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| **Table e-1. Clinical manifestations of the 269 NAMDC Clinical Registry Subjects with Canonical Syndromes** | | | | | |
|  | **MELAS**  **N=71**  **Freq. (%)** | **LHON**  **N=28**  **Freq. (%)** | **cPEO/cPEO+**  **N=55**  **Freq. (%)** | **Leigh syndrome**  **N=97**  **Freq. (%)** | **MERRF**  **N=13**  **Freq. (%)** |
| **CNS** | **68 (95.8)** | **18 (64.3)** | **33 (60.0)** | **87 (89.7)** | **13 (100.0)** |
| Ataxia | 24 (33.8) | 1 (3.6) | 10 (18.2) | 44 (45.4) | 11 (84.6) |
| Dementia | 16 (22.5) | - | 1 (1.8) | - | 1 (7.7) |
| Dystonia | 3 (4.2) | 1 (3.6) | 1 (1.8) | 44 (45.4) | 2 (15.4) |
| Hearing loss | 46 (64.8) | 2 (7.1) | 13 (23.6) | 6 (6.2) | 6 (46.2) |
| Migraine | 22 (31.0) | 3 (10.7) | 6 (10.9) | 7 (7.2) | 1 (7.7) |
| Seizures | 52 (73.2) | 3 (10.7) | 1 (1.8) | 38 (39.2) | 8 (61.5) |
| **Skeletal Muscle** | **60 (84.5)** | **6 (21.4)** | **53 (96.4)** | **73 (75.3)** | **13 (100.0)** |
| Exercise intolerance | 41 (57.7) | 2 (7.1) | 30 (54.5) | 19 (19.6) | 6 (46.2) |
| Dysphagia | 18 (25.4) | - | 15 (27.3) | 40 (41.2) | 5 (38.5) |
| Myopathy | 25 (35.2) | 2 (7.1) | 34 (61.8) | 20 (20.6) | 11 (84.6) |
| Ophthalmoparesis | 4 (5.6) | 1 (3.6) | 46 (83.6) | 5 (5.2) | 2 (15.4) |
| Ptosis | 21 (29.6) | 1 (3.6) | 49 (89.1) | 15 (15.5) | 6 (46.2) |
| **Heart** | **21 (29.6)** | **3 (10.7)** | **7 (12.7)** | **10 (10.3)** | **1 (7.7)** |
| Arrhythmia | 11 (15.5) | 2 (7.1) | 3 (5.5) | 5 (5.2) | - |
| CCB | 3 (4.2) | 1 (3.6) | 2 (3.6) | - | - |
| WPW | 2 (2.8) | - | - | 1 (1.0) | 1 (7.7) |
| Structural Abnormalities | 9 (12.7) | 1 (3.6) | 3 (5.5) | 6 (6.2) | - |
| **Developmental** | **22 (31.0)** | **3 (10.7)** | **2 (3.6)** | **91 (93.8)** | **5 (38.5)** |
| Dev. delay | 16 (22.5) | 2 (7.1) | 1 (1.8) | 84 (86.6) | 3 (23.1) |
| Dev. regression | 5 (7.0) | - | - | 42 (43.3) | 1 (7.7) |
| **Constitutional** | **39 (54.9)** | **-** | **15 (27.3)** | **34 (35.1)** | **1 (7.7)** |
| Thinness | 28 (39.4) | - | 12 (21.8) | 19 (19.6) | 1 (7.7) |
| Short stature | 27 (38.0) | - | 7 (12.7) | 30 (30.9) | - |
| **Psychiatric** | **23 (32.4)** | **4 (14.3)** | **19 (34.5)** | **10 (10.3)** | **4 (30.8)** |
| Anxiety | 11 (15.5) | 2 (7.1) | 10 (18.2) | 9 (9.3) | 3 (23.1) |
| Depression | 16 (22.5) | 3 (10.7) | 10 (18.2) | 6 (6.2) | 1 (7.7) |

Manifestations grouped by clinical system (bold), numbers (percent) designate individuals with involvement in clinical system.

**Table e-2 Clinical features of classical syndromes vs commonly associated mtDNA mutations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **m.3243A>G**  **N = 138** | **MELAS**  **N = 71** | **m.8344A>G**  **N = 23** | **MERRF**  **N = 13** | **Del DNA**  **N = 67** | **KSS**  **N = 17** |
| **Age of Onset\***   * Missing | 24 (17.4) | 6 (8.5) | 6 (26.1) | 4 (30.8) | 9 (13.4) | - |
| * <2 yrs | 13 (9.4) | 2 (2.8) | 5 (21.7) | 4 (30.8) | 11 (16.4) | 3 (17.6) |
| * ≥2 and <5 yrs | 5 (3.6) | 1 (1.4) | - | - | 12 (17.9) | 3 (17.6) |
| * ≥5 and <12 yrs | 23 (16.7) | 18 (25.4) | 5(21.7) | 2 (15.4) | 13 (19.4) | 4 (23.5) |
| * ≥12 and <18 yrs | 15 (10.9) | 11 (15.5) | 2 (8.7) | - | 4 (6.0) | 2 (11.8) |
| * ≥18 yrs | 58 (42.0) | 33 (46.5) | 5 (21.7) | 3 (23.1) | 18 (26.9) | 5 (29.4) |
| **Sex\***   * Missing | 1 | 1 | - | - | - | - |
| * Male | 48 (35.0) | 28 (40.0) | 10 (43.5) | 6 (46.2) | 29 (43.3) | 8 (47.1) |
| * Female | 89 (65.0) | 42 (60.0) | 13 (56.5) | 7 (53.8) | 38 (56.7) | 9 (52.9) |
| **CNS** | 127 (92.0) | 68 (95.8) | 23 (100.0) | 13 (100.0) | 44 (65.7) | 13 (76.5) |
| * Stroke | 53 (38.4) | 60 (84.5) | 1 (4.3) | - | 4 (6.0) | 1 (5.9) |
| * Seizures | 55 (39.9) | 52 (73.2) | 5 (21.7) | 8 (61.5) | 8 (11.9) | 1 (5.9) |
| * Ataxia | 35 (25.4) | 24 (33.8) | 15 (65.2) | 11 (84.6) | 13 (19.4) | 7 (41.2) |
| * Myoclonus | 9 (6.5) | 11 (15.5) | 16 (69.6) | 10 (76.9) | 1 (1.5) | - |
| **Neuropathy** | 16 (11.6) | 11 (15.5) | 8 (34.8) | 4 (30.8) | 7 (10.4) | 2 (11.8) |
| * Axonal | 12 (8.7) | 8 (11.3) | 8 (34.8) | 3 (23.1) | 3 (4.5) | 1 (5.9) |
| * Demyelinating | 6 (4.3) | 4 (5.6) | 2 (8.7) | 3 (23.1) | 4 (6.0) | 1 (5.9) |
| **Ophthalmoparesis** | 11 (8.0) | 4 (5.6) | 3 (13.0) | 2 (15.4) | 38 (56.7) | 13 (76.5) |
| **Ptosis** | 37 (26.8) | 21 (29.6) | 8 (34.8) | 6 (46.2) | 47 (70.1) | 16 (94.1) |
| **Deafness** | 92 (66.7) | 46 (64.8) | 13 (56.5) | 6 (46.2) | 18 (26.9) | 8 (47.1) |
| **DM** | 57 (41.3) | 25 (35.2) | 1 (4.3) | - | 7 (10.4) | 3 (17.6) |
| **Short Stature** | 42 (30.4) | 27 (38.0) | 3 (13.0) | - | 22 (32.8) | 12 (70.6) |
| **Low BMI** | 37 (26.8) | 28 (39.4) | 4 (17.4) | 1 (7.7) | 23 (34.3) | 9 (52.9) |

Manifestations grouped by clinical system (bold), numbers (percent) designate individuals with involvement in clinical system.

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| --- | --- | --- |
| Table e-3. Demographic, Clinical, and Muscle Biopsy Features of 981 NAMDC Registry Subjects with and without Genetic Diagnoses | | |
|  | **With Genetic Diagnosis (N=722)**  **Freq. (%)** | **Without Genetic Diagnosis (N=619)**  **Freq. (%)** | |
| Gender\* |  |  | |
| Female | 418 (58.0) | 370 (60.0) | |
| Male | 303 (42.0) | 247 (40.0) | |
| Missing | 1 | 2 | |
| Racial Composition\* |  |  | |
| White | 617 (85.6) | 546 (88.5) | |
| Asian | 24 (3.3) | 19 (3.1) | |
| More than one | 25 (3.5) | 11 (1.8) | |
| Black/African-American | 20 (2.8) | 6 (1.0) | |
| Other | 35 (4.9) | 35 (5.7) | |
| Missing | 1 | 2 | |
| Age of Onset\* |  |  | |
| <18 yrs | 416 (69.3) | 330 (69.6) | |
| ≥18 yrs | 184 (30.7) | 144 (30.4) | |
| Missing | 122 | 145 | |
| Clinical Syndromes | | |
| Multisystemic syndrome | 113 (15.7) | 145 (23.4) | |
| Other clinical diagnosis | 75 (10.4) | 132 (21.3) | |
| Leigh syndrome | 97 (13.4) | 55 (8.9) | |
| Encephalomyopathy | 32 (4.4) | 40 (6.5) | |
| MELAS | 71 (9.8) | 15 (2.4) | |
| Myopathy | 25 (3.5) | 46 (7.4) | |
| CPEO-plus | 37 (5.1) | 18 (2.9) | |
| Encephalopathy | 38 (5.3) | 22 (3.6) | |
| LHON | 28 (3.9) | 10 (1.6) | |
| CPEO | 18 (2.5) | 26 (4.2) | |
| KSS | 17 (2.4) | 14 (2.3) | |
| SANDO | 19 (2.6) | 1 (0.2) | |
| DAD | 16 (2.2) | 4 (0.6) | |
| Alpers syndrome | 15 (2.1) | 1 (0.2) | |
| Pearson syndrome | 10 (1.4) | 7 (1.1) | |
| MNGIE | 10 (1.4) | 5 (0.8) | |
| MERRF | 13 (1.8) | 7 (1.1) | |
| NARP | 8 (1.1) | 5 (0.8) | |
| Maternal inherited deafness | 5 (0.7) | 3 (0.5) | |
| Cardiomyopathy | 5 (0.7) | 3 (0.5) | |
| Hepatocerebral syndrome | 6 (0.8) | 3 (0.5) | |
| RIM with COX deﬁciency | 2 (0.3) | 1 (0.2) | |
| Barth syndrome | 2 (0.3) | 1 (0.2) | |
| Leukoencephalopathy | 4 (0.6) | 4 (0.6) | |
| No clinical symptoms | 56 (7.8) | 50 (8.1) | |
| Missing | 0 (0.0) | 1 (0.2) | |
| Muscle Biopsy |  |  | |
| Yes | 100 (13.9) | 139 (22.5) | |
| No | 619 (85.7) | 459 (74.2) | |
| Missing | 3 (0.4) | 21 (3.4) | |
| Ragged-Red Fibers |  |  | |
| Yes | 41 (5.7) | 28 (4.5) | |
| No | 32 (4.4) | 56 (9.0) | |
| Missing | 649 (89.9) | 535 (86.4) | |
| COX-DeficientFibers |  |  | |
| Yes | 39 (5.4) | 35 (5.7) | |
| No | 24 (3.3) | 43 (6.9) | |
| Missing | 659 (91.3) | 541 (87.4) | |
| ᵟ From Fisher’s Exact Tests.  \*Percentages exclude missing cases. | | |