

Supporting Information

Table SI. Distributions of the *ELANE* mutations observed in the 143 patients: 3 in-frame, 5 initiation, 85 missense, 32 splicing defects and 18 truncated. Variant nomenclature using the reference sequence NM_001972.2.

Exon	Variant nucleotide effect, protein effect	Type of variants	Diagnosis subtype	Occurrence
1	c.1A>G, p.Met1?	Initiation	SCN	3
1	c.1A>T, p.Met1?	Initiation	SCN	1
4	c.3G>A, p.Met1?	Initiation	SCN	1
2	c.125C>T, p.Pro42Leu	Missense	SCN	1
2	c.127T>C, p.Phe43Leu	Missense	CyN	3
2	c.129C>A, p.Phe43Leu	Missense	CyN	2
2	c.129C>G, p.Phe43Leu	Missense	SCN	1
2	c.136T>C, p.Ser46Pro	Missense	SCN	1
2	c.137C>T, p.Ser46Phe	Missense	SCN	1
		Missense	CyN	2
2	c.140T>C, p.Leu47Pro	Missense	SCN	2
		Missense	CyN	3
2	c.158A>T, p.His53Leu	Missense	SCN	1
2	c.170C>T, p.Ala57Val	Missense	SCN	1
2	c.178A>T, p.Ile60Phe	Missense	SCN	2
2	c.179_204delinsGTGCACAT, p.Ile60_Ala68delinsSerAlaHis	In-Frame	SCN	1
2	c.193G>T, p.Val65Phe	Missense	SCN	1
2	c.197T>G, p.Met66Arg	Missense	SCN	1
2	c.199_207del, p.Ser67_Ala69del	In-frame	SCN	1
2	c.215T>G, p.Val72Gly	Missense	SCN	1
3	c.241_246del, p.Arg81_Val82del	In-frame	SCN	1
3	c.242G>C, p.Arg81Pro	Missense	SCN	1
3	c.244G>A, p.Val82Met	Missense	CyN	1
3	c.251T>C, p.Leu84Pro	Missense	SCN	5
3	c.253G>A, p.Gly85Arg	Missense	SCN	1
3	c.308G>A, p.Arg103His	Missense	CyN	1
3	c.308G>T, p.Arg103Leu	Missense	SCN	1
		Missense	CyN	2
3	c.333_336dup, p.Asn113fs	Truncating	SCN	1
3	c.359T>C, p.Ile120Thr	Missense	SCN	1
3	c.362T>C, p.Leu121Pro	Missense	SCN	1
4	c.370A>C, p.Asn124His	Missense	SCN	1
4	c.377C>T, p.Ser126Leu	Missense	SCN	7
		Missense	CyN	11
4	c.379G>C, p.Ala127Pro	Missense	SCN	1
4	c.416C>T, p.Pro139Leu	Missense	SCN	5
		Missense	CyN	6
4	c.451T>C, p.Cys151Arg	Missense	SCN	1
4	c.455T>C, p.Leu152Pro	Missense	SCN	1
4	c.458C>A, p.Ala153Asp	Missense	SCN	1
4	c.466T>C, p.Trp156Arg	Missense	SCN	1
4	c.561C>A, p.Cys187*	Truncated	SCN	5
4	c.580C>T, p.Gln194*	Truncated	SCN	1
4	c.584_588dup, p.Val197fs	Truncated	SCN	2
4	c.584_588dup, p.Val197fs	Truncated	SCN	1
4	c.597+1G>A, p.Val190_Phe199del	Splicing defect	SCN	4

		Splicing defect	CyN	7
4	c.597+1G>C, p.Val190_Phe199del	Splicing defect	CyN	2
4	c.597+1G>T, p.Val190_Phe199del	Splicing defect	SCN	1
		Splicing defect	CyN	2
4	c.597+5G>A, p.Val190_Phe199del	Splicing defect	SCN	9
		Splicing defect	CyN	3
4	c.597+6T>G, p.Val190_Phe199del	Splicing defect	CyN	2
5	c.600_606del, p.Asp201fs	Truncated	SCN	1
5	c.640G>A, p.Gly214Arg	Missense	SCN	7
5	c.640G>T, p.Gly214*	Truncated	SCN	1
5	c.656del, p.Val219fs	Truncated	SCN	1
5	c.659G>A, p.Arg220Gln	Missense	SCN	2
		Missense	CyN	3
5	c.669C>A, p.Cys223*	Truncated	SCN	5
5	c.688del, p.Asp230fs	Splicing defect	SCN	2
5	c.723G>T, p.Trp241Cys	Missense	SCN	1
Total				143

Fig S1. Examples of infections in *ELANE* patients. (A) Case #5205: a 26-year-old woman developed cellulitis after an insect bite, while she was taking G-CSF (10 µg/kg, 3 times a week); no microorganism was identified. (B) Case #5172: hypertrophic gingivitis in 12-year-old boy, who, despite profound neutropenia, was not treated with G-CSF; surgical excision was done later. (C) Case #5852: aphthosis in an 8-year-old girl not treated with G-CSF. (D) Case #6228: computed-tomography (CT) scan of an 18-month-old boy (c.193G>T p.Val65Phe) showing adenitis that developed despite G-CSF (20 µg/kg/day). No microorganism was identified in a node biopsy by culture or 16S RNA. He later underwent HSCT and died of acute grade IV GVHD and thrombotic microangiopathy. (E & F) Case #6231: CT scan and radiogram, respectively, showing pneumonia with pleuritis in a 9-month-old boy. No microorganism was isolated and the pneumonia was treated with G-CSF (10 µg/kg/day) in combination with vancomycin and Tazocillin. (G & H) Case #6231: a boy diagnosed at birth with ELANE severe chronic neutropenia (SCN) (*ELANE* c.253G>A, p.Gly85Arg) during the work-up for paronychia. At 2 months, he developed his first episode of pneumonia successfully treated with IV antibiotics. Antibacterial prophylaxis was prescribed along with G-CSF (5 µg/kg/day). At 21 months, he developed bilateral pneumonitis. CT images (G & H) show bilateral pulmonary cavitating consolidations, masses and nodules. G-CSF was increased to 15 µg/kg/day. ANC remained mostly <500/mm³ on that G-CSF dose and exceeded 1500/mm³ only when G-CSF was increased to 30 µg/kg/day. Despite a thorough work-up (bronchoalveolar lavage (BAL), fungal polymerase chain reaction, β-D-glucan...), only *Staphylococcus aureus* was identified. When the CT scan revealed a cystic lesion, and several bronchial dilatations, combined antibiotic and anti-fungal therapy (voriconazole) was prescribed for 4 weeks. Despite long-term G-CSF, he developed several mild infections (pneumococcal otitis/adenitis) and a new episode of pneumonitis, with two distinct pulmonary condensations, at 3 years 7 months. G-CSF (32 µg/kg/day) was prolonged, in combination with antibiotic and itraconazole. The latter was withdrawn when only *S. aureus* was isolated from BAL and no fungi were isolated. With high-dose G-CSF and anti-staphylococcus therapy, the cystic lung lesion disappeared. Because of high-dose

G-CSF dependence and severe infection recurrence, at 5 years 2 months, he underwent HSCT (matched unrelated donor), which achieved full recovery of blood counts and good clinical status. Now 9 years old, he is healthy and pursuing his normal education. (I, J & K) Case #7156: a girl diagnosed at birth with ELANE SCN because of familial ELANE. She has the c.640G>A, p.Gly214Arg *ELANE* variant. At birth, antibiotic prophylaxis with penicillin was prescribed, followed by co-trimoxazole. At 5 months, a skin lesion appeared on her buttock; *Escherichia coli* was identified on the skin and successfully treated with antibiotics. G-CSF (10 µg/kg/day) was started at 8 months of age but ANC did not rise >500/mm³. She remained infection-free until 14 months, when her first episode of fever with frank inflammation (C-reactive protein (CRP) 200–300 mg/l) occurred. No microorganisms were identified. The situation improved with IV antibiotics (Tazocillin, switched to meropenem, and vancomycin) and G-CSF was increased to 20 µg/kg/day. Despite transient improvement, at 15 months, fever resumed and CRP rose to 300 mg/l). Although the routine work-up was negative, β-D-glucan was positive (221 pg/ml); its interpretation was difficult because ongoing antibiotics can lead to a false-positive result. Positron-emission-tomography scan revealed a 4-cm diameter liver lesion (SUV 7) (I), compatible with an abscess. A new abdominal ultrasound (J) and a CT scan (K) confirmed the existence of that lesion (42 × 39 × 32 mm). (J & K) Because a direct biopsy appeared difficult, antibiotics (Tazocillin and caspofungin) were adjusted empirically and combined with G-CSF, increased from 20 to 100 µg/kg/day, notably without any ANC increase. The situation deteriorated, with persistent high CRP with no visible CT scan improvement; a liver biopsy was obtained at 18 months and *Escherichia coli* highly resistant to penicillinase was isolated. Antibiotic therapy was switched to ertapenem and ciprofloxacin, while G-CSF was pursued. The liver abscess was later controlled. At 26 months, she underwent HSCT (umbilical cord-blood donor), which unfortunately failed. At 29 months, a second HSCT, haploidentical with her mother, achieved full engraftment. Now 4 years old, this little girl is in good health, with no current therapy and a normal CBC.

Fig S2. Etiologies of most common severe infections. The results are expressed in percentage of microorganisms, if documented.

Supplemental Figure 1.

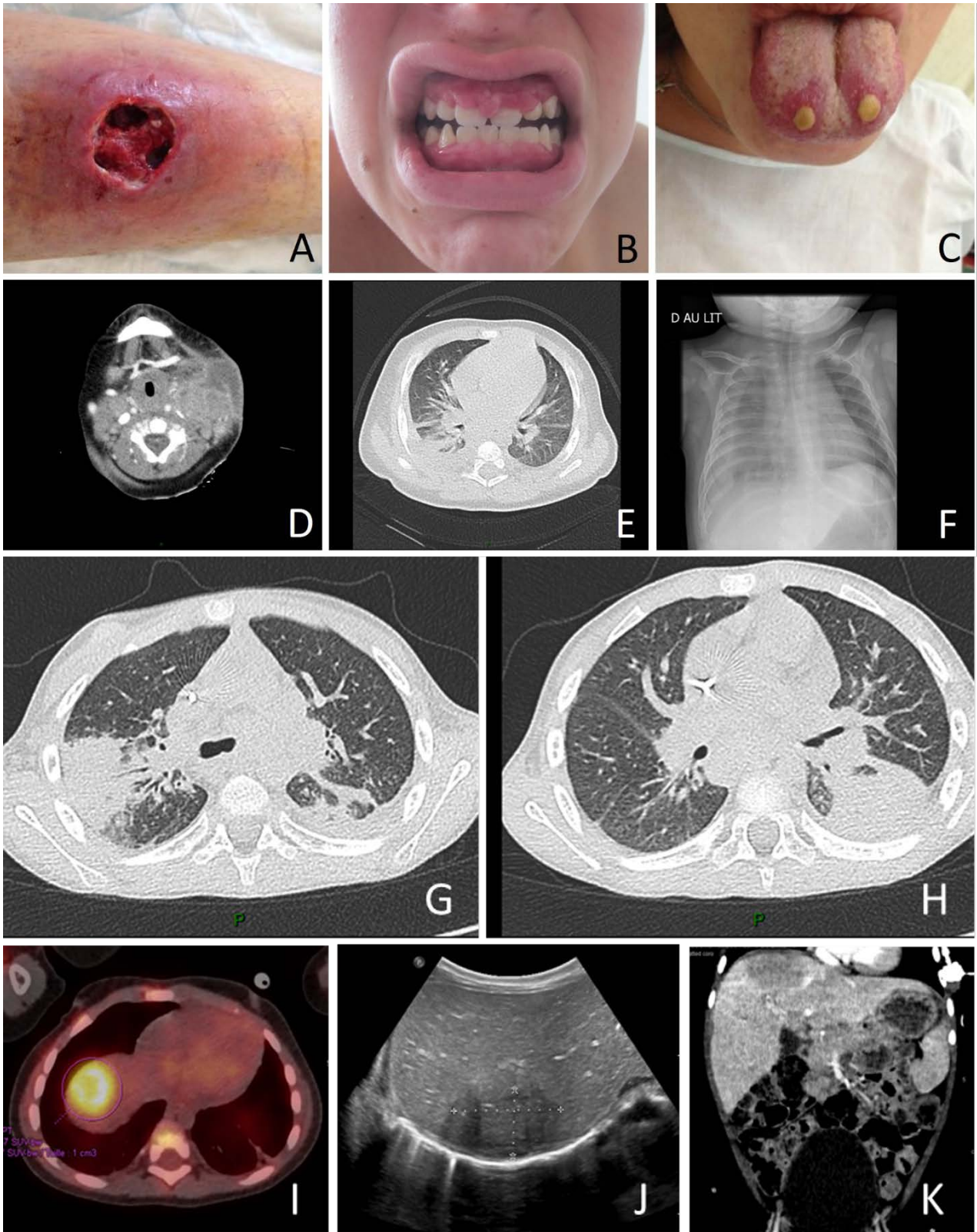


Figure S2.

