Supplementary Material

**Supplementary Table 1.** English translation of the questionnaire administered to the patients

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| --- |
| 1. Did your son/daughter ever need hospital admission for treatment with intravenous antibiotics because of an infection? |
| a. | Never |  |
| b. | Once |  |
| c. | More times |  |
|  |  | - Less than once a year |
|  |  | - Two or more times a year |
| 2. How many times did your son/daughter need oral antibiotics for non-serious infections? |
| a. | Never |  |
| b. | Once |  |
| c. | More times |  |
|  |  | - Less than once a year |
|  |  | - Two or more times a year |
| 3. If he/she had serious infections, what was the site? (Check all that applies) |
| a. | Systemic (sepsis/meningitis) |  |
| b. | Upper respiratory tract (ear, nose and throat) |  |
| c. | Lower respiratory tract (pneumonia) |  |
| d. | Gastrointestinal |  |
| e. | Bones |  |
| f. | Kidney |  |
| g. | Skin |  |
| h. | Mouth and teeth |  |
| 4. If he/she had non-serious infections requiring antibiotics, what was the site? (Check all that applies) |
| a. | Systemic (sepsis/meningitis) |  |
| b. | Upper respiratory tract (ear, nose and throat) |  |
| c. | Lower respiratory tract (pneumonia) |  |
| d. | Gastrointestinal |  |
| e. | Bones |  |
| f. | Kidney |  |
| g. | Skin |  |
| h. | Mouth and teeth |  |

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| 5. Did your son/daughter undergo surgical procedures? If yes, which ones? |
| a. | No procedure |  |
| b. | Yes |  |
|  |  | - Appendicectomy |
|  |  | - Adenoidectomy/tonsillectomy |
|  |  | - Other (please, specify) |
| 6. How often has your son/daughter gotten sick with infections not requiring antibiotic therapy so far? |
| a. | Never |  |
| b. | Once |  |
| c. | 2-4 times |  |
| d. | 5-8 times |  |
| e. | >9 times |  |
| 7. In the last year, how many times has your son/daughter gotten sick with infections treated with antibiotics? |
| a. | Never |  |
| b. | Once |  |
| c. | 2-4 times |  |
| d. | 5-8 times |  |
| e. | >9 times |  |
| 8. Does one of the following conditions apply to your son/daughter? |
| a. | Four or more episodes of acute otitis media in the last year |  |
| b. | Two or more episodes of sinusitis in the last year |  |
| c. | Two or more episodes of pneumonia in the last year |  |
| d. | Any infection that doctors considered unusual (unusual pathogen, severe course) |  |
| e. | Recurrent infections caused by the same bacteria |  |
| f. | Severe clinical course after common trivial infection |  |
| g. | Need for prolonged treatment with antibiotics because of a protracted infection |  |
| h. | No one of the above |  |
| 9. Do you feel that your son/daughter is more prone to infections than his/her peers? |
| a. | Yes |  |
| b. | No |  |
| 10. Has your son/daughter ever gotten sick with mononucleosis? |
| a. | Yes |  |
|  |  | - He/she was admitted to hospital because of it |
|  |  | - He/she was treated at home |
| b. | No |  |

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| --- |
| 11. Did your son/daughter ever complain of swelling of lymph nodes in neck or in other sites? |
| a. | Yes |  |
|  |  | - Please, specify the site/s |
| b. | No |  |
| 12. Did your son/daughter ever complain of medical conditions involving the liver or the spleen? |
| a. | Yes |  |
|  |  | - Please, specify the site/s |
| b. | No |  |

**Supplementary Table 2.** Baseline demographic and clinical characteristics of the study population.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Genetics | Age (y) | Cafè-au-lait spots | Freckling | Skin neurofibroma | PleXiform neurofibroma | Xanthogranuloma | Pigmentid macules of penis | Intestinal hamartomatous polyposis | Lipomas | macrocephaly | Short stature | Cognitive retardation | learning and/or behavioral problems | Congenital heart defects | Splenomegaly | Lymphadenopathy | Eye anomalies | Skeletal anomalies | Genitourinary disorders | SNC anomalies | Pulmonary anomalies | Autoimmunity | Deafness | RBE | DNT | RTE |
| 1 | NF1 | 2 | X | X |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   | ND | ND | ND |
| 2 | NF1 | 5 | X | X |   |   |   |   |   |   | X |   | X  |   |   | X | X |  |   | X |   |   |   |   | ND | ND | ND |
| 3 | NF1 | 5 | X | X | X |   |   |   |   |   | X |   | X  |  |   | X |   |  |   | X  |   |   |   |   | ND | ND | ND |
| 4 | NF1 | 29 | X | X | X | X |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   | **10.9** | 1.0 | 18.3 |
| 5 | NF1 | 16 | X | X |   |   |   |   |   |   |   |   |   |   |   | X |   |  |   |   |   |   |   |   | 6.9 | 0.9 | 34.8 |
| 6 | NF1 | 11 | X | X |   |   |   |   |   |   |   |   |   |   |   |   |   |  |   |   |   |   |   |   | **19.1** | 1.8 | 40.7 |
| 7 | PTEN | 15 | X |   |   |   |   | X | X |  X | X |   | X |  |   |   |   |   |   |   |   |   |   |   | **22.6** | 0.6 | 30.9 |
| 8 | NF1 | 11 | X | X | X | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X  |   |   |   | **16.4** | 1.2 | 43.3 |
| 9 | NF1 | 32 | X | X | X | X |   |   |   |   |   |   |   |   |   |   |   |   | X  |  X |   |   | X | X | ND | ND | ND |
| 10 | Neg | 13 | X | X | X |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  | **23.1** | 1.4 | **30.1** |
| 11 | NF1 | 10 | X | X | X |  |  |  |  |  |  |  |  | X  |  |  |  |  | X |  |  |  |  |  | **19.4** | 2.0 | 51.2 |
| 12 | NF1 | 11 | X | X | X |  |  |  |  |  | X |  |  | X |  |  |  | X |  |  |  |  |  |  | **17.2** | 1.5 | 48.4 |
| 13 | NF1 | 41 | X | X | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X | X  |  |  |  | **9.2** | 1.3 | 14.8 |
| 14 | Neg | 8 | X | X |  |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  | **12.5** | **7.3** | 58.6 |
| 15 | PTPN11 | 16 |  |  |  |  |  |  |  |  |  | X |  |  | X |  |  |  |  |  |  |  |  |  | **9.2** | 1.0 | 41.2 |
| 16 | NF1 | 2.5 | X | X | X | X |  |  |  |  | X |  |  |  |  |  |  |  |  |  | X  |  |  |  | ND | ND | ND |
| 17 | Neg | 11 | X | X |  |  |  |  |  |  |  | X | X  | X | X  |  |  |  |  |  |  |  |  |  | ND | ND | ND |
| 18 | Neg | 10 | X | X |  |  |  |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  | ND | ND | ND |
| 19 | Neg | 12 | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **26.1** | 2.3 | 52.8 |
| 20 | Neg | 8 | X | X |  |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ND | ND | ND |
| 21 | NF1 | 18 | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **8.9** | **2.6** | 27.3 |
| 22 | NF1  | 12 | X | X | X |  | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ND | ND | ND |
| 23 | NF1  | 37 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | ND | ND | ND |
| 24 | PTPN11 | 12 |   |   |   |   |   |   |   |   |   | X  |  | X  | X  |  |   | X  | X  |  X |   |   |   |   | **16.4** | 2.2 | 47.8 |
| 25 | NF1 | 13 | X | X | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | **18.0** | 0.7 | 47.0 |
| 26 | NF1 | 16 | X | X |  |  |  |  |  |  |  |  |  | X |  | X |  |  | X  |  |  |  |  |  | **28.8** | 1.4 | 45.4 |
| 27 | NF1 | 26 | X | X | X | X |  |  |  |  |  |  |  |  |  |  |  |  | X  |  |  |  |  |  | **19.8** | 1.9 | 35.3 |
| 28 | PTPN11 | 10 |   |   |   |   |   |   |   |   |   | X |  |   | X |  |   | X | X |   |   |   |   |   | **23.5** | 1.2 | 54.7 |
| 29 | NF1 | 12 | X | X |   |   |   |   |   |   |   |   |   |   |   | X |   |   | X  |   |   |   |   |   | **20.1** | 0.8 | 43.4 |
| 30 | KRAS | 13 |   |   |   |   |   |   |   |   |   | X | X  |   | X  |  |   |  | X  |   |   |   |   |   | **10.3** | 1.7 | 39.1 |
| 31 | PTPN11 | 9 |  |  |  |  |  |  |  |  |  |  | X |  | X |  |  |  | X |  |  |  |  |  | **20.9** | **3.5** | 48.5 |
| 32 | NF1 | 14 | X | X | X | X |  |  |  |  |  |  | X |  |  |  |  |  | X |  | X |  |  |  | **16.9** | **3.5** | 43.5 |
| 33 | NF1 | 20 | X | X |  |  |  |  |  |  |  |  |  | X  |  |  |  |  | X  |  |  |  |  |  | **12.3** | **3.6** | 32.6 |
| 34 | PTNP11  | 2 | X |  |  |  |  |  |  |  |  |  | X |  | X |  |  |  |  |  |  |  |  |  | **20.3** | 1.7 | 71.9 |
| 35 | PTEN | 12 |   |   |   |   |   | X |   | X | X |   |   | X  |   |   |   |   |   |   |   |   | X |   | **30.3** | 2.0 | 41.0 |
| 36 | PTNP11  | 12 |   |   |   |   |   |   |   |   |   | X |   |   | X |  |  | X | X |   | X |  |   |   | **16.1** | 1.5 | 51.1 |
| 37 | NF1 | 10 | X | X |  | X |  |  |  |  |  |  | X |  |  |  |  | X | X |  |  |  |  |  | **17.1** | 1.8 | 57.3 |
| 38 | NF1 | 9 | X | X |  |  |  |  |  |  |  |  | X | X |  |  |  | X |  |  |  |  |  |  | **25.6** | 1.4 | 47.2 |
| 39 | PTPN11 | 21 |   |   |   |   |   |   |   |   |   | X  |  |   | X |   |   | X | X  |   |   | X  |  |   | **27.7** | 2.0 | 10.7 |
| 40 | NF1 | 15 | X | X | X | X |  |  |  |  |  |  |  |  |  | X |  |  | X  |  |  |  |  |  | **34.3** | **2.7** | 53.1 |
| 41 | Neg | 17 | X |  |  |  |  |  |  |  |  | X | X |  |  |  |  | X |  | X |  |  |  |  | **17.5** | 0.9 | 42.0 |
| 42 | PTEN | 3 |   |   |   |   |   |   |   | X | X |   | X |   |   |   |   |   |   |   |   |   |   |   | **22.7** | **2.9** | **39.8** |
| 43 | SHOC2 | 19 |   |   |   |   |   |   |   |   |   | X  | X |   |   | X |   |   |   |   |   |   |   |   | **19.8** | 0.8 | 27.6 |
| 44 | NF1  | 3 | X | X |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  | X | X |  |  |  | **28.7** | 2.2 | 68.6 |
| 45 | PTPN11  | 8 |   |   |   |   |   |   |   |   |   | X  |  |   | X |   |   |   | X  |   | X  |  |   | X  | **17.9** | **2.9** | **36.3** |
| 46 | NF1 | 12 | X | X | X | X |  |  |  |  |  |  | X | X |  |  |  |  |  |  | X  |  |  |  | **9.8** | **3.3** | 44.2 |
| 47 | NF1  | 2 | X | X |  |  |  |  |  |  | X |  |  |  |  |  | X |  |  |  |  |  |  | X | 14.2 | 1.7 | 67.9 |

**Supplementary Table 3.** Clinical characteristics of the study population.

|  |  |  |  |
| --- | --- | --- | --- |
| **Phenotype** | **NF** | **NS** | **BRRS** |
| Number of patientsSex | 3316 Male | 116 Male | 33 Male |
| Genes (mutated) | NF1 27 (82%)*Negative* 6 (18%) | PTPN11 8 (73%)KRAS 1 (9%)SHOC2 1 (9%)*Negative* 1 (9%) | PTEN 3 (100%) |
| **Skin and soft tissue features** Café-au-lait spot Lentigines Cutaneous neurofibromas Plexiform neurofibromasXantogranulomas Thin/absent hair Genital lentiginosis Lipomas |  33 (100%) 33 (100%) 32 (97%) 15 (45%) 10 (30%) 2 (6%) 0 0 0 | 3 (27%)2 (18%)00001 (9%)00 | 3 (100%)0000002 (67%)3 (100%) |
| **Short stature** requiring growth hormone therapy |  1 (3%) | 9 (82%) | 0 |
| **Developmental anomalies**Cognitive impairment Learning/behavioral problems | 11 (33%)7 (21%)7 (21%) | 6 (54%)5 (45%)1 (9%) | 3 (100%)2 (66%)1 (33%) |
| **Macrocephaly** | 10 (30%) | 0 | 3 (100%) |
| **Congenital heart defects** | 2 (6%) | 8 (73%) | 0 |
| **Ocular anomalies \***Glaucoma Exotropia Peters’anomaly | 3 (9%)1 (3%)2 (6%)0 | 5 (45%)05 (45%)1 (9%) | 0 |
| **Deafness** | 2 (6%) | 1 (9%) | 0 |
| **Genitourinary anomalies**Renal anomalies Cryptorchidism Uterine anomalies Gonadal dysgenesis | 5 (15%)3 (9%)1 (3%)1 (3%)1 (3%) | 2 (18%)2 (18%)1 (9%)00 | 0 |
| **Skeletal anomalies**ScoliosisLimb length discrepancy Chest wall anomalies | 9 (27%)4 (12%)3 (9%)0 | 7 (63%)4 (36%)2 (18%)3 (27%) | 0 |
| **Pulmonary anomalies** | 0 | 1 (9%) | 0 |
| **Feeding difficulties** | 0 | 1 | 0 |
| **SNC anomalies**Optic pathway gliomaChiari I malformationEmpty sellaEpilepsy | 6 (18%)2 (6%)2 (6%)1 (3%) 1 (3%) | 2 (18%)02 (18%)00 | 0 |
| **Splenomegaly\*\*** | 6 (18%) | 1 (9%) | 0 |
| **Lymphadenopathy** | 2 (6%) | 0 | 0 |
| **Autoimmunity**Autoimmune thyroiditisAlopecia areata | 1 (3%)1 (3%)0 | 0 | 1 (33%)01 (33%) |