Understanding Your Genetic Report
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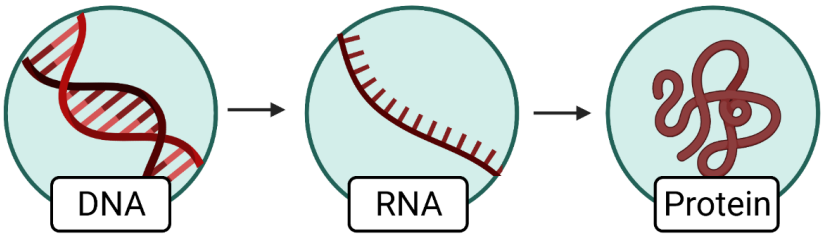
Basic Genetics of NR2F1:

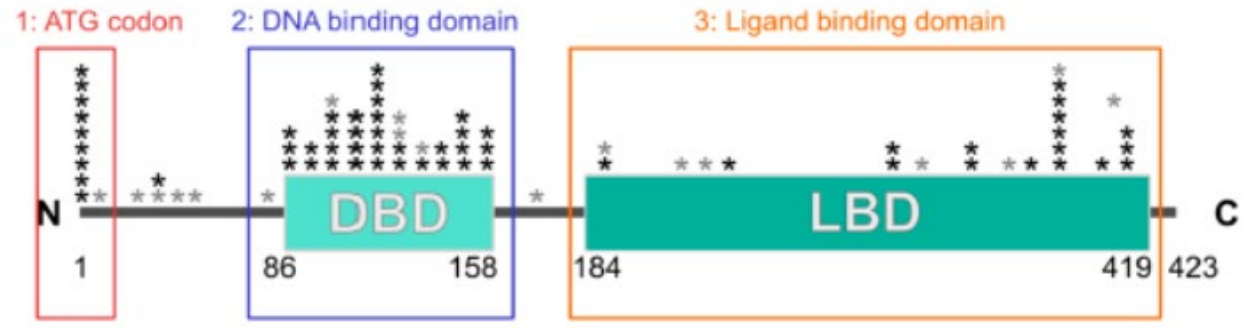
- *NR2F1* is a gene located on chromosome 5.
- The DNA in chromosomes provide instructions for making RNA for each gene.
- RNA of a gene provides instructions to make a specific protein.



- Proteins are long chains made up of a variety of different molecules called *amino acids*.
- Every protein made in cells has a different function to perform in cells.
- The *NR2F1* gene makes *NR2F1* RNA, which makes NR2F1 proteins.
- The NR2F1 gene in the DNA ultimately describes the NR2F1 protein that will be made.

There are Two Main Types of Genetic Mutations (aka variants):

1. Simple point mutations (aka missense mutations): This is a mutation causing a change of just one letter in the DNA. In Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS), these mutations occur most often in the:
    - DNA Binding Domain (DBD)
      OR
    - Ligand Binding Domain (LBD)



2. Truncations: These are deletions in the DNA, or a specific type of point mutation in the DNA which prevent the full NR2F1 protein from being made. The different types are:
    - Mutations at the beginning of the gene (Start Codon).
    - “Nonsense” mutations

- “Frameshift” mutations

Translating Your Genetic Report:

1. Find in the report where the variant (aka mutation) in the *NR2F1* gene is reported.

   ★ Usually, a small table identifying “Pathogenic Variants” is included on the first page of the report. The table might have categories like “Gene”, “Coding Sequence”, and “Amino Acid/ Protein Change”, among others.

   ★ (The specific location of this information on the actual report will vary depending on the organization which performed the genetic testing.)

2. In this table, under the *NR2F1* gene, find the series of numbers and letters starting with “**c.**” and/or “**p.**”.
   Notation using “**c.**” refers to the DNA. Notation using “**p.**” is referring to the protein.

   Example:
   c.123 T>C This describes a Point Mutation.
   - In this example, this means that at position **123** in the coding (**c.**) DNA, the nucleotide (letter) in their DNA should be a **T** but has changed to a **C**.

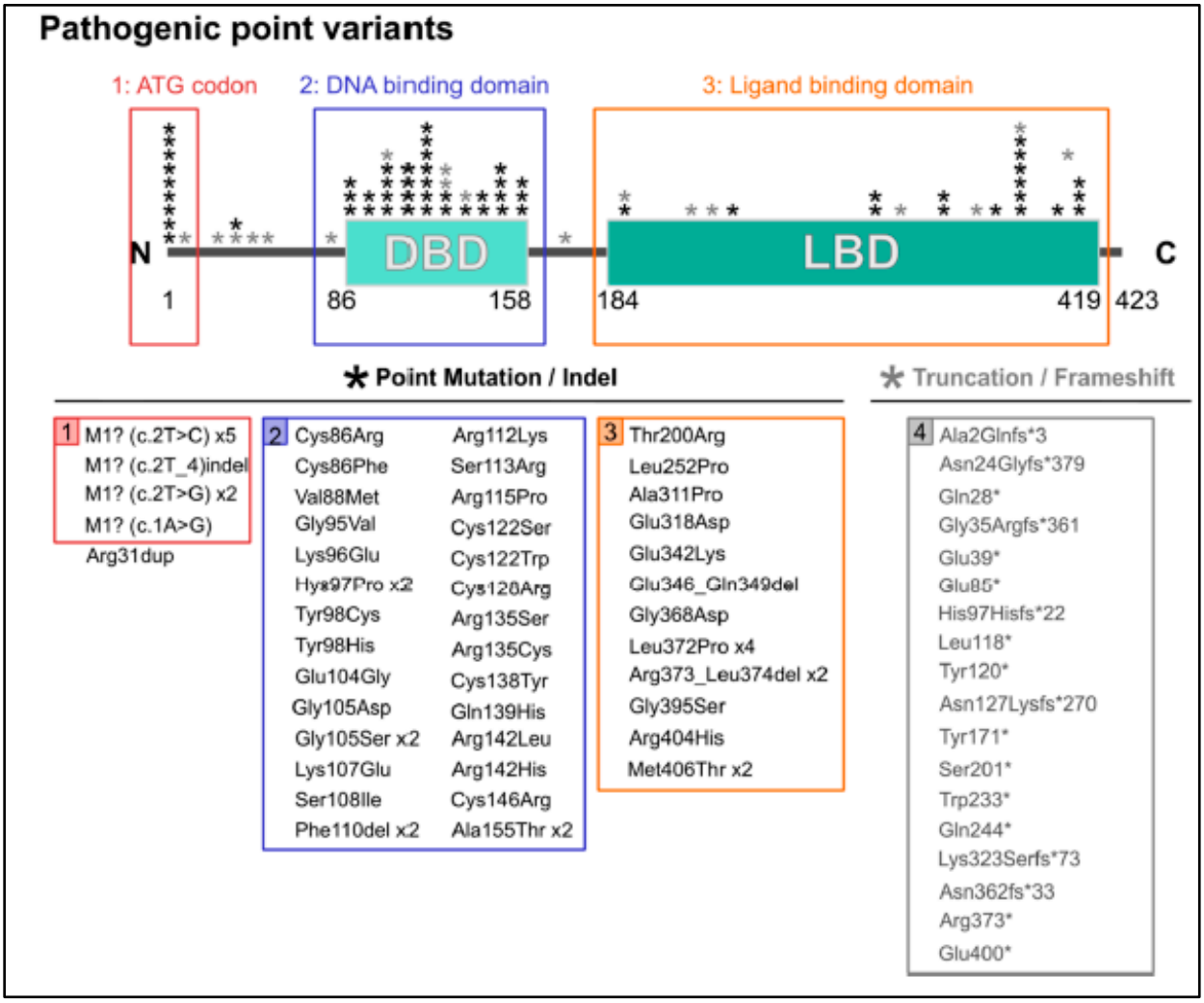
   p.F41S This is the same point mutation as above, just described in a different way.
   - This describes the type of *amino acid* in the NR2F1 protein (**p.**). Here, the *amino acid* at position **41** of the NR2F1 protein changes from **F** to **S**.
   - You don’t need to worry about the different amino acid letters or what they each stand for!

   *** Beware that “**c.**” positions are not the same as the “**p.**” positions***

   Other Examples:
   - **M1?** c.2T>C, or anything similar using “**M1?**”, denotes a mutation in the Start Codon (aka ATG Codon).
   - p.R373_L374 **del** denotes a Deletion from position 373 to 374.
   - p.L118***** or p.L118**X** denotes a Nonsense Mutation at position 118.
   - p.A2Q **fs** denotes a Frameshift Mutation at position 2.

3. Identify which example is closest to you and/or your child's. See Figure 1

Figure 1. Map of Known Mutations in the NR2F1 Protein:



(Figure taken from Bertacchi et al 2022)

Your and/or Your Child's Mutation to Other Patients:

Using the c. and p. information in your genetic report, along with the ranges below, you can classify almost every BBSOAS individual into one of six different groups:

1. Point Mutations in the DBD (**p.** 86 to 158)
2. Point Mutations in the LBD (**p**. 184 to 419)
3. Point Mutations in the Start Codon ("**M1?**")
4. Deletions ("**del**")
5. Frameshift mutations ("**fs**")
6. Truncations (***** or **X**)

*** Note that “p.” locations are not the same as the “c.” locations!

Table 1. Outcomes of Patients with Similar Mutations:

	All variants	*Variants in the DBD*	*Variants in the LBD*	*Deletions*	*Variants in the Start Codon*	*Truncations*	*Frameshift*
	(N = 92)	***(N = 32)***	***(N = 17)***	***(N = 15)***	***(N = 9)***	***(N = 11)***	***(N = 7)***
Morphology							
Myelin defects	14.13%	25%	11.76%	6.67%	0%	18.18%	0%
	13/92	8/32	2/17	1/15	0/9	2/11	0/7
Corpus callosum malformations	32.61%	46.88%	0%	13.33%	33.33%	63.64%	42.86%
	30/92	15/32	0/17	2/15	3/9	7/11	3/7

	All variants	*Variants in the DBD*	*Variants in the LBD*	*Deletions*	*Variants in the Start Codon*	*Truncations*	*Frameshift*
Development & behavior	***(N = 92)***	***(N = 32)***	***(N = 17)***	***(N = 15)***	***(N = 9)***	***(N = 11)***	***(N = 7)***
Developmental delay	88.04%	90.62%	70.59%	93.33%	88.89%	90.91%	100%
	81/92	29/32	12/17	14/15	8/9	10/11	7/7
Delayed motor development	30.43%	40.63%	11.67%	20.00%	66.67%	9.09%	42.86%
	28/92	13/32	2/17	3/15	6/9	1/11	3/7
Intellectual disability/ speech delay	86.95%	93.75%	70.59%	86.67%	88.89%	90.91%	85.71%
	80/92	30/32	12/17	13/15	8/9	10/11	6/7
Autism spectrum disorder (ASD)	38.04%	40.63%	29.41%	26.67%	33.33%	45.45%	71.43%
	32/92	13/32	5/17	4/15	3/9	5/11	5/7
ASD-like traits	14.13%	28.13%	0.00%	6.67%	22.22%	0.00%	14.29%
	13/92	9/32	0/17	1/15	2/9	0/11	1/7
ADHD (Attention deficit hyperactivity disorder)	18.48%	9.38%	5.88%	26.67%	22.22%	36.36%	42.86%
	17/92	3/32	1/17	4/15	2/9	4/11	3/7

	All variants	*Variants in the DBD*	*Variants in the LBD*	*Deletions*	*Variants in the Start Codon*	*Truncations*	*Frameshift*
Visual System	***(N = 92)***	***(N = 32)***	***(N = 17)***	***(N = 15)***	***(N = 9)***	***(N = 11)***	***(N = 7)***
CVI (Cerebral visual impairment)	42.39%	53.13%	47.06%	26.67%	33.33%	27.27%	42.86%
	39/92	17/32	8/17	4/15	3/9	3/11	3/7
Optic atrophy	67.39%	78.13%	47.06%	53.33%	77.78%	72.73%	71.43%
	62/92	25/32	8/17	8/15	7/15	8/11	5/7
Optic nerve hypoplasia	21.74%	12.50%	29.41%	0.00%	44.44%	27.27%	57.14%
	20/92	4/32	5/17	0/15	4/9	3/11	4/7
Pallid or small optic disk (P/SOD)	19.56%	18.75%	11.76%	33.33%	22.22%	18.18%	14.29%
	18/92	6/32	2/17	5/15	2/9	2/11	1/7

	All variants	*Variants in the DBD*	*Variants in the LBD*	*Deletions*	*Variants in the Start Codon*	*Truncations*	*Frameshift*
Others	***(N = 92)***	***(N = 32)***	***(N = 17)***	***(N = 15)***	***(N = 9)***	***(N = 11)***	***(N = 7)***
Epilepsy	45.65%	62.50%	29.41%	26.67%	55.56%	45.45%	42.86%
	42/96	20/32	5/17	4/15	5/9	5/11	3/7
Hypotonia	61.96%	75.00%	35.29%	60.00%	88.89%	54.55%	57.14%
	57/92	24/32	6/17	9/15	8/9	6/11	4/7

(Tables adapted from Bertacchi et al 2022)

References:

1. Bertacchi, M.; Tocco, C.; Schaaf, C.P.; Studer, M. Pathophysiological Heterogeneity of the BBSOA Neurodevelopmental Syndrome. Cells 2022, 11, 1260. https://doi.org/10.3390/ cells11081260