived growth factor receptor and repress its downstream signaling[19]. Interestingly, a selective increase in red blood cells (isolated erythrocytosis) was observed in two individuals with the *SH2B3* missense mutations E208X and A215V[20]. However, SH2B3 sequencing in 23 erythrocytosis patients uncovered only one non-synonymous polymorphism of unclear relevance[6]. Systematic SH2B3 sequencing analysis in 42 patients with chronic phase myeloproliferative neoplasms detected a missense mutation in 7% of cases, either in the SH2 domain or in the C-terminal domain, which were always accompanied by a *JAK2* mutation[21]. Myeloproliferative *SH2B3* mutations within the PH domain were also shown to reduce SH2B3 function without altering its binding properties to JAK2, CBL and 14-3-3[22]. An analysis of peripheral mononuclear blood cells stimulated with anti-CD28 and anti-CD3 antibodies detected an increased proliferation of T-lymphocytes in carriers of the W262R missense SH2B3 variant, independent of the presence of juvenile type 1 diabetes[23]. *In vitro* studies had previously shown SH2B3 to attenuate the ability of SH2B1 to promote JAK2 activation and subsequent tyrosine phosphorylation of insulin receptor substrate-1 by JAK2[24]. SH2B3-deficient hematopoietic stem cells displayed an increased postnatal expansion and enhanced thrombopoietin responsiveness[25]. In subsequent studies they showed increased resistance to apoptosis due to enhanced expression of Bcl-xL upon thrombopoietin stimulation[26]. A limitation of growth by SH2B3 was also observed in the rat neuronal PC12 cell line and in primary cortical neurons, where neurotrophin-induced neurite outgrowth was downregulated by the binding of SH2B3 to the phosphorylated neurotrophin receptor TrkA and the repression of downstream signaling[27].

AUTOIMMUNE DISEASES (EOSINOPHIL NUMBERS, COELIAC DISEASE, JUVENILE IDIOPATHIC ARTHRITIS, RHEUMATOID ARTHRITIS, THROMBOTIC ANTIPHOSPHOLIPID SYNDROME, LUPUS ERYTHEMATOSUS, MULTIPLE SCLEROSIS, HYPOTHYROIDISM, VITILIGO) MAY BE MODULATED BY SH2B3

Possibly as an effect of SH2B3 on B-lymphocyte proliferation, the 12q24 locus modulates the risk for various autoimmune diseases. A GWAS in the Icelandic popula-

tion studying eosinophil counts observed association with the *SH2B3* SNP rs3184504[28]. A GWAS into coeliac disease found the *SH2B3* SNP rs3184504 and the *ATXN2* intronic SNP rs653178 to be associated[29]. Follow up studies of coeliac disease focusing on 9 and 11 candidate SNPs confirmed the association with *SH2B3*[30,31], and reported upregulation of *SH2B3* mRNA expression levels in intestinal mucosa to be triggered by coeliac disease and by the risk allele T of the *SH2B3* SNP rs3184504[31]. Further haplotype studies were confirmatory, and functional experiments indicated that carriers of the rs3184504 risk allele show stronger activation of the NOD2 recognition pathway in response to lipopolysaccharides and muramyl dipeptide[32]. A candidate study of sixteen SNPs known from coeliac disease and from T1D found an association of the *ATXN2* SNP rs653178 with juvenile idiopathic arthritis[33]. GWAS studies into rheumatoid arthritis indicated association with *SH2B3* particularly among rheumatoid-factor-positive patients[34]. A GWAS meta-analysis confirmed that the *ATXN2* intronic SNP rs653178 is associated not only with coeliac disease, but also with rheumatoid arthritis[35]. A study of thrombophilia in antiphospholipid antibody positive individuals by array-comparative genomic hybridization analysis of copy number variations with subsequent fine mapping identified a risk haplotype comprising one *SH2B3* SNP and two *ATXN2* SNPs[36]. A GWAS of systemic lupus erythematosus observed association with the SNP rs17696736 within the *ERP29* gene downstream from *SH2B3*[9]. A candidate study of 12 SNPs in almost 3000 Spanish multiple sclerosis patients detected association with the *SH2B3* SNP rs3184504[37]. A GWAS into hypothyroidism reported the *SH2B3* SNP rs3184504 to be associated, with autoimmune Hashimoto thyroiditis as a likely explanation for this observation[38]. A GWAS into the autoimmune skin disease vitiligo reported an association with the 12q24 locus extending from the *SH2B3* across the *ATXN2* gene[39].

T1D MELLITUS

The first GWAS into T1D encountered a maximal association with the 12q24 SNP rs17696736 in an intron of the *C12ORF30/NAA25* gene, while the effect was consistently observed also in its neighbourhood across a 1.5 Mbp LD block[10]. An extended GWAS confirmed this observation and pointed out that the association with the W272R missense variant encoded in exon 3 of SH2B3 was sufficient to model the regional effect[40]. GWAS of additional cases corroborated the association with *SH2B3*[41], a further GWAS with meta-analysis and combined comparisons supported the association with rs3184504[42], and also a GWAS of affected sib-pair families showed association with the region from the *SH2B3* SNP rs739496 across the *ERP29* SNP rs17696736 until the SNP rs10850061 beyond PTPN11[11,43]. GWAS of autoantibody positive T1D patients again detected the association with SH2B3[44,45]. GWAS of soluble intercellular adhesion molecule-1 levels as an endothelium-derived inflammatory biomarker in diabetes and infarction also showed the association with the *SH2B3* SNP rs3184504[46]. Candidate studies of 2 and 21 SNPs in T1D cases from Russia and United States, respectively, replicated the SH2B3 association[47,48]. Since the effect is so consistent, *SH2B3* SNP genotyping was integrated into a signature of 8 polymorphisms that provide optimal prediction of T1D risk[49]. However, it is likely that the *SH2B3* sequence variant rs3184504 is not biologically responsible by itself, since sequencing studies failed to find similar SH2B3 variants in NOD mice that model many T1D features[50].

EVIDENCE FROM MOUSE MUTANTS IMPLICATES *ATXN2* IN METABOLIC SYNDROME

While the autoimmune component of T1D might be explained by the SH2B3 effect on lymphocyte proliferation, some metabolic features of T1D might be exacerbated by the ataxin-2 effect on glucose and lipid metabolism. Mice with targeted deletion of Atxn2 exon 1 and frameshift in homozygous state displayed marked obesity and infertility in two independently generated mutant lines[51,52]. Hepatic lipid and glycogen accumulation was evident already at age 6 mo. As in other insulin resistance syndromes, pancreatic and blood serum insulin levels were increased, in parallel to a reduction of insulin receptor (IR) protein levels in the liver, in spite of increased IR mRNA levels. Serum cholesterol was significantly increased[52]. Although ataxin-2 is mostly localized at the rough endoplasmic reticulum and has strong effects on mRNA processing[53-59], its effect on the IR is possibly explained through interactions with the endocytic internalization machinery of receptor tyrosine kinases[60,61]. TDP-43 is an interactor protein of ataxin-2 *via* joint RNA-binding[57], was also demonstrated to regulate glucose homeostasis and fat deposition, with its levels showing direct correlation with the expression levels of the obesity gene *Tbc1d1*, while its deletion affects the splicing of apolipoprotein A-Ⅱ[62-64].

EVIDENCE FROM HUMAN MUTATIONS IMPLICATES *ATXN2* IN OBESITY

The investigation of obesity in 92 children by systematic sequencing of the *ATXN2* coding regions demonstrated a greatly increased frequency of the SNP rs695872 allele C and an overrepresentation of (CAG)-repeat sizes > 22[65]. Indeed, obesity and polyphagia were marked features of infants in middle stages of the neurodegenerative process caused by (CAG)-repeat expansions in ATXN2[66]. Thus, monogenic evidence links obesity to ATXN2 both in mice and in human. This is possibly reflected by a genome-wide SNP genotyping analysis, where SH2B3 variants were associated with low-density lipoprotein (LDL) cholesterol[67]. Interestingly, an association with obesity was also observed for the ataxin-2

binding protein 1 (A2BP1 or RBFOX1) both in a GWAS among Pima Indians and in a candidate approach among French Caucasian adults[68].

ATXN2 IS IMPORTANT FOR NEURODEGENERATIVE DISEASES

The polyglutamine (polyQ) domain at the N-terminal end of ataxin-2 normally has a size of Q22-23, usually encoded by a $(CAG)_8CAA(CAG)_4CAA(CAG)_8$ sequence in exon 1 of the *ATXN2* gene on chromosome 12q24. Its unstable expansion to large sizes beyond $(CAG)_{31}$ is the monogenic cause of an autosomal dominant multisystem atrophy of the nervous system, which was named spinocerebellar ataxia type 2[69-86]. CAG-repeat expansions with cytosine adenosine adenosine (CAA) interruptions may also manifest as Parkinson's disease[87,88]. Intermediate CAG-repeat sizes of 26-31 units, sometimes with CAA interruptions, act as polygenic risk factor for the motor-neuron disease amyotrophic lateral sclerosis[57,89]. Intermediate CAG-repeat expansions enhance also the risk for progressive supranuclear palsy[90]. Published evidence suggests that the polyglutamine expansions increase the half-life of ataxin-2 and that a gain-of-toxic-function through accumulation of ataxin-2 aggregates with sequestration of interactor proteins such as the poly(A)-binding-protein PABPC1 underlies the neurodegenerative process[57,91]. In spite of the vast evidence that excess ataxin-2 is the biological cause for neuronal death, SNP genotyping and association studies curiously found an *SH2B3* allele haplotype to be more informative and to better predict amyotrophic lateral sclerosis risk than the ATXN2 alleles[92]. This observation underscores old experiences that maximal linkage logarithm of odds scores and maximal haplotype association scores within any chromosomal region depend on random population stratification effects and on the frequency/informativity of alleles. Thus, they are not suitable for the fine mapping of disease genes.

LONGEVITY

Interestingly, the discovery set of a GWAS of exceptional longevity in centenarians detected a significant association with the *ATXN2* SNP rs653178, in parallel to several other disease associated SNPs, while the strongest effect correlated with the SNP rs2075650 at the *TOMM40*/apolipoprotein E (*APOEO* locus. TOMM40 encodes the channel forming subunit of the translocase across the mitochondrial outer membrane, while APOE encodes the apolipoprotein E, which mediates the binding and clearance of lipoprotein particles such as chylomicrons and very LDLs. Apolipoprotein E polymorphisms are the main known genetic factors associated with the risk of Alzheimer's disease[93,94]. While it remained unclear in this longevity GWAS, whether an LD effect was consistently observed also for SNPs that surround ATXN2, and whether blood cell traits, autoimmune disorders, obesity, neurodegenerative processes or vascular pathology were underlying this observation, the authors reported their observation of a reduced frequency of the *ATXN2* SNP rs653178 allele T among centenarians [with a log10(BayesFactor) of 1.2] in the light of previous ATXN2 GWAS association data with hypertension[93,94].

KIDNEY DISEASE, MICROCIRCULATION, HYPERTENSION AND CARDIOVASCULAR INFARCTION

Indeed, several independent GWAS found renal function (estimated glomerular filtration rate on the basis of cystatin c) and chronic kidney disease to be modulated by the rs653178 variant within an intron of the *ATXN2* gene in populations of European and African ancestry[5,95-97]. Also a GWAS into plasma levels of beta-2-microglobulin as a biomarker of kidney function, cardiovascular diseases and mortality reported an association with the *ATXN2* SNP rs653178[98]. Furthermore, a recent GWAS into serum urate concentrations uncovered an association with the *ATXN2* SNP rs653178[99]. The analysis of 83 candidate SNPs showed kidney disease variants to be associated with vascular phenotypes only in the case of rs653178 within the *ATXN2* gene and two SNPs at the *SH2B3* locus[100]. A GWAS studying microcirculation as measured by retinal venular caliber reported 4 loci, with only the rs10774625 SNP within an *ATXN2* intron showing also significant association with hypertension and coronary heart disease[12]. The *ATXN2* SNP rs653178 and the *SH2B3* SNP rs3184504 association with diastolic as well as systolic blood pressure, mean arterial pressure and pulse pressure was reported in three independent GWAS of populations with European and African ancestry[7,101-103]. Similarly, an association of the *SH2B3* SNP rs3184504 with diastolic and systolic blood pressure and hypertension was detected in a GWAS of 200000 individuals of European descent[104]. A GWAS association of the *ATXN2* SNP rs653178 with myocardial infarction was shown in Icelandic individuals[28]. A recent candidate SNP study replicated the association between the *SH2B3* SNP rs3184504 and coronary heart disease also in South Asian patients[105]. Thus, it appears that the 12q24 locus has a marked effect on vascular pathology.

RED BLOOD CELL TRAITS

It is unclear whether the above vascular disorders are consequences of vessel wall pathology or of blood cell pathology. It may therefore be relevant that a GWAS into the genetic basis of six traits of erythrocytes (including hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell count) also showed associations with the 12q24 locus from *SH2B3* across the *ATXN2* gene[106].

CONCLUSION

For further mechanistic insights it will be important to

generate and characterize rodent mutants for each of the genes in the pleiotropic 12q24 disease susceptibility locus.

With the limited knowledge available so far, it is credible that SH2B3 modulates B-lymphocyte proliferation and autoimmune traits. Ataxin-2 gain-of-function is a well-established modulator of several neurodegenerative diseases, while its deficiency appears to predispose to insulin resistance, blood cholesterol elevation, hepatic glycogen and lipid accumulation with overall obesity. Thus, downstream effects of both genes might cooperate to enhance the risk for type 1 diabetes.

Since T1D is an age-associated disease, it will be important to age Atxn2-null mice beyond 6 mo to the end of their natural lifespan around 2 years. This will allow us to assess whether their obesity leads to hypertension and vascular pathology, *e.g.*, in kidneys, whether red blood cell traits are altered, and whether their longevity is abnormal. In particular, the insulin resistance/obesity/dyslipidemia/hepatosteatosis induced by *Atxn2*-null mutations should be studied regarding their long-term consequences. Mechanistically, it will be intriguing to elucidate how the RNA processing effects of ataxin-2 lead to this pathology.

In view of the polyQ expansion effects extending the protein half-life and causing a gain-of-function of ataxin-2, it is conceivable that the polyQ shrinkage sizes (Q13-21) could mediate a decreased half-life of the protein and a partial loss-of-function. Thus, these rare variants might be associated with phenotypes that were observed in the Atxn2-null mouse, such as obesity, insulin-resistance and diabetes mellitus.

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