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# Genetic burden linked to founder effects in Saguenay–Lac-Saint-Jean illustrates the importance of genetic screening test availability

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Received 25 February 2021

Revised 27 March 2021

Accepted 14 April 2021

Published Online First 28 April 2021

## ABSTRACT

The Saguenay–Lac-Saint-Jean (SLSJ) region located in the province of Quebec was settled in the 19th century by pioneers issued from successive migration waves starting in France in the 17th century and continuing within Quebec until the beginning of the 20th century. The genetic structure of the SLSJ population is considered to be the product of a triple founder effect and is characterised by a higher prevalence of some rare genetic diseases. Several studies were performed to elucidate the historical, demographic and genetic background of current SLSJ inhabitants to assess the origins of these rare disorders and their distribution in the population. Thanks to the development of new sequencing technologies, the genes and the variants responsible for the most prevalent conditions were identified. Combined with other resources such as the BALSAC population database, identifying the causal genes and the pathogenic variants allowed to assess the impacts of some of these founder mutations on the population health and to design precision medicine public health strategies based on carrier testing. Furthermore, it stimulated the establishment of many public programmes.

We report here a review and an update of a subset of inherited disorders and founder mutations in the SLSJ region. Data were collected from published scientific sources. This work expands the knowledge about the current frequencies of these rare disorders, the frequencies of other rare genetic diseases in this population, the relevance of the carrier tests offered to the population, as well as the current available treatments and research about future therapeutic avenues for these inherited disorders.

## INTRODUCTION

Located 200 km northeast of Quebec City, Canada, the Saguenay–Lac-Saint-Jean (SLSJ) region is a relatively geographically isolated region with approximately 279 000 inhabitants (<https://www.stat.gouv.qc.ca>). The genetic structure of its population is considered to be the product of three successive migration waves corresponding to a triple founder effect (**figure 1**): (a) the first founder effect took place during the French regime (1608–1760) when approximately 10 000 immigrants settled in the Saint Lawrence valley, in the west of the Province of Quebec. They account for the major part of the contemporary French-Canadian gene pool<sup>1</sup>; (b) the

second founder effect started at the end of the 17th century, when inhabitants from Quebec city and C ote-de-Beaupr e (on the north shore of the Saint Lawrence river) moved to the Charlevoix region where 600 individuals settled between 1675 and 1840<sup>2</sup>; (c) the third founder effect corresponds to the colonisation of the SLSJ region. It started in the 1830's with the arrival of inhabitants coming first mostly from the nearby Charlevoix region, and afterwards from other regions of the Saint Lawrence valley.<sup>3</sup> From 1838 to 1911, almost 30 000 individuals migrated to the SLSJ, 70% of them from Charlevoix.<sup>4,5</sup> Thus, SLSJ provides a great example of a founder population.

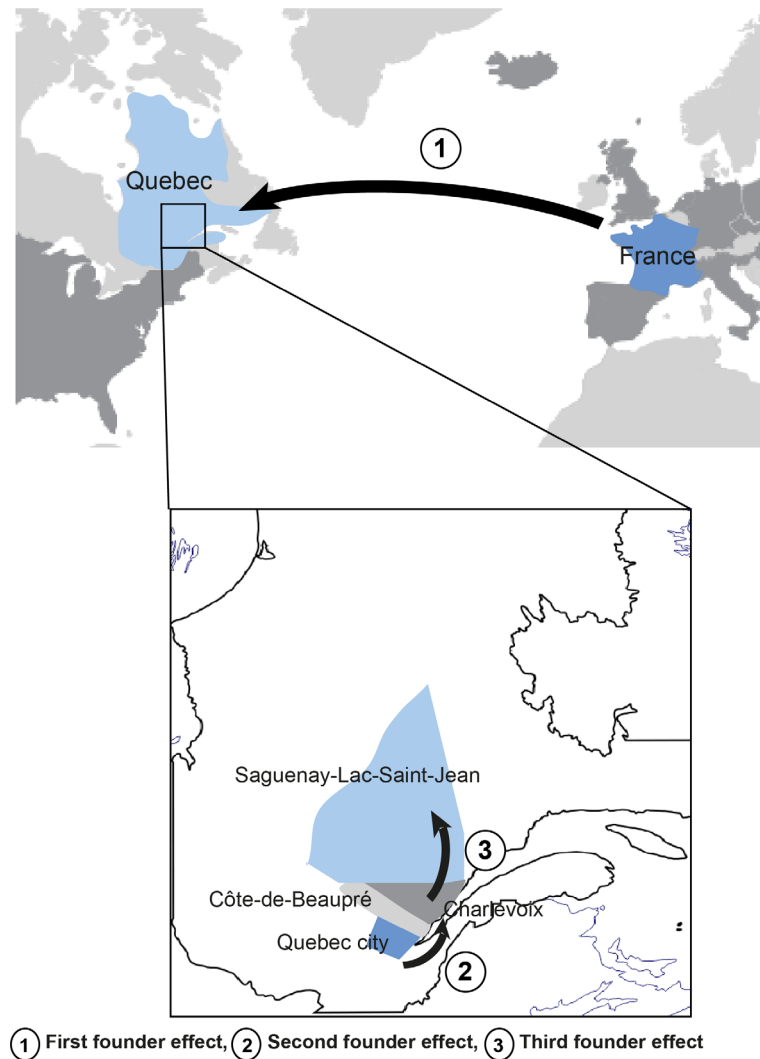
In the last decades, many studies have investigated rare genetic disorders or susceptibility genes showing higher frequency in the SLSJ population. Altogether, these studies indicate that hereditary disorders in this population follow a specific pattern consistent with a founder effect: the ‘founder’ diseases have a higher prevalence explained by a lower genetic variability whereas some others (eg, phenylketonuria) are ultra-rare or not reported in the SLSJ population.<sup>6–8</sup> Also consistent with the characteristics of settlement history, many reports documented that most of the genetic disorders found in the SLSJ region are also found in Charlevoix.<sup>9</sup> As the existing founder effect increases haplotype homozygosity and reduces genetic diversity, many geneticists and physicians worked on the SLSJ population for gene discovery as well as for clinical and epidemiological studies.<sup>10–13</sup>

From a research standpoint, the SLSJ population has also been of great interest to demographers and population geneticists. A research programme was developed in the 1980s through the use of the complete genealogy of the SLSJ population available in the BALSAC database (<https://balsac.uqac.ca/>). A major goal of these studies was to understand and explain the role of demographic dynamics and population history in the origin and spread of genetic diseases. Results have confirmed the impact of the founder effect and its associated factors, such as drift and remote inbreeding. These studies have also clearly established that, contrary to a widely held belief, consanguineous marriages were similar and even less frequent than in the other regions of the Province of Quebec. Consanguinity therefore cannot explain the observed higher frequency of rare genetic diseases in the SLSJ.<sup>6,8,14,15</sup>



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**To cite:** Bchetnia M, Bouchard L, Mathieu J, et al. *J Med Genet* 2021;**58**:653–665.



**Figure 1** Three main migratory events contributing to the founder effect in Saguenay–Lac-Saint-Jean (SLSJ) region. During the 17th and 18th centuries, between 10 000 and 12 000 immigrants, mainly from France, settled in the Saint Lawrence Valley (first founder effect). From the end of the 17th century, inhabitants of the Saint-Lawrence Valley, more particularly from Quebec City and the Côte-de-Beaupré area, settled in the Charlevoix region (second founder effect). Finally, settlers from Charlevoix moved to the SLSJ region from the 1830s (third founder effect). They were later followed by settlers from other Quebec regions, but they represent the majority of the founders of the SLSJ population.

A better understanding of the genetic characteristics of these diseases has made it possible to offer genetic counselling for affected patients and their families and free carrier testing screening for the Quebec people with at least one grandparent born in the SLSJ, Charlevoix or Côte-Nord regions (<https://www.sante.gouv.qc.ca/tests4maladies>). Currently, the carrier test includes four selected diseases with increased incidence in SLSJ (autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS | MIM 270550), agenesis of the corpus callosum with/without peripheral neuropathy (ACCPN | MIM 218000), Leigh syndrome French-Canadian type (LSFC | MIM 220111) and hereditary tyrosinemia type 1 (TYRSN1 | MIM 276700)).<sup>16</sup> The carrier frequency of these diseases is between 1/19 and 1/23 meaning that 20% of the SLSJ inhabitants carry the mutated allele of at least one pathogenic variants causal of these recessive diseases.

In this review, we present some of the most frequent hereditary diseases identified in SLSJ and published in the literature. PubMed, Google Scholar and other documentary sources were explored using the following key words: Saguenay–Lac-Saint-Jean (SLSJ), Charlevoix, French-Canadian origin, genetic

disease, founder mutation and carrier test. When available, updated data are provided (table 1). We describe the estimated frequency, clinical and genetic characteristics, available or emerging treatments and potential impacts on public health of these diseases. Finally, we discuss the clinical utility and highlight some issues related to a recently developed multiplex recessive diseases carrier testing programme offered to couples originating from the SLSJ.

### Rare autosomal recessive diseases with higher prevalence in Saguenay–Lac-Saint-Jean population

#### Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS, MIM 270550)

Autosomal recessive spastic ataxia of Charlevoix-Saguenay is an early-onset neurodegenerative disorder due to progressive degeneration of the spinal cord and the cerebellum.<sup>17</sup> ARSACS manifests between 12 and 18 months with early-onset ataxia, and leads to peripheral neuropathy, spasticity, hypermyelination of the retinal nerve fibres, and finger and foot deformities.<sup>18</sup> It was first described among a cohort of

**Table 1** Inherited disorders in Saguenay–Lac-Saint-Jean (SLSJ)

Autosomal recessive diseases									
Disease	OMIM	Worldwide frequency	Frequency in SLSJ	Carrier rate in SLSJ	Gene	Founder mutations in SLSJ	Founder allele frequency in SLSJ	Founder allele frequency (gnomAD)**	References
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	270550	N/A	1/1932	1/22	<i>SACS</i>	► c.8844del (p.Ile2949fs) ► c.7504C>T (p.Arg2502X)	0.926 0.037	610 <sup>-5</sup> 10 <sup>-5</sup>	19 25 28
Agensis of corpus callosum and peripheral neuropathy (ACCPN)	218000	N/A	1/2117	1/23	<i>SLC12A6</i>	► c.2436delG (p.Thr813Profs) ► c.1584-1585delCTinsG (Phe529fsX531)	0.99 N/A	310 <sup>-5</sup> N/A	31 32
Leigh syndrome, French-Canadian type (LSFC)	220111	1/40 000	1/2000	1/23	<i>LRPPRC</i>	► c.1061C>T (p.Ala354Val)	0.99	510 <sup>-5</sup>	10 35
Tyrosinemia type I (TYRSN1)	276700	1/120 000	1/1846	1/20	<i>FAH</i>	► c.1062 5G>A (IVS12+5G+A)	0.9	310 <sup>-4</sup>	38 39
Cystic fibrosis (CF)	219700	1/2000	1/902	1/15	<i>CFTR</i>	► c.1521-1523delCT (p.Phe508del) ► c.489+1G>T (621+1G>T) ► c.1364C>A (p.Arg347Pro)	N/A N/A N/A	710 <sup>-3</sup> 610 <sup>-5</sup> 210 <sup>-5</sup>	49 51
Mucopolipidosis (I-cell disease)	252500	N/A	1/6184	1/39	<i>GNPTAB</i>	► c.3503_3504delTC (p.Leu1168Glnfs)	N/A	410 <sup>-4</sup>	4 64
Vitamin D–dependent rickets type 1 (VDDR1)	264700	N/A	1/2916	1/27	<i>CYP27B1</i>	► c.262delG (p.Val88Trpfs) ► c.958delG (frameshift after 877Tyr)	N/A N/A	310 <sup>-5</sup> N/A	76 77
Familial dysbetalipoproteinemia (type III hyperlipoproteinemia)	617347	1/5000	1/1000	1/7	<i>APOE</i>	► Apo E2 allele	N/A	N/A	81–84
Lipoprotein lipase deficiency (LPLD)	238600	1–2/ 1 000 000	1/5000	1/40	<i>LPL</i>	► c.644G>A (p.Gly215Glu) ► c.701C>T (p.Pro234Leu) ► c.829G>A (p.Asp277Asn)	N/A N/A N/A	10 <sup>-4</sup> 410 <sup>-5</sup> 210 <sup>-5</sup>	87 160
Cystinosis	219800	0.5–1.0/100 000	1/11 939	1/39	<i>CTNS</i>	► c.414G>A (p.Trp138X)	N/A	410 <sup>-5</sup>	4
Zellweger syndrome (ZS)	601539	N/A	1/12 191	1/55	<i>PEX6</i>	► c.802_815del (p.Asp268fs)	N/A	10 <sup>-5</sup>	6 11
Naxos disease (NXD)	601214	N/A	N/A	N/A	<i>JUP</i>	► c.902A>G (p.Glu301Gly)	N/A	10 <sup>-5</sup>	147 148
Autosomal dominant diseases									
Myotonic dystrophy type 1 (DM1)	160900	2.1–14.3/100 000	158/100 000	-	<i>DMPK</i>	► (CTG) repeat expansion	N/A	N/A	12 98
Familial hypercholesterolaemia (FH)	143890	Heterozygous 1/250 Homozygous 1/300 000	Heterozygous 1/120	-	<i>LDLR</i>	► prom_e1 deletion >15 kb ► c.259T>G (p.Trp87Gly) ► c.2000G>A (p.Cys667Tyr) ► c.1467C>G (p.Tyr489Ter)	N/A N/A N/A N/A	N/A 210 <sup>-5</sup> 310 <sup>-6</sup> 310 <sup>-6</sup>	81 107 108 113
Epidermolysis bullosa simplex (EBS)	131760 131900 131800	6–30/100 000	N/A	-	<i>KRT5</i> <i>KRT14</i>	<i>KRT5</i> : ► c.74C>T (p.Pro25Leu) ► c.449C>T (p.Leu150Pro) <i>KRT14</i> : ► c.1130T>C (p.Ileu377Thr)	N/A N/A N/A N/A	N/A N/A N/A	152 153

\*<https://gnomad.broadinstitute.org>.  
-, not applicable; N/A, not available.

about 325 French-Canadian patients from 200 families originating from the Charlevoix and SLSJ regions<sup>19</sup> where a higher incidence has been observed: the estimation of incidence and carrier frequency were 1/1932 live born infants and 1/22, respectively.<sup>19 20</sup> ARSACS was for a long time recognised as a form of early-onset ataxia limited to Quebec, due to a founder effect. However, over time, several studies showed that ARSACS occurs elsewhere in the world, including in Europe and Asia, with significant clinical variability between patients.<sup>17 21–24</sup> Pathogenic variants in the gene Spastic Ataxia of Charlevoix-Saguenay (*SACS*) were first described in French-Canadian patients.<sup>25</sup> The product of this gene is a very large cytoplasmic protein, saccin, with a suggested potential chaperone activity. Over the years, the number of individuals with ARSACS harbouring pathogenic variants in the *SACS* gene has rapidly increased worldwide and close to

200 pathogenic variants have been reported.<sup>26 27</sup> Two founder mutations in the *SACS* gene have been identified in French-Canadian patients, c.8844del (p.Ile2949fs) and c.7504C>T (p.Arg2502Cys).<sup>28</sup> Up to now, there is no effective treatment for ARSACS. Physiotherapy and exercises tailored to ataxia and medications such as baclofen to control spasticity in the early stage of the disease may joint contractures and prevent tendon shortening and, hence, may help postpone functional impairments.<sup>29</sup> Urinary urgency and incontinence may be controlled with specific treatments.<sup>29</sup> An Ataxia Charlevoix-Saguenay Foundation was established in 1972 in Montreal in order to help the management and diagnosis of patients with ARSACS. In SLSJ, the *Clinique des maladies neuromusculaires* (CMNM) provides specialised adaptation and rehabilitation services to people with neuromuscular diseases

such as ARSACS, and support to their families (<https://santesaglac.gouv.qc.ca/soins-et-services/deficience-physique/clinique-des-maladies-neuromusculaires/>).

#### Agenesis of the corpus callosum and peripheral neuropathy (ACCPN, MIM 218000)

Agenesis of the corpus callosum and peripheral neuropathy (Andermann syndrome) is an autosomal recessive motor and sensory neuropathy with agenesis of the corpus callosum. ACCPN manifests with progressive axonal degeneration and peripheral neuropathy leading to absence of deep tendon reflexes, atypical psychosis, mental retardation and growth delay.<sup>30</sup> On cerebral imaging, around 67.2% of patients present partial or total corpus callosum agenesis.<sup>31</sup> The mean age at death is 33 years.<sup>32</sup> Children usually begin to walk at a mean age of 3.8 years and lose the ability to walk at a mean age of 13.8 years (Muscular Dystrophy Canada, 2013). The prevalence of this condition in the world is very low, as only a few cases have been reported outside Quebec.<sup>31,33</sup> In the population of SLSJ, the prevalence is 1/2117 live births, and 1/23 individuals is a carrier of the founder mutation.<sup>32</sup> The causal gene is solute carrier family 12 member 6 (*SLC12A6*) located on chromosome band 15q14. It encodes the potassium-chloride cotransporter 3 (*KCC3*). Two pathogenic variants have been found in French-Canadians, c.2436delG (p.Thr813Profs) (161/162 alleles) and c.1584-1585delCTinsG (Phe529fsX531).<sup>30</sup> No treatments are currently available. As the disease progresses, orthoses for upper and lower limbs and physiotherapy are beneficial to prevent contractures. Early developmental/educational intervention addresses cognitive delays. Neuroleptics may be used to treat psychiatric manifestations.<sup>30</sup>

#### Leigh syndrome, French-Canadian type (LSFC, MIM 220111)

Leigh syndrome, French-Canadian type or congenital lactic acidosis specific to SLSJ is an autosomal recessive form of cytochrome oxidase deficiency (COX, respiratory chain complex IV). This mitochondrial disease is diagnosed in children aged between 0 and 4 years and is characterised by developmental delay, hypotonia, elevated lactate levels in blood and cerebrospinal fluid, and high mortality in infancy.<sup>34</sup> It affects 1/40 000 newborns worldwide.<sup>10</sup> In SLSJ, this disorder affects 1/2000 births, with a carrier rate of 1/23 individuals.<sup>35</sup> A genome-wide linkage-disequilibrium scan carried in 13 families from SLSJ localised the candidate region for the SLSJ cytochrome oxidase deficiency on chromosome 2p16.<sup>10</sup> Two years later, the responsible gene was identified as the leucine-rich pentatricopeptide repeat containing protein (*LRPPRC*) gene. It encodes for a mitochondrial and nuclear protein predicted to bind mRNA and thus regulates post-transcriptional mechanisms such as RNA stability, RNA modifications or RNA degradation.<sup>36,37</sup> The majority of patients from SLSJ carry the homozygous founder mutation c.1061C>T (p.Ala354Val) in *LRPPRC*.<sup>35</sup> To date, there is no treatment for this disease. Patients are encouraged to eat several small meals throughout the day in order to reduce the high-energy demands of digestion. During acute acidotic crises, management involves control of acidosis and provision of life-supporting care.<sup>35</sup> In 1991, a patient and family association was established in SLSJ as well as an international multidisciplinary consortium in order to better understand the pathophysiology of this disease and advance the development of diagnosis and treatment.

#### Tyrosinemia type I (TYRSN1, MIM 276700)

Tyrosinemia type I (hepatorenal tyrosinemia) is an autosomal recessive metabolic disease. It manifests with renal tubulopathy, hypophosphatemic rickets and mild renal Fanconi syndrome, cirrhosis, hepatocellular carcinoma, and acute neurological crises and sometimes paralysis.<sup>8</sup> The worldwide prevalence of hereditary tyrosinemia type I is 1/120 000 live births.<sup>38</sup> However, the prevalence is much higher in SLSJ, where around 1/1846 newborns is affected and 1/20 individuals is a carrier.<sup>39</sup> The responsible gene is fumarylacetoacetate hydrolase (*FAH*), located on chromosome 15q23-25 and encoding fumaryl acetoacetate hydrolase (Fah). Pathogenic variants in this gene lead to a deficiency in Fah, involved in the catabolism of tyrosine.<sup>40</sup> This deficiency causes an accumulation of metabolic products with high toxicity in the liver, kidneys and peripheral nerves.<sup>41,42</sup> The founder splice mutation c.1062 5G>A (IVS12+5G+A) is the main allele found in patients from the SLSJ region.<sup>43</sup> Before 2005 and prior to the availability of nitisinone (a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase), the only available curative therapy for tyrosinemia type I was liver transplantation. Since 2005, the pharmacological medication nitisinone or NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) combined with a strict diet and close monitoring of disease progression is the standard management.<sup>42,44,45</sup> Liver transplantation is still offered to those with severe complications or if therapeutic response is not achieved.<sup>46</sup> Recently, a CRISPR-Cas9-mediated correction of a *FAH* pathogenic variant in hepatocytes of a mouse model resulted in expression of the wild-type Fah protein in liver cells.<sup>47</sup> This is promising for a future therapeutic avenue. Newborn screening for this condition is routinely offered in Quebec since 1970 as part of the provincial newborn screening programme.<sup>48</sup>

#### Cystic fibrosis (CF, MIM 219700)

Cystic fibrosis (CF) (mucoviscidosis) is an autosomal recessive disorder classically described as a triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency and congenital bilateral agenesis of the vas deferens.<sup>8</sup> In the world, CF incidence is approximately 1/2000 and carrier rate about 1/22.<sup>49</sup> In the population of European descent, CF has an incidence of 1/2500 and a carrier rate of 1/25.<sup>50</sup> In Quebec, CF incidence is 1/2500 and a carrier rate of 1/22. In SLSJ, the incidence of cystic fibrosis reached 1/902 live births between 1975 and 1988. This corresponds to a carrier rate of 1/15.<sup>51</sup> CF is caused by pathogenic variants in the gene cystic fibrosis transmembrane conductance regulator (*CFTR*) on chromosome 7q31.2.<sup>52</sup> Over 2000 disease-causing pathogenic variants have been reported in *CFTR*.<sup>53</sup> Three mutations are particularly frequent in the SLSJ population (c.1521-1523delCTT (p.Phe508del), c.489+1G>T (621+1G>T) and c.1364C>A (p.Arg347Pro)). As in most populations, p.Phe508del is the most frequent one.<sup>54</sup> Three other pathogenic variants are present in at least three different families (c.579+1G>T (711+1G>T), c.3067\_3072del (p.Ile1023Val1024del) and c.3276C>A (p.Tyr1092X)) in SLSJ.<sup>55,56</sup> CF treatment is supportive, with pancreatic enzyme supplementation, antibioprophyllaxis and respiratory therapy.<sup>57,58</sup> Patients homozygous for the p.Phe508del mutation, treated with a combination of a corrector and a potentiator of the mutated *CFTR* protein, showed some amelioration of respiratory function.<sup>59,60</sup> Since 2017, screening for CF is available for all Quebec newborns, allowing for early diagnosis and management of children with



CF. Cystic Fibrosis Canada, a national charitable not-for-profit corporation, was created in 1960 in order to help patient management and treatment development for CF. In SLSJ, a CF clinic was also established and offers diagnosis and treatment for children and adults with CF.

#### Mucopolysaccharidosis (MLII, MIM 252500)

Mucopolysaccharidosis (MLII) (I-cell disease) is a rare autosomal recessive form of lysosomal storage disorder. This disease is fatal in childhood and causes developmental delay, coarse facial features with hyperplastic gums, dislocation of the hips, short stature, thickened skin and generalised hypotonia.<sup>61 62</sup> MLII prevalence at birth in SLSJ was reported to be 1/6184, with a carrier rate of 1/39 which is the highest frequency documented worldwide.<sup>4</sup> MLII is caused by a deficiency of the lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase (GNPTAB), an enzyme required for the mannose 6-phosphate tagging of newly synthesised lysosomal enzymes.<sup>63</sup> A single founder mutation c.3503\_3504delTC (p.Leu1168Glnfs) was present in 100% of MLII obligatory carriers of SLSJ origin and is responsible for MLII in this population.<sup>64</sup> Although this mutation has been observed elsewhere, it reaches the highest reported frequency in SLSJ.<sup>65 66</sup> No cures or specific therapies for MLII currently exist. Management of symptoms and supportive care are the only treatments available. For example, interactive programmes to stimulate cognitive development, physical and/or speech therapy may be beneficial for patients (<https://www.orpha.net>). For those with severe mouth pain and infections, gingivectomy may be considered.<sup>67 68</sup> Respiratory support and assisted ventilation may be required for some patients.<sup>69</sup>

#### Vitamin D-dependent rickets type 1 (VDDR1, MIM 264700)

Vitamin D plays an essential role in ensuring bone growth, mineral metabolism and cellular differentiation.<sup>70</sup> Vitamin D dependency type I (VDDR1), also referred to as pseudo-vitamin D-deficiency rickets (PDDR), is an autosomal recessive disease due to renal 25(OH)-vitamin D 1 $\alpha$ -hydroxylase deficiency, the key enzyme in vitamin D metabolism. This results in impaired synthesis of 1,25-dihydroxyvitamin D, the active form of vitamin D.<sup>71–73</sup> VDDR1 is characterised by early onset of rickets, hypocalcemia, hypophosphatemia and secondary hyperparathyroidism that appeared in the first or second year of life.<sup>74</sup> This disorder is rarely described in the world but was reported to be particularly common in the French-Canadian population. In SLSJ, it was recognised for the first time in 1970<sup>75</sup> and its prevalence was estimated to be 1/2916 live births giving a carrier frequency of 1/27 inhabitants.<sup>4</sup>

VDDR1 is caused by pathogenic variants in the 25-hydroxyvitamin D 1 $\alpha$ -hydroxylase gene (*CYP27B1*) that was mapped to chromosome 12q14 by genotyping French-Canadian families.<sup>72</sup> Two founder mutations were identified in French-Canadian patients, the c.262delG (p.Val88Trpfs) mutation was found in three patients at the homozygous state<sup>76</sup> and c.958delG (frameshift after 87Tyr) mutation was described on 11/12 alleles.<sup>77</sup> This suggests the existence of more than one founder effect of this disease in that population. The clinical phenotype of this disorder is completely corrected by daily administration of physiological doses of hormonally active, synthetic, vitamin D analogue (calcitriol).<sup>78</sup>

#### Autosomal recessive lipid disorders

The molecular genetic basis is well established for 25 monogenic dyslipidemias affecting blood levels of low-density lipoprotein

cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), other lipids or fat metabolism.<sup>79</sup> Although the majority of known monogenic dyslipidemias are encountered among French Canadians, familial dysbetalipoproteinemia and lipoprotein lipase deficiency (LPLD) are two autosomal recessive disorders having a significantly higher-than-expected prevalence in the Charlevoix-SLSJ population. Familial dysbetalipoproteinemia (MIM 617347), formerly known as type III hyperlipidemia, is a treatable hypertriglyceridemic phenotype most often associated with lipoprotein remnants accumulation, apolipoprotein E2 (APOE2) homozygosity, palmar xanthomas, and increased risk of coronary and peripheral artery disease.<sup>80</sup> Its estimated worldwide prevalence is 1/5000 but it is fivefold more frequent in the SLSJ due to a higher prevalence of APOE2, as estimated from the regional sample of the Quebec Heart Health Survey in 1991<sup>81</sup> and other sources.<sup>82–84</sup> LPLD (MIM 238600) is the main cause of the familial chylomicronemia syndrome (FCS) which is due to the presence of null variants in the *LPL* gene or in genes directly affecting LPL bioavailability, such as *APOC2*, *GPIIIBP1*, *APOA5* or *MLF1*.<sup>85</sup> LPLD is characterised by chylomicronemia (very severe hypertriglyceridemia), lipemia retinalis, eruptive xanthomas, and increased risk of recurrent acute pancreatitis and other morbidities. The prevalence of FCS is estimated at 1–2 cases per million worldwide, but it is 200-fold more frequent in the SLSJ-Charlevoix population.<sup>81 86</sup> The higher prevalence of LPLD in the SLSJ is due to the high frequency of the c.701C>T (p.Pro234Leu) variant<sup>87 88</sup> and, to a lesser extent, the c.644G>A (p.Gly215Glu) variant in *LPL* gene,<sup>88</sup> although other loss-of-function pathogenic variants, in both *LPL* and *LPL*-related genes, also contribute to the FCS phenotype in this region. The treatment of LPLD is a very strict low-fat diet. Effective therapies are in advanced clinical development for LPLD, including apoC-III antisense oligonucleotides (ASO) or small interfering RNA.<sup>89–91</sup> *LPL* gene replacement therapy has been used and a next generation is in development.<sup>92 93</sup> ANGPTL3 inhibitors (monoclonal antibodies, ASO or siRNA) are also in clinical development for severe hypertriglyceridemia and chylomicronemia.<sup>94</sup> Oligogenic and polygenic causes of chylomicronemia also exist and are 50- to 100-fold more common than monogenic, autosomal recessive, causes.<sup>95</sup>

#### Rare autosomal dominant diseases with higher prevalence in Saguenay–Lac-Saint-Jean population

##### Myotonic dystrophy type 1 (DM1, MIM 160900)

Myotonic dystrophy type 1 (DM1), also known as dystrophia myotonica or Steinert disease, affects the muscular system and also the central nervous, ocular, respiratory, cardiovascular, digestive, endocrine and reproductive systems.<sup>96 97</sup> Its prevalence ranges between 2.1 and 14.3/100 000 worldwide.<sup>98</sup> In SLSJ, the prevalence was estimated in 2010 to be 158/100 000, which is the highest reported prevalence in the world.<sup>12</sup> In 1985, 406 patients with DM1 were known in SLSJ. From 1985 to 2010, 352 new patients with DM1 were identified and 321 patients died.<sup>12</sup> The local founder effect of this disease in SLSJ was confirmed by haplotype analysis.<sup>99</sup> The genetics of this condition is characterised by anticipation due to a highly unstable trinucleotide (CTG) repeat expansion within the 3' untranslated region of the dystrophia myotonica protein kinase gene (*DMPK*) at chromosome 19q13.3.<sup>100</sup> Treatment is palliative and can include the use of ankle-foot orthoses, wheelchairs, or other assistive tools, special education programmes for children with DM1, and when appropriate, treatment of hypothyroidism, management of pain, consultation with a cardiologist for symptoms

or electrocardiogram evidence of arrhythmia, and removal of cataracts if present.<sup>101 102</sup> In SLSJ, patients can benefit from services offered by the *Clinique des maladies neuromusculaires* (CMNM). Roussel *et al* showed that strength/endurance training programmes in patients with DM1 leads to skeletal muscle adaptations linked to muscle growth.<sup>103</sup>

#### Familial hypercholesterolaemia (FH, MIM 143890)

Familial hypercholesterolaemia (FH) is an autosomal codominant disorder of cholesterol metabolism. The world prevalence is estimated at 1/250 for heterozygous FH and 1/300 000 for homozygous FH.<sup>104–106</sup> The overall prevalence of FH is known to be higher in several founder clusters, including French Canadians. Although the FH prevalence varies from one Quebec region to another,<sup>107</sup> it was estimated at 1/80 in the SLSJ region in the early 1990s.<sup>108</sup> FH is most often caused by loss-of-function pathogenic variants in the low-density lipoprotein (LDL)-receptor (*LDLR*) gene, although variants in *APOB*, *PCSK9* and *LDLRAP1* genes are also FH causing. The most frequent mutation in SLSJ is the non-null c.259T>G (p.Trp87Gly) in *LDLR* gene.<sup>109</sup> For a long time, a large (>15 kb) deletion was considered as the most frequent mutation in Quebec, but this was due to the severity of the FH phenotype associated with this null deletion. Despite the clinical utility of molecular testing, the diagnosis of FH is primarily clinical.<sup>110–112</sup> On top of life habits, statin therapy, with or without ezetimibe, is the standard of care for HeFH and can be started during childhood.<sup>113–115</sup> Monoclonal antibodies or siRNA agents inhibiting proprotein convertase subtilisin/kexin type 9 (*PCSK9*), a serine protease that binds and promotes the lysosomal degradation of the *LDLR*, and incrementally decrease LDL-C in HeFH by more than 50% are now available in affected adults<sup>116–119</sup> and are currently under advanced clinical investigation in the severe paediatric HeFH population.<sup>120–122</sup> *PCSK9* inhibitors, however, require some residual *LDLR* receptor bioavailability and are therefore less effective or non-effective in homozygous FH (HoFH) patients. For HoFH and refractory FH, *LDLR* receptor-independent agents have been developed, including lomitapide, a microsomal triglyceride transfer protein (*MTTP*) inhibitor,<sup>123–125</sup> and evinacumab, an Angiopoietin-like 3 (*ANGPTL-3*) inhibitor.<sup>126–128</sup> Given the prevalence of FH in SLSJ, the use of expensive therapies such as *PCSK9* inhibitors, lomitapide or evinacumab might constitute an important socioeconomic hurdle.<sup>124</sup>

#### Other rare Mendelian diseases in Saguenay–Lac-Saint-Jean population

As discussed previously, on top of recessive or dominant disorders being more prevalent in SLSJ, several other genetic disorders are regularly diagnosed in this region and are the object of clinical intervention or clinical research. These include well-documented lipid disorders such as elevated lipoprotein (a) (Lp(a)), abetalipoproteinemia, ATP-binding cassette A1 (*ABCA1*) deficiency, lecithin-cholesterol acyltransferase (*LCAT*) deficiency, chylomicron retention disease, lipid storage diseases and rare causes of non-alcoholic steatohepatitis (NASH) to name a few, as well as the diseases described later.

#### Cystinosis (MIM 219800)

Cystinosis (MIM 219800) is a lysosomal storage disease with autosomal recessive transmission. It is characterised by high accumulation of the amino acid cystine inside the lysosomes of cells due to a defect in cystine transport.<sup>129 130</sup> This cystine deposits begins during fetal life and affects various tissues

leading to failure to thrive, disturbance of renal function, ocular impairment and hypothyroidism.<sup>131 132</sup> The worldwide incidence of this metabolic disorder is estimated to 0.5–1.0/100 000 live births.<sup>133</sup> In SLSJ, between 1971 and 1990, eight cases were identified and thus the incidence was calculated to be 1/11 939 births and carrier rate to 1/39.<sup>4</sup> High incidence rate was also observed in the founder population in the province of Brittany, France (1/26 000 live births).<sup>134</sup>

In 1998, Town *et al* mapped the gene cystinosis, lysosomal cystine transporter (*CTNS*) on chromosome 17p13 and confirmed its responsibility of cystinosis. This gene is encoding for the lysosomal membrane protein cystinosis, transporting cystine out of the lysosomal compartment.<sup>135</sup> More than 100 pathogenic variants have been further reported within this gene in the literature.<sup>133</sup> Mutational analysis of 20 cystinosis French-Canadian families identified five pathogenic variants, from which two are novel. One mutation, c. 414G>A (p.Trp138X), previously found in the Irish population (but not French), accounted for 40%–50% of cystinosis alleles in Quebec suggesting a probable Irish origin of this mutation in French-Canadian patients.<sup>131</sup>

For over 20 years, cysteamine is used for the treatment of cystinosis. This agent decreases intracellular cystine resulting in slows organ deterioration and delaying the onset of end-stage renal disease.<sup>136 137</sup> Although this cystine-depleting agent does not treat the disease, it highly improves the overall prognosis.<sup>132 138</sup> The side effects of cysteamine include stomach problems, unusual breath, sweat odour and allergic reactions.<sup>139</sup> A novel aminoglycoside (ELX-02) is now under investigation as a novel read-through therapy without cytotoxicity.<sup>140</sup>

#### Zellweger syndrome (ZS, MIM 601539)

Zellweger syndrome (ZS) is an autosomal recessive condition due to a peroxisome biogenesis dysfunction. This leads to developmental defects and progressive neurological involvement and often results in death in the first year of life.<sup>141</sup> The world incidence of ZS is 1/50 000–100 000 live births.<sup>142</sup> For some years, increased incidence of ZS has been suspected in French Canadians in SLSJ<sup>6</sup> and was calculated to be 1/12 191 live births, with a carrier rate of 1/55.<sup>11</sup> ZS is genetically heterogeneous and can be caused by pathogenic variants in any of 13 peroxisomal biogenesis factor (*PEX*) genes.<sup>143</sup> *PEX1* and *PEX6* pathogenic variants account for 70% and 10%–16% of all cases, respectively.<sup>143 144</sup> The homozygous pathogenic variant c.802\_815del (p.Asp268fs) in *PEX6* was identified in five SLSJ patients.<sup>11</sup> This pathogenic variant was observed only one time in the literature, in a US patient with unknown ethnicity.<sup>145</sup> No close relationship between the five patients with ZS from SLSJ was identified which provides strong evidence that the c.802\_815del variation in *PEX6* is a founder mutation in SLSJ and suggests that this could be a relevant target for carrier screening in this population. If we consider an a priori estimated carrier frequency of 1/55, about 3000 individuals would have to be screened to find one carrier couple at 25% risk of having an affected child.<sup>11</sup> There is currently no cure or effective treatment for ZS. Management is supportive and based on the signs and symptoms. For example, infants with feeding issues may require placement of a feeding tube to ensure proper intake of calories. Symptomatic therapy may also include hearing aids, cataract removal in infancy, corrective lenses, vitamin supplementation, primary bile acid therapy, adrenal replacement, antiepileptic drugs, and possibly monitoring for hyperoxaluria.<sup>141</sup>

### Naxos disease (NXD, MIM 601214)

Naxos disease (NXD) is an autosomal recessive disorder that combines palmoplantar keratoderma, peculiar woolly hair and arrhythmogenic right ventricular cardiomyopathy. It was first described in the island of Naxos, Greece.<sup>146</sup> Since then, other cases were reported in Turkey, other Aegean Islands, Italy, Israel, Saudi Arabia, India, Argentina and Ecuador.<sup>147</sup> In 2017, seven unrelated patients of French-Canadian descent were diagnosed with this disease. Five of these patients came from the SLSJ or Charlevoix regions. All the cases shared the same novel homozygous pathogenic variant in exon 5 of the plakoglobin (*JUP*) gene on chromosome 17q21: c.902A>G (p.Glu301Gly).<sup>148</sup> Authors suggest that could be a founder mutation. Further studies are needed to confirm the pathogenicity of this variation and to confirm its founder origin. Management of NXD includes implantation of an automatic cardioverter defibrillator to prevent sudden cardiac arrest, antiarrhythmic drugs to prevent recurrences of episodes of sustained ventricular tachycardia and classical pharmacological treatment for congestive heart failure, while heart transplantation is used for patients with late-stage heart failure.<sup>149</sup>

### Epidermolysis bullosa simplex (EBS-loc, MIM 131800; EBS-gen intermed, MIM 131900; EBS-gen sev, MIM 131760)

Epidermolysis bullosa simplex (EBS) is a clinically and genetically heterogeneous skin disorder characterised by blistering of the skin following minor trauma as a result of cytolysis within the basal layer of the epidermis. Most subtypes are autosomal dominant inherited. The localised form is characterised by blistering primarily on the hands and feet. The other two main types of EBS include the milder generalised intermediate type and the generalised severe types.<sup>150</sup> All three forms are caused by pathogenic variants in the keratin 5 (*KRT5*) or keratin 14 (*KRT14*) genes.<sup>151</sup> EBS worldwide prevalence is estimated to be approximately 6–30/1 000 000 live births.<sup>152</sup> There are 230 known causative pathogenic variants for EBS in *KRT5* and *KRT14* including 123 in *KRT5* and 107 in *KRT14* (<http://www.interfil.org/>). From 2007 to 2019, ten EBS French-Canadian patients were described in Quebec, including four from SLSJ. Two SLSJ patients carried pathogenic variants in *KRT5* (c.74C>T (p.Pro25Leu), c.449C>T (p.Leu150Pro)) and the two others share the same pathogenic variant in *KRT14* gene (c.1130T>C (p.Ileu377Thr)) with no known familial relationship.<sup>153</sup> There is no treatment for EBS and the clinical management is primarily palliative, focusing on supportive care to protect the skin from blistering, and the use of dressings that will not further damage the skin and will promote healing. Blister formation can be limited by applying aluminium chloride to palms and soles. Hyperkeratosis of the palms and soles can be prevented by using keratolytics and softening agents. Treatment with topical and/or systemic antibiotics or silver-impregnated dressings or gels can be used for limiting secondary infections. Avoiding higher weather temperature and activities that damage the skin is typically recommended.<sup>150</sup> Several potential attempts of protein therapy and gene therapy to cure EBS were initiated and are under development.<sup>154</sup>

### Organisation of resources and services for patients and families

In 1980, a not-for-profit organisation (*La Corporation de recherche et d'action sur les maladies héréditaires*; CORAMH) ([www.coramh.org](http://www.coramh.org)) was founded by Gérard Bouchard and colleagues.<sup>155</sup> Its mission is educating the SLSJ population and providing information about severe hereditary diseases known

to have a higher frequency in the region (table 1). CORAMH was of great help to raise awareness about the medical implications for individuals in SLSJ, including modes of transmission, clinical features and reproductive options. Moreover, CORAMH contributes at the community level to the offer of support to individuals affected by genetic diseases and their families, and also contributes to promote scientific research on various issues linked to these diseases and to the needs of affected individuals. Throughout the years, this expertise has facilitated the implementation and the development of specialised services in the region, including the *Clinique des maladies neuromusculaires* (1982) which currently provides services to over 1000 individuals with neuromuscular diseases and the regional chapters of Muscular Dystrophy Canada (1983). Moreover, CORAMH participated to the creation of the tyrosinemia association (1984) (*Groupe d'Aide aux Enfants Tyrosinémiques du Québec*, <https://gaetq.org>), as well as the creation of the lactic acidosis association (1990) (*Association de l'acidose lactique du Saguenay-Lac-Saint-Jean*, [www.aal.qc.ca](http://www.aal.qc.ca)). CORAMH has always supported and has promoted research activities. It has participated in several committees and task forces with government organisations, including the implementation of a reliable screening test to identify carriers of tyrosinemia in SLSJ in 1995 in collaboration with the Applied Genetic Medicine Network. CORAMH was one of the most important partners of the first international community genetics meeting, which has been held in June 2000 under the sponsorship of the World Health Organization (WHO) and Health Canada.<sup>155–157</sup> The CORAMH experience has also been presented in Geneva at the WHO consensus meeting on FH (Gaudet and Hegele, as coauthors of the WHO FH experts consensus (World Health Organization 1998)) and has participated in a consultative committee for the Quebec government about orientations in human genetics in the last years (figure 2). Patient associations, local healthcare professionals and specialised clinics have joined CORAMH to get involved in their education and research programme (figure 3).

In 2000, CORAMH joined and received support from the Canadian Institute for Health research (CIHR) Community Alliance on Health Research (CAHR) in community genetics (CIHR grant #CAR43283) and from the Canada research Chair in community genetics.<sup>155 156</sup> At the end of the CIHR/CAHR programme in 2005, CORAMH, the SLSJ health authorities and the *Institut national de santé publique du Québec* (INSPQ) joined the 5-year CIHR Interdisciplinary Health Research Team (IHRT) in community genetics (ECOGENE-21). Both the CAHR and IHRT (CIHR grant #CTP-82941) programmes provided support to the conception and development of the community carrier screening programme. During this period, CORAMH pursued the development of mobilisation and knowledge transfer tools and participated in the activities of a multidisciplinary working group whose mandate was to document the situation of genetic, orphan diseases in the SLSJ region. This committee submitted a brief to the provincial government that recommended the implementation of a pilot project on carrier testing for four autosomal recessive disorders. In 2010, the CIHR decided to not renew the IHRT programme and ECOGENE-21 became a not-for-profit organisation dedicated to access to health innovations for unmet medical needs. After almost 10 years of studies and planning, the Quebec Ministry of Health and Social Services (MSSS) launched a pilot population-based carrier-screening programme in SLSJ to offer carrier screening for a selected set of autosomal recessive diseases: spastic ataxia of Charlevoix-Saguenay (ARSACS), the agenesis of the corpus callosum with/without peripheral neuropathy (ACCPN), the Leigh syndrome, French-Canadian





Missions	Support	Education/Information/Prevention	Research
<b>Objectives</b>	<ul style="list-style-type: none"> <li>- To promote respect of the rights of individuals affected with inherited diseases or carriers of genes associated to these disorders;</li> <li>- To ensure quality of services and promote development of specialized resources;</li> <li>- To carry out community projects helping affected individuals and their families.</li> </ul>	<ul style="list-style-type: none"> <li>- To develop awareness and inform the Saguenay-Lac-St-Jean population on genetics and hereditary diseases.</li> </ul>	<ul style="list-style-type: none"> <li>- To promote and support research.</li> </ul>
<b>Actions</b>	<ul style="list-style-type: none"> <li>- Promotion of the implementation of specialized clinics;</li> <li>- Participation to the creation of parent associations and support groups.</li> </ul>	<ul style="list-style-type: none"> <li>- Information sessions (high school, colleges, universities, etc);</li> <li>- Information tools (brochures, posters, documentaries, web site);</li> <li>- Information campaigns on hereditary diseases and available services.</li> </ul>	<ul style="list-style-type: none"> <li>- Implication in research programs through partnership with researchers;</li> <li>- Financial support to research projects.</li> </ul>

**Figure 2** CORAMH in the Saguenay–Lac-Saint-Jean (SLSJ) region. The *Corporation de recherche et d'action sur les maladies héréditaires* (CORAMH) activities combine education programmes, support to affected individuals and their families, research promotion and community involvement. The main goal of CORAMH is to provide information on the basics of genetics and heredity and on the most frequent hereditary diseases in SLSJ and to describe the available services (eg, specialised clinics, genetic counselling, *Regroupement québécois des maladies orphelines* (RQMO) and support groups) through presentations in high schools, vocational schools, colleges and university health programmes. The CORAMH programmes also target workers in their workplaces as well as members of various social clubs and lay organisations. CORAMH has also developed a plethora of information and prevention tools that present the problematic hereditary diseases in the region and its consequences on affected individuals and their families. These tools include brochures, posters and documentaries, as well as a website ([www.coramh.org](http://www.coramh.org)). CORAMH also supports and has promoted research about genetic diseases at the national and international level.

type (LSFC) and the hereditary tyrosinemia type 1 (TYRSN1) (<https://www.sante.gouv.qc.ca/tests4maladies>). The carrier screening testing for the four mentioned disorders includes all five frequent mutations reported in the region. This allows a carrier detection rate in this population between 97% and 100% depending on the disease tested which is relatively high considering only five mutations were tested (this is an advantage of the founder effect).

The test is free and offered to couples planning a pregnancy (preconception) and couples with an ongoing pregnancy (prenatal). To be eligible for this test, individuals needed to be over 18 years of age and either are planning to have children or have an ongoing pregnancy under 16 weeks of pregnancy (later during pregnancy, they are seen in a prenatal clinic). For this pilot programme, they also had to live in SLSJ and have at least one grandparent born in SLSJ (<https://www.inesss.qc.ca>). Before doing the carrier screening test, all individuals had a face-to-face 45 min information session given by a well-trained nurse about the target diseases, the risks and benefits of the test, and its possible results. Information about all reproductive options available to carrier couples was also presented. All individuals needed to sign a consent form before doing the screening test and were advised they can withdraw from the test at any time after blood collection.<sup>16</sup> After the samples were analysed, all received a letter reporting their results: carriers were informed about their status by phone call with the nurse who collected the samples and carrier couples were in addition offered genetic counselling sessions. In 2012, the INSPQ, with the support of the CIHR/IHRT (CIHR grant #82941), completed the evaluation of the pilot programme. At that time, a total of 3915 individuals were already screened and 846 carriers identified.<sup>158 159</sup> The report acknowledged the pilot project was a success and recommended the carrier screening tests should be offered on a continuous basis.

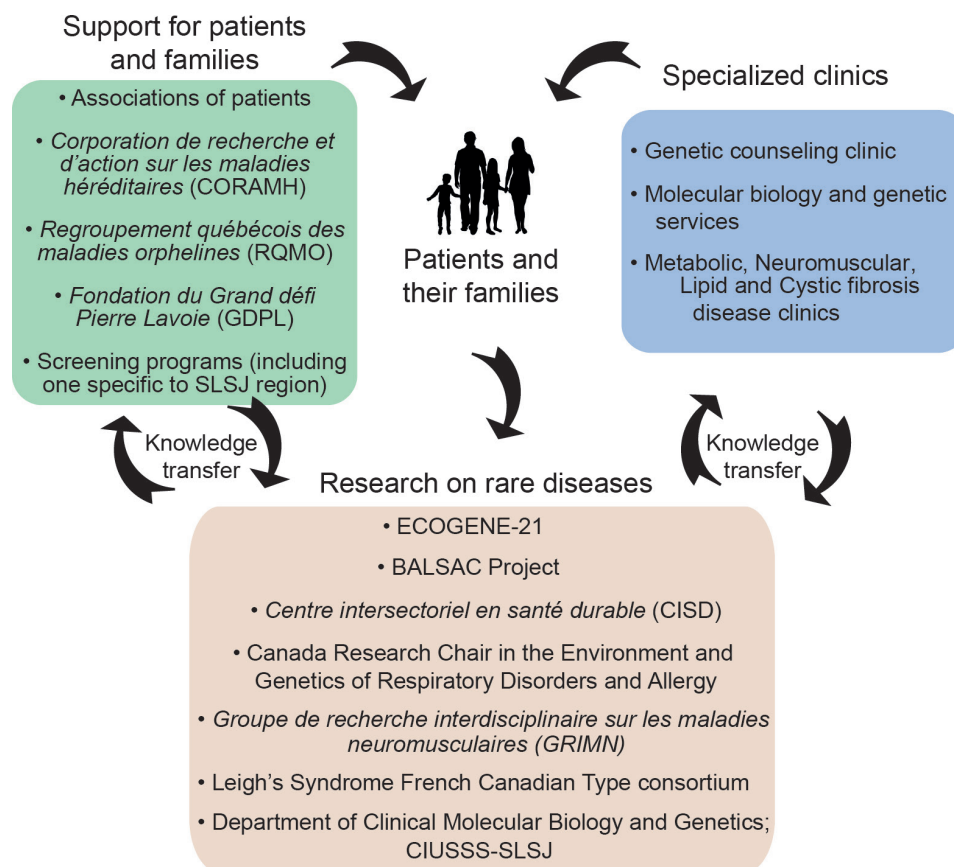
In 2018, the MSSS announced the deployment of the screening tests offer in the Province of Quebec for all potential carriers of at least one of the four diseases with increased incidence in SLSJ. As the same diseases affected Charlevoix and Haute-Côte-Nord (on the north of SLSJ) regions, these populations were also prioritised for the screening test. Admissible individuals need to (1) be over 18 years; (2) have at least one of their four biological grandparents born in SLSJ, Charlevoix or Haute-Côte-Nord regions; and (3) plan to have children (preconception or within 16 weeks of pregnancy) (<https://www.sante.gouv.qc.ca/tests4maladies>). The test remains free but is now made at home on self-sampled buccal cells. After an online registration, which includes an information session about the test, the four genetic diseases and the possible results, the collection kit (two buccal swabs, instructions and consent form) is sent and returned by mail. Results are shared following the same procedures as in the pilot project.

## CONCLUSION

The initial founder effect and subsequent population movements on the Quebec territory have strongly impacted the genetic load of the current population of French-Canadian descent. These migrations have resulted in a series of regional and local founder effects leading to an increased frequency of specific deleterious mutations and shaping their geographical distribution. In the SLSJ region, numerous research projects have been conducted over the past 40 years on the clinical, epidemiological and demogenetic aspects of some of these mutations and the associated genetic conditions. This work has confirmed that the elevated frequency of these disorders is the consequence of subsequent founder effects and cannot be explained by consanguineous marriages.<sup>14 15</sup>

These studies have also led to the creation in 1980 of a community association (CORAMH) aiming at developing public





**Figure 3** The network of organisations specialising in genetic diseases in Saguenay–Lac-Saint-Jean (SLSJ) region. Many resources of information on diseases exist in SLSJ region (patients associations, the Corporation de recherche et d'action sur les maladies héréditaires (CORAMH), the Réseau Québécois sur les maladies orphelines (RQMO), the Grand défi Pierre Lavoie (GDPL) and specialised clinics). These organisations support patients and their families by different means and services. ECOGENE-21 is devoted to access to innovation for unmet medical needs, helps to identify new biological pathways and disease markers, and develops diagnostic and screening tools, innovative treatments and new knowledge and technologies, through genetic research and its application to clinical practice and disease prevention. Canada Research Chair in the Environment and genetics of respiratory disorders and allergy, the Centre intersectoriel en santé durable (CISD) and Leigh's syndrome French-Canadian consortium are working on promoting scientific research on these disorders in order to improve treatment and alleviate their burden on the SLSJ population.

awareness on the various issues linked to the genetic disorders found in the region, promoting research and offering support to affected individuals and their families. CORAMH and partners have supported the implementation in 2010 of a pilot project aimed at offering screening tests on a voluntary basis for four genetic disorders with a higher prevalence in the region. These diseases are rare in the world and usually have no treatment, which increases the challenges for patients who are affected, clinicians, researchers and the SLSJ population as a whole. Since 2018, the programme is offered in the entire Province of Quebec.

Finally, there is a need to pursue the study of the current genetic make-up of the SLSJ population and take into account the evolution of the population including ageing and the decrease of the population size, outmigration of individuals with SLSJ ancestry and the arrival of newcomers from other regions of Quebec or with other ethnocultural backgrounds. This is essential to better understand the prevalence and distribution of genetic diseases in the population and organise genetic screening and testing services accordingly.

Our paper summarises key elements of the recent literature about genetic disorders in SLSJ and offer a portrait for geneticists, clinicians, health professionals and scientists of the current situation in SLSJ. In doing so, we hope to contribute to the sound management of genetic diseases and to the development

of intervention strategies that meet the needs of the SLSJ population and abroad.

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**Correction notice** This article has been corrected since it was published Online First. The name of Dr Philippe M Campeau, and references 81, 116 and 126 have been corrected.

**Acknowledgements** CL is the director of the *Centre intersectoriel en santé durable de l'UQAC* and the chair holder of the Canada Research Chair tier one in the Environment and Genetics of Respiratory Disorders and Allergies ([www.chairs](http://www.chairs)).

gc.ca). CL, PC and MB are scientific members of the CERMO-FC ([www.cermofc.uqam.ca/](http://www.cermofc.uqam.ca/)). LB is a senior research scholar from the *Fond de la recherche du Québec - santé* (FRQS) and a member of the FRQS-funded *Centre de recherche du CHUS* (affiliated to the *Centre hospitalier universitaire de Sherbrooke*). DG is the scientific director of ECOGENE-21 and the Université de Montréal Community Genomic Medicine Centre (CMGC). We thank Anne-Marie Boucher-Lafleur for her help in producing the figures.

**Contributors** MB performed the research and wrote the first version. CL designed, supervised and contributed to the manuscript, as well as revised and approved the version for publication. LB, DB, PC, DG, A-ML, JM, CL, CM and HV are involved in rare diseases research projects. LB, DB, PC, DG, A-ML, JM, CM and HV contributed to the writing and editing of specific sections. All the listed authors have reviewed the manuscript and have approved its final version for publication.

**Funding** Soft funds from the Canada Research Chair in the Environment and genetics of respiratory diseases and allergy.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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