Recessively Inherited *LRBA* Mutations Cause Autoimmunity Presenting as Neonatal Diabetes

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GENETICS/GENOMES/PROTEOMICS/METABOLOMICS

Young-onset autoimmune diabetes associated with additional autoimmunity usually reflects a polygenic predisposition, but rare cases result from monogenic autoimmunity. Diagnosing monogenic autoimmunity is crucial for patients' prognosis and clinical management. We sought to identify novel genetic causes of autoimmunity presenting with neonatal diabetes (NDM) (diagnosis <6 months). We performed exome sequencing in a patient with NDM and autoimmune lymphoproliferative syndrome and his unrelated, unaffected parents and identified compound heterozygous null mutations in *LRBA*. Biallelic *LRBA* mutations cause common variable immunodeficiency-8; however, NDM has not been confirmed in this disorder. We sequenced *LRBA* in 169 additional patients with diabetes diagnosed <1 year without mutations in the 24 known NDM genes. We identified recessive null mutations in 8 additional probands, of which, 3 had NDM (<6 months). Diabetes was the presenting feature in 6 of 9 probands. Six of 17 (35%) patients born to consanguineous parents and with additional early-onset autoimmunity had recessive *LRBA* mutations. *LRBA* testing should be considered in patients with diabetes diagnosed <12 months, particularly if they have additional autoimmunity or are born to consanguineous parents. A genetic diagnosis is important as it can enable personalized therapy with abatacept, a CTLA-4 mimetic, and inform genetic counseling.

Clustering of diabetes with early-onset autoimmunity in very early childhood is usually due to a combination of extreme polygenic risk and environmental exposure. Rarely, a mutation in a single gene is the etiological cause, and the identification of the underlying monogenic defect can give important insights into mechanisms of β-cell autoimmunity and pathways of immune tolerance (1–14). Because of significant clinical overlap, discriminating patients with causative mutations in a single gene from those with a polygenic etiology remains a challenge.

A prompt diagnosis of monogenic autoimmunity is crucial as it informs clinical management and targeted therapies may be possible. *FOXP3* mutations in males cause immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome (14), which can be treated with a hematopoietic stem cell transplant (HSCT). If performed early, HSCT can cure the life-threatening enteropathy as well as prevent the onset of autoimmune-mediated diabetes (15). In an individual with polyarthritis, scleroderma, and autoimmune hemolytic anemia resulting from an activating *STAT3* mutation, treatment with tocilizumab, a monoclonal antibody against IL-6, resulted in marked improvement in the symptoms (16). Patients with common variable immunodeficiency-8 (CVID-8), caused by recessively inherited mutations in lipopolysaccharide-responsive beige-like anchor

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protein (*LRBA*), can be successfully treated with abatacept, a mimetic for CTLA-4. CTLA-4 is a potent suppressive receptor that acts as an immune checkpoint and is posttranslationally regulated by LRBA (1).

Monogenic autoimmune disease often presents extremely early; for example, mutations in the *STAT3*, *FOXP3*, or *IL2RA* genes commonly present with neonatal diabetes (13,14,17). Mutations in *LRBA* typically presents with severe autoimmune disease early in childhood and diabetes is a feature in 22% of patients; however, neonatal diabetes has not been confirmed (2).

We identified biallelic mutations in *LRBA* in an individual with neonatal diabetes diagnosed at 7 weeks and additional early-onset autoimmunity of unknown cause. We go on to show that this is a relatively common etiology of neonatal or infancy-onset diabetes when patients have additional early-onset autoimmune disease and are born to consanguineous parents.

RESEARCH DESIGN AND METHODS

Gene Discovery Using Exome Sequencing

The initial case presented with diabetic ketoacidosis (blood glucose concentration 53 mmol/L) at the age of 7 weeks and developed thrombocytopenia and autoimmune lymphoproliferative disease at age 3 years. To define the genetic etiology, having excluded all 24 known causes of neonatal diabetes, we used exome sequencing and trio analysis of the proband and his unaffected, unrelated parents to search for de novo heterozygous mutations and/or compound heterozygous mutations. Exome sequencing was performed using Agilent SureSelect Human All Exon kit (v5) with paired end 100 bp read length sequencing undertaken on an Illumina HiSEq 2500. For single nucleotide variant identification, the resulting reads were aligned to the hg19 reference genome according to Genome Analysis Toolkit (18,19) best practice guidelines. An in-house script was used to remove synonymous variants, those outside the coding region or conserved splice site, and variants present in dbSNP131 or the Exome Aggregation Consortium (ExAC) database with a minor allele frequency >0.1%, as previously reported (13). We used the R software package ExomeDepth (20) to detect copy number variation. Coverage and read depth data for the trio is provided in Supplementary Table 1.

Follow-up Testing in Selected Neonatal/Infancy-Onset Diabetes

In our cohort of 1,561 patients diagnosed with diabetes before the age of 12 months, 169 did not have a mutation in a known gene and were screened for mutations in *LRBA* (Fig. 2). Of these, 54 patients were consanguineous, and within this group, 17 individuals had autoimmune disease. Autoimmune disease was also present in 25 of 116 nonconsanguineous patients. Consanguineous unions were defined as previously described (21), either known related parents ($n = 25$) or patients who were from regions with high levels of consanguineous unions ($n = 29$) (21). The additional autoimmune disease was diagnosed before 5 years and included hypothyroidism (15/42), celiac disease/autoimmune enteropathy (16/42), and inflammatory arthritis (3/42) (further details are provided in Supplementary Table 2).

The 24 known causes of neonatal diabetes had been previously excluded by next-generation sequencing (13,22) and methylation-specific multiplex ligation-dependent probe amplification (MLPA; MRC-Holland, Amsterdam, the Netherlands) in all 169 patients. Targeted next-generation sequencing of the 58 exons and flanking intronic regions of *LRBA* (NM_006726.4) was performed as previously described (23) in the 169 patients with diabetes diagnosed before 1 year. Putative mutations were confirmed by Sanger sequencing or by droplet digital PCR (details available on request). When available samples from affected siblings and unaffected parents underwent mutation testing, clinical information was collected from the patient's medical records by the referring clinician. All subjects and/or their parents gave informed consent for genetic testing. The study was approved by the Genetic Beta Cell Research Bank (Exeter, U.K.) with ethics approval from the North Wales Research Ethics Committee.

RESULTS

Molecular Genetics

We initially searched for de novo mutations in the proband and unrelated, unaffected parent trio. This identified four coding variants in the proband, all of which were present in the ExAC database (24) of >60,000 patients not diagnosed with any severe pediatric disease (Supplementary Table 3). We considered these unlikely to be causative and switched our analysis to look for recessive causes.

We identified compound heterozygous mutations in *LRBA* and *PKHD1L1*. The two novel null mutations in *LRBA* (p.D1053fs*2; c.3156del and p.S2659*; c.7976C>G) were considered likely to be pathogenic as biallelic mutations in this gene are known to cause CVID-8 (7). Variants in *PKHD1L1* have not been associated with Mendelian disease, and there are 549 individuals in the ExAC database (control subjects without severe pediatric disease) with homozygous loss-of-function mutations (24), suggesting that loss of *PKHD1L1* does not cause childhood-onset disease.

Although diabetes has been reported as a feature in 11 of 57 patients (1–12) with *LRBA* mutations, only 2 patients were diagnosed before the age of 1 year; 1 at 4 months and 1 at 7 months. The median age of diabetes diagnosis in the other patients was 2 years (range 1–9 years). *LRBA* encodes the LRBA protein, an essential posttranslational regulator of the CTLA-4 receptor involved in the suppression of regulatory T cells (1).

Sequence analysis of *LRBA* in 169 patients diagnosed with diabetes before 12 months identified homozygous null mutations in 8 additional probands and 1 affected sibling (Table 1, Fig. 1, and Supplementary Fig. 2). All mutations introduce premature termination codons (three nonsense, four frameshift, and two mutations affecting splicing and one whole-exon deletion) and are predicted to result in

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Table 1—Clinical features of patients with *LRBA* mutations

	Patient									
	1	2.1	2.2	3	4	5	6	7	8	9
Genotype	p.D1053fs/ p.S2659* (c.3156del/ c.7976C>A)	p.R2348* (c.7042C>T)	p.R2348* (c.7042C>T)	p.R1271* (c.3811C>T)	p.? (c.5581 –1G>A)	p.M589fs (c.1764dup)	p.P816fs (c.2447del)	p.? (c.(4729+ 1_4730–1)_ (5171+1_ 5172–1)del)	p.? (c.5172– 2A>G)	p.I1330fs (c.3988dup)
Birth weight, g (gestational weeks)	2,600 (35)	3,200 (39)	3,200 (unknown)	2,700 (40)	3,200 (38)	2,750 (39)	3,200 (40)	2,965 (40)	2,970 (40)	3,000 (40)
Sex	Male	Male	Male	Male	Female	Female	Male	Male	Female	Male
Current age (years)	Deceased	1	Deceased	8	Deceased	2	6	26	1	4
Known consanguinity	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Ethnicity	Turkish	Moroccan	Moroccan	Omani	Omani	Iranian	Egyptian	Chinese	Turkish	Pakistani
Diabetes features										
Age at onset	7 weeks	6 weeks	15 months	4 months	5 months	9 months	9 months	10 months	8 months	7 months
Treatment (dose, units/kg/day)	Insulin (1)	Insulin (1)	Insulin (1.2)	Insulin (1)	Insulin (0.6)	Insulin (0.7)	Insulin (2)	Insulin (0.6)	Insulin (0.9)	Insulin (1.7)
HbA_{1c}, % (mmol/mol)†	7.0 (53)	7.1 (54)	6.6 (49)	7.1 (54)	8.3 (67)	ND	ND	8.7 (72)	7.2 (55)	ND
Antibody status	GAD negative	GAD/IA2/ ZnT8 negative	ND	GAD/IA2 negative	GAD positive	ND	ND	GAD negative	GAD/IA2 negative	ND
Immune dysregulatory features										
Hematological disorders	Thrombocytopenia, autoimmune lymphoproliferative disease	–	Thrombocytopenia, autoimmune lymphoproliferative disease	Agammaglobulinemia, autoimmune lymphoproliferative disease	–	–	Thrombocytopenia, autoimmune hemolytic anemia	Pernicious anemia	–	–
Gastrointestinal disorders	–	Autoimmune enteropathy	Autoimmune enteropathy, hepatosplenomegaly	Hepatosplenomegaly	Autoimmune enteropathy	–	Episodes of diarrhea	Celiac disease	–	Chronic diarrhea
Endocrine disorders	–	–	–	–	–	–	Autoimmune hypothyroidism	TPO Ab positive (subclinical hypothyroidism)	–	–
Recurrent infections	–	–	Died of septic shock following unknown infection	Recurrent chest infections (*Aspergillus* spp.)	–	–	Pneumonia	–	Pneumonia, otitis media	URTI, septicemia
Other features	Cleft lip, developmental delay, hemiparesis. Died of intracranial bleed	–	–	Lymphocytic interstitial pneumonia	Died of nephroblastoma	–	History of convulsions, multiple cerebral infarctions	Parenchymal calcification of kidneys	–	–

All mutations are homozygous unless otherwise indicated and are described according to Human Genome Variation Society guidelines based on the longest isoform, NM_006726.4. Disorders reported are based on the clinical diagnosis made by the patients' physician and were not always confirmed by diagnostic investigations such as biopsies. ND, no data; TPO Ab, thyroid peroxidase antibody; URTI, upper respiratory tract infections. †Most recent HbA_{1c} recorded.

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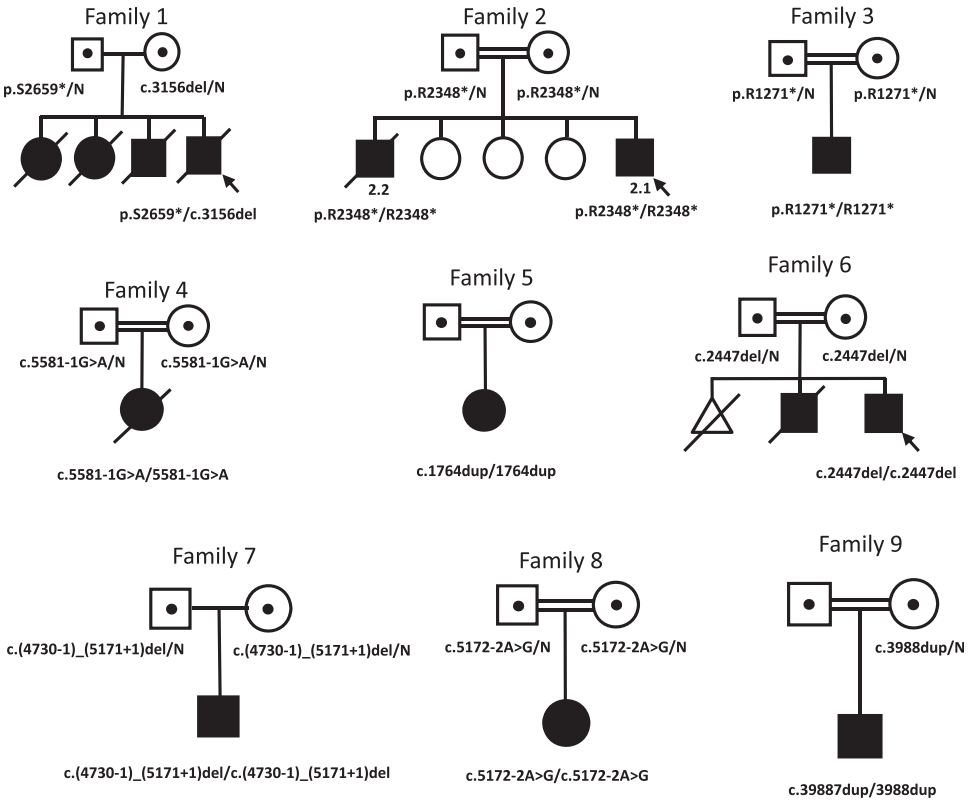

Figure 1—Family pedigrees of patients with *LRBA* mutations. Filled symbols represent affected individuals and dots within symbols represent heterozygous unaffected carriers. Double lines signify parents are related. Symbols with lines through represent deceased individuals. Genotypes are provided below affected individuals and carriers. When no genotype is given, samples were unavailable for testing.

complete loss of the LRBA protein. Carrier status was confirmed in parents when samples were available (Fig. 1).

Table 2 shows the distribution of individuals with *LRBA* mutations by age of diabetes diagnosis and parental consanguinity. Interestingly, the highest proportion of those with a mutation was diagnosed with diabetes between 6 and 12 months. We identified *LRBA* mutations in 9 of 1,561 patients diagnosed with diabetes before 12 months, giving a minimum prevalence of 0.6% in our cohort (Table 2).

Seven of 54 (13%) consanguineous patients had *LRBA* mutations, whereas a mutation was identified in only 2 of 25 (8%) nonconsanguineous patients with autoimmunity. Strikingly, when the criteria of consanguinity and autoimmunity were combined, 6 of 17 (35%) patients harbored mutations in *LRBA* (Fig. 2). Using these two criteria therefore greatly increased the likelihood of identifying an *LRBA* mutation.

Clinical Characteristics

The proband presented in severe diabetic ketoacidosis at the age of 7 weeks (blood glucose 53 mmol/L). He was treated with a full replacement dose of insulin, was negative for anti-GAD antibodies, and had an HbA_{1c} prior to his death of 7.0% (53 mmol/mol). Thrombocytopenia and autoimmune lymphoproliferative disease were reported at the age of 3 years, with additional features including right hemiparesis and neuromotor retardation noted at this time. The patient died shortly before his fourth birthday as a result of an intracranial hemorrhage caused by thrombocytopenia.

Table 2—Minimum prevalence of *LRBA* mutations in our cohort of patients diagnosed with diabetes before 12 months

	<6 months		6–12 months		<12 months	
	Consang	Nonconsang	Consang	Nonconsang	Consang	Nonconsang
Total number of patients	338	892	63	268	401	1,160
Number with other known genetic cause	299	761	17	56	316	817
Number *LRBA* tested in	31	74	23	41	54	116
Number of *LRBA* cases identified	3	1	4	1	7	2
Minimum prevalence (%)	0.9	0.1	6.3	0.4	1.7	0.2

Consang, born to consanguineous parents; Nonconsang, born to unrelated parents.

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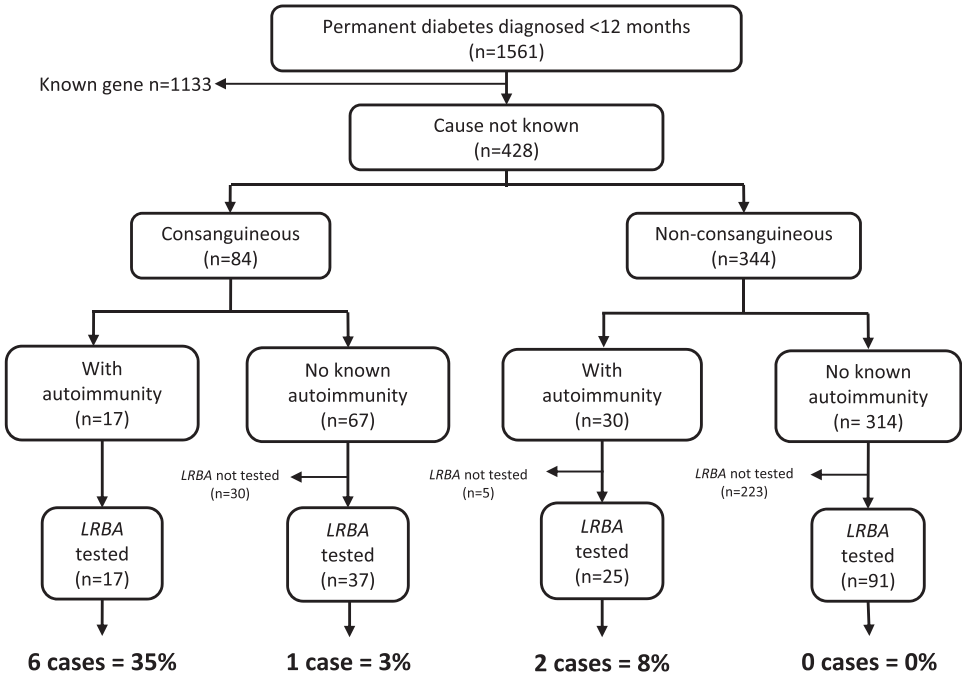

Figure 2—Flow diagram showing the testing strategy for *LRBA* screening in individuals diagnosed with diabetes before 12 months of age. The pick-up rates of *LRBA* mutations, when individuals are subgrouped according to consanguinity and additional autoimmune disease, are provided.

Detailed follow-up after genetic analysis revealed the proband's three elder siblings had also died in childhood at another hospital; two older sisters died at ages 12 years and 3.5 years due to complications relating to immunodeficiency and his older brother died at the age of 6.5 years as a result of immunodeficiency and severe enteropathy. Diabetes was not reported in these individuals and DNA was not available for testing. This family history suggests the siblings were also compound heterozygous for the *LRBA* mutations, fitting with the inheritance pattern of *LRBA*. The parents were unaffected in keeping with previous reports that haploinsufficiency of *LRBA* does not cause CVID-8 (5,6)

All 10 patients with biallelic *LRBA* mutations were diagnosed with diabetes in the first 15 months of life (median 7.5 months, range 6 weeks–15 months), and 4 of these patients met the criteria for neonatal diabetes, having been diagnosed with diabetes before the age of 6 months. All had insulin doses suggesting full replacement was required (Table 1). Positivity for anti-GAD antibodies (90 units/mL; normal range <25 units/mL) was detected in just 1 of the 6 patients in whom pancreatic antibody screening with GAD/IA2/ZnT was possible (Table 1). This low prevalence of autoantibodies is in keeping with these patients having autoimmunity with a distinct mechanism to that seen in type 1 diabetes.

In 6 of the 9 probands, diabetes was the presenting feature. Autoimmune disorders were present in 8 of the 9 probands (Table 1) and included hematological manifestations (5/8), autoimmune enteropathy (3/8), and hypothyroidism (1/8). The remaining proband is the result of a consanguineous union and presented with diabetes at 9 months, which is still the only clinical feature at 2 years. In 3 patients, recurrent respiratory infections were reported. The prognosis is poor as three of the patients are deceased: the original proband died of a cerebral hemorrhage likely caused by thrombocytopenia, a second patient developed complications associated with nephroblastoma, and a third patient died of sepsis (Table 1).

DISCUSSION

We have identified 10 different loss-of-function *LRBA* mutations in nine probands and one sibling (Fig. 1 and Table 1) with four patients having neonatal diabetes. This study increases the total number of genetic causes of neonatal diabetes to 25, and the genetic causes of severe early-onset autoimmunity that includes neonatal diabetes to 4; the others being *FOXP3* (14), *IL2RA* (17), and *STAT3* (13).

In our cohort of patients with diabetes diagnosed before 12 months, 0.6% had recessively inherited *LRBA* mutations. In contrast to other monogenic autoimmune diabetes subtypes, the highest pick-up rate for *LRBA* mutations was in those individuals diagnosed with diabetes between 6 and 12 months. The combined criteria of autoimmune disease and consanguinity identified a high proportion of patients with *LRBA* mutations. Six of the nine probands with *LRBA* mutations were suspected or proven to be consanguineous and have additional autoimmune disease. Using these criteria

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in our patients with infancy-onset diabetes, we identified a causative mutation in 35% (6 of 17) of patients (Fig. 2). We therefore recommend that testing for *LRBA* mutations be considered in all patients diagnosed with diabetes before the age of 12 months, particularly those who have additional autoimmunity and are the result of consanguineous union.

Identifying *LRBA* mutations early is crucial as it may allow for the introduction of optimal treatment strategies before the disease progresses. Genetic testing of all causes of neonatal diabetes is now predominantly by targeted panels (23,25,26) occurring immediately after the diagnosis of diabetes within the first 6 months of life (22). Targeted sequencing should include *LRBA*, as in all four probands with neonatal diabetes, diabetes was the first feature of their multisystem autoimmune disorder and for one proband is currently the only feature at the age of 2 years.

Recessive mutations in *LRBA* are a known cause of CVID-8 (MIM #614700) (7), which often include early-onset autoimmunity, immune dysregulation, recurrent infections, and hypogammaglobinemia with variable penetrance (1–12,27). Neonatal diabetes had not been confirmed as a feature of this disorder. The extrapancreatic features observed in our cohort are at a similar prevalence to those reported in patients with biallelic *LRBA* mutations (Supplementary Fig. 1), consistent with a diagnosis of CVID-8.

Five of the six patients in whom testing was possible were negative for pancreatic antibodies. This suggests that the mechanism of autoimmunity may be distinct to that observed in early-onset type 1 diabetes. It may be that the autoantigens that are the target of the immune response are as-yet uncharacterized or are not islet specific or that the autoimmunity is cell based rather than antibody driven. Further work to elucidate the true mechanism underlying the development of diabetes in CVID-8 is warranted and may give new insights into the pathophysiology of type 1 diabetes.

All patients we describe have functionally similar biallelic null mutations, but despite this, there is considerable variation in their phenotype. For example, patient 3 presented with neonatal diabetes (diagnosed at 4 months) and has immunodeficiency, autoimmune lymphoproliferative disease, hepatosplenomegaly, lymphocytic interstitial pneumonia, and recurrent chest infections diagnosed before the age of 8 years, whereas patient 7 was diagnosed with diabetes at the age of 10 months and has celiac disease, pernicious anemia, and subclinical hypothyroidism at the age of 26 years (Table 1). The variable phenotype of patients with homozygous missense mutations seen in previous studies was not statistically different from those with protein-truncating mutations; the age of onset of the first symptom is similar in both groups (median age of onset, missense mutations 1.75 years vs. nonsense mutations 2 years, $P = 0.79$) (1,5,7,8,11). It therefore seems likely that additional genetic and/or environmental factors influence the severity of the disease and the specific organs affected in these patients.

The autoimmunity observed in patients with *LRBA* mutations is thought to result from the loss of an essential immune regulatory pathway and a reduction in the suppressive action of regulatory T cell and therefore a disruption of immune tolerance (1). It was recently shown that LRBA prevents the lysosomal degradation of the CTLA-4 receptor, facilitating its trafficking to the surface of T cells during T-cell receptor stimulation (1). CTLA-4 is a potent suppressor, blocking costimulation of the T-cell receptor and therefore negatively regulating immune responses (28). A loss of LRBA therefore results in increased CTLA-4 degradation diminishing this inhibitory pathway on T-cell activation and resulting in unchecked activation of immunological responses.

Identifying the underlying genetic etiology is clinically important for these patients as understanding the disease mechanism may allow the use of personalized therapy. Abatacept, a CTLA-4 mimetic that replaces the action of the lost suppressive receptor, has been used to treat 12 patients with *LRBA* mutations so far and all showed improvement in their autoimmune features (1,5). Therapy with abatacept had not been attempted in our patients at the time of reporting. HSCT is also an option for these patients, with successful outcome reported in three of four patients with *LRBA* mutations in whom it has been attempted (5,10,12).

In conclusion, we have identified *LRBA* mutations in nine probands with early-onset diabetes (<1 year), of whom, eight had additional autoimmune features. In four of these patients, diabetes was diagnosed before 6 months confirming the role of this gene in the etiology of neonatal diabetes. As diabetes was the presenting feature in six of nine individuals, we recommend that testing for *LRBA* mutations is considered in all patients with newly diagnosed neonatal diabetes and in those with infancy-onset diabetes (<12 months), especially when a recessive inheritance is suspected or additional autoimmune features are present. A genetic diagnosis is critical not only for counseling on recurrence risk but also for allowing immunomodulatory agents such as abatacept to be considered as part of the treatment regimen.

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patients, provided clinical information, and contributed to discussion. S.E., A.T.H., and S.E.F. designed the study. A.T.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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